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Message from the Editor-in-Chief

Evolving variants suggest the COVID-19 pandemic will last longer than expected. The success of vaccines is evident; however, there is still no cure for COVID-19 to reduce the adverse outcomes in severely affected people who are generally at advanced ages. Meanwhile, more liberal restrictions have been announced in many regions, although by far the most contagious variant of the coronavirus is on the scene.

Gülhane Medical Journal enters 2022 with an affluent issue. We have prepared more articles in the current issue, from basic research to clinical, including interesting papers on COVID-19.

With this opportunity, I would like to express my gratitude to all submitting authors, reviewers, and editors for their contributions.

Prof. Dr. M. Ali Gülçelik
Editor-in-Chief

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Applications of platelet rich fibrin in dentistry

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ABSTRACT

Platelet-rich fibrin (PRF), a second-generation platelet concentrate, comprises a fibrin matrix containing numerous growth factors. These growth factors are involved with the cells responsible for the processes of tissue repair, regeneration, and growth. The applications of PRF have surpassed those of other platelet concentrates such as platelet-rich plasma due to the ease and economical method of its preparation, as well the elimination of the need for supplemental exogenous compounds like bovine thrombin and calcium chloride during preparation. This brief communication highlights the applications of PRF in dentistry and medicine and focuses on its preparation method, as it involves low risks and satisfactory results with minimally invasive techniques.

Introduction

Platelet concentrates collected from the whole blood were first introduced in medicine more than 20 years ago. The first attempts to use concentrated platelet growth factors were derived from the knowledge that supra-physiological doses of these growth factors could be obtained from platelets to promote wound healing during and after surgery. The idea was later established into what is known today as platelet-rich plasma (PRP) which was introduced also in dentistry in the 1990s by several leading clinician-scientists such as Whitman and Marx (1,2).

One of the main disadvantages of currently used biomaterials in tissue engineering is that the majority are typically avascular by nature, therefore, they do not provide the necessary vascular supply to provide successful regeneration of either soft or hard tissues (1,3).

Platelets are the key components in the early phases of tissue regeneration as they release many growth factors, coagulation factors, adhesion molecules, cytokines/chemokines, and various other angiogenic factors that promote the proliferation and activation of cells involved in wound healing (4).

However, despite the growing success and use PRP of in the initial years, several limitations prevented its full potential. The technique of collection and processing was lengthy and therefore required the use of an additional anticoagulant such as bovine thrombin or $CaCl_2$ (both known inhibitors of wound healing) to prevent clotting of the collected blood. These limitations brought the need to investigate new modalities for successful tissue regeneration (2,5).

From this perspective, a second-generation platelet concentrate that does not require anticoagulants was developed, allowing a shorter preparation time, named platelet-rich fibrin (PRF) (6).

Platelet concentrates are classified into pure platelet-rich plasma, PRF, leukocyte and platelet-rich plasma, pure PRF, liquid PRF. The platelet concentrate obtained using the centrifugation process is used for regenerative treatment in periodontal disease.

Preparation of PRF

PRF was introduced as the first total autologous concept without additional anticoagulants. The lack of a need for an anticoagulant significantly reduces the risk of trans-contamination (7). It also allows the physiological cell functions to continue after centrifugation (8). The main goal is to simplify the preparation process and minimize the required preparation steps and time for more suitable clinical applications. In this method, 10 mL peripheral venous blood is collected from a peripheral vein patient in a glass test tube. This is followed by immediate centrifugation at 3000 rpm for 10 min. If not immediately centrifuged, diffuse fibrin polymerization occurs, resulting in clot formation and reduction in quantity and quality (Figure 1) (1).

After processing PRF, the blood sample in the test tube is left to settle, allowing separation into three layers (8). The acellular plasma, or platelet-poor plasma, is the topmost straw-colored layer and, as the name suggests, lacks platelets. This step is followed by the PRF clot rich in fibrin and includes growth factors and cytokines in polymerized structure. The lowest, red fraction consists of erythrocytes.

When blood is collected in the test tube, it undergoes intrinsic coagulation due to contact with the glass, separating the blood into the clot and plasma.

During centrifugation, fibrinogen in the plasma fraction combines with the thrombin and forms the PRF region between the acellular plasma and the lower-packed red blood cell-rich fraction (8).

The superficial acellular fraction is removed, and the middle PRF fraction is collected using pliers along with the attached erythrocytes from the test tube. The fibrin clot is placed on a sterile surface and erythrocytes are scrapped off (Figure 2) (8).

Inflammatory cells and platelets are observed in abundance in the PRF matrices obtained by low-speed centrifugation force. Injectable PRF matrices also increase the number of platelets and leukocytes, which is obtained by low-speed centrifugation force (8).

Uses of PRF in dentistry

A. Extraction socket management

Extraction sockets have been managed using PRF as it is a natural fibrin matrix (8).

PRF can be used alone, replacing either a bone grafting material and/or barrier membrane. Since it is not necessary to use other biomaterials to cover an exposed flap, it offers the added advantage of exposing it to the oral cavity without risk of infection. PRF speeds the natural wound healing process without generating an immune response or foreign body reaction (4,5).

PRF is typically stabilized by simply using an X-suture within the socket. Primary closure is not required. It has been shown that within a 3-month healing period, the fibrin matrix transforms into new tissue, bone in the socket with overlying soft tissue. The

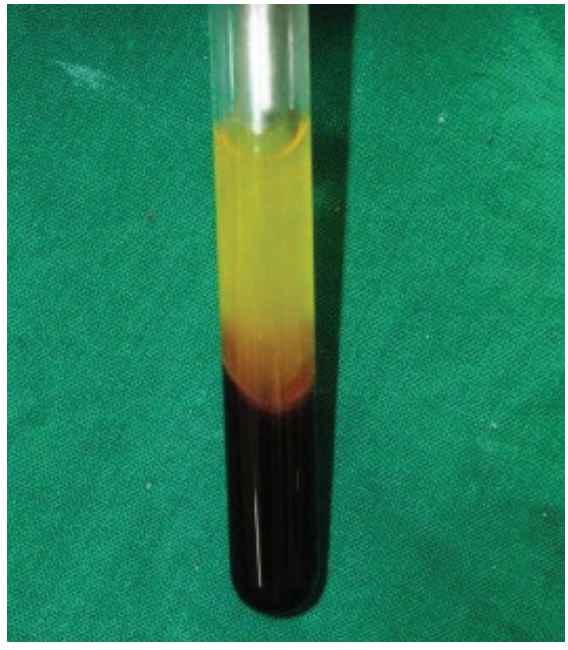

Figure 1. Test tube showing platelet rich fibrin after centrifugation of blood

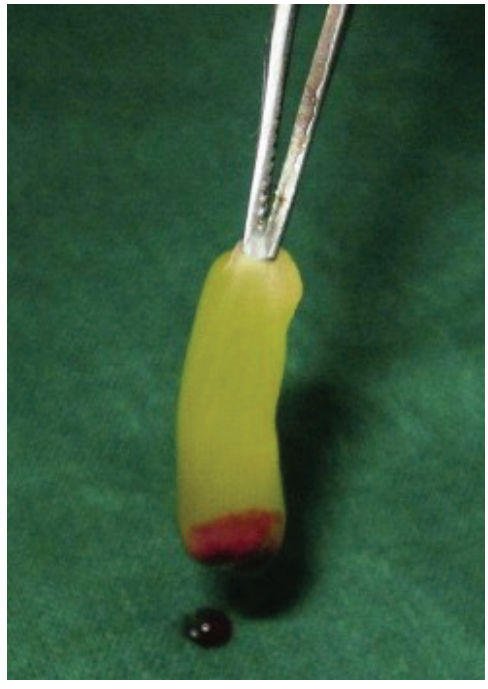

Figure 2. Platelet rich fibrin after centrifugation

rationale is to apply pro-angiogenic, pro-inflammatory cytokines, and growth factors from PRF to stimulate healing in extraction sockets (8).

B. Sinus elevation procedures

PRF is used to repair the Schneiderian membrane, as sole grafting material and close the window during the lateral sinus approach (9). While the success rate of the above-mentioned procedures has been reported very high, very few comparative studies have been conducted so far (9). Others have shown that PRF could be combined with a bone grafting material for sinus lift augmentation to reduce the overall healing time (1).

C. Soft tissue root coverage

One of the other most widespread use of PRF has been reported for managing root exposure (10). Since PRF acts more directly on soft-tissue regeneration, numerous clinical studies have focused on the use of PRF during periodontal surgery of mucogingival defects. These studies have investigated the potential of PRF for soft-tissue management of Miller Class I and II defects (11). PRF can be used instead of connective tissue grafts in Miller Class I and II defects with a thick biotype, resulting in improved vascularization, wound healing, and patient morbidity (11). With a proper patient selection, PRF can be as effective as a connective tissue graft or using a collagen-derived xenograft material for Miller Class I and II recession defects (12). It improves wound healing and speeds the re-vascularization of tissues with similar root coverage without the need for a second surgical site from the palate or using a foreign body collagen membrane (10).

Millers Class I gingival recession can be effectively treated by coronally advanced flap with PRF or with a subepithelial connective tissue graft (10). Studies have shown better root coverage with the combination of subepithelial connective tissue graft and coronally advanced flap compared with the coronally advanced flap with PRF (10). PRF can be a better alternative in root coverage procedures, provided that they do not require a second surgical site.

D. Periodontal regeneration

The regeneration of periodontal tissues is much more complex than most tissues as it comprises many tissues/cell types from different embryonic origins (8).

The PRF matrix releases the growth factor slowly over an extended period, helping the regeneration process. PRF improves tissue repair and helps blood clot formation (8).

In periodontal diseases, the bone defect occurs due to bacteria and its byproducts, suggesting treatment with PRF can be useful since it contains leukocytes and macrophages capable of eliminating the pathogens.

PRF affects different types of cells like gingival fibroblasts, chondrocytes, osteoblasts, and endothelial cells by influencing their recruitment, proliferation, differentiation and helps in hard and soft tissue repair of the tissues (13).

E. Guided bone regeneration

Guided tissue regeneration (GTR) and guided bone regeneration (GBR) exhibit successful and predictable results (11). PRF can either be cut into small pieces and combined with various bone biomaterials/grafting materials or subsequently flattened and used as a barrier membrane in GTR/GBR procedures (12). It offers numerous advantages compared to traditional collagen membranes as it contains autologous growth factors and living host-immune leukocytes (12). These cells fight against incoming pathogens, reducing the rate of infection by as much as 10-fold (12). For this reason, PRF membranes bear the advantage in that they may be left exposed to the oral cavity without increased risk of contamination (14).

To date, there exist two methods to combine PRF with GBR procedures (14). The first acts as a barrier membrane, whereby the PRF scaffolds can be flattened into natural autologous barrier membranes with a resorption time of between 10 and 14 days and provides additional wound healing properties to the overlying soft tissues (14). The second aim is to supply bone-grafting particles with PRF by cutting PRF membranes into small “fragments” and mixing them with bone-grafting materials (14). The latter improves the handling properties of bone grafts by making them “stickier” but also provides the proteins and growth factors responsible for facilitating angiogenesis in bone biomaterials (1,3).

F. Implant placement and ridge augmentation

A study on the effect of PRF placed in the maxillary posterior region and its association with implant stability after 4 to 6 weeks after implant placement showed that the implant placed with PRF showed better post insertion stability assessed by the resonance frequency analysis, compared with the contralateral region where implant placement was performed without PRF (15). The improved outcome was linked to the growth factors and the healing properties of PRF (16).

A review article concluded that, since PRF contains high number of growth factors, it has been used in healing extraction sockets, also in alveolar ridge augmentation procedures along with other bone grafts (16).

PRF is widely used by maxillofacial surgeons for the reconstruction of bone defects before implant placement. Evidence has shown improved osseous growth when PRF was used in intrabony defects (15).

PRF used in extraction sockets showed alveolar ridge preservation by decreasing alveolar width and height loss compared with the bone grafts used in alveolar sockets (16).

Dhote and colleagues suggested that bone filling by PRF after enucleation of cyst followed by tooth extraction showed complete filling of bony defects (17).

A comparative study showed that PRF improved the preservation of the alveolar ridge, preventing bone resorption compared with the group in which no filling material was used (18). Studies have also shown successful closure of oral antral closure after extraction of maxillary first molar using PRF (19).

Another study that used PRF with and without flapless split crest in elderly patients showed positive results with PRF as it does not require the second stage surgery as well as improved healing and regenerative properties (20).

The application of PRF in medicine

PRF has been very useful in middle ear surgery as it helps a faster healing process, by accelerating cell proliferation and matrix remodeling (9).

PRF was shown to help angiogenesis and proliferation of preadipocytes, having a beneficial role in the consolidation of an adipocyte graft in the technique of facial aesthetic lipostructure procedure (21).

PRF can be used as an alternative to conventional myringoplasty as it has certain advantages like improved healing properties and reduced postoperative pain with minimal risk when used multiple times in a procedure (21). It was reported that treatment with PRF was successful when used for the repair of tympanic membrane perforations (21).

Topical application of PRF was used with inlay butterfly cartilage myringoplasty for tympanic perforation patients to assess healing of tympanic membrane and complications (22). The success rate of this technique improved with topical application of PRF (21). The autologous PRF not only enhances the healing of the graft but also protects it from infection (22).

In non-healing ulcers of patients with diabetes, which occurs due to various local and systemic factors, the autologous PRF matrix was found useful as it helped in painless healing of the wounds (23). PRF is a very economical and safe adjuvant to treat difficult wounds (23).

Advantages (24)

- No need for additional anticoagulants and chemicals are not required
- Favorable healing due to natural and slower healing
- Preparation protocol is standardized
- Cost-effectivity and simplicity
- PRF matrix has elasticity and flexibility properties that also help hemostasis

Disadvantages (24)

- The quantity of autologous blood samples and PRF is low
- Not useful for large wounds
- Need for quick handling after collection
- Storage impossible
- High antigenicity due to circulating immune cells (donor specific).

Conclusion

PRF offers the advantage of utilization and safely and efficiently delivery at supra-physiological doses of autologous growth factors to host tissues without the fear of a foreign body reaction or tissue rejection.

Regeneration of the periodontal tissues after treatment is a complex process as new cementum, periodontal ligament and alveolar bone are to be formed. The role of PRF in the formation of new tissues in the regeneration process needs to be confirmed by histological studies. It is crucial to assess the effect of PRF on soft and hard tissues based on histological evidence similar to well-researched recombinant protein. Another area of research is to determine whether the strength, stiffness, or toughness of PRF scaffolds should be modified via centrifugation protocols for the different clinical indications proposed.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.S., Design: M.S., Data Collection or Processing: M.S., Analysis or Interpretation: M.S., Literature Search: S.B., Writing: S.B.

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Characteristics that distinguish leiomyoma variants from the ordinary leiomyomas and recurrence risk

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Keywords: Cellular leiomyoma, leiomyoma variant, leiomyoma with bizarre nuclei, mitotically active leiomyoma, recurrence

ABSTRACT

Aims: To evaluate the clinical characteristics that distinguish the leiomyoma variants from the ordinary ones, as well as the recurrence risk and patterns of these tumors.

Methods: This retrospective, case-control study included women diagnosed with uterine leiomyoma between 2009 and 2019 at a tertiary referral center in Turkey. The clinical characteristics of patients diagnosed with cellular leiomyoma (CL), leiomyoma with bizarre nuclei (LBN), mitotically active leiomyoma (MAL), and ordinary leiomyoma (OL) were examined. Disease recurrence and patterns of variants were evaluated.

Results: Among the 1,581 women with uterine leiomyoma, the incidence of CL, LBN, and MAL were 2.9%, 1.2%, and 1.3%, respectively. The occurrence for a single mass (63% in CL, 78.9% in LBN, 61.9% in MAL, 38.8% in OL; p=0.001) was more common, and the diagnosis of intramural leiomyoma (67.4% in CL, 73.7% in LBN, 71.4% in MAL, 90.8% in OL; p=0.002) was less frequent in the leiomyoma variant groups compared with the OL group. Recurrent leiomyosarcoma was observed in one woman with MAL.

Conclusions: This study showed that single mass rate was higher and intramural leiomyoma rate was lower in leiomyoma variants than in ordinary variants. Although rare, leiomyoma variants carry a risk of malignant recurrence after hysterectomy, suggesting the need for long-term follow-up.

Introduction

Leiomyoma variants are rare pelvic tumors. The variant rate is 1-4% (1,2). Cellular leiomyoma (CL), leiomyoma with bizarre nuclei (LBN) (atypical leiomyoma, symplastic leiomyoma, bizarre leiomyoma), and mitotically active leiomyoma (MAL) are the three variants. These tumors have some leiomyosarcoma (LMS) characteristics but do not have all the characteristics together. MAL has increased mitotic count of 5-20 mitotic figures per 10 high power fields but no nuclear atypia or tumor necrosis. LBN has moderate-to-severe nuclear atypia with low mitotic counts and no coagulative tumor cell necrosis (3). In the case of CL, there is increased cellularity of the lesion compared to the surrounding myometrial tissue (4,5).

Leiomyoma variants have similar symptoms and findings in the pelvic examinations of patients with ordinary leiomyoma (OL) and LMS. Immunohistochemistry, molecular-genetic analysis, and imaging techniques have a limited benefit for the differential diagnosis of these uterine mesenchymal tumors (6-9). It was reported that LMS and bizarre leiomyoma had significant overlapping staining patterns and immunoreactivity for p16, p53, and Ki-67 (7). Atypical leiomyoma and LMS share similar microRNA signatures (8). MED12 mutations were common in both OL and MAL (8). Magnetic resonance imaging (MRI), positron emission tomography and computed tomography have a limited utility to differentiate leiomyoma variants from OL and LMS (9). A definitive diagnosis is still currently carried out by a histopathological examination of myomectomy or hysterectomy specimens. Whether leiomyoma variants differ from one another in terms of clinical characteristics and behavior patterns is also unclear.

The management of variants after diagnosis is currently similar to the management of OL. However, the recurrence risk of these non-malignant variants has not been fully characterized yet, and rare malignant recurrent cases have been reported previously (10-12). Considering this knowledge, this study aims to evaluate the clinical characteristics that distinguish the leiomyoma variants from the ordinary ones, as well as the recurrence risk and patterns of these tumors.

Methods

In this retrospective study, medical records were reviewed for women who underwent hysterectomy or myomectomy due to a preoperative diagnosis of leiomyoma between January 2009 and August 2019 at a tertiary referral center. Written informed consent that allowed the use of their medical records in scientific research was obtained from all participants before the surgery. The study protocol was approved by the Institutional Review Board of University of Health Sciences Turkey, Etlik Zubeyde Hanim Women's Health Training and Research Hospital (protocol number: 2019/15, date: 10.10.2019) and complied with the Helsinki Declaration including current revisions.

The histopathological reports of the participants were reviewed. Women with OL and leiomyoma variants were included in the study. Women with adenomyosis, smooth muscle tumors of uncertain malignant potential (STUMP), uterine sarcomas, and concomitant endometrial, ovarian, and cervical malignancies were excluded from the study. According to the histopathological diagnosis, the study population was divided into four groups: the CL group, the LBN group, the MAL group, and the OL group. The control group consisted of OL cases. The sample size of the control group was determined to be approximately twice that of the largest variant group. The demographic, clinical, and histopathological characteristics of the four groups were compared.

Postmenopausal status was defined as no menstrual bleeding within (at least) one year before the operation in the absence of amenorrhea due to other reasons (such as intrauterine synechia, hyperprolactinemia, etc.). Regular or irregular bleeding, heavy and prolonged bleeding and intermenstrual bleeding were all identified as abnormal uterine bleeding. Surgery indications were described as previously reported (4,13).

The number of leiomyomas, as well as their size and localization, were determined according to histopathological reports in women who underwent hysterectomy. These details were also determined on the basis of ultrasonography reports in women who underwent myomectomy or hysteroscopic resection. The presence of atypia, degeneration, and necrosis in the surgical specimen was noted on the basis of information from the histopathological reports. Histopathologically confirmed recurrence according to reoperation reports was accepted as recurrence.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Statistics for Windows (Version 23.0, Armonk, NY: IBM Corp., 2015). Normality for continuous variables was checked using the Shapiro-Wilk test. The descriptive statistics were expressed as a frequency and mean±standard deviation or median (minimum-maximum). One-way ANOVA or the Kruskal-Wallis test was used to compare the differences among the groups where appropriate. Tukey test or the Dunn test was used for post-hoc analyses. The chi-square test or Fisher exact tests was used to compare the differences in categorical variables. A $p<0.05$ was accepted statistically significant.

Results

The medical records of 1,638 women with a preoperative diagnosis of uterine leiomyoma were evaluated. Nine women with LMS, 14 women with STUMP, two women with a mixed stromal tumor, four women with endometrial stromal sarcoma, 26 women with adenomyosis, and 2 women with concomitant ovarian carcinoma were excluded from the study. A total of 86 women diagnosed with leiomyoma variants (46 with CL, 19 with LBN, and 21 with MAL), as well as 98 women with OL were included in the study. The participants' recruitment is as shown in Figure 1. Of the 1,581 women with uterine leiomyoma, the incidence of CL, LBN, and MAL were 2.9%, 1.2%, and 1.3%, respectively.

As shown in Table 1, the demographic and clinical characteristics of the four groups were similar except in age. The mean age of the OL group was higher than the LBN group (46.5±5.8 y vs. 42.3±6.7 y, p=0.037). Most women included in the study were in the premenopausal period.

The postmenopausal rates of the groups were not significantly different. Ultrasonographic and histopathological findings of the women did not reveal any significant difference between the four groups in terms of tumor size and rates of degeneration and necrosis in leiomyoma specimens (Table 2). The median number of leiomyomas was higher in the OL group [3 (1-9)] than in the others [1 (1-7) in the CL group, 1 (1-7) in the LBN group, and 1 (1-6) in the MAL group] (p<0.001). The single mass rate was higher in the leiomyoma variant groups than in the OL group (63% in CL, 78.9% in LBN, 61.9% in MAL, 38.8% in OL; p=0.001). The rate of intramural leiomyoma was higher in the OL group than in the others (90.8% in the OL group, 67.4% in the CL group, 73.7% in the LBN group, and 71.4% in the MAL group; p=0.002). The rates of submucosal and subserous leiomyoma of the four groups were similar.

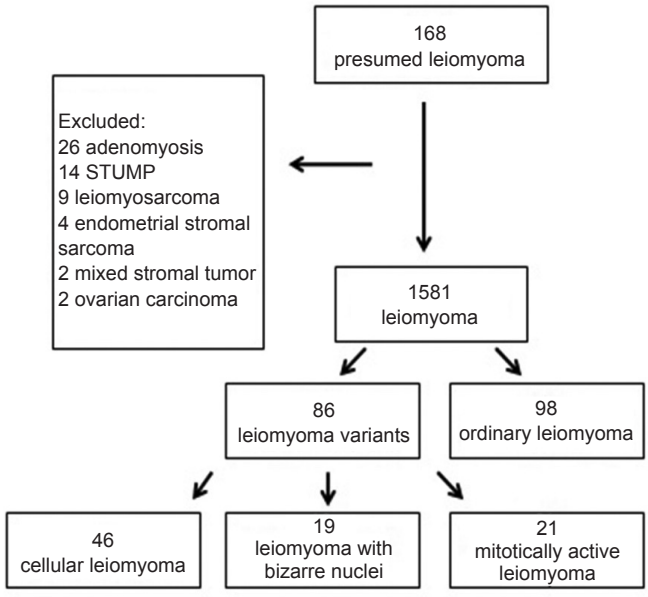

Figure 1. Flowchart of participants

STUMP: Smooth muscle tumors of uncertain malignant potential

Follow-up records of 73 women with leiomyoma variants were available. The mean follow-up period was 14.4±17.6 months with a range of 1-72 months. During the follow-up period, recurrence was observed in one woman with the MAL. She was 46 years old. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy due to an 18 cm in diameter degenerated myoma. The histopathological diagnosis of the hysterectomy specimen was MAL. In the follow-up visit 15 months after surgery, multiple semisolid recurrent masses were observed in the abdominal MRI examination. Tumoral debulking was carried out in the second operation. LMS was detected in a histopathological diagnosis of the recurrent mass. The length of survival for the woman-administered chemotherapy after the second operation was 32 months.

Discussion

The study results show that no significant demographic and clinical characteristics differentiated the three leiomyoma variants from the other. However, the women with OL were significantly older than the women with LBN when they underwent surgery. Ultrasonographic and histopathological findings showed that the leiomyoma variants tended to be a single mass, whereas

Table 1. Demographic and clinical characteristics of groups

	CL (n=46)	LBN (n=19)	MAL (n=21)	OL (n=98)	p value
Age (years), mean±SD	44.7±7.2	42.3±6.7	43.5±5.1	46.5±5.8	**0.017***
Gravidity, median (IQR)	3 (0-8)	3 (0-5)	2 (1-8)	3 (0-9)	0.581
Parity, median (IQR)	2 (0-6)	2 (0-4)	2 (1-4)	2 (0-7)	0.926
Postmenopausal, n (%)	4 (8.7)	1 (5.3)	0 (0)	7 (7.1)	0.689
Irregular menses, n (%)	20 (43.5)	11 (57.9)	14 (66.7)	50 (53.2)	0.330
Operation indication					0.252
Symptomatic leiomyoma, n (%)	39 (84.8)	16 (84.2)	21 (100)	86 (87.8)	
Enlarging leiomyoma, n (%)	7 (15.2)	3 (15.8)	0 (0)	12 (12.2)	
Symptom					
Abnormal uterine bleeding, n (%)	31 (67.4)	12 (63.2)	19 (90.5)	69 (70.4)	0.190
Postmenopausal bleeding, n (%)	1 (2.2)	0 (0)	0 (0)	0 (0)	0.467
Pelvic pain, n (%)	10 (21.7)	5 (26.3)	3 (14.3)	17 (17.3)	0.710
Urinary symptom, n (%)	0 (0)	1 (5.3)	0 (0)	1 (1.0)	0.328
Preoperative hemoglobin (gr/dL), median (IQR)	12.2 (5.8-15.6)	11.8 (9.6-14.9)	11.6 (7.7-14.1)	12.2 (5.8-15.2)	0.500

*Comparison of CL and LBN (p=0.497), comparison of CL and MAL (p=0.878), comparison of CL and OL (p=0.355), comparison of LBN and MAL (p=0.935), comparison of LBN and OL (p=0.037), comparison of MAL and OL (p=0.177).
CL: Cellular leiomyoma, LBN: Leiomyoma with bizarre nuclei, MAL: Mitotically active leiomyoma, OL: Ordinary leiomyoma, SD: Standard deviation, IQR: Interquartile range

Table 2. Ultrasonographic and histopathological findings of groups

	CL (n=46)	LBN (n=19)	MAL (n=21)	OL (n=98)	p value
Leiomyoma size, median (IQR)	8 (1.5-20)	8 (2.5-17)	7.5 (1-9)	7.5 (2.5-18.5)	0.529
Number of leiomyoma, median (IQR)	1 (1-7)	1 (1-7)	1 (1-6)	3 (1-9)	**<0.001**
Single leiomyoma, n (%)	29 (63.0)	15 (78.9)	13 (61.9)	38 (38.8)	**0.001**
Leiomyoma localization, n (%)					
Submucosal, n (%)	7 (15.2)	1 (5.3)	5 (23.8)	9 (9.2)	0.188
Intramural, n (%)	31 (67.4)	14 (73.7)	15 (71.4)	89 (90.8)	**0.002***
Subserous, n (%)	8 (17.4)	4 (21.0)	1 (4.8)	29 (29.6)	0.065
Degeneration, n (%)	9 (20.0)	5 (26.3)	2 (9.5)	12 (12.2)	0.284
Atypia, n (%)	0 (0)	19 (100)	0 (0)	0 (0)	**<0.001**
Necrosis, n (%)	1 (2.2)	0 (0)	0 (0)	0 (0)	0.467

*Comparison of CL and LBN (p>0.99), comparison of CL and MAL (p>0.99), comparison of CL and OL (p<0.001), comparison of LBN and MAL (p>0.99), comparison of LBN and OL (p=0.001), comparison of MAL and OL (p=0.015).
CL: Cellular leiomyoma, LBN: Leiomyoma with bizarre nuclei, MAL: Mitotically active leiomyoma, OL: Ordinary leiomyoma, IQR: Interquartile range

ordinary cases had multiple leiomyomas. The rate of intramural mass was also higher in ordinary cases than in the leiomyoma variants. In this series, one woman with MAL had a recurrence diagnosed as LMS.

Like previous reports, the incidence of leiomyoma variants was less than 5% in our series (1,2,14). As previously reported, most women with leiomyoma variants were in the fifth decade of their life and in the premenopausal period when they underwent surgery. This was the same for the OL cases (4,8,12,15). Symptoms of leiomyoma variants were also similar to OL cases in our series. Unlike our findings, Taran et al. (4) reported that menometrorrhagia and pelvic pressure symptoms were more likely in women with CL than OL.

Leiomyoma variants usually appear as a single mass (4,8,13). In the Taran et al. (4) series, one leiomyoma was found amongst the CL cases and three were found amongst the women with OL, as was the case in our series. Rothmund et al. (13) reported the 51.3% rate of single uterine masses in women with CL. We also found that the rate of the intramural tumor was lower in leiomyoma variants than in the OL cases. Prayson and Hart (16) reported that more than 60% of the MAL cases were submucosal. In our series, the rate of submucosal MAL was 23.8%, and it was not significantly different from the other groups.

The evolution of minimally invasive and uterine-conserving therapies requires a better understanding of the clinical behavior of leiomyoma variants. Although leiomyoma variants are accepted as benign pelvic masses, previous reports suggest that these tumors have a malign behavior. Molecular genetic studies showed that transcriptional profiles of CL with a 1p deletion were more likely to those of LMS than to profiles of OL on hierarchical cluster analysis (17). A metastasis of CL to the rib and vertebra three years after myomectomy (18), a pulmonary metastasis of CL 10 years after vaginal hysterectomy (4), and the recurrence of LBN (10) and MAL (11) as LMS were also reported previously. Cooney et al. (10) reported an atypical leiomyoma case recurring as LMS in the vagina 22 months after laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Gregová et al. (12) reported two LMS cases eight months after hysterectomy and seven years after myomectomy due to LBN. Kim et al. (11) reported a malignant recurrence of MAL with hyaline degeneration after a total hysterectomy. LMS was detected seven months after the first operation in a 68-year-old postmenopausal woman. The recurrent variant cases reported in the literature are shown in Table 3 (4,10-13,15,18-22). In our series, the recurrent case was a premenopausal woman. She was 46 years old and underwent a total hysterectomy due to MAL with degenerative changes. LMS occurred 15 months after the surgery. Based on previous reports and current findings, close postoperative follow-up appointments are necessary for patients with leiomyoma variants, especially those with degenerative changes.

The retrospective design, incomplete data such as the amount of decrease in hemoglobin levels that lead to operation decision and histopathological evaluation of surgical specimens by different pathologists are the limitations of this study. Nevertheless, the examination of all surgical specimens by experienced gynecopathologists at a single tertiary care center compensated for these limitations. The relatively small sample size of the variant groups and short follow-up periods were the other limitations of the study. Prospective studies with a larger series and longer follow-up periods are needed to confirm the presented results. A better understanding of the clinical characteristics and behavior of these tumors will lead to choosing an adequate surgical treatment modality and follow-up period.

Table 3. Recurrent leiomyoma variant cases reported in the literature

Author year	Study	Leiomyoma variant	Age (y)	Menopausal status	Tumor number	Tumor localization	Tumor size (cm)	The first operation	Recurrence time	Recurrence rate	Recurrent mass	Recurrence localization
Sharma et al. (20) 2004	Case report	CL (n=1)	55	Postmenopausal	1	Intraabdominal	7	Excision	7 m		LMS	Omentum
Taran et al. (4) 2010	Retrospective case control	CL (n=99)	44.7	82.8% Premenopausal	53.6% single	-	8.8	Hysterectomy	120 m	1/99	BML	Pulmonary
Kim et al. (11) 2010	Case report	MAL (n=1)	68	Postmenopausal	Multiple	Subserosal	10	Hysterectomy	7 m	-	LMS	Pelvis
Kang et al. (18) 2011	Case report	CL (n=1)	27	Premenopausal	1	-	13	Myomectomy	3y	-	BML	The rib and vertebrae
Guan et al. (19) 2012	Retrospective case control	CL (n=78)	45.3	6.4% Postmenopausal	-	-	7.5	Myomectomy	5 y	1/41	CL	Uterus
Rothmund et al. (13) 2013	Retrospective cohort	CL (n=76)	39.6	92.1% Premenopausal	1.9	-	6.1	Myomectomy	43 m	1/50	CL	Uterus
Ly et al. (15) 2013	Retrospective cohort	AL (n=51)	42.5	-	-	-	6.8	Hysterectomy	87.5 m	1/51	AL	Retroperitoneum
Cooney et al. (10) 2015	Case report	AL (n=1)	53	Postmenopausal	1	-	-	Hysterectomy	22 m	-	LMS	Vagina
Liang et al. (21) 2015	Retrospective cohort	AL (n=32)	47	-	-		6.4	Myomectomy	65 m and 84 m	2/32	AL	Uterus
Guraslan et al. (22) 2015	Case report	CL (n=1)	52	-	3	Intramural	-	Hysterectomy	10 y	-	CL	Pelvis
Gregová et al. (12) 2019	Retrospective cohort	LBN (n=108)	43	-	-	-	0.5-15	Hysterectomy/ myomectomy	8 m-7 y	5/108	LBN (2) MAL (1) LMS (2)	Vaginal stump, uterus

Y: Year, CL: Cellular leiomyoma, M: Month, LMS: Leiomyosarcoma, BML: Benign metastasing leiomyoma, MAL: Mitotically active leiomyoma, AL: Atypical leiomyoma, LBN: Leiomyoma with bizarre nuclei

Conclusion

In conclusion, the leiomyoma variants had a higher rate of single masses and a lower rate of intramural localization than the ordinary ones. It should be kept in mind that there may be a leiomyoma variant in women with a single leiomyoma other than intramural localization. Additionally, this study showed that the leiomyoma variants have a risk of malign recurrence after hysterectomy, even if this is rare. Long-term follow-up will be needed after hysterectomies or myomectomies are carried out due to these rare tumors.

Ethics

Ethics Committee Approval: The study were approved by the Institutional Review Board of University of Health Sciences Turkey, Etlik Zubeyde Hanim Women's Health Training and Research Hospital, of Local Ethics Committee (protocol number: 2019/15, date: 10.10.2019).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: T.K., F.K., Design: T.K., S.Y.E., F.K., Ç.G.M., Ş.K.A., Ö.L.T., Data Collection or Processing: T.K., S.Y.E., G.D., F.A., Analysis or Interpretation: Ç.G.M., J.K., Ş.K.A., Ö.L.T., F.KÜ., Literature Search: T.K., S.Y.E., G.D., F.A., Writing: T.K., J.K.

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Determining knowledge and willingness regarding stem cell donation among health science students: A cross-sectional study

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ABSTRACT

Aims: This study evaluated health science students' knowledge of stem cell donation, their willingness to become potential stem cell donors, and their perceived incentives and barriers to becoming potential stem cell donors.

Methods: This cross-sectional study was conducted in the faculty of health sciences of a university in Turkey. Data were collected using a questionnaire administered to health science students enrolled in the department(s) of child development, health management, midwifery, nursing, nutrition and dietetics, and physiotherapy and rehabilitation in October 2019.

Results: The sample included 541 students (80.8% women) with a mean age of 19.70±1.52 years. Most (80.8%) of the students stated that they did not know what stem cell donation is. Of those who knew what stem cell donation is (n=104), 5.8% reported that they were registered as potential stem cell donors, and 68.3% stated that they would like to be a potential stem cell donor. The most common reason for wanting to be a potential stem cell donor was the belief that the donation saves lives (n=71, 83.1%), and the most common reason for unwillingness or indecision about being a stem cell donor was the belief that there may be side effects (n=33, 57.6%).

Conclusions: We determined that most health science students did not know what stem cell donation is. Moreover, a large proportion of the students who knew about the stem cell donation expressed willingness to become potential stem cell donors, but very few of them were registered with the stem cell bank.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an effective and life-saving method in treating many malignant and nonmalignant diseases. HSCT is classified as allogeneic, syngeneic, or autologous. Allogeneic transplantation is performed using stem cells obtained from a donor whose human leukocyte antigens (HLA) are compatible with those of the recipient (1). A factor limiting the applicability of this treatment is the low rate of HLA-compatible related donors (2). If there is no related match, allogeneic transplantation can also be performed from HLA-compatible unrelated donors (1). However, one of the main obstacles to this is the lack of potential unrelated bone marrow donors (3).

There are three stem cell banks in Turkey where volunteer potential stem cell donors are registered. These stem cell banks organize recruitment drives to increase the number of volunteer donors (4). Having more donors increases the likelihood of finding an HLA-compatible donor, resulting in more transplantations (5). It has been reported that there are now 470,000 volunteer donors registered with the Turkish Stem Cell Coordination Center. A quarter of this number consists of potential donors between the ages of 18 and 25 years, who are expected to remain active in the system long term (6). Young donors are also preferred because they have fewer medical risks and tend to provide better posttransplant outcomes. As university students are generally young, healthy, educated, open-minded, and active in the community, they represent an important group in stem cell donor recruitment (7).

Various reasons for not wanting to donate stem cells or register with stem cell banks have been reported in the literature. These include lack of knowledge about stem cell donation (8-11), health concerns (8,9,11), the idea of compromising bodily integrity (12), fear of pain (11,13), financial issues (13), and fear of complications (13). Few studies have examined these issues in the young population in Turkey. Evaluating young people's knowledge and willingness to donate stem cells will facilitate efforts to recruit more donors by helping to determine the factors that encourage and inhibit them from becoming potential stem cell donors and identify issues that should be emphasized when educating the public. University students comprise an important segment of the young population and can provide valuable insight into other young people in their age group. Simultaneously, considering that health science students will enter the health system in the future and may affect recruiting stem cell donors, it is important to determine their knowledge and perceptions of stem cell donation. This study evaluated health science students' knowledge of stem cell donation, their willingness to become potential stem cell donors, and their perceived incentives and barriers to becoming potential stem cell donors.

Research questions

1. Do health science students know what stem cell donation is?

2. Do health science students want to be potential stem cell donors?

3. What are health science students' incentives for and barriers to becoming potential stem cell donors?

Methods

Study design

This research was designed as a cross-sectional study and was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cross-sectional research (14).

Setting and participants

The study was conducted with students enrolled in the department(s) of child development, health management, midwifery, nursing, nutrition and dietetics, and physiotherapy and rehabilitation in the health sciences faculty of a university in Turkey. No sampling method was applied. Eligibility criteria were being a registered student in a department listed above, volunteering to participate in the study, and fully completing the study questionnaire. The study population consisted of 766 students. Of these, 559 students were reached during the study period due to absenteeism or leave. Two of the students did not consent to participate, and 16 were excluded because they did not complete the questionnaire thoroughly. Therefore, the study was completed with 541 students (70.6%).

Measurement

Data were collected using a 14-item questionnaire created by the researchers based on relevant literature (8-13,15-22). This questionnaire consisted of three parts. The first part of the questionnaire included six questions about descriptive characteristics such as the student's age, gender, and place of residence before coming to university. The second part of the questionnaire consisted of four questions evaluating the student's knowledge about stem cell donation, and the third part comprised four questions about their willingness to become a potential stem cell donor.

Data collection

Data were collected using the face-to-face interview method in the classrooms of the faculty of health sciences in October 2019. We contacted the instructor responsible for each course to schedule the date and time of data collection. At the beginning of a class session, we provided information about the study and informed the students that participation was voluntary, they had the right not to answer the questions, and they could withdraw from the study. We also explained to the participants that the information obtained through the study would be anonymized and used for scientific purposes only. After obtaining informed consent from the students who agreed to participate, we distributed the questionnaires. The students were informed that they did not have to write their names on the questionnaire forms. To prevent bias, we asked the students to complete the questionnaire independently, without getting information from any other person or source. We collected the questionnaires immediately after the students completed them. The average time to complete the questionnaire was 10 to 15 minutes.

Statistical Analysis

IBM Statistical Package for the Social Sciences Statistics for Windows, version 24.0 (Armonk, NY: IBM Corp.) was used for

data analyses. Descriptive statistics were expressed as number (n), percentage (%), and median (first quartile-third quartile). Kolmogorov-Smirnov test was used to determine whether continuous data were normally distributed. Chi-square test was used to analyze categorical variables, and Mann-Whitney U test was used to analyze continuous variables with non-normal distribution. P<0.05 was accepted as an indicator of statistical significance.

Ethics

Ethical approval was obtained from the Cankiri Karatekin University Local Ethics Committee (decision no: 2019/145, date: 23.10.2019). After receiving ethical approval, institutional permission to conduct the study was obtained from the faculty of health sciences of the university. This study was conducted following the principles of the Declaration of Helsinki.

Results

The descriptive characteristics of the 541 students included in the study are summarized in Table 1. The average age of the students participating in the study was 19.70±1.52 years, 80.8% were women, 55.3% came to the university from urban areas, 59.9% were nursing students, and 56.2% were first-year students. A family history of cancer was reported by 17.6% of the students.

Table 2 presents the self-reported knowledge status of the students participating in the study regarding stem cell donation. Most (80.8%) of the students stated that they did not know what stem cell donation is, and 88.5% did not know what the bone marrow bank is. However, 88.4% stated that they wanted to be informed about the stem cell donation. Of the students who knew what stem cell donation is (n=104), 60.6% reported that they obtained this information from online resources and 53.8% from school.

Of the students who knew what stem cell donation is (n=104), 5.8% reported that they were registered as potential stem cell donors, 68.3% stated that they want to be a potential stem cell donor, 20.2% were undecided, and 11.5% did not want to be a stem cell donor (Table 3). The most common reason for wanting to be a potential stem cell donor was the belief that the donation saves lives (n=71, 83.1%). The most common reason for unwillingness or indecision about being a stem cell donor was the belief that there may be side effects (n=33, 57.6%).

Table 1. Descriptive characteristics of the students (n=541)

Characteristic	
Age (years), mean±SD	19.70±1.52
Gender, n (%)	
Female	437 (80.8)
Male	104 (19.2)
Pre-university residence, n (%)	
Urban center	299 (55.3)
Non-urban area	242 (44.7)
Department, n (%)	
Nursing	324 (59.9)
Child development	59 (10.9)
Midwifery	57 (10.5)
Nutrition and dietetics	46 (8.5)
Health management	32 (5.9)
Physiotherapy and rehabilitation	23 (4.3)
Year of education, n (%)	
First	304 (56.2)
Second	121 (22.4)
Third	78 (14.4)
Fourth	38 (7.0)
Family history of cancer, n (%)	
Yes	95 (17.6)
No	446 (82.4)

Data presented as mean±SD or n (%).
SD: Standard deviation

Table 2. Students' knowledge of stem cell donation (n=541)

		n (%)
Knows what stem cell donation is	Yes	104 (19.2)
	No	437 (80.8)
Source(s) of information about stem cell donation if known (n=104)*,#	Internet	63 (60.6)
	School education	56 (53.8)
	Television/radio	34 (32.7)
	Health professionals	30 (28.8)
	Signs/posters/billboards	18 (17.3)
	Newspaper/magazine	15 (14.4)
	Relative/friend	13 (12.5)
Wants detailed information about stem cell donation	Yes	478 (88.4)
	No	63 (11.6)
Knows what the bone marrow bank is	Yes	62 (11.5)
	No	479 (88.5)

*Percentages calculated based on those who knew what stem cell donation is (n=104).
#Respondents could select multiple options

Table 3. Health sciences students' willingness to become potential stem cell donors (n=104)*

		n (%)
Registered potential stem cell donor	Yes	6 (5.8)
	No	98 (94.2)
Willingness to be potential stem cell donor	Yes	71 (68.3)
	No	12 (11.5)
	Undecided	21 (20.2)
Perceived incentives for being a potential stem cell donor (n=71)#, **	Believing that donation saves lives	59 (83.1)
	Wanting to help others	45 (63.4)
	Hearing about patients who benefited from stem cell transplantation	33 (46.5)
	Believing that a relative/friend needs/may need stem cells	19 (26.8)
	Being informed about the donation process and related risks	8 (11.3)
	Wanting to be appreciated by others for this action	3 (4.2)
	Having relatives/friends who are potential stem cell donors	2 (2.8)
Perceived barriers to being a potential stem cell donor (n=33)#, ***	Believing that there may be side effects	19 (57.6)
	Not being informed of the risks	16 (48.5)
	Fear (of medical procedures, pain, blood donation, infectious disease, death)	13 (39.4)
	Not knowing about the procedures involved	10 (30.3)
	Believing that it will harm his/her health	10 (30.3)
	Not having the opportunity	7 (21.2)
	Believing that his/her family will not approve	6 (18.2)
	Having poor health/believing they are not eligible to donate	3 (9.1)
	Believing it will be expensive	3 (9.1)
	Concern about not being able to opt out of the registry later	2 (6.1)

#Respondents could select multiple options.
*Percentages calculated based on those who knew what stem cell donation is (n=104).
**Percentages calculated based on number willing to become potential stem cell donor (n=71).
***Percentages calculated based on number unwilling/undecided about becoming potential stem cell donor (n=33)

Table 4 shows the comparison of sociodemographic data of students based on their knowledge of stem cell donation. The median age was significantly higher among students who knew what stem cell donation is compared with those who did not ($z=-4.294$, $p<0.001$), and significantly fewer first-year students knew what stem cell donation is ($\chi^2=32.803$, $p<0.001$).

Table 5 shows the comparison of descriptive characteristics based on their willingness to become potential stem cell donors. The data were calculated for students who reported that they knew what stem cell donation is (n=104). It was found that older students ($z=-2.971$, $p=0.003$) and those in higher classes ($\chi^2=8.373$, $p=0.039$) were more willing to become potential stem cell donors.

Discussion

This study determined that most health science students did not know what stem cell donation is. Of the students who knew what stem cell donation is (19.2%), a small proportion (5.8%) were registered with the stem cell bank, but a high proportion (68.3%) stated that they wanted to be registered as potential stem cell donors.

Kim and Shin (23) provided hematopoietic stem cell donation education to nursing students and found that knowledge, attitudes, and willingness were better among students who received this education than those who did not. Azzazy and Mohamed (24) also reported improvement in the knowledge and attitudes of nursing students who received education about stem cell therapy. In a study of medical and law students in Turkey, a 15-minute brief education about HSCT increased students' knowledge and awareness (18). These findings indicate that education interventions can raise knowledge among university students in the age group expected to remain in the stem cell donation system for the long term. In this study, most students stated that they did not know what stem cell donation is. These students can be educated to increase their knowledge of stem cell donation.

In this study, the majority (88.4%) of the students stated that they want to receive detailed information about stem cell donation. Available literature indicates that information about stem cell donation or stem cell transplantation has been obtained from various sources. Preferred sources of information reported in previous studies included health professionals, the internet, and other media such as television, newspapers, radio (8,11,12,18).

Table 4. Comparison of students' knowledge of stem cell donation according to sociodemographic data

	Knowledge of stem cell donation			
	Knows (n=104)	**Does not know (n=437)**	**Test**	**p**
Age (years), median (Q1-Q3)	20.0 (19-21)	19.0 (19-20)	-4.294[a]	**<0.001**
Gender, n (%)				
Female	82 (18.8)	355 (81.2)	0.309[b]	0.578
Male	22 (21.2)	82 (78.8)		
Pre-university residence, n (%)				
Urban center	58 (19.4)	241 (80.6)	0.013[b]	0.909
Non-urban area	46 (19.0)	196 (81.0)		
Department, n (%)				
Nursing	73 (22.5)	251 (77.5)	8.032[b]	0.155
Child development	8 (13.6)	51 (86.4)		
Midwifery	7 (12.3)	50 (87.7)		
Nutrition and dietetics	10 (21.7)	36 (78.3)		
Health management	4 (12.5)	28 (87.5)		
Physiotherapy and rehabilitation	2 (8.7)	21 (91.3)		
Year of education, n (%)				
First	39 (12.8)	265 (87.2)	32.803[b]	**<0.001**
Second	22 (18.2)	99 (81.8)		
Third	27 (34.6)	51 (65.4)		
Fourth	16 (42.1)	22 (57.9)		
Family history of cancer, n (%)				
Yes	24 (25.3)	71 (74.7)	2.707[b]	0.100
No	80 (17.9)	366 (82.1)		

Data are shown as n (%) or median [first quartile (Q1)-third quartile (Q3)].
[a]Mann-Whitney U test, [b]Chi-square test

Table 5. Comparison of students' descriptive characteristics based on their willingness to become potential stem cell donors (n=104)*

	Willingness to become potential stem cell donor			
	Willing (n=71)	**Unwilling/undecided (n=33)**	**Test**	**p**
Age (years), median (Q1-Q3)	20.0 (20-21)	19.0 (19-20)	-2.971[a]	**0.003**
Gender, n (%)				
Female	59 (72.0)	23 (28.0)	2.426[b]	0.119
Male	12 (54.5)	10 (455)		
Pre-university residence, n (%)				
Urban center	42 (72.4)	16 (27.6)	1.040[b]	0.308
Non-urban area	29 (63.0)	17 (37.0)		
Department, n (%)				
Nursing	52 (71.2)	21 (28.8)	0.993[b]	0.319
Other[#]	19 (61.3)	12 (38.7)		
Year of education, n (%)				
First	21 (53.8)	18 (46.2)	8.373[b]	**0.039**
Second	18 (81.8)	4 (18.2)		
Third	18 (66.7)	9 (33.3)		
Fourth	14 (87.5)	2 (12.5)		
Family history of cancer, n (%)				
Yes	19 (79.2)	5 (20.8)	1.710[b]	0.191
No	52 (65.0)	28 (35.0)		

*Percentages calculated based on those who knew what stem cell donation is (n=104).
[#]Child development, health management, midwifery, nutrition and dietetics, physiotherapy and rehabilitation.
Data are shown as n (%) or median [first quartile (Q1)-third quartile (Q3)].
[a]Mann-Whitney U test, [b]Chi-square test

In this study, we determined that most of the students who knew about the stem cell donation obtained this information via the internet, formal education, and television/radio. These findings suggest that using these information sources is effective in education aiming to inform the public. Reliable information about stem cell donation can be disseminated through the education provided by health professionals, detailed study of the subject in schools, the inclusion of educational content on television/radio, and especially the internet and social media, which are widely used by the new generation. In this way, awareness can be raised among the young population, increasing their likelihood of registration and enlarging the donor pool. Simultaneously, students who will work as health professionals after graduation should have enough knowledge and positive attitudes about stem cell donation. This will enable them to serve as a reliable source of information that can support the community in their decisions about becoming stem cell donors.

Kwok et al. (11) reported that individuals with more knowledge about HSCT were more likely to be hematopoietic stem cell donors. In contrast, in this study, many students who knew about the stem cell donation were willing to donate, but few were registered as potential stem cell donors. This raises the question of why these students were not registered despite their knowledge and willingness. Possible reasons may be a lack of motivation, lack of chance, and easy access to a registration site. We predict that more willing individuals can be registered in the donor pool by increasing students' motivation, organizing donor campaigns, and increasing the accessibility of the mobile blood donation team. However, the answer to this question should be investigated with a qualitative study.

Knowing the factors that encourage people to become a stem cell donor is important for expanding the potential donor pool (17). The main incentives stated by the students in this study who knew about the stem cell donation included the belief that donation saves lives, the desire to help others, and having heard about patients who benefited from stem cell transplantation. Suluhan et al. (12) also determined that the idea of saving lives was one of the main reasons for wanting to be a stem cell donor. In a study by Aurelio et al. (15), helping patients was a participant' primary motivators for registering as donors. Bart et al. (10) found that the prospect of saving lives, solidarity with fellow humans, and the prospect of increasing patients' chances of recovery were the main incentives for registering with stem cell banks. Emphasizing these motivating factors in the education provided to university students can increase their willingness, thereby helping to increase the number of potential stem cell donors.

The students in this study stated concerns about possible side effects, lack of knowledge about the risks, and fear (of medical procedures, pain, blood donation, infectious diseases, or death) as the main reasons for their unwillingness or indecision about being a potential stem cell donor. Barriers to registration reported in other studies have included pain, health concerns, fear of complications, and lack of information (8,10,11). These perceived barriers to being a potential stem cell donor are issues that should be focused on and addressed in the education provided to students. Additionally, it may be helpful to include information about common misperceptions and barriers to registration in all forms of educational material containing information about stem cell donation.

This study found that older students more frequently stated that they knew what stem cell donation is, while new students stated this less frequently. We also observed a greater willingness to be potential stem cell donors among older and higher classes. This finding may be attributable to the accumulation of theoretical and practical knowledge as they progress in their program in the faculty of health sciences.

Study Limitations

This study has several limitations. One of these is that the study was conducted with health science students of a single university. Therefore, the results obtained in this study cannot be generalized to society at large. Another limitation is that our results are based on an analysis of quantitative data. Qualitative studies are needed for a more comprehensive evaluation of experiences and opinions related to stem cell donation. Moreover, the students' knowledge and willingness regarding stem cell donation were evaluated using a questionnaire we prepared based on a literature review. Valid and reliable scales measuring awareness, knowledge, attitudes, and willingness about stem cell donation are needed to obtain more quantitative data on this subject.

Conclusion

This study determined that most health science students did not know what stem cell donation is. Moreover, many students who knew about the stem cell donation expressed willingness to become potential stem cell donors, but very few of them were registered with the stem cell bank. Older students and those in higher classes more frequently knew what stem cell donation is and expressed greater willingness to be potential donors. Our study sample included students from different geographical regions of Turkey and different cultures. Therefore, we believe that our results offer insight into the awareness and attitudes of young people in this age group. Modifying health science curricula to address the stem cell donation in more detail may improve knowledge in these students, who will join the health workforce after they graduate. Ensuring that health professionals know stem cell donation and transplantation will also facilitate the provision of reliable information to the community and registration of donors. The contents of educational and promotional materials related to stem cell donation should be

developed considering the factors that encourage and hinder individuals from donating stem cells.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Cankiri Karatekin University Local Ethics Committee (decision no: 2019/145, date: 23.10.2019).

Informed Consent: Informed consent was obtained from the students.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.B., F.İ.Ç., Design: D.B., F.İ.Ç., Data Collection or Processing: D.B., F.İ.Ç., Analysis or Interpretation: D.B., F.İ.Ç., Literature Search: D.B., F.İ.Ç., Writing: D.B., F.İ.Ç.

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Dermatology consultations in patients with hematological and solid organ malignancies

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ABSTRACT

Aims: Patients with hematological or solid organ malignancies are susceptible to various skin disorders. This study described the cutaneous problems related to the underlying diseases or their management in hematology and oncology inpatients.

Methods: In this retrospective study with a cross-sectional analysis, we examined the medical records of inpatients with hematologic or solid organ malignancy who consulted the dermatology department from January 2018 through March 2021. Sociodemographic characteristics, medical history and comorbidities, cancer type, and dermatological findings and diagnoses were noted. Patients who have consulted the outpatient clinic and those with inadequate medical records were excluded.

Results: The study included 200 patients (age, mean±standard deviation, minimum-maximum: 51.4±18.2, 18-89 years; female 51%). Most of the consultations were from the internal medicine clinic (26.4%), followed by the hematology and oncology clinics (12.5%). A quarter of the patients had acute myeloid leukemia, the most frequent disease among hematological malignancies. Breast cancer (7%) and testis cancer (7%) were the most common solid organ malignancies. The most common dermatological diagnoses were cutaneous infections (33.5%) and drug reactions (13.5%). Skin biopsies were performed in 19.5% (n=39) of the patients. The evaluation of the patient by a dermatologist for a cutaneous symptom or finding led to modifications of disease management in 67 patients (33.7%).

Conclusions: Dermatology consultations are frequently required in hematological or solid organ malignancies. A successful evaluation of skin manifestations in these patients may improve the quality of care in this vulnerable population.

Introduction

Hospitalized patients frequently need multidisciplinary care. Dermatologists may play a pivotal role in managing inpatients, usually more complicated and challenging than many outpatients (1). A study examining 591 dermatology consultations showed that 78% of the inpatients were misdiagnosed by non-dermatologists (2). Dermatology consultations change the diagnoses made by the primary team in more than 60% of the patients and affect the treatment plan of most (1,3-5). Despite some discrepancy among the published studies, the most frequent requesting service is internal medicine, while hematology and oncology are among the most common subspecialties (4,6).

However, dermatology is among the top five consultations requested from oncology clinics (7). Due to underlying diseases, chemotherapy, stem cell transplantation, and multi-drug treatments, immunosuppression makes this group prone to cutaneous conditions (7,8). Recently, there have been promising advances in cancer therapeutics with many new treatment agents, including immune checkpoint inhibitors, associated with cutaneous immune-related side effects (7-10). Therefore, there is an increasing need for closer collaboration between hematology, oncology, and dermatology departments (7,8).

Few studies have described the characteristics of skin findings in detail in hematology and oncology patients so far. In this study, we aimed to 1) categorize the frequent dermatological

diseases in hospitalized patients with malignancy, 2) analyze the role of dermatologists in diagnosing associated dermatological conditions, and 3) demonstrate the effect of dermatologists in the treatment strategies of patients.

Methods

This was a retrospective, cross-sectional study conducted using the medical records of patients diagnosed with hematologic and oncological malignancies who were referred to the dermatology clinic for cutaneous manifestations. The study included inpatient admissions between January 2018 and March 2021. Patients under the age of 18, not hospitalized, or with insufficient medical history were excluded. The study was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital Ethics Board (decision no: 2021/123, date: 06.01.2022).

We used the data from the Department of Dermatology and Venereology of the University of Health Sciences Turkey, a tertiary referral care hospital that provides consultant services for inpatients and outpatients. Sociodemographic and medical information, including cancer characteristics (cancer type, current therapeutics) and dermatological findings, were collected from the electronic medical records and patient charts.

Cutaneous conditions evaluated

Cutaneous conditions were classified into ten groups according to etiology:

1. Cutaneous infections (viral eruption, cellulitis, herpes zoster, fungal infection, scabies),
2. Drug eruptions,
3. Inflammatory disorders (subtypes of dermatitis),
4. Malignant tumors (cutaneous metastasis or primary skin cancer),
5. Steroid-induced acneiform eruption,
6. Deep vein thrombosis and thrombophlebitis,
7. Chemotherapy skin side effects,
8. Xerosis and pruritus,
9. Graft-versus-host disease (GVHD) and,
10. Other skin conditions.

Skin biopsy results following the dermatologist's evaluation were recorded. Recommendations by the dermatologist and whether the consultation changed the patient's immediate treatment plan were also analyzed.

The accuracy of the prediagnoses, if any, specified by the primary care team was also evaluated.

Additionally, we evaluated the effect of Coronavirus disease-2019 (COVID-19) on dermatology consultations requested for hematology and oncology patients.

Statistical Analysis

Statistical analyses were performed by Statistical Package for the Social Sciences for Windows version 22.0 (IBM, Armonk, NY, USA). Categorical variables were presented by frequency and percentage. Normally distributed continuous variables were expressed as mean±standard deviation. Non-normally distributed continuous variables were expressed as median (interquartile ranges, minimum-maximum).

Results

Demographics

A total of 2120 inpatient referrals were made during the study period. Of these, 265 (12.5%) were from the hematology and oncology clinics. Dermatology consultations were ordered most commonly from the internal medicine clinic (26.4%), followed by the intensive care unit (9.5%) and surgical clinics (8.3%). Among the internal medicine clinics, the highest number of referrals were from the hematology and oncology clinics (12.5%), followed by rheumatology (6.5%) and nephrology (4.7%).

The number of total consultations requested by years was 42 in 2018 (21%), 45 in 2019 (22.5%), 81 in 2020 (40.5%), and 53 in the only first three months of 2021 (26.5%). About half of the consultations (48%) (n=96) were requested during the COVID-19 pandemic, corresponding to the last 12 months of the 39-month study period. Of the 265 hematology-oncology consultations requested in total, 65 were follow-up consultations of the same patients. Of these patients, 37.5% had at least one medical comorbidity (Table 1).

Characteristics of underlying malignancies

Various hematologic (n=113) or solid organ malignancies (n=87) were encountered (Table 1). Distant organ metastases were present by 7.5%. The overall mortality rate was 2% (n=4). Among the deceased patients, orolabial herpes (n=2), contact dermatitis, and cutaneous metastasis of testis cancer were the dermatological diagnoses following consultations. These patients died within one week of the consultation request.

Role of the dermatology consultation

In this study, 47 different dermatological diagnoses were made in 10 major disease categories. All consultations were evaluated within 8 h of the consultation request.

The most common diagnoses were cutaneous infections (33.5%) and drug eruptions (13.5%), followed by dermatitis (11.5%), cutaneous metastasis (7.5%) (Figure 1a, 1b), xerosis and pruritus (5.5%), steroid-induced acne (5%), deep vein thrombosis and thrombophlebitis (%3), chemotherapy skin side effects (%3) (Figure 1c, 1d), GVHD (2.5%), and miscellaneous skin disorders (11.5%) (Table 2).

Table 1. Demographic and clinical characteristics of the patients (n=200)	
Age, years, mean±standard deviation (minimum-maximum)	51.4±18.2 (18-89)
<30, mean (standard deviation)	36 (18)
30-49, mean (standard deviation)	59 (29.5)
50-65, mean (standard deviation)	54 (27)
>65, mean (standard deviation)	51 (25.5)
Sex (female/male)	98/102
Comorbidity (n=74)	n (%)
Hypertension	28 (14)
Diabetes mellitus	18 (9)
Cardiac disease	11 (5.5)
Benign prostate hypertrophy	6 (3)
Pulmonary disease	5 (2.5)
Thyroid disease	5 (2.5)
Psychiatric disorder	5 (2.5)
Hematologic malignancy (n=113)	n (%)
Acute myeloid leukemia	50 (25)
Multiple myeloma	18 (9)
Acute lymphoblastic leukemia	14 (7)
Non-Hodgkin lymphoma	14 (7)
B-cell lymphoma	4 (2)
Mantle cell lymphoma	4 (2)
Burkitt lymphoma	4 (2)
Other (chronic myeloid leukemia, intestinal T-cell lymphoma, large B-cell lymphoma, natural killer T-cell lymphoma, follicular lymphoma)	5 (25)
Solid organ malignancy (n=87)	n (%)
Breast	14 (7)
Testis	14 (7)
Colon	12 (6)
Lung	9 (4.5)
Pancreas	5 (2.5)
Malignant melanoma	4 (2)
Stomach	4 (2)
Other [Ewing sarcoma (n=3), ovarian cancer (n=3), glioblastoma multiforme (n=3), osteosarcoma, peripheral nerve sheath tumor, cholangiocellular cancer, renal cell cancer, osteosarcoma, liposarcoma, hepatoblastoma, hepatocellular cancer, bladder cancer, rectum cancer, peripheral nerve sheath tumor, malignant mesenchymal tumor, gastrointestinal stromal tumor, endometrium, cervix, unknown origin]	25 (12.5)

Drug reaction was the second most common diagnosis. Steven Johnson syndrome (SJS)-toxic epidermal necrolysis (TEN) overlap (Figure 1e) due to the use of phenytoin-valproic acid and fluconazole was observed in two patients with lung and bladder cancers, respectively. Urticarial drug reaction (n=1) and symmetrical drug-related intertriginous and flexural exanthema (n=1) were recorded following administration of ciprofloxacin and piperacillin-tazobactam, respectively. The use of multiple antibiotics (≥3 antibiotics simultaneously) was recorded in three patients diagnosed with fixed drug eruptions. In 8 (40%) patients with maculopapular drug eruptions (n=20), simultaneous dual broad-spectrum antibiotic use was recorded; a combination of meropenem-teicoplanin was the most common suspicious dual-antibiotic (n=4). Meropenem (n=7), teicoplanin (n=5), piperacillin-tazobactam (n=3), and trimethoprim-sulfamethoxazole (n=3) were the most common individual suspicious antibiotics leading to a maculopapular (morbilliform) drug eruption. The majority (73.9%) of patients with maculopapular drug eruption had a hematological malignancy twice as common in patients with solid organ malignancies (13.3% vs. 5.7%).

Hematology and oncology services mentioned a suspicious diagnosis of their own in 34.5% (n=69) of dermatology consultations but no preliminary diagnosis in 65.5% of the patients. The dermatology team confirmed the preliminary

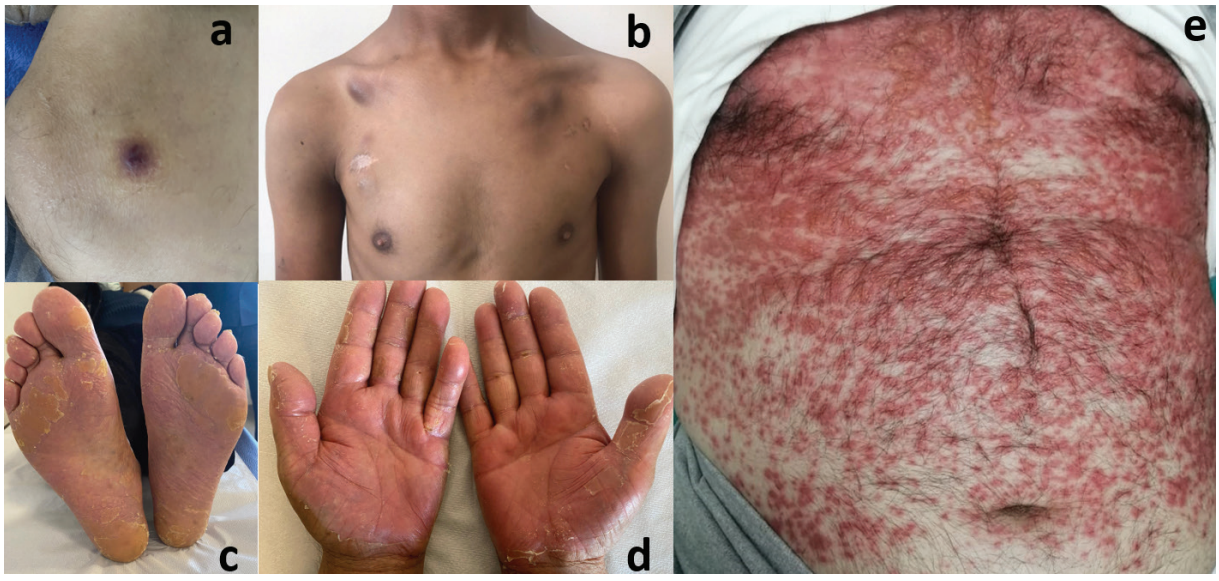

Figure 1. Cutaneous metastasis: **a)** A 64-year-old male patient with angiosarcoma and bone metastases. Purple-brown nodule, approximately 1*1 cm in size, on the medial side of the right knee. Histopathological examination confirmed angiosarcoma skin metastasis. **b)** A 22-year-old male patient was diagnosed with acute myeloid leukemia. Subcutaneous nodules are darker than normal skin, appearing on the trunk one month ago. The biopsy was compatible with leukemia cutis.
Acral peeling syndrome: **c, d).** A 76-year-old male patient diagnosed with colon cancer complained of peeling on the hands and feet after the 3rd course of capecitabine treatment. His symptoms were relieved with a potent topical steroid and moisturizer**.**
Steven Johnson Syndrome-toxic epidermal necrolysis overlap: **e)** A 68-year-old male patient was diagnosed with prostate cancer (2010) and lung cancer (2019). Fenotion was started due to brain metastases three weeks ago. Nikolsky signs positive areas with the involvement of more than 10% of the total body. In the early period, intravenous immunoglobulin was planned for the patient. And phenytoin, as well as suspicious other drugs, were stopped immediately

diagnosis by the hematologist or medical oncologist in 70.1% of 69 patients. The highest diagnostic accuracy was observed in GVHD and cutaneous side effects of cancer therapeutics (100%). However, stasis dermatitis was consulted as cellulitis in 30% of the cases, and 44.4% of the cutaneous metastases were mistaken for zona zoster or folliculitis. Steroid-induced acne, which can be observed in malignancy patients receiving high-dose steroids according to the treatment schedule, was the least accurately recognized dermatological diagnosis by primary physicians (Table 3).

Evaluation of the histopathological results

Histopathological examination was used in 19.5% (n=39) of the patients to confirm the dermatological diagnosis. Dermatology consultations led to changes in the medical management of 63 patients (31.5%) through the modification of antibiotic treatment (9%), current chemotherapy sessions (17.5%), or chemotherapeutic options and treatment plans (5%). Treatments recommended for the medical management of patients are listed in Table 4.

Discussion

In this study, the most common cutaneous disorder among dermatology inpatient consultations in hematology and oncology clinics was cutaneous infections followed by drug eruptions. Since oncology and hematology inpatients are immunosuppressed and predisposed to neutropenia due to cancer therapeutics, they are more susceptible to mucocutaneous infections and drug reactions due to multiple drug use and prophylaxis schemes (8-13). Although GVHD (2.5%) and cutaneous side effects of chemotherapeutics (3%) have been commonly reported in previous studies (8,10-13), they were rarely observed in our study. The current study included only the patients consulted in the dermatology department; therefore, all inpatients in hematology and oncology clinics were not examined. Since our hospital is a tertiary referral center for bone marrow transplantation and cancer treatment, hematologists and oncologists might be more familiar with skin conditions specifically related to their specialties, such as GVHD and the side effects of chemotherapeutics. Therefore, they might have managed some other patients without the need for a dermatology consultation. The correct preliminary diagnoses for these two dermatological diseases also support our suggestion.

The most common diagnoses in our study were cutaneous infections. More than half of them did not relate to any significant risk of mortality and morbidity, such as localized fungal or bacterial infections. The most frequently observed subgroups were zona zoster, cellulitis, and tinea unguium. Interestingly,

Table 2. Dermatological diagnoses in hematology and oncology inpatients		
Cutaneous infections (n=67), n (%)		
Viral	Herpes zoster	10 (7)
	Orolabial herpes	5 (2.5)
	Chicken pox	3 (1.5)
Bacterial	Cellulite	10 (6)
	Folliculitis	6 (3)
	Paronychia	3 (1.5)
Fungal	Tinea unguium	10 (5)
	Tinea pedis	6 (3)
	Pityriasis versicolor	5 (2.5)
	Tinea corporis	4 (2)
	Candidiasis	3 (1.5)
	Deep fungal (actinomyces)	1 (0.5)
Parasitic	Scabies	1 (0.5)
Drug eruptions (n=27), n (%)		
	Maculopapular	20 (10)
	Fixed drug	3 (1.5)
	SJS	2 (1)
	Urticarial	1 (0.5)
	Symmetrical drug-related intertriginous and flexural exanthema	1(0.5)
Dermatitis (n=23), n (%)		
	Contact dermatitis	7 (3.5)
	Seborrheic dermatitis	6 (3)
	Stasis dermatitis	5 (2.5)
	Perianal dermatitis	3 (1.5)
	Dermatitis (noted without specification)	2 (1)
Malignant skin tumors (n=19), n (%)		
Cutaneous metastasis	Acute myeloid leukemia	4 (2)
	Breast cancer	3 (1.5)
	Testis cancer	3 (1.5)
	Unknown origin	2 (1)
	Other (Burkitt lymphoma, intestinal T-cell lymphoma, lung cancer, angiosarcoma, colorectal)	5 (2.5)
Primary	Basal cell carcinoma	2 (1)
Steroid-induced acneiform eruption (n=10)		
Xerosis and accompanying pruritus (n=10)		
Deep vein thrombosis and thrombophlebitis (n=6)		
Cutaneous side effects of cancer therapeutics (n=6), n (%)		
	Acral peeling syndrome (capecitabine, cytarabine, bleomycin- etoposide-cisplatin, regorafenib)	3 (1.5)
	Palmar erythema (docetaxel)	2 (1)
	Nail discoloration (paclitaxel)	1 (0.5)
GVHD (n=5)		
Miliaria (n=2)		

Miscellaneous (n=25) (intertrigo, Still's disease, dystrophic calcification, amyloidosis, bullous pemphigoid, epidermal cyst, insect bite, vasculitis, stasis-related bulla, traumatic ecchymosis, acrochordon, leukocytoclastic vasculitis, terra firma forme dermatosis, petechiae secondary to thrombocytopenia).
GVHD: Graft-versus-host disease, SJS: Steven Johnson syndrome

Table 3. Diagnostic concordance and the influence of dermatology consultation

Cutaneous condition	Consulted with provisional diagnose/n	Diagnostic accuracy (%)*
Graft-versus-host disease	4/4	4/4 (100)
Cutaneous side effects of cancer therapeutics	5/6	5/5 (100)
Zona zoster	8/10	7/8 (87.5)
Tinea pedis and unguium	5/16	4/5 (80)
Cellulite	13/15	9/13 (69.2)
Drug eruption	14/27	9/14 (64.2)
Orolabial herpes	5/5	3/5 (60)
Cutaneous metastasis	9/19	5/9 (55.5)
Steroid-induced acneiform eruption	5/10	1/5 (20)

n: the total number of patients with that diagnosis. *Patients whose preliminary diagnosis by the physician was confirmed by the dermatologist / patients who were consulted with a preliminary diagnosis

Table 4. Treatments for medical management

Topical (n=145), n (%)		Systemic (n=78), n (%)	
Corticosteroids	55 (27.5)	Antihistamine drugs	26 (13)
Emollients	30 (15)	Antibiotics	19 (9.5)
Antibiotics	25 (12.5)	Antiviral	17 (8.5)
Antifungals	21 (10.5)	Corticosteroids	14 (7)
Acne treatments	10 (5)	Antifungal	6 (3)
Wet dressings	6 (3)		
Antivirals	3 (1.5)		

these infections are some of the essential topics of dermatology education in medical school, which could be better recognized by the primary team and primarily described in the consultation note. Nevertheless, the diagnostic accuracy of cellulitis was relatively low by the primary physicians. Stasis dermatitis was present approximately in one of every three patients consulted dermatology with the diagnoses of cellulitis. One study at two separate centers showed that 20-35% of patients admitted for cellulitis by the emergency department were mistakenly diagnosed as cellulitis by physicians other than dermatologists and infectious diseases specialists (14). Although stasis dermatitis is a clinical mimicked of cellulitis, bilateral, chronic, and non-tender erythema with usually long-standing pitting edema mainly indicates stasis dermatitis (1,15). A history of trauma in the affected area or accompanying tinea pedis or unguium with tenderness, warmth, swelling, and indistinct borders in a unilateral erythematous plaque, points to cellulitis. Additionally, rapid onset, presence of systemic symptoms such as fever, immunosuppression, and satisfactory response to antibiotics are findings in favor of cellulitis. However, in indistinguishable cases, Doppler ultrasonography could be considered (15,16). These observations suggest that postgraduate dermatology training programs help physicians better assess and manage patients with underlying malignancies and build more proper collaboration with dermatologists.

Drug reactions are another common dermatological condition with a higher risk of morbidity and mortality in patients with underlying malignancies. The frequency of adverse drug reactions in hematology consultations varies between 13 and 38% (8,17,18). In our study, drug reactions were recorded in 13.5% of 200 patients, and most of them were morbilliform drug eruptions (10%) in line with previous literature 9-17.3% (8,10,18). As in our study, most morbilliform drug reactions were uncomplicated conditions. Morbilliform or maculopapular drug eruptions usually present 1 to 2 weeks after initial exposure of the causative drug, may also show up sooner on rechallenge. Although most cases regress within 1-2 weeks, dermatology consultation is critical in confirming the diagnosis and excluding imitators such as viral exanthema seen in the immunosuppressive patient group (19,20). A dermatologist can help determine the suspected drug(s). More importantly, dermatologists may help to recognize the early signs of severe cutaneous drug reactions (SJS and TEN) such as mucosal involvement, skin tenderness, blistering, dusky red and coalescent macular exanthema, atypical target lesions, and Nikolsky sign (ready removal of the epidermis with slight unrelated pressure) (20,21). Therefore, dermatology consultations should be considered in the early period for patients with diffuse maculopapular eruptions.

The current study demonstrates the possible dermatological diagnoses encountered by physicians working with patients with

hematology and oncological malignancies. Although 47 different dermatological diagnoses were made in 10 main disease categories, most patients (72.5%) were managed with topical therapy, and only 39% required systemic medications. These data suggested that most skin conditions could be governed without aggressive treatments.

This study presents the 39-month experience of an advanced tertiary center. The last 12 months of the study period corresponds to the COVID-19 pandemic, which has rapidly affected the world and caused severe morbidity and mortality. While our center was mainly in charge of managing patients with COVID-19 infection in this period, hematology and oncology services were at the forefront of the departments that tried maintaining inpatient service properly. In this period, dermatology consultations are essential due to various skin manifestations of COVID-19 infections including urticarial, purpuric, erythema multiforme-like, chickenpox-like rash, acro-ischemia, chilblain-like eruptions, and pityriasis rosea like eruptions (22-25). Intense anxiety among patients and physicians and cutaneous side effects of several systemic medications are likely to increase dermatology consultations during the pandemic period. All these factors are potential causes of the increasing number of dermatology consultations in hematology and oncology inpatients during the pandemic period.

The retrospective design and lack of long-term follow-up are the main limitations of this study. The major strength is documenting a three-year experience of a large population from an advanced tertiary center.

Conclusion

In conclusion, the current study indicates that dermatology inpatient consultations of hematological or solid organ malignancies play an essential role in determining skin manifestations associated with underlying malignancy or treatment of the disease. A close collaboration between hematologists, oncologists, and dermatologists helps manage patients with underlying malignancies appropriately.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital Ethics Board (decision no: 2021/123, date: 06.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., S.N.Ç., G.A., Design: P.E., S.N.Ç., G.A., Data Collection or Processing: P.E., S.N.Ç., G.A., Analysis or Interpretation: P.E., S.N.Ç., G.A., Literature Search: P.E., S.N.Ç., G.A., Writing: P.E., S.N.Ç., G.A.

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Monitoring of gentamicin blood level in one-week-of-life neonates admitted to a special care nursery ward

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ABSTRACT

Aims: Gentamicin is routinely used in neonates as an empirical antibiotic for suspected sepsis at a dose of 4.0 mg/kg, either 24 or 36 hourly based on premenstrual age. Regularly, therapeutic drug monitoring is performed. This study was conducted to determine gentamicin blood level in one-week-of-life neonates on 4 mg/kg treatment.

Methods: Neonates who received gentamicin in a special care nursery ward were identified from the records retrospectively. The included subjects were neonates between 3 and 7 days old treated with gentamicin for at least three days. Admission diagnoses, dosing protocol (including dosage, the timing of the doses, and timing of blood samples) and measured gentamicin trough and peak levels were recorded.

Results: A total of 290 neonates met the inclusion criteria (male: 57.6%). Over 30% of the subjects treated with gentamicin experienced potential toxicity with trough levels above 1.0 µg/mL, and 15.9% of them had sub efficacy of the drug (peak level below 5 µg/mL). Six neonates had trough levels above 2.0 µg/mL. The percentage of potential toxicity was higher in subjects with presumed sepsis, in those with bodyweight between 2.5-2.99 kg and with 24-hour dosing interval.

Conclusions: We propose a trough-only monitoring protocol in non-critically ill neonates, as the practice of monitoring pre and post often necessitate additional blood sampling. The decision of not determining the peak levels routinely can be based on the outcome that gentamicin dosage of 4.0 mg/kg likely provides peak levels in desired range without any added risk of toxicity.

Introduction

Gentamicin is routinely used in neonates as an empirical antibiotic for suspected sepsis. It is given together with ampicillin or penicillin (cloxacillin if a staphylococcal infection is suspected) as recommended by World Health Organization. Due to its narrow therapeutic index, gentamicin required therapeutic drug monitoring (TDM) during treatment to ensure efficacy, reduce the potential for ototoxicity and nephrotoxicity, and reduce the potential for resistance.

There is considerable variation in dosing regimen guidelines, but the common dosage regimen used is between 4 and 7 mg/kg every 24 to 36 h, depending on the gestational age. In a study from Thailand, once-daily gentamicin therapy of 4 mg/kg in neonates of more than 34-week gestation resulted in appropriate peak and lower trough concentrations (1). The study suggested that routine collection of serum gentamicin concentration may not be necessary for neonates with normal renal function receiving a 3-day, once-daily gentamicin of 4 mg/kg for suspected sepsis. It was concluded that once-daily gentamicin dosing was preferable to any other dosing interval because of the simplicity of the regimen, which achieves desirable drug levels (1). In another study, neonates who received once-daily gentamicin at a dose of 5 mg/kg/day reported unacceptably high trough levels (2).

In Raja Perempuan Zainab II Hospital (HRPZ II), stable neonates with risk factors associated with neonatal sepsis such as maternal Group B Streptococcus infection, maternal fever, low birth weight, or preterm are treated in Special Care Nursery (SCN) Ward. Gentamicin is prescribed empirically combined with a penicillin drug, at a dose of 4.0 mg/kg, either 24 or 36 hourly based on the premenstrual age. Regularly, TDM is used for both trough and peak samples of gentamicin in SCN. In this study, we examined the peak and trough serum gentamicin level in one-week-of-life neonates on a 4 mg/kg dosing schedule.

Methods

In this single-center and retrospective study, neonates who received gentamicin at the SCN ward were identified from the database of TDM 2019 records for a one-year interval. TDM forms were reviewed for diagnoses, dosing history, including dosage, the timing of the doses, and timing of blood samples, and measured gentamicin trough and peak levels (Figure 1). We only included neonates between 3 and 7 days old admitted to the SCN ward in 2019 who were treated with gentamicin for at least three days. The study was approved by the Medical Research and Ethics Committee of the Ministry of Health, Malaysia (NMRR-20-254-53622 IIR date: 09.04.2020). Informed consent was not required due to the retrospective design of the study. Patients' information was anonymized and de-identified before analyses. The study protocol conforms to the 1975 Helsinki Declaration.

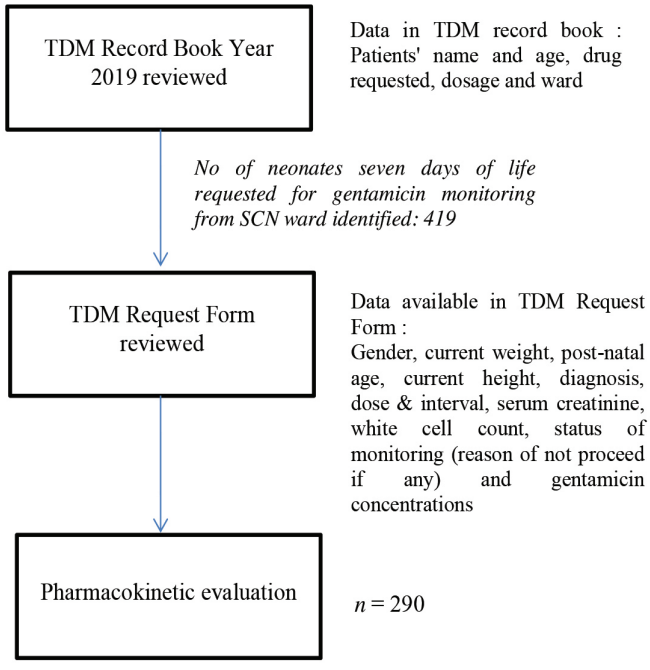

Figure 1. Flow chart of patients recruitment

TDM: Therapeutic drug monitoring

Neonates treated with gentamicin received an initial dose of 3.5-4 mg/kg daily. Gentamicin was diluted and infused over 60 min according to the calculated doses. TDM was performed by measuring the peak and trough gentamicin blood level 1.0 h and 23.5h or 35.5h after the infusion of the third dose.

The trough serum gentamicin level was measured 30 min before the third dose, and the peak was measured 60 min after infusion on the third dose. Determination of gentamicin was performed using the COBAS INTEGRA analyzer according to the instructions provided in the manufacturer's manual. The steady-state Sawchuk-Zaske method was used to calculate the actual trough and peak levels (3). Peak is associated with efficacy of gentamicin while trough is associated with gentamicin toxicity.

Statistical Analysis

Descriptive statistics were performed using Statistical Package for the Social Sciences version 22.0 (Armonk, NY). Data are expressed as the mean±standard deviation and median. The chi-square test was used to analyze categorical data, and simple linear regression was carried out to investigate the relationship between post-natal age, weight, and creatinine clearance with gentamicin concentrations. $P<0.05$ indicated statistical significance.

Results

Patients

Overall, 419 TDM requests were reviewed and 291 cases were analyzed. One hundred twenty-eight cases were not included in the analyses because blood specimens exceeded stability time (n=89), and insufficient samples were obtained (n=39). Another admission was also excluded due to missing documentation of age. Table 1 shows the demographic data. Presumed sepsis, clinical sepsis, and congenital pneumonia were the common clinical diagnoses (Table 2).

Table 1. Demographic and clinical characteristics (n=290)

Post-natal age; days, mean±SD	3.54±1.05
Male, n (%)	167 (57.6)
Body weight, kg, mean±SD	3.0±0.63
Height, cm, mean±SD	46.4±5.14
Total daily gentamicin dose, mg, mean±SD	11.9±2.56
Dosing interval 24 hourly, n (%)	248 (85.5)
Dosing interval 36 hourly, n (%)	42 (14.5)
Total dose/kg body weight, mg/kg, mean±SD	3.98±0.26
Serum creatinine, µmol/L, mean±SD	56.19±16.14
Creatinine clearance, ml/min, mean±SD	33.97±10.02
White cell count, K/uL x10^3, mean±SD	19.71±35.72

SD: Standard deviation

Gentamicin serum concentrations

Gentamicin was started in the majority of the neonates on the first days of life. Table 3 shows gentamicin serum concentrations. A trough level above 1.0 µg/mL is considered potentially toxic, and a peak level of 5.0 µg/mL and above is considered effective. Renal function (presented as creatinine clearance) showed a negative relationship with the trough level of gentamicin. The same relationship was also observed between the weight of neonates and the peak level of gentamicin (Table 3). Concomitant antibiotics were documented in 165 cases. Most of the combined antibiotic therapy included ampicillin or penicillin.

Over 30% of neonates treated with gentamicin experienced potential toxicity with trough levels above 1.0 µg/mL, and 15.9% of them had sub-efficacy of the drug (peak level below 5 µg/mL). Only six neonates had trough levels above 2.0 µg/mL. The percentage of potential toxicity was higher in presumed sepsis neonates; in subjects with bodyweight between 2.5-2.99 kg and in subjects who received 24-hour dosing (Table 4).

Table 2. Initial diagnosis of neonates before starting empirical gentamicin (n=290)

Presumed sepsis, n (%)	108 (37.2)
Clinical sepsis, n (%)	79 (27.2)
Congenital pneumonia, n (%)	73 (25.2)
Respiratory distress syndrome, n (%)	23 (7.9)
Group B *Streptococcus pneumoniae*, n (%)	5 (1.7)
Community acquired pneumonia, n (%)	2 (0.7)

Discussion

Gentamicin is one of the most commonly prescribed antibiotics for culture-proven or suspected sepsis in neonates. Since the development and organ maturation influences gentamicin pharmacokinetics in neonates, interest has increased in refining dosing regimens for improved efficacy and decreased toxicity. In this population, variability in kidney function and body composition, in particular, is responsible for the large interpatient variability in clearance and volume of distribution of gentamicin.

Table 3. Relationship of demographic characteristics and gentamicin levels

	Gentamicin trough concentration[a]		Gentamicin peak concentration[a]	
	Beta (95% CI)	**p**	**Beta (95% CI)**	**p**
Postnatal age	-0.112 (-0.317, 0.092)	0.279	0.003 (-0.03, 0.036)	0.87
Weight	-0.035 (-0.157, 0.087)	0.575	-0.025 (-0.045, -0.006)	**0.012**
Creatinine clearance	-3.66 (-6.79, -0.534)	**0.022**	-0.562 (-1.18, 0.057)	0.075

[a]Simple linear regression, CI: Confidence interval

Table 4. Percentage of potential toxic and sub efficacy of total case, based on most common diagnosis, body weight category and dosing interval (n=290)

	Potential toxicity	**Sub-efficacy**
Total n (%)	94 (32.4)	46 (15.9)
Diagnosis, n (%)		
Presumed sepsis (n=108)	41 (38)	25 (23.1)
Clinical sepsis (n=79)	22 (27.8)	10 (12.7)
Congenital pneumonia (n=73)	21 (28.8)	7 (9.6)
	p=0.257[a]	p=0.031[a, *]
Body weight category, n (%)		
≤2 kg (n=23)	7 (30.4)	2 (8.7)
<2-2.5 kg (n=37)	13 (35)	4 (10.8)
>2.5-2.99 kg (n=77)	29 (37.7)	15 (19.5)
≥3 kg (n=153)	45 (29.4) p=0.623[a]	25 (16.3) p=0.498[a]
Dosing interval, n (%)		
24 hourly (n=248)	86 (34.7)	42 (16.9)
36 hourly (n=42)	8 (19.0)	4 (9.5)
	p=0.045[a]*	p=0.224[a]

[a]Chi-square test.
*Significant.

The clearance of gentamicin is almost entirely dependent on glomerular filtration (4).

In this retrospective study, the rejection rate of gentamicin analysis in SCN neonates over one year was 30.5%. Most of the samples (69.5%) were rejected due to delays in the transport of the sample to the laboratory, which may cause erroneous test results. Inaccurate gentamicin levels may cause miss-interpretation and consequently inappropriate management as either under-treatment or over-treatment that leads to nephrotoxicity or ototoxicity. Therefore, delayed samples were not analyzed.

Delayed transport of the sample is a human error but the percentage was quite high in the current study. The blood samples (especially pre-level) were kept in the wards for more than four hours before transport to the laboratory. The reason for the delay in the transportation of blood samples was waiting for the post-level samples from the same patient. Delayed administration of gentamicin or difficulty in taking blood samples were also among the probable causes. Other than delays in transportation, insufficient blood samples (30.5%) was another reason for the rejection of the sample by the laboratory. Insufficient means that there was not enough specimen volume to perform the TDM assay.

Specimen rejection and subsequent recollection require extra communication between the pharmacist, medical laboratory technician, and the clinician, extra working hours, and additional resources for recollection and reanalysis, resulting in discomfort and stress imposed on neonates. The blood volume of a neonate is approximately 75 to 107 mL/kg (5). Small neonates may have a total blood volume as low as 50 mL. This means drawing just 1.0-mL blood from a neonate could significantly reduce his or her blood volume. Blood loss attributable to laboratory testing is acknowledged as the primary factor leading to anemia in infants in the first weeks of life (6). Therefore, it is important to reduce the number of unnecessary gentamicin blood sampling.

Optimal dosing of gentamicin in neonates is still a matter of debate although it is commonly used. In our hospital setting, 4.0 mg/kg of gentamicin is given as once-daily dosing for full-term neonates and 36 hourly for pre-term neonates according to local guidelines (7). With this protocol, 84.1% achieve an appropriate peak of at least 5.0 µg/mL. Thai neonates also achieved an appropriate peak with a similar dosage whereby 97% of their neonates had a peak above 4.0 µg/mL (1). The percentage increased to 100% when gentamicin dosage was increased to 5.0 mg/kg but 21% of the Thai neonates had higher peak levels above 12.0 µg/mL (2). The generally accepted peak concentrations are 4.0-10.0 µg/mL in neonates, however, many guidelines and researchers target peaks above 5.0 µg/mL for optimization of gentamicin effectiveness (8).

In our setting, 92.8% of the neonates had a peak concentration above 4.0 µg/mL. Collectively, these findings suggest that the current practice of 4.0 mg/kg dosage is appropriate to achieve the desired peak level in our population. A pharmacokinetic-pharmacodynamic model that describes the time course of the bactericidal activity of gentamicin and its adaptive resistance in neonates also demonstrated that 4.0 mg/kg of gentamicin every 24 hours is the most effective in the newborn infant as the bacteria remained below the starting inoculum for the longest time. The model also supported an extended dosing interval of 36 to 48 hourly in preterm neonates that were as effective as a 24 hourly dosing interval for the same total dose (9). In full-term neonates, the bacterial count reached the initial starting inoculum (5x105 CFU/mL) in 48 hours for 4.0 mg/kg every 24 hours. The model also predicted using different initial doses of 4.0 to 7.0 mg/kg for the extreme preterm (gestational age of 25 weeks) and term (gestational age of 40 weeks) neonates and displayed minor differences in bacteria-killing between the different doses during the first 6 h (9).

In our setting, trough level is targeted at below 1.0 µg/mL since trough level of more than 1.0 mg/L suggests accumulation (potentially toxic) and above 2.0 µg/mL is toxic (10). Based on the target, the percentage of a potential toxic incident in overall neonates with a dosage of 4.0 mg/kg is 32.4% and is between 19-38% according to the most common diagnoses, body weight, or dosing interval. Gestational age was not documented in TDM forms reviewed, therefore we were uncertain whether neonates with a bodyweight of two kilograms and below were premature or not. All three neonates with 24 hourly intervals had potential toxic trough levels (above 1.0 µg/mL). One neonate with a bodyweight of more than 3 kilograms was prescribed with 36 hourly intervals and his trough level was not detected. This is indicative that 36 hourly interval is inappropriate for the body weight. Our findings are suggestive of 36 hourly intervals for neonates of 2.0 kg and below regardless of gestational age. Increasing the interval between doses can maintain maximal antibacterial activity while minimizing side effects.

The percentage of neonates with trough levels above 2.0 µg/mL was comparably low in our population compared to Thai neonates whereby incidence was only 2.0%. In Thai neonates, the incidence is 6.67% (1). The principal adverse effects of gentamicin therapy are renal toxicity, which nearly always is reversible, and ototoxicity which generally is irreversible. The amount of drug that accumulates in the kidney and inner ear increases with higher plasma concentrations and longer periods of exposure. The elimination of a drug from these organs, on the other hand, occurs more slowly than from plasma and is retarded by high plasma concentrations. Back diffusion from these sensitive organs to the blood, thereby lowering end-organ drug levels, is dependent primarily on the trough rather than the peak concentration of the drug in the serum. This accounts for the association between toxicity and high plasma trough concentrations. Once-daily dosing or extended-interval dosing,

despite the higher peak concentration, provides a longer period when serum concentrations are below the threshold for toxicity, leading to a reduced risk of toxicity (10).

Current findings suggest that the monitorization of trough levels alone is generally sufficient in non-critically ill neonates treated in the SCN to verify that gentamicin is being adequately eliminated. Peak levels are typically not required, as the larger doses used are expected to produce concentrations well above those required for clinical efficacy.

Limitations of the current study include the small volume of drug administered to neonates less than 2.0 kg, with possible administration error, which influences the reported concentrations, and impacts on subsequent pharmacokinetic calculations. Other limitations relate to clinical acuities such as hydration levels, gestational age, and birth weight which were not documented in the TDM request form. Patients' medical records were not reviewed due to time constraints, therefore data on the culture of infection was not available to confirm infection.

Conclusion

We propose trough-only monitoring in non-critically ill neonates admitted to SCN as the current practice of monitoring pre and post often necessitates additional blood sampling. The decision not to determine peak levels routinely is based on the present outcome that gentamicin dosage of 4.0 mg/kg is likely to provide peak levels in desired range without any added risk of toxicity, lesser trauma, and blood sampling.

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Ethics

Ethics Committee Approval: This research was conducted in accordance with the 1975 Helsinki Declaration and approval from Medical Research and Ethics Committee of Ministry of Health, Malaysia (NMRR-20-254-53622 IIR, date: 09.04.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.R., Concept: S.M., R.R., W.N.W.Y., Design: S.M., R.R., W.N.W.Y., Data Collection or Processing: S.M., S.L.A.M.N., Analysis or Interpretation: S.M., S.L.A.M.N., W.N.W.Y., Literature Search: S.M., S.L.A.M.N., Writing: S.M., S.L.A.M.N., R.R., W.N.W.Y.

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Assessment of cardiac autonomic parameters in patients with uncomplicated familial Mediterranean fever

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ABSTRACT

Aims: Cardiac dysautonomia and arrhythmias can occur in chronic inflammatory conditions such as familial Mediterranean fever (FMF). The aim of this study was to evaluate the cardiac autonomic functions in patients with FMF.

Methods: This was a retrospective case-control study. Electrocardiography (ECG) and 24-hour Holter ECG recordings were obtained from the medical records. T-peak to T-end intervals (Tp-e) and Tp-e/corrected QT (QTc) ratio were calculated on ECG. Heart rate variability (HRV) parameters and heart rate turbulence (HRT) parameters including turbulence onset (TO) and turbulence slope (TS) were evaluated using the 24-hour Holter ECG. All subjects were divided into three groups according to HRT parameters (HRT-0: normal TO and TS; HRT-1: abnormal TS or TO; and HRT-2: abnormal TO and TS).

Results: The study included 115 individuals (age, years, mean±standard deviation: 34.5±9.6 years, 57% female, 61 FMF patients and 54 controls). Patients with FMF exhibited an increased ratio of Tp-e, Tp-e/QTc ratio ($p<0.001$ for both), and impairment in all HRV parameters ($p<0.05$ for all). Disease duration was correlated with Tp-e ($r=0.402$, $p=0.001$), Tp-e/QTc ratio ($r=0.382$, $p=0.003$) and HRV parameters ($r>0.264$, $p<0.05$ for all). Of patients with FMF, 32 (52.5%) were in the HRT-1 group, and 9 (14.8%) were in the HRT-2 group. Patients using anakinra showed more impairment in the HRV parameters ($p<0.05$ for all) and Tp-e/QTc ratio ($p=0.041$) compared to patients who were not on anakinra.

Conclusions: This study showed cardiac autonomic system impairments in patients with FMF without complications, which correlated with the disease duration.

Introduction

Familial Mediterranean fever (FMF) is a chronic inflammatory disease that is usually inherited as an autosomal recessive disorder (1,2). Although it is a widespread disease, some ethnic groups, such as Turks, Arabs, and Hebrews, have a higher prevalence (1,3). FMF is characterized by recurrent attacks of fever, accompanied by abdominal and joint pain (2). Besides these clinical features, chronic inflammation and amyloid deposits have been linked to significant cardiovascular complications such as pericarditis, atherosclerosis, cardiomyopathy, and pulmonary hypertension (4). Colchicine is recommended to reduce attacks and prevent complications (5). In recent studies, anakinra, an interleukin-1 (IL-1) receptor antagonist, is effective and safe in colchicine-resistant patients (6).

The cardiac autonomic nervous system (ANS) is crucial in the regulation of the cardiovascular system. Regardless of the underlying disease, cardiac autonomic dysfunction can cause ventricular arrhythmias, which can lead to sudden death (7). Cardiac arrhythmias, which are associated with poor prognosis, can occur in chronic inflammatory diseases such as FMF due to cardiac dysautonomia (8). Chronic inflammation can cause

adverse cardiovascular outcomes such as atrial fibrillation and ventricular arrhythmias (9). Cardiometabolic events are also one of the leading causes of death in chronic inflammatory diseases (10).

Cardiac ANS functions can be evaluated using several non-invasive methods. One of these is the 24-hour Holter electrocardiography (ECG), which is a simple and practical method. Heart rate variability (HRV) and heart rate turbulence (HRT) are parameters in 24-hour Holter ECG that provide information about the cardiac ANS (11). ECG examination is another simple method to evaluate cardiac ANS. The measurement of the time course for the repolarization of myocardial Moe cells, which is believed to be related to cardiac arrhythmia, has recently been reported to be a valuable tool for evaluating cardiac ANS (12). This measurement is recorded at resting ECG and is defined as the peak-to-end interval of the T wave (Tp-e). Prolonged Tp-e and Tp-e/corrected QT interval (QTc) ratios, as well as aberrant HRV and HRT parameters, were associated with malignant ventricular arrhythmias and cardiac death (13).

Some studies found that cardiac autonomic functions were impaired in FMF patients without amyloidosis, while others found the opposite (14,15). This study investigated whether the cardiac ANS is impaired in FMF patients by evaluating the 24-hour Holter parameters as well as the Tp-e and Tp-e/QTc ratio on the ECG.

Methods

Study population

This retrospective case-control study reviewed the records of 61 patients with FMF and 54 control subjects who presented to our cardiology outpatient clinic for any reason between April 2019 and January 2020 and underwent a 24-hour Holter record. In the FMF group's hospital records, there was no history of FMF attacks in the last 3 months preceding the 24-hour Holter ECG. We excluded control patients who had some form of cardiac disease or comorbidity. Those without a suitable 24-hour Holter ECG recording (with artifacts and <5 premature ventricular complexes) and those without an appropriate ECG recording (with T negativity, biphasic T waves, and U waves) were excluded from the study. Additionally, patients with a history of documented diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation or rhythm abnormalities, additional chronic inflammatory diseases, active infections, malignancies, or diagnosed with amyloidosis, structural heart disease, proteinuria in 24-hour urine test (to exclude amyloidosis), as well as those using medications known to affect cardiac autonomic function (antidepressants, b-blockers, calcium channel blockers, antiarrhythmics), were excluded. In our hospital, where the study was conducted, the number of patients using biological agents other than anakinra was very low. Therefore, only the patients who used anakinra were included in the study, and the patients who used other biological agents were excluded.

The Local Ethics Committee approved the study (Yozgat Bozok University, approval no: 2017-KAEK-189_2021.04.28_10), and its protocol conformed to the principles of the Declaration of Helsinki.

ECG examination

Medical records were used to produce resting ECG recordings with an amplitude of 10 mV at a rate of 25 mm/sec. All of the ECG recordings were transferred to a computer and measurements of the peak-to-end interval of the T wave (Tp-e) were performed from the precordial leads. An average value of two readings was calculated for each lead. The following ventricular repolarization parameters were calculated: QT interval, QT interval corrected for heart rate, and Tp-e (Figure 1). The results of standard transthoracic echocardiography and 24-hour Holter monitoring (GE medical systems information technologies, Inc., software version 8.0.3, Milwaukee, USA) with 3-lead analog devices were evaluated independently by two different cardiologists.

Heart rate variability and heart rate turbulence

Holter monitoring recordings were exported to the computer and manually scanned to remove artifacts and analyzed with the Holter software. HRV and HRT parameters were automatically documented by the Holter software as numerical data.

In HRV analysis were obtained time-domain parameters, including the standard deviation (SD) of all NN intervals for a given period (SDNN), SD of the 5 min mean R-R intervals tabulated over an entire day (SDANN), square root of the mean of the sum of the squares of differences between adjacent R-R intervals (rMSSD), and the proportion of differences in successive NN intervals greater than 50 ms (pNN50) as well as frequency domain parameters, including high frequency (HF) component (0.15-0.40 Hz), low frequency (LF) component

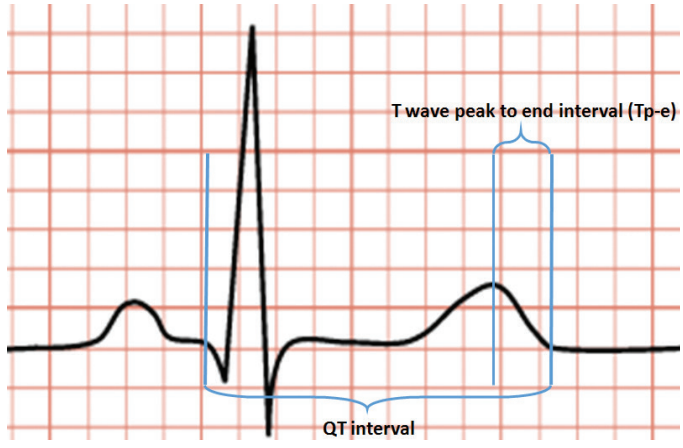

Figure 1. Demonstration of the T wave peak to end and QT intervals

(0.04-0.15 Hz) and very LF (VLF) component (0-0.04 Hz) and LF/HF ratio (16).

HRT analysis was carried out by an automatic computer program. To minimize false evaluations, patients having at least five ventricular extrasystoles were included in the assessment. The two phases of HRT were numerically quantified as turbulence onset (TO) and turbulence slope (TS). TO was defined as the percentage change in the RR intervals following premature ventricular beats (PVBs) versus (vs.) the pre-PVB period. TO represents the initial acceleration of heart rate following PVB. TO ≤0% (negative TO) whereas TS >2.5 ms/RR (positive TS) were accepted as normal values. The study population was separated into three groups based on their HRT data. HRT-0 means that both values are within normal limits, HRT-1 implies that one of the two parameters is abnormal and HRT-2 means both parameters are abnormal (17).

Statistical Analysis

The IBM Statistical Package for the Social Sciences for Windows, version 21.0, IBM.Corp., Armonk, NY, 2012 was used for the statistical analysis. The Kolmogorov-Smirnov test was used to test the normality of distribution. Continuous variables were presented as mean ± SD, and categorical variables were expressed as a number and a percentage (%). The Student's t-test or the Mann-Whitney U test was used to compare continuous variables. The chi-square test or Fisher's exact test was used to compare categorical variables. Pearson's correlation test was used for the normally distributed data, and Spearman's correlation test was used for non-normally distributed data. A two-sided p<0.05 was considered significant.

Results

A total of 115 individuals were included in the study. The demographic characteristics of the patients (n=61, 43 females; mean±SD, 34.3±10.0 years) and the control group (n=54, 33 females; mean±SD, 34.7±9.3 years) are presented in Table 1. There were no significant differences between the two groups in terms of age, gender, smoking, or body mass index. The median disease duration was 7.0 (3.0-10.5) years. All patients were on colchicine (1-1.5 mg/day); however, eight patients were receiving anakinra+colchicine (1.5-2 mg/day) due to colchicine resistance. The median duration of anakinra treatment was 45 (19.5-69) months. The most common mutations seen in patients were M694V (n=35; 57.3%), M680I (n=8; 13.1%), V726A (n=7; 11.4%), and E148Q (n=6; 9.8%). There was no mutations in six patients (9.8%). Of the 55 patients with mutations, 18 (29.5%) were heterozygous, 22 (37.7%) were compound heterozygous, and 15 (22.9%) were homozygous. ECG and 24-hour Holter ECG parameters in FMF patients did not differe by gender. Although C-reactive protein levels were within normal ranges, they were statistically higher than in the control group [1.62 (0.59-4.59) vs. 0.80 (0.47-1.72), p=0.012]. All other biochemical and transthoracic echocardiographic parameters were comparable between the two groups (Table 2).

The resting ECGs of all individuals were in sinus rhythm. Although corrected QT intervals were similar between the two groups, ventricular repolarization parameters [Tp-e (86.91±16.49 vs. 70.20±5.02, p<0.001) and Tp-e/QTc ratio (0.21±0.04 vs. 0.17±0.02, p<0.001)] were significantly prolonged in FMF patients (Table 1).

Table 1. Baseline characteristics and 12-lead electrocardiographic parameters of the study population (n=115)

	FMF group (n=61)	Control group (n=54)	p
Age, years, mean±SD	34.3±10.0	34.7±9.3	0.838
Sex, male, n (%)	18 (29.5)	21 (38.9)	0.288
BMI, kg/m^2, mean±SD	24.8±2.4	25.6±2.8	0.144
Smoking, n (%)	18 (29.5)	14 (25.9)	0.670
EF, %, mean±SD	62.3±3.0	61.9±4.5	0.620
Sedimentation rate, mm/h, median (IQR)	14.00 (6.00-21.50)	11.00 (8.75-14.00)	0.154
C-reactive protein, mg/L, median (IQR)	1.62 (0.59-4.59)	0.80 (0.47-1.72)	**0.012**
Sodium, mmol/L, median (IQR)	138.00 (137.00-140.00)	138.00 (137.00-140.00)	0.826
Potassium, mmol/L, mean±SD	4.23±0.39	4.20±0.43	0.781
TSH, mU/L, mean±SD	1.27±0.77	1.34±0.81	0.885
Heart rate, beats/min, median (IQR)	78.0 (73.0-89.0)	75.5 (72.0-82.3)	0.103
QRS interval, ms, mean±SD	78.34±9.65	75.50±9.01	0.130
QTc interval, ms, mean±SD	414.72±20.12	406.92±31.23	0.122
Tpe, ms, mean±SD	86.91±16.49	70.20±5.02	**<0.001**
Tpe/QTc ratio, mean±SD	0.21±0.04	0.17±0.02	**<0.001**

Statistically significant results (p<0.05) were showed in bold type.
FMF: Familial Mediterranean fever, SD: Standard deviation, BMI: Body mass index, EF: Ejection fraction, IQR: Interquartile range, TSH: Thyroid-stimulating hormone, QTc: Corrected QT interval, Tpe: Transmural dispersion of repolarization

Table 2. 24-hour Holter parameters of the study population (n=115)

	FMF group (n=61)	Control group (n=54)	p
Minimum HR, beats/min, mean±SD	45.7±7.3	45.9±9.1	0.867
Average HR, beats/min, mean±SD	80.7±7.4	79.1±7.5	0.254
Maximum HR, beats/min, mean±SD	149.1±15.7	145.1±15.6	0.168
Total QRS, per 24 hour, mean±SD	111488.0±15259.8	105196.5±14588.8	0.122
VLF, ms^2, median (IQR)	29.08 (24.22-35.85)	32.58 (27.82-42.53)	**0.006**
LF, ms^2, mean±SD	22.93±7.36	27.74±8.96	**0.002**
HF, ms^2, median (IQR)	13.56 (10.65-18.57)	18.22 (13.14-26.25)	**0.001**
LF/HF ratio, mean±SD	1.67±0.48	1.46±0.42	**0.012**
SDNN, ms, mean±SD	136.31±32.06	152.83±33.85	**0.008**
SDANN, ms, mean±SD	124.29±32.53	137.79±31.58	**0.026**
ASDNN, ms, mean±SD	56.37±18.21	66.53±22.46	**0.009**
rMSSD, ms, mean±SD	34.50±13.10	40.38±12.58	**0.016**
pNN50, %, median (IQR)	10.00 (6.79-18.32)	18.55 (9.85-25.10)	**<0.001**
Tonset, %, median (IQR)	-0.34 (-2.19-1.46)	-1.05 (-1.86-(-0.60))	0.112
Tslope, ms/RR, median (IQR)	6.00 (1.93-9.67)	3.57 (2.98-5.14)	0.073
VPBs, per 24 hour, median (IQR)	13.0 (8.0-27.5)	18.5 (12.0-38.5)	**0.020**
HRT-0, n (%)	20 (32.8)	43 (79.6)	**<0.001**
HRT-1, n (%)	32 (52.5)	11 (20.4)	**<0.001**
HRT-2, n (%)	9 (14.8)	0 (0)	**0.003**

Statistically significant results (p<0.05) were showed in bold type.
FMF: Familial Mediterranean fever, HR: Heart rate, SD: Standard deviation, VLF: Very low frequency, IQR: Interquartile range, LF: Low frequency power, HF: High frequency power, LF/HF ratio: Ratio of power in low/high frequency, SDNN: Standard deviation of normal to normal R wave in the entire recording, SDANN: Standard deviation of the averages of all normal to-normal RR intervals in all 5-min segments of the entire recording, ASDNN: Average of the standard deviation of NN intervals, rMSSD: Root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms, VPBs: Ventricular premature beat, HRT: Heart rate turbulence

While the minimum-maximum-mean heart rates and total QRS were similar between the two groups, all other HRV parameters, including SDNN (136.31±32.06 vs. 152.83±33.85, p=0.008), SDANN (124.29±32.53 vs. 137.79±31.58, p=0.026), rMSSD (34.50±13.10 vs. 40.38±12.58, p=0.016), pNN50 [10.00 (6.79-18.32) vs. 18.55 (9.85-25.10), p<0.001], VLF [29.08 (24.22-35.85) vs. 32.58 (27.82-42.53), p=0.006], LF (22.93±7.36 vs. 27.74±8.96, p=0.002), HF [13.56 (10.65-18.57) vs. 18.22 (13.14-26.25), p=0.001] were significantly lower in the FMF group. Compared to the control group, the LF/HF ratio (1.67±0.48 vs. 1.46±0.42, p=0.012) was significantly higher (Table 2).

HRT parameters were normal in 20 (32.8%) of the FMF patients and 43 (79.6%) of the control subjects. Thirty-two (52.5%) patients were in the HRT-1 group (FMF vs. control; 32/61 vs. 11/54, p<0.001), whereas 9 (14.8%) patients were in the HRT-2 group (9/61 vs. 0/54, p=0.003) in the FMF group (Table 2).

There was a moderate negative correlation between disease duration and HRV parameters and a moderate positive correlation between Tp-e and Tp-e/QTc ratio (Table 3). No significant difference was observed in resting ECG, HRV, and HRT parameters with regards to the mutations.

There were no significant differences in terms of demographic characteristics, Tp-e, and QTc intervals between anakinra-treated and non-anakinra-treated patients. Tp-e/QTc ratio (0.24±0.05 vs. 0.21±0.04, p=0.041) was prolonged in patients using anakinra (Table 4). Both groups had similar minimum-mean-maximum heart rates, total QRS, and ventricular extrasystole counts. All HRV variables VLF (22.45±5.45 vs. 31.42±8.17, p=0.004), LF (17.02±4.99 vs. 23.82±7.28, p=0.014), HF (10.42±3.42 vs. 15.67±6.71, p=0.035), SDNN (114.00±15.60 vs. 139.67±32.63, p=0.034), SDANN (87.50±12.50 vs. 129.84±30.99, p<0.001), ASDNN (39.75±13.84 vs. 58.88±17.54, p=0.005), rMSSD (26.12±10.41 vs. 35.77±13.07, p=0.039), pNN50 [7.04 (1.20-8.12) vs. 11.10 (7.55-18.70), p<0.001] were significantly lower in anakinra-treated patients than in non-anakinra-treated patients. Additionally, all patients using anakinra had abnormal HRT values (Table 5).

Discussion

This study found that Tp-e, Tp-e/QTc ratios were prolonged, and HRV and HRT parameters were impaired in patients with FMF versus the control group. Additionally, disease duration and anakinra treatment were associated with the impairment of these parameters.

Table 3. Correlation analysis of disease duration, Tpe, Tpe/QTc and 24-hour Holter parameters of FMF patients

	Disease duration, years	Tpe, msn	Tpe/QTc ratio	VLF, ms²	LF, ms²	HF, ms²	SDNN, ms	SDANN, ms	ASDNN, ms	rMSSD, ms	pNN50, %
Disease duration, years											
R	-	0.402	0.382	-0.370	-0.304	-0.319	-0.544	-0.398	-0.314	-0.304	-0.332
P	-	0.001	0.003	0.004	0.020	0.012	<0.001	0.002	0.014	0.017	0.009
Tpe, msn											
R	0.402	-	0.974	-0.401	-0.368	-0.390	-0.437	-0.311	-0.433	-0.284	-0.380
P	0.001	-	<0.001	0.001	0.003	0.002	<0.001	0.014	0.001	0.031	0.002
Tpe/QTc ratio											
R	0.382	0.974	-	-0.351	-0.377	-0.359	-0.431	-0.350	-0.366	-0.264	-0.341
P	0.003	<0.001	-	0.006	0.002	0.004	0.001	0.006	0.004	0.042	0.007

Tpe: Transmural dispersion of repolarization, QTc: Corrected QT interval, FMF: Familial Mediterranean fever, VLF: Very low frequency, LF: Low frequency power, HF: High frequency power, SDNN: Standard deviation of normal to normal R wave in the entire recording, SDANN: Standard deviation of the averages of all normal to-normal RR intervals in all 5-min segments of the entire recording, ASDNN: Average of the standard deviation of NN intervals, rMSSD: Root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms

Table 4. Baseline characteristics and 12-lead electrocardiographic parameters of FMF patients (n=61)

	Anakinra group (n=8)	Non-anakinra group (n=53)	p
Age, years, mean±SD	34.5±7.6	34.3±10.4	0.971
Sex, male, n (%)	4 (50)	14 (26.4)	0.218
BMI, kg/m², mean±SD	24.2±2.5	24.9±2.4	0.484
Smoking, n (%)	3 (37.5)	15 (28.3)	0.677
Disease duration, years, median (IQR)	5.8 (3.5-15.0)	7.0 (3.0-10.0)	0.468
EF, %, mean±SD	62.6±3.9	62.2±2.9	0.743
Sedimentation rate, mm/h, median (IQR)	9.00 (3.75-20.25)	14.00 (6.50-22.00)	0.312
C-reactive protein, mg/L, median (IQR)	1.18 (0.30-6.53)	1.66 (0.60-4.60)	0.777
Heart rate, beats/min, mean±SD	75.2±13.5	81.9±10.4	0.214
QRS interval, ms, mean±SD	85.62±14.59	77.24±8.33	0.151
QTc interval, ms, mean±SD	405.62±14.36	416.09±20.61	0.172
Tpe, ms, mean±SD	96.50±19.08	85.47±15.77	0.084
Tpe/QTc ratio, mean±SD	0.24±0.05	0.21±0.04	**0.041**

Statistically significant results (p<0.05) were showed in bold type.
FMF: Familial Mediterranean fever, SD: Standard deviation, BMI: Body mass index, IQR: Interquartile range, EF: Ejection fraction, QTc: Corrected QT interval, Tpe: Transmural dispersion of repolarization

Cardiovascular events are the leading causes of death and morbidity in FMF and many other autoimmune diseases (4). Cardiac autonomic dysfunction is associated with ventricular arrhythmias and sudden death (18). Conduction disorders and arrhythmias are common symptoms of adverse cardiac outcomes in autoinflammatory diseases such as FMF (19). Cardiac autonomic dysfunction related to amyloidosis has been observed in patients with FMF (20). However, some studies have shown that patients with FMF without complications (without amyloidosis) also develop autonomic dysfunction (21). Moog et al. (22) stated that patients with FMF have impaired pupillomotor function which is controlled by the parasympathetic nervous system. Cardiac autonomic dysfunction (reduced parasympathetic dominance) has also been observed in many other autoimmune diseases, and it has been associated with disease activity and poor prognosis (23). The 24-hour Holter ECG monitoring, which is a cost-effective, reliable, and easily accessible method, is commonly used to evaluate cardiac ANS. HRV and HRT parameters obtained automatically from 24-hour Holter recordings are useful in evaluating cardiac ANS (24,25). Some HRV parameters were depressed in diseases such as diabetes mellitus, hypertension, myocardial infarction, heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and hypothyroidism (26). It was also reported that decreased HRV parameters could predict the mortality risk in heart failure and myocardial infarction (26). Depressed HRV parameters and increased LF/HF ratio are predictors of decreased parasympathetic dominance and increased cardiac

Table 5. 24-hour Holter parameters of FMF patients (n=61)

	Anakinra group (n=8)	Non-anakinra group (n=53)	P
Minimum HR, beats/min, mean±SD	46.3±7.1	45.6±7.4	0.811
Average HR, beats/min, mean±SD	78.0±6.4	81.2±7.5	0.270
Maximum HR, beats/min, mean±SD	139.4±14.7	150.5±15.4	0.082
Total QRS, per 24 hour, mean±SD	104867.9±11250.9	108275.8±15814.4	0.564
VLF, ms^2, mean±SD	22.45±5.45	31.42±8.17	**0.004**
LF, ms^2, mean±SD	17.02±4.99	23.82±7.28	**0.014**
HF, ms^2, mean±SD	10.42±3.42	15.67±6.71	**0.035**
SDNN, ms, mean±SD	114.00±15.60	139.67±32.63	**0.034**
SDANN, ms, mean±SD	87.50±12.50	129.84±30.99	**<0.001**
ASDNN, ms, mean±SD	39.75±13.84	58.88±17.54	**0.005**
rMSSD, ms, mean±SD	26.12±10.41	35.77±13.07	**0.039**
pNN50, %, median (IQR)	7.04 (1.20-8.12)	11.10 (7.55-18.70)	**<0.001**
Tonset, %, median (IQR)	-0.04 (-3.36-1.07)	-0.54 (-2.19-1.58)	0.679
Tslope, ms/RR, median (IQR)	1.72 (1.53-5.82)	6.47 (3.09-10.05)	0.786
VPBs, per 24 hour, median (IQR)	37.5 (11.5-51.8)	13.0 (7.5-24.5)	0.131
HRT-0, n (%)	0 (0)	20 (37.7)	**0.034**
HRT-1, n (%)	4 (50)	28 (52.8)	1.000
HRT-2, n (%)	4 (50)	5 (9.4)	**0.013**

FMF: Familial Mediterranean fever, SD: Standard deviation, HR: Heart rate, VLF: Very low frequency, LF: Low frequency power, HF: High frequency power, SDNN: Standard deviation of normal to normal R wave in the entire recording, SDANN: Standard deviation of the averages of all normal to-normal RR intervals in all 5-min segments of the entire recording, ASDNN: Average of the standard deviation of NN intervals, rMSSD: Root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms, IQR: Interquartile range, VPBs: Ventricular premature beats, HRT: Heart rate turbulence. Statistically significant results (p<0.05) were showed in bold type

sympathetic dominance (25). If the parasympathetic nervous system's dominance in the heart weakens, arrhythmias are unavoidable (27). It has been shown that the evaluation of only one of the HRV parameters does not provide reliable information on the cardiac ANS. Therefore, it is important to evaluate all HRV parameters together (26). Canpolat et al. (28) found that many HRV parameters were impaired in FMF patients without amyloidosis. In our study, as in the literature, both time-domain (SDNN, SDANN, pNN50, rMSSD) and frequency domain (VLF, LF, HF) parameters decreased, while the LF/HF ratio increased in patients with FMF compared to the control group. Furthermore, disease duration was associated with the impairment of these parameters.

HRT, a more specific and sensitive method than HRV, provides data on cardiac ANS (29). Additionally, HRT gives information on the baroreceptor response (30). Impaired HRT was associated with arrhythmias and sudden death in patients with heart failure and myocardial infarction (31). HRT parameters were found to be impaired in chronic inflammatory disorders such as systemic sclerosis and systemic lupus erythematosus (32,33). There are two separate variables in the HRT analysis; TO and TS. Cardiovascular deaths are higher among patients with impaired TO and TS (34). In our study, most patients with FMF had impairment in HRT variables (67.5%).

Tp-e interval and Tp-e/QTc ratio are cost-effective and reliable parameters that can be used to quickly evaluate the transmural repolarization dispersion of the myocardium using a resting ECG (35). Impairment of these parameters may predict ventricular arrhythmias and sudden cardiac death. Also, these parameters can be used to assess cardiac risk in various diseases and the general population (35). It has been reported that a prolonged Tp-e interval may be a predictor of the cardiovascular mortality risk in inflammatory diseases (36). Some studies showed that ventricular repolarization parameters were impaired in patients with FMF compared to the healthy group (37,38). In our study, we found that the Tp-e interval and Tp-e/QTc ratio were significantly longer in FMF patients than those in the control group. Moreover, we determined that these variables were correlated with disease duration and HRV parameters.

Colchicine is the cornerstone of FMF treatment. However, in colchicine-resistant cases, anakinra, the IL-1 receptor antagonist, is recommended, but its long-term effect on mortality is still unknown (39). Few studies have examined the relationship between anakinra use and cardiac arrhythmias. It has also been reported that anakinra may prevent arrhythmias after *myocardial infarction* (40). Conversely, in our study, we found that all HRV and HRT parameters were significantly impaired in patients using anakinra compared to those who did not use it. While

there was no significant difference in Tp-e values, we found a significant impairment in the Tp-e/QTc ratio in anakinra-treated patients. Although the small number of patients using anakinra, this is the first study to evaluate 24-hour Holter and ECG in these patients. Patients who were using anakinra were more likely to have uncontrolled chronic inflammation for a longer period. This may explain why abnormal cardiac autonomic functions in these patients were more pronounced.

Our study has shown that patients with FMF may have autonomic dysfunction even if they do not have any cardiovascular symptoms. Therefore, patients with FMF should be constantly monitored for cardiovascular complications, particularly arrhythmias. It is difficult to perform 24-hour Holter ECG on all patients, however, Tp-e, a basic ECG measurement that correlates with 24-hour Holter ECG parameters, can be evaluated in daily practice. ECG should, in our opinion, be performed on patients who have been following up with FMF for a long period.

The higher number of patients, evaluating the relationship between resting ECG and 24-hour Holter ECG parameters in patients with FMF, and evaluating 24-hour Holter ECG recordings in patients using anakinra are the strengths of our study. Our study has some limitations. Since the study was designed retrospectively, the contribution of the impaired cardiac autonomic system to cardiovascular adverse events could not be evaluated in the long-term follow-up. Since some common comorbidities (such as hypertension, diabetes mellitus ...) were excluded from the study, our results may not be representative of the real world. Although there were no statistically significant differences in any parameters based on gender, the higher proportion of females is considered a limitation. Additionally, the number of colchicine-resistant cases treated with anakinra was low.

Conclusion

In conclusion, the ventricular repolarization, HRV, and HRT parameters were impaired in parallel with the disease duration in patients with FMF without complications compared to the control group. This impairment was common in anakinra-treated patients. Therefore, cardiac autonomic system dysfunction and arrhythmias, which may increase morbidity and mortality in patients with FMF, can be evaluated using easy and non-invasive methods such as standard ECG and 24-hour Holter ECG. On the other hand, studies with larger sample size and a long-term follow-up are required to further confirm these findings.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee (Ethical Committee of Yozgat Bozok University, approval no: 2017-KAEK-189_2021.04.28_10).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.C., B.C., Design: M.C., B.S., S.G.N., Data Collection or Processing: B.C., S.G.N., Analysis or Interpretation: M.C., B.C., Literature Search: M.C., B.S., Writing: B.S., M.C., B.C.

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Mehran risk score model for predicting contrast-induced nephropathy after cardiac resynchronization therapy in patients with heart failure

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ABSTRACT

Aims: Contrast-induced nephropathy (CIN) is a challenging condition after cardiac procedures. Mehran risk score (MS) is a simple tool for predicting CIN. We investigated the role of MS to predict CIN development following cardiac resynchronization therapy (CRT) implantation in heart failure (HF) patients.

Methods: This single-center, retrospective study included HF patients who underwent CRT implantation. The patients had New York Heart Association class II-IV disease, wide QRS in electrocardiogram (>130 ms), and diminished left ventricular ejection fraction (<35%). Patients with active bleeding, acute renal failure before the CRT procedure, liver cirrhosis, autoimmune disease, chronic or acute inflammatory diseases, end-stage malignancy, and receiving dialysis were excluded. Mehran CIN risk score was calculated using the patient records.

Results: The study included 144 patients (age, mean±standard deviation: 63±10, male sex: 75%). Patients who developed CIN had significantly higher MS than those who did not (10.4±3.3 vs. 7.6±2.7, p<0.001). Multivariate logistic regression analyses showed that contrast volume [Odds ratio (OR): 1.02, 95% confidence interval (CI): 1.00-1.04, p=0.029] and MS (OR: 1.34 95% CI: 1.10-1.63, p=0.004, respectively) were independently associated with development of CIN.

Conclusions: This study showed that higher MS was independently associated with CIN in HF patients who underwent CRT implantation.

Introduction

Heart failure (HF) is the most prevalent reason for morbidity and mortality worldwide. Management of HF consists of pharmacotherapy and device-based therapy (1). Cardiac resynchronization therapy (CRT) has been developed as a potent treatment for advanced HF patients with prolonged QRS duration greater than or equal to 130 ms despite optimal pharmacotherapy (2). CRT improves mechanical synchrony by pacing both the LV free wall and septal. The CRT improves left ventricular (LV) ejection fraction (LVEF), survival, 6-min-walk distance, and QRS duration (3). Due to the progressive increase in the incidence of HF population and broadened indications for CRT, it is being performed more frequently worldwide (4).

A detailed coronary sinus (CS) anatomy evaluation via coronary venous angiography, which is the gold standard, is essential to ensure optimal placement of the LV lead (5).

Nevertheless, this procedure necessitates contrast material administration to identify and cannulate the CS. The most common reason for failure in CRT devices is the failure to cannulate CS ostium (6). However, the contrast administration in this set of patient populations brings the risk of contrast-induced nephropathy (CIN). Major risk factors for the progression of CIN involve congestive HF, pre-existing reduced kidney function, older age, diabetes mellitus (DM), and contrast material load (7-9). CIN has been revealed to be more common than the most recognized complications of CRT implantation (10).

Besides, the development of CIN following CRT has an important negative impact on morbidity and long-term prognosis (11). Therefore, it is essential to determine risk factors for CIN to take preventive precautions. Mehran et al. (12) developed a risk score in 2004 to predict the risk of CIN after percutaneous coronary interventions (PCI). The Mehran risk score (MS) is the most widely accepted and simple to calculate tool for estimating CIN. Several risk factors have been described for CIN MS based on hypotension, use of an intra-aortic balloon, congestive HF, advanced age, anemia, DM, contrast material volume, and glomerular filtration rate (GFR). It is categorized into 4 groups according to the scores obtained from these parameters. This single-center study aimed to assess the prediction of MS on the CIN of chronic HF patients with CRT.

Methods

This single-center, retrospective study included medically refractory HF patients who underwent CRT implantation between February 2019 and February 2021. The inclusion criteria were New York Heart Association (NYHA) class II-IV disease, wide QRS in electrocardiogram (ECG) (>130 ms), and diminished LVEF (<35%) (13). Patients with active bleeding, acute renal failure before CRT procedure, liver cirrhosis, autoimmune disease, chronic or acute inflammatory diseases, end-stage malignancy, and receiving dialysis were excluded. Additionally, subjects on angiotensin receptor-neprilysin inhibitor (ARNI), renin-angiotensin-aldosterone system blockers, mineralocorticoid receptor antagonists (MRA), diuretics, and digoxin 24-48 hours before the procedure were excluded from the study.

The successful CRT implantation was defined as implantation of LV lead into the appropriate branch of the CS, a right ventricular lead in the optimal position, and a right atrial lead if needed.

Clinical assessment included the evaluation of the NYHA functional class. All patients' 2-dimensional and Doppler echocardiographic examinations were recorded to calculate EF in terms of suitability for CRT. A 2-4 MHz transducer (Philips Affiniti 50, Philips Healthcare, Andover, Netherlands) is used for echocardiographic examinations in our clinic (14). White blood cell count, platelet count, creatinine, and hemoglobin level were obtained from the patient records.

CIN was defined as an increase in creatinine concentration 0.5 mg/dL (44 mol/L), or 25% above baseline, within 48 h of contrast administration (12). Patients were divided into two groups according to the development of CIN.

MS was calculated for all patients, which Mehran et al. (12) defined. It is calculated by summing the scores from the following findings: hypotension (5 points, if systolic blood pressure <80 mmHg for at least 1 hour requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive HF (5 points, if class III/IV by NYHA classification or history of pulmonary edema), age (4 points, if >75 years), anemia (3 points, if hematocrit <39% for men and <36% for women), DM (3 points), contrast media volume (1 point per 100 mL), and estimated GFR (GFR; in mL/min per 1.73 m^2; 2 points, if GFR 60 to 40; 4 points, if GFR 40 to 20; 6 points, if GFR <20). It is categorized into 4 groups: low risk, <6 points; moderate risk, 6-10 points; high risk, 11-15 points; and very high risk, >15 points). Contrast material volume was estimated using the amount for visualization of the CS.

The study was approved by the Ankara City Hospital Institutional Ethics Committee (decision no: E2-20-57, date: 16.12.2020).

Statistical Analysis

IBM Statistical Package for the Social Sciences Statistics for Macintosh, version 24.0 (IBM Corp., Armonk, New York, USA) was used to perform the statistical calculations. The results were displayed as mean±standard deviation (SD), median (interquartile range), and number (percentage), where appropriate. Kolmogorov-Smirnov test was used to test the normality of distribution. Student's t-test and Mann-Whitney U were used for the comparison of continuous variables according to the normality. The chi-square test was used to compare the categorical variables. Logistic regression analysis was performed to explore the variables that were independently associated with a CIN diagnosis. Potential confounding factors for developing CIN were tested in univariate analysis, including age, gender, DM, hypertension, coronary artery disease, dyslipidemia, ischemic HF, treatment with an MRA, or renin-angiotensin-aldosterone system blocker, contrast material volume, baseline creatinine level, LVEF, and MS. The variables that showed a crude association with a $p<0.100$ in univariate analysis were entered in the multivariate model. The goodness-of-fit assumption was examined by the Hosmer-Lemeshow method and satisfied when the p-value was above 0.05. Receiver operating characteristic (ROC) curve analyses

were performed to define the cut-off values for the sensitivity and specificity of MS and contrast material volume to predict the diagnosis of CIN. The area under the ROC curve (AUC) was assessed with a 95% confidence interval (CI) in addition to specificity and sensitivity. A two-sided p-value of less than 0.05 was defined to be statistically significant.

Results

Basic characteristics

The study included 144 patients (age, mean±SD: 63±10, male sex: 75%). Table 1 shows the demographic, clinical, laboratory, and treatment characteristics of the study population. Compared with CIN (-) patients, CIN (+) patients were significantly older, had higher mean creatinine levels, and lower lymphocyte count and platelet count (p=0.010, p=0.019, p=0.007, and p=0.031, respectively). There was no statistically significant difference in the frequency of smoking, DM, hypertension, dyslipidemia, chronic obstructive pulmonary disease, anemia, coronary artery disease, cerebrovascular disease, ischemic HF, peripheral artery disease, treatments, and other laboratory variables in patients with and without CIN.

In the whole group, ECG revealed a left bundle branch block in one hundred thirty-nine patients (Table 2). The remaining had the right bundle branch block. Patients with CIN had a longer length of hospital stay and received higher contrast material volume (p=0.001, and p<0.001, respectively). Patients with CIN had lower EF than CIN (-) patients (22±6% vs. 26±7%, p=0.005), and higher NYHA class III-IV (38% vs. 18%, p=0.023) (Table 2).

Mehran score evaluation

As demonstrated in Table 3, univariate logistic regression analyses showed that age [Odds ratio (OR): 1.06, 95% CI: 1.01-1.11, p=0.021], contrast volume (OR: 1.03, 95% CI: 1.02-1.05, p<0.001), creatinine level (OR: 2.85, 95% CI: 1.12-7.22, p=0.027), LVEF (OR: 0.92, 95% CI: 0.86-0.98, p=0.008), and MS (OR: 1.35, 95% CI: 1.17-1.56, p<0.001) showed association with the development of CIN. Multivariable logistic regression analyses showed contrast volume (OR: 1.02, 95% CI: 1.00-1.04, p=0.029) and MS (OR: 1.34, 95% CI: 1.10-1.63, p=0.004) independently associated with the development of CIN.

Sensitivity and specificity analysis

On admission, MS of 8.5 showed a sensitivity of 69% and specificity of 71% (AUC: 0.743, 95% CI: 0.645-0.841, p<0.001) for the prediction of CIN in this study population (Table 4). The cut-off for the contrast material volume for predicting CIN was 43 mL, with a sensitivity of 65% and specificity of 80% (AUC: 0.819, 95% CI: 0.751-0.886, p<0.001) (Figure 1, Table 4).

Discussion

This study showed that MS can be used as a predictor of CIN in patients undergoing CRT implantation, with a cut-off value of 8.5 and more than 65% sensitivity and specificity. This is the first study demonstrating that MS is an independent CIN predictor among patients undergoing CRT implantation.

CRT implantation complicated with CIN has higher mortality and morbidity than those without CIN (11). Therefore, determining the factors that may cause CIN in the preoperative period will help identify the patients in the risky group.

CIN is one of the most important complications of percutaneous cardiovascular procedures with an important effect on the long-term prognosis in this set of patients (11,15,16). Several potential pathophysiological pathways that can cause CIN have been reported. However, the pathogenesis of kidney damage is still not precisely elucidated. Nonetheless, iodinated contrast causes direct cellular damage to renal tubular cells leading to swelling, blebbing, and apoptosis in tubular cells (17). Additionally, microembolism due to catheter manipulation, which is not easily identifiable clinically may, at least in part, lead to CIN (18).

Although PCI and coronary angiography are the most common causes for developing CIN, the incidence of CIN after CRT implantation is similar to that of coronary procedures. CIN is a serious and frequent procedural complication of CRT implantation with a significant negative influence on long-term survival. Generally, less contrast volume is used in CRT implantation than PCI. Besides, patients with chronic HF have more comorbid chronic kidney disease. Therefore, although less contrast is required in the CRT procedure, the risk of developing CIN is increased (11).

CIN incidence was 20.1% in our study. This number is higher than the findings published by other authors despite the use of less amount of contrast medium (10,11,19). Our study sample received a mean contrast volume of 36 mL. In other studies, however, more than 100 mL contrast volume was used (10,11,19). Nonetheless, our study repeatedly confirmed that CIN is the most common procedural complication in patients undergoing CRT implantation. Less contrast usage was not associated with failed LV lead implantation. The decrease in failed LV lead implantation is associated with increased operator experience (19). Thus, CRT implantation by experienced operators is an essential preventive strategy in patients with high-risk factors.

HF and lower EF are among the most significant risk factors for CIN development in patients receiving CRT implantation (10,12). In our study, patients with CIN had lower EF compared to patients without CIN. However, lower EF was not found as an independent risk factor for the development of CIN. This finding may be related to the small number of patients in the study.

Table 1. Demographic, clinical and laboratory features of the study population

	Total (n=144)	CIN (+) (n=29)	CIN (-) (n=115)	p
Demographic and clinical features				
Age, years, mean±SD	63±10	67±9	62±10	**0.010**
Gender, n (%)				0.187
Male	108 (75)	19 (65)	89 (77)	
Female	36 (25)	10 (35)	26 (23)	
Diabetes mellitus, n (%)	66 (46)	17 (59)	49 (43)	0.122
Hypertension, n (%)	97 (67)	17 (59)	80 (70)	0.261
Coronary artery disease, n (%)	85 (59)	20 (69)	65 (56)	0.223
Dyslipidemia, n (%)	74 (51)	16 (55)	58 (50)	0.648
COPD, n (%)	20 (14)	7 (24)	13 (11)	0.078
Peripheral artery disease, n (%)	4 (3)	2 (7)	2 (2)	0.131
Cerebrovascular disease, n (%)	15 (10)	3 (10)	12 (10)	0.989
Smoker, n (%)	59 (41)	12 (41)	47 (42)	0.983
Ischemic heart failure, n (%)	82 (57)	19 (66)	63 (55)	0.297
Anemia, n (%)	27 (19)	10 (34)	17 (15)	0.116
Treatments				
Beta-blockers, n (%)	142 (99)	29 (100)	113 (99)	0.475
ARNI, n (%)	6 (4)	0 (0)	6 (5)	0.209
MRA, n (%)	110 (76)	21 (72)	89 (77)	0.573
Non-dihydropyridine CCBs, n (%)	11 (8)	4 (14)	7 (7)	0.163
Dihydropyridine CCBs, n (%)	144 (100)	29 (100)	115 (100)	-
RAAS blockers, n (%)	126 (87)	25 (86)	101 (88)	0.814
Furosemide, n (%)	112 (78)	25 (86)	87 (76)	0.222
Thiazide, n (%)	29 (20)	5 (17)	24 (21)	0.663
Ivabradine, n (%)	13 (9)	1 (3)	12 (10)	0.241
Statins, n (%)	56 (39)	9 (31)	47 (41)	0.332
Digoxin, n (%)	6 (4)	2 (7)	4 (4)	0.410
Laboratory parameters				
WBC, K/uL x10^3, median (25^{th}-75^{th} IQR)	7.6 (6.5-9.1)	7.6 (5.8-8.8)	7.55 (6.6-9.1)	0.221
Neutrophil, K/uL x10^3, mean±SD	5.1±1.8	5.1±2.1	5.0±1.7	0.786
Lymphocyte, K/uL, x10^3, median (25^{th}-75^{th} IQR)	1.9 (1.3-2.3)	1.5 (12.-1.9)	2.1 (1.4-2.3)	**0.007**
Platelets, K/uL, x10^3, median (25^{th}-75^{th} IQR)	233 (195-281)	215 (178-244)	239 (202-287)	**0.031**
Hemoglobin, g/dL, mean±SD	13.4±1.67	12.8±1.92	13.5±1.57	0.066
Hematocrit, mean±SD	40.5±4.9	39.0±5.6	40.9±4.7	0.100
RDW, mean±SD	14.7±1.7	15.1±1.6	14.6±1.8	0.144
MPV, fL, mean±SD	8.5±1.0	8.7±0.9	8.5±1.1	0.496
Total cholesterol, mg/dL, mean±SD	168±42	172±50	166±39	0.565
HDL, mg/dL, mean±SD	39±10	39±10	40±10	0.718
LDL, mg/dL, mean±SD	97±34	104±39	95±32	0.286
Triglycerides, mg/dL, median (25^{th}-75^{th} IQR)	136 (102-195)	123 (95-189)	136 (104-204)	0.526
Total protein, g/dL, mean±SD	6.7±0.7	6.7±0.8	6.7±0.6	0.960
Albumin, g/dL, mean±SD	4.1±0.4	4.1±0.5	4.2±0.4	0.503

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, ARNI: Angiotensin receptor-neprilysin inhibitor, MRA: Mineralocorticoid receptor antagonist, CCBs: Calcium channel blockers, RAAS: Renin-angiotensin-aldosterone system, GFR: Glomerular filtration rate, IQR: Interquartile range, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: Whole blood count, RDW: Red cell distribution width, MPV: Mean platelet volume

CIN also negatively influences the recovery of EF and survival in patients undergoing CRT implantation (20). Cardiorenal syndrome (CRS) type 3 is a subtype of the CRS. This type of CRS leads to acute kidney injury that aggravates and contributes to acute cardiac injury (21). This association can be explained by the close relationship between renal and cardiac function. As the reduction in cardiac output damages kidney functions, impaired kidney functions may also cause worsening in cardiac performance. Survival benefit in CRT responders is reduced if CIN occurs after the procedure (20).

MS has been developed to detect patients at risk of CIN in patients undergoing PCI. Although persistent renal dysfunction requiring routine hemodialysis after CIN is extremely rare, up to 45.9% of patients with CIN may have permanent renal failure (22). This complication is also associated with higher mortality and morbidity (11).

There are some limitations of this study. Firstly, this is a single-center study with relatively small sample size. Second, it is a retrospective study, and the results need to be further

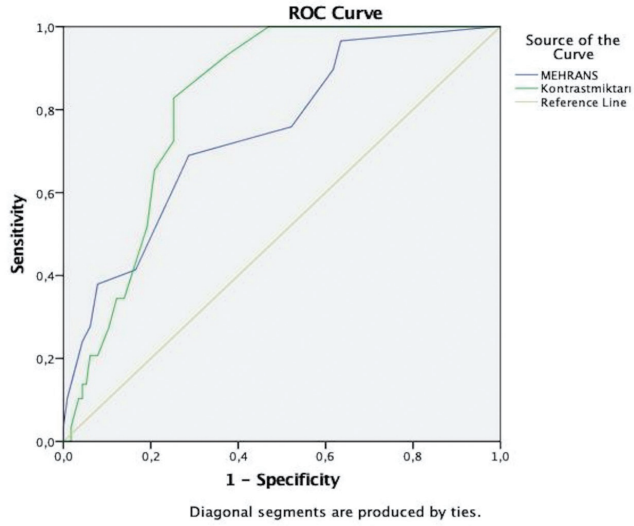

Figure 1. Mehran risk score cut-off value at admission for predicting contrast induced nephropathy based on receiver-operating characteristic curve analysis

ROC: Receiver-operating characteristic

Table 2. Mehran risk score and cardiovascular features of the study population

	Total (n=144)	CIN (+) (n=29)	CIN (-) (n=115)	p
Left-bundle branch block	139 (96)	28 (97)	111 (96)	0.994
Length of hospitalization, days, median (25^{th}-75^{th} IQR)	4 (2-11)	8 (4.5-17.5)	3 (1-8)	**0.001**
Contrast volume, mL, mean±SD	36±24	55±24	31±23	**<0.001**
LVEF, %, mean±SD	25±7	22±6	26±7	**0.005**
NYHA, n (%)				
Class I-II	112 (78)	18 (62)	94 (82)	**0.023**
Class III-IV	32 (22)	11 (38)	21 (18)	
Mehran risk score, mean±SD	8.2±3.0	10.4±3.3	7.6±2.7	**<0.001**

IQR: Interquartile range, SD: Standart deviation, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association

Table 3. Independent predictors of development of contrast-induced nephropathy by logistic regression analyses

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.06 (1.01-1.11)	**0.021**	1.03 (0.98-1.09)	0.236
Gender	1.80 (0.74-4.35)	0.191		
Diabetes mellitus	1.91 (0.84-4.36)	0.125		
Hypertension	0.62 (0.27-1.43)	0.264		
Coronary artery disease	1.71 (0.72-4.07)	0.226		
Dyslipidemia	1.21 (0.53-2.74)	0.649		
Ischemic heart failure	1.57 (0.67-3.66)	0.299		
MRA	0.77 (0.30-1.93)	0.573		
RAAS blockers	0.87 (0.26-2.86)	0.814		
Contrast volume, mL	1.03 (1.02-1.05)	**<0.001**	1.02 (1.00-1.04)	**0.029**
Creatinine	2.85 (1.12-7.22)	**0.027**	0.63 (0.17-2.31)	0.490
LVEF	0.92 (0.86-0.98)	**0.008**	0.94 (0.86-1.02)	0.132
Mehran risk score	1.35 (1.17-1.56)	**<0.001**	1.34 (1.10-1.63)	**0.004**

OR: Odds ratio, CI: Confidence interval, MRA: Mineralocorticoid receptor antagonist, RAAS: Renin-angiotensin-aldosterone system, LVEF: Left ventricular ejection fraction

Table 4. ROC curve analysis for the prediction of contrast induced nephropathy

	Cut off value	AUC	Sensitivity, %	Specificity, %
Mehran risk score	8.5	0.743 (0.645-0.841)	69	71
Contrast volume, mL	43	0.819 (0.751-0.886)	65	80

ROC: Receiver operating characteristic, AUC: Area under the curve

verified by prospective studies. Finally, the results are cross-sectional, precluding the establishment of a causal relationship.

Conclusion

We found a higher MS as an independent risk factor for developing CIN in HF patients undergoing CRT implementation. A score of MS above 8.5 may warn the operators to take stricter preprocedural precautions and modify the potential risk factors for CIN after CRT implantation. Therefore, the data obtained from this study suggest that MS can be used in risk stratification for CIN following CRT implementation in individuals with advanced HF.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital Institutional Ethics Committee (decision no: E2-20-57, date: 16.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.E., M.Ö., A.A., Design: M.A.E., M.Ö., M.K., Data Collection or Processing: M.E., K.D., A.A., Analysis or Interpretation: A.E., A.B.A., S.T., Literature Search: A.C.Ö., M.E., K.D., Ç.Y., Writing: M.A.E., M.K., A.B.A.

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The prevalence of peripheral artery disease in older adults with chronic kidney disease

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ABSTRACT

Aims: Not only severe but also mild to moderate chronic kidney disease (CKD) is an independent risk factor for peripheral artery disease (PAD). In this study, we examined the prevalence of PAD among older adults with mild-to-moderate CKD.

Methods: The study was performed using the dataset of participants registered to a previous single-center, cross-sectional study that included non-institutionalized older adults aged 65 years or older in a geriatric outpatient setting. The subjects were patients with mild to moderate CKD. Ankle brachial index (ABI) was measured using a hand-held Doppler. PAD was diagnosed using an ABI value <0.9. The crude and adjusted prevalence of PAD were calculated.

Results: A total of 554 patients were included (age: 75.4±6.2 years; female: 67.3%). PAD was detected by 8.2%, 27.1%, 60.0%, and 4.7%, in stage 1, 2, 3 and 4 CKD, respectively, with significant difference in stage 2 (p=0.003) and stage 3 (p=0.011) CKD compared with the stage 1 disease. PAD was also more prevalent in patients with reduced estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2: 19.6% vs. 10.9%, p=0.005). However, after adjustment for potential confounders, the increase in the prevalence of PAD in subjects with lower eGFR was no longer significant (Odds ratio: 1.48, 95% confidence interval: 0.87-2.53, p=0.148).

Conclusions: This study showed a higher prevalence of PAD among older adults with mild-to-moderate CKD; however, the difference appears to depend on existing confounders.

Introduction

The occlusive atherosclerotic disease of the aorta and lower extremities are known as peripheral artery disease (PAD). PAD is classified as an atherosclerotic cardiovascular disease (ASCVD) with coronary artery disease (acute coronary syndrome, history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization), stroke, and transient ischemic attack (1-3).

The prevalence of PAD in the general population is around 3-10% (4,5). Also, independent of cardiovascular disease (CVD) risk factors, the incidence of the PAD progresses with age and reaches 15-20% in patients aged 70 years or older (4,5). In the CAREFUL study, the first multicenter national study that investigated the prevalence of PAD in Turkey, subjects aged 70 years or older, or subjects aged 50-69 years with at least one cardiovascular risk factor were enrolled (6). The results of the study demonstrated that the prevalence of PAD was 20% in the study population, and 30% in patients aged 70 years or older (6). PAD accompanies complex chronic diseases of older age, as was shown in different types of dementia (7).

Although the gold-standard test for the diagnosis of PAD is conventional or computed tomography angiography, the ankle-brachial index (ABI) measurement, a non-invasive, simpler, efficient, and cheaper diagnostic tool, became a preferable option in the diagnosis of PAD with sensitivity (Sen) and specificity (Spe) above 90% in all age groups (8,9). Another alternative non-invasive technique used in the diagnosis of PAD is the arterial Doppler ultrasonography of the lower extremities (10). However, its preference is limited due to its poor performance in the diagnosis of infrapopliteal disease, inter-observer variability of the technique, and higher costs (10). Pulse wave velocity measurement, a non-invasive tool for the assessment of arterial stiffness, and Edinburgh Claudication Questionnaire, a screening tool for the detection of intermittent claudication were also studied as alternative methods for ABI, but results revealed that these tools cannot be used instead of each other (11,12).

Chronic kidney disease (CKD) is prevalent among older adults and is associated with increased morbidity and mortality (13). Most older adults have a mild to moderate decrease in estimated glomerular filtration rate (eGFR) and a higher frequency of CKD due to the comorbidities (14). The overall prevalence of CKD in the general population is around 11%, reaching greater than 40% after the 6th decade (15).

Mild-to-moderate CKD is associated with a higher risk of ASCVD (16), which is more pronounced for older adults (17). However, most studies have focused on coronary artery disease (16). Only a few studies have been published on the association of PAD in patients with renal insufficiency (18). Thus, current knowledge on the frequency of PAD among older adults with CKD is considered limited. In this study, we investigated the prevalence of lower extremity PAD in older adults with mild-to-moderate CKD.

Methods

Study population

This study was performed using the dataset of participants registered to a previous single-center, cross-sectional study that included non-institutionalized older adults aged 65 years or older in a geriatric outpatient setting (19). Subjects receiving renal replacement therapy, having a history of lower extremity revascularization, recent major surgery, or extremity amputation, severely impaired in daily activities, residing in a nursing home, wheelchair bounded, or considered to have a short life expectancy due to malignancies or any other medical conditions and those who declined to participate were excluded from the original cohort. For the current analysis, subjects diagnosed with dementia were further excluded.

The institutional review board approved the study, and the participants provided written, informed consent when enrolled to the original study. The study protocol conforms to the Helsinki Declaration of 1975, as revised in 1983.

Working protocol

The basic characteristics of the subjects including age, gender, and self-reported education attained in years, current or past smoking status, and comorbidities including diabetes mellitus, hypertension, hypercholesterolemia, cardiovascular disease (CVD), coronary heart disease, stroke, anemia, hypothyroidism, vitamin B12 deficiency, and folate deficiency, body mass index (BMI), and laboratory results were available in the registry dataset.

Calculation of GFR and determination of CKD stages

Serum creatinine level was used to calculate eGFR (mL/min/1.73 m^2) by using the Modification of Diet in Renal Disease (MDRD) study equation to determine the degree of kidney impairment (20). Stages of CKD was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline as follows: stage 1 CKD: GFR ≥90 mL/min/1.73 m^2; stage 2 CKD: GFR 60 to 89 mL/min/1.73 m^2; stage 3 CKD: GFR 30 to 59 mL/min/1.73 m^2; stage 4 CKD: GFR 15 to 29 mL/min/1.73 m^2; stage 5 CKD: GFR <15 mL/min/1.73 m^2 or treatment by dialysis. However, individuals with CKD stage 5 (n=2) were not included due to the very low number of subjects in the analyses because they were excluded from the original study.

Measurement of ABI

ABI was measured in an improved facility by the conventional method as previously described (7,21-23). Briefly, patients were placed on a stretcher in the supine position with both arms slightly open. Two metal armrests of 30 cm width and 90 cm length were placed to the stretcher with an angle of 30º degrees to support both arms. In addition, sponge rubbers were placed under the heels and elbows to slightly elevate the extremities from the surface below the heart level to allowing the operator to place the cuff ideally. Four fully calibrated and identical aneroid sphygmomanometers with Velcro cuffs (ERKA, D-83646, Bad Tölz, Germany) of 12 cm width and 29 to 42 cm length were wrapped on four extremities at the same time. After resting at least for five minutes in supine, measurements were performed using a handheld 8-MHz Doppler instrument (Hadeco, Kawasaki, Japan). The measurements were started from the right upper arm and followed by the right ankle left ankle and left upper arm. This cycle was performed twice. The first sound of blood flow heard during the deflation of the cuff for both brachial pulses in the upper arms and dorsalis pedis and tibialis posterior pulses in both ankles were recorded. The mean value of the two measurements was recorded as the result for the respective vessel.

Calculation and interpretation of ABI results

The ABI was calculated based on the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) guidelines (9). The right and left ABIs were calculated separately by dividing the highest systolic blood pressures of each lower extremities (a. dorsalis pedis or a. tibialis posterior) to the systolic blood pressure of the brachial artery on the same side. Finally, the lower ABI value on the left or right side was recorded as the final ABI value. Individuals who had an ABI value of 0.9 or lower were diagnosed with PAD. Besides, subjects with an ABI value greater than 1.40 (n=3) were excluded as it indicates noncompressible arteries that interfere with the correct assessment of the ABI.

Statistical Analysis

Results are displayed as the mean and standard deviation for normally distributed continuous variables. The normality of distribution was tested using the Shapiro-Wilk test. Categorical data are displayed as absolute numbers and a percentage of the total. The differences between the continuous variables were tested by the t-test. The chi-square test was used to compare the categorical variables. The Sen and Spe analysis was conducted to determine the effects of different stages of CKD on PAD. The study sample was divided into 3 tertiles according to the eGFR, as follows; tertile 1: eGFR <49.4 mL/min/1.73 m^2 (n=138, 25 percentile), tertile 2: eGFR between 49.5-72.2 mL/min/1.73 m^2 (n=277, 50 percentile), tertile 3: eGFR >72.3 mL/min/1.73 m^2 (n=139, 75 percentile). Tertile 1 had the lowest and tertile 3 had the highest eGFR. The analysis of continuous variables across tertiles was performed using one-way ANOVA or the Kruskal-Wallis test, and the analysis of categorical variables was performed using the chi-square test. Multivariable logistic regression analysis was used to test the independent association between the eGFR and PAD. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. Statistical significance was set at p value <0.05. Statistical Package for the Social Sciences for Windows, version 26.0, IBM. Corp., Armonk, NY, 2019 was used for statistical analysis for all data.

Results

Study population

The study included 554 older adults (mean age: 75.4±6.2 years, women: 67.3%). Women were significantly younger than men (mean age: 74.8±6.3 vs. 76.8±5.8; p<0.001). Basic demographics and clinical characteristics are given in Table 1. The mean eGFR was 62.0±20.6 mL/min/1.73 m^2, and men have lower mean value than woman (59.5±17.2 mL/min/1.73 m^2 vs. 63.2±22.0 mL/min/1.73 m^2; p=0.032).

Frequency of PAD according to the stages of CKD and tertiles

In the whole study group, the frequency of patients with a 0.9 or lower ABI was 15.3% (n=85). The prevalence of PAD among

Table 1. Basic characteristics of the subjects

	Total (n=554)	Female (n=373, 67.3%)	Male (n=181, 32.7%)	p
Age, mean (SD)	75.4 (6.2)	74.8 (6.3)	76.8 (5.8)	**<0.001**
65-74, n (%)	277 (50.0)	203 (36.6)	74 (13.4)	**0.001**
75-84, n (%)	231 (41.7)	143 (25.8)	88 (15.9)	**0.041**
>84, n (%)	46 (8.3)	27 (4.9)	19 (3.4)	**0.029**
eGFR, mean (SD)	62.0 (20.6)	63.2 (22.0)	59.5 (17.2)	**0.032**
BMI, mean (SD)	29.8 (5.6)	30.8 (5.9)	27.7 (4.3)	**<0.001**
Lower education, n (%)	390 (70.5)	316 (57.1)	74 (13.4)	**<0.001**
Past/current smoking, n (%)	152 (27.4)	40 (7.2)	112 (20.2)	**<0.001**
Diabetes mellitus, n (%)	146 (26.4)	107 (19.3)	39 (7.0)	0.074
Hypertension, n (%)	432 (78.0)	300 (54.2)	132 (23.8)	**0.046**
Hypercholesterolemia, n (%)	224 (40.4)	160 (28.9)	64 (11.6)	0.090
Anemia, n (%)	92 (16.6)	78 (14.0)	14 (2.6)	**0.007**
Hypothyroidism, n (%)	62 (11.5)	48 (8.9)	14 (2.6)	0.056
Vitamin B12 deficiency, n (%)	168 (30.3)	107 (19.3)	61 (11.0)	0.228
Folate deficiency, n (%)	62 (11.9)	35 (6.7)	27 (5.2)	0.085
CVD, composite, n (%)	138 (24.9)	66 (11.9)	72 (13.0)	**<0.001**
Coronary heart disease, n (%)	109 (19.7)	50 (9.0)	59 (10.6)	**<0.001**
Stroke, n (%)	36 (6.5)	19 (3.4)	17 (3.1)	0.054

Lower education: <5 years of attained education level, anemia: hemoglobin <12 g/dL in woman, and hemoglobin <13 g/dL in man, hypothyroidism: thyroid stimulating hormone >5 mIU/mL, vitamin B12 insufficiency: <200 pg/mL, folate deficiency: <5 ng/mL, CVD: Presence of either coronary heart disease or stroke. Significant p values are in bold. See text for other details.
SD: Standard deviation, eGFR: Estimated glomerular filtration rate, BMI: Body mass index, CVD: Cardiovascular disease

subjects with stage 1, 2, 3 and 4 CKD was given in Table 2. Stage 1 and stage 4 CKD groups showed similar proportion of PAD (8.2% vs. 7.9%, p=0.914, and 3.0% vs. 4.7%, p=0.410, respectively). The frequency of PAD was lower in stage 2 CKD (27.1% vs. 44.1%, p=0.003), and higher in stage 3 CKD (60.0% vs. 45.0%, p=0.011) (Table 2). Also, the prevalence of PAD was higher in patients with a reduced (<60 mL/min/1.73 m^2) vs. higher eGFR (19.6% vs. 10.9%, p=0.005). However, after adjustment for potential confounders (age, gender, smoking, diabetes mellitus), the increase in the prevalence of PAD in subjects with reduced eGFR was no longer significant [OR: 1.48, 95% confidence interval (CI): 0.87-2.53, p=0.148] (Hosmer-Lemeshow test, p=0.890).

The frequency of PAD between the eGFR tertiles was significantly different (tertile 1: 36.5%, tertile 2: 48.2%, and tertile 3: 15.3%, p=0.010) (Table 2). The comparison of patients in the lowest and highest tertiles showed that the mean ABI value was significantly higher (T1: 0.99±0.19 vs. T3: 1.07±0.14, p<0.001), and the prevalence of PAD was significantly lower (T1: 22.5% vs. T3: 9.4%, p=0.003) in the highest tertile (Table 3).

The Sen and Spe of each CKD stages and reduced eGFR to detect PAD were as follows; stage 1 CKD=8.2% Sen and 92.1% Spe; stage 2 CKD=27.1% Sen and 55.9% Spe; stage 3 CKD=60.0% Sen and 55.0% Spe; stage 4 CKD=4.7% Sen and 97.0% Spe, and eGFR <60 mL/min/1.73 m^2=64.7% Sen and 57.0% Spe.

Discussion

The results of this study showed that an eGFR value below <60 mL/min/1.73 m^2 is associated with a higher frequency of PAD among older patients. Also, the comparison of subjects in the lowest and highest eGFR tertiles showed that PAD was more prevalent, and the mean ABI value was lower in the lowest eGFR tertile. However, adjusted for age, gender, smoking status, and diabetes mellitus, the difference in the prevalence of PAD patients with eGFR below and above 60 mL/min/1.73 m^2 became saturated.

The risk of ASCVD associated ischemic events is higher in CKD patients than in individuals with preserved kidney function (24). The PAD, similar to other ASCVD, is also more frequent in CKD patients than in the general population (25). Although the association between severe CKD and PAD in the general population is well established (25), the data related to the association of mild to moderate CKD and PAD among older adults are limited. Most of the studies that focused on the association of ASCVD and reduced eGFR among older adults excluded patients with PAD (17,26). Either the rate of PAD patients in the study cohort was limited (27), or the participants were mostly younger than 65 years in other studies (18).

Table 2. Frequency of peripheral artery disease according to the stages of chronic kidney disease and tertiles

	Total (n=554)	Peripheral artery disease (n=85, 15.3%)	No peripheral artery disease (n=469, 84.7%)	p
Stage 1 CKD, n (%)	44 (7.9)	7 (8.2)	37 (7.9)	0.914
Stage 2 CKD, n (%)	230 (41.5)	23 (27.1)	207 (44.1)	**0.003**
Stage 3 CKD, n (%)	262 (47.3)	51 (60.0)	211 (45.0)	**0.011**
Stage 4 CKD, n (%)	18 (3.2)	4 (4.7)	14 (3.0)	0.410
eGFR tertiles, n (%)				
Tertile 1	138 (24.9)	31 (36.5)	107 (22.8)	
Tertile 2	277 (50)	41 (48.2)	236 (50.3)	**0.010**
Tertile 3	139 (25.1)	13 (15.3)	126 (26.9)	

Stage 1 CKD: eGFR ≥90 mL/min/1.73 m^2, stage 2 CKD: eGFR between 89-60 mL/min/1.73 m^2, stage 3 CKD: eGFR between 59-30 mL/min/1.73 m^2, stage 4 CKD: eGFR between 29-15 mL/min/1.73 m^2, tertile 1: eGFR <49.4 mL/min/1.73 m^2, tertile 2: eGFR between 49.5-72.2 mL/min/1.73 m^2, tertile 3: eGFR >72.3 mL/min/1.73 m^2. Significant p values are in bold.
CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate

Table 3. Comparison of the frequency of peripheral artery disease and the mean ankle brachial index values in subjects with reduced and preserved estimated glomerular filtration rate and in lowest and highest tertiles

	Estimated glomerular filtration rate		
	Reduced (n=280)	Preserved (n=274)	p
PAD, n (%)	55 (19.6)	30 (10.9)	**0.005**
	Tertile 1 (n=138)	**Tertile 3 (n=139)**	
PAD, n (%)	31 (22.5)	13 (9.4)	**0.003**
ABI, mean (SD)	0.99 (0.19)	1.07 (0.14)	**<0.001**

Reduced eGFR: <60 mL/min/1.73 m^2, preserved eGFR: ≥60 mL/min/1.73 m^2, significant p values are in bold.
PAD: Peripheral arterial disease, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, ABI: Ankle-brachial index

In a study conducted in Spain with 102 older adults with CKD, patients with reduced eGFR (<60 mL/min/1.73 m^2) were diagnosed with PAD by 32%, markedly higher than the prevalence of PAD in Spanish population without CKD (6.9%) (28). However, the authors performed only unadjusted analyses. Although we diagnosed more patients with PAD among CKD patients with a reduced eGFR (<60 mL/min/1.73 m^2) in crude comparisons, the difference was no longer significant in the adjusted analysis.

In a longitudinal study conducted with 4893 subjects aged 65 years or older, participants were followed up for a mean of 4.33 years to determine the relationship between baseline kidney function and the development of ASCVD (29). The authors identified that 25.1% (n=1229) of the participants were diagnosed with ASCVD during follow-up, but only 1.5% (n=18) were PAD. The authors also reported that each 10 mL/min/1.73 m^2 decline in eGFR was associated with an increased risk of ASCVD, including PAD. However, the number of PAD diagnoses in that study was limited. Also, the authors did not perform a subgroup analysis with PAD patients to investigate whether the increased risk of ASCVD due to a decrease in eGFR could have been similarly attributed to the PAD patients or not.

According to results of the National Health and Nutrition Examination Survey of 1999-2000, the prevalence of PAD among patients with an eGFR <60 mL/min/1.73 m^2 vs. higher was found 24% vs. 3.7%, respectively (25). Moreover, the association of PAD and CKD remained significant after adjustment for potential confounders, which contrasts with our results of frequency analysis as the difference in the prevalence of PAD among subjects with low vs. preserved eGFR was not significant controlling for potential covariates. The exclusion of patients with stage 5 CKD/renal replacement therapy and significantly older age of the study population in our study may explain the difference between the two studies (30,31).

In a prospective follow-up study by Wattanakit et al. (26), a total of 14280 participants with a mean age of 54 years were followed up for a mean of 13.1 years to investigate whether the level of kidney function was an independent risk factor for PAD. Age and gender-adjusted relative risk (RR) for PAD was 1.04 (95% CI: 0.91-1.18) for those with stage 1 and 2 CKD, and 1.82 (95% CI: 1.34-2.47) for those with stage 3 and 4 CKD. After adjustment for confounders of ASCVD development, although the RR was reduced, patients with CKD were still at an increased risk of incident PAD (RR of 1.56; CI: 1.13-2.14). The findings suggested an inverse correlation between the risk of PAD and kidney functions across all stages of CKD. We were unable confirm that finding among mild-to-moderate CKD patients in our study. On the explanation may be the unexpectedly high frequency of PAD in patients with preserved renal functions due to the advanced age of our cohort.

PAD is more frequent in CKD patients than in the general population (25). However, the causal relationship between CKD and PAD has not yet been fully elucidated. The prevailing opinion on this subject is that CKD is probably a marker of metabolic diseases leading to progressive dysfunction of vascular structure (32,33). This suggestion is mostly based on studies that have investigated the association of atherosclerosis and albuminuria that is a marker of endothelial dysfunction (34). The association between albuminuria, medial arterial calcification and PAD is well established (35,36). In addition to the direct impact of CKD on arteries, the risk factors for both CKD and PAD development are quite similar, though not identical (37,38). In the Chronic Renal Insufficiency Cohort study, novel risk factors associated with an increased prevalence of PAD in patients with CKD were oxidative stress, inflammation, insulin resistance, and a prothrombotic state (39).

This study has some limitations. First, this was a retrospective analysis of a dataset created to explore the association of ABI and bone mineral density (19). Therefore, the study may be underpowered to study the relationship between severely reduced kidney functions and ABI or peripheral arterial disease. Second, we calculated eGFR by using serum creatinine level at study entry using the MDRD study equation, which requires stable kidney function (39). Although the participants were community-dwelling outpatients, the current study did not specifically assess the course of kidney functions for at least three months. Third, it is well-known that the prevalence of PAD is significantly higher among dialysis patients (25) and end-stage CKD patients (36). However, we excluded stage 5 CKD patients and patients receiving renal replacement therapy, which might have caused a similar distribution of PAD between lower and higher eGFR groups after adjustment for confounders.

Conclusion

In conclusion, this study showed evidence of a higher prevalence of PAD in older people with CKD. However, the observed difference appeared to depend on existing confounders in multivariable regression analyses, suggesting that the risk of PAD in older adults with CKD is not modified independently from other risk factors for atherosclerotic diseases. Based on the findings in our study and current literature, future prospective studies with larger sample size must better identify the association of mild to moderate CKD with PAD among older adults.

Ethics

Ethics Committee Approval: The Kecioren Training and Research Hospital Institutional Review Board approved the study (approval number: 2012-KAEK-15/1256-2017, date: 11.01.2017).

Informed Consent: This study is an analysis of a data set from a prospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.T., Design: İ.T., Data Collection or Processing: B.B.B., İ.T., Analysis or Interpretation: B.B.B., İ.T., Literature Search: B.B.B., İ.T., Writing: B.B.B., İ.T.

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Neuroma prevalence and neuroma-associated factors in patients with traumatic lower extremity amputation

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Keywords: Amputation, neuroma, pain, ultrasound, radiography

ABSTRACT

Aims: There is limited understanding of factors related to the development of symptomatic neuromas. The aims of this study were to determine the prevalence of neuroma in amputees with residual limb pain (RLP) and to examine factors associated with neuromas.

Methods: A retrospective and cross-sectional study was conducted at the amputee rehabilitation unit of a tertiary hospital in Turkey. Demographic, clinical, ultrasonographic and radiographic records between September 2016 and April 2020 were evaluated. Bone anatomy in the affected limb was evaluated by radiographic examination. Both neuroma site and size were evaluated with ultrasonography.

Results: A total of 85 patients (107 amputations) were included in the study. Neuroma was detected in 47.1% of the patients with RLP. Sixty percent of the patients with neuroma had a duration of longer than 5 years since amputation. The most common amputation level was transtibial (below-the-knee, 61.9%). Neuroma was more frequently identified in patients with landmine injury (57.5%) than without (37.8%). A correlation was found between the time after amputation and the neuroma size (r=0.47, p=0.001). There was no correlation between visual analog scale scores and neuroma size (r=-0.09, p=0.570). There was also no relationship between bone spurs and neuromas.

Conclusions: Half of lower limb amputees with RLP were found to have neuromas. Clinicians should be aware of the high prevalence of neuroma among the causes of RLP to manage the rehabilitation procedure of these patients appropriately.

Introduction

About 185.000 upper or lower limb amputations are done annually (1). Limb amputations caused by trauma and diseases is a devastating condition and causes psychological and functional disabilities (2,3). Residual limb pain (RLP), defined as pain felt in the rest of the amputated limb, is one of the chronic complications of amputations (1). Neuromas, the tumor-like thickening of a nerve stump in the scar area after amputation of a limb sensitive to pressure are among the causes of RLP (4). Patients with neuroma usually describe the pain as intense paroxysmal burning pain or low-intensity dull pain, often provoked by external stimuli like temperature and touch. The diagnosis of symptomatic neuromas can be made with the medical history, response to a diagnostic proximal nerve block, physical symptoms, the Tinel sign, and imaging (5).

Both magnetic resonance imaging (MRI) and ultrasonography (US) are useful to detect the suspected neuromas (6,7). While MRI is expensive and not widely available, US is inexpensive, commonly available, and cheaper (8). The classic appearance of the neuroma, which may be well-circumscribed or have irregular margins, is hypoechoic, oval mass in direct contiguity with the nerve (7,9).

The prevalence of symptomatic neuroma in patients with extremity amputation varies extensively, and there is uncertainty about their actual prevalence in the literature (5). There is also a limited understanding of the factors related to the development of

symptomatic neuromas. Landmine injury, nerve trunk indentation of bone spurs, and central pain phenomenon may be associated with neuroma development (10-13). Nonetheless, there are limited studies on the association of the aforementioned factors with neuroma. Examining the factors that cause stump neuroma formation and the features of neuroma may help develop new rehabilitative strategies for the prevention and management of neuroma in patients with amputation.

This study aimed to determine the prevalence of neuroma in amputees with RLP and to examine the potential factors associated with neuromas.

Methods

A retrospective and cross-sectional study was conducted. The study population consisted of patients with traumatic lower extremity amputation referred to the Amputee Rehabilitation Unit of a tertiary hospital, between September 2016 and April 2020 (Ankara Gaziler Physical Medicine and Rehabilitation Training and Research Hospital). Patients with RLP between the ages of 18-65 years were included in the study. The exclusion criteria were age over 65 years, partial foot or toe loss, congenital limb deficiency, phantom limb pain, nontraumatic etiology, absence of radiographic view, and the absence of stump US record. The study protocol was approved by the Committee on Human Research Ethics at Ankara City Hospital (Nr.: E1-20-839, date: 25.06.2020).

Each amputation was considered an individual case in patients with more than one amputation. Age, gender, height, weight, comorbidities, amputation type, time since amputation, amputation level, amputation etiology, US findings, and radiological findings were obtained from the medical records. Bone anatomy in the affected limb was evaluated by radiographic examination and spur formation was recorded if any. The perception of pain by the patient was evaluated using the visual analog scale (VAS) (0-10 points) at initial admission [VAS; from 0 (no pain) to 10 (worst pain)].

All sonographic evaluations were performed by a radiologist experienced in musculoskeletal sonography. Both neuroma site and size were identified using US imaging. The size of each neuroma in the amputation stump was measured along two axes (Figure 1). If there was more than one neuroma in an amputation stump, the size of the largest neuroma was recorded. Mainly three types of neuroma associated with RLP have been identified: 1) fusiform/lobulated shaped neuroma formed of a radiating network of tiny nerves, 2) cylindrical-shaped neuroma, 3) neuroma that keeps the morphology of a normal but swollen nerve (10).

We hypothesized that neuroma sizes may differ depending on the duration of the disease. Therefore, patients were divided into 3 groups according to the duration after amputation (<1 year, 1-5 years, and >5 years).

Statistical Analysis

The Statistical Package for the Social Sciences Statistics for Windows (version 23.0, Armonk, NY: IBM Corp., 2015) was used for statistical analysis. Continuous variables were expressed as mean and standard deviation (SD) or minimum-maximum values. Categorical variables were presented in frequency (%). Student's t-test and Mann-Whitney U tests were used for comparison of mean values between groups. The chi-square test was used for frequency comparisons. Spearman or Pearson coefficient used for correlation analysis. One-way ANOVA was used to compare neuroma sizes among the amputation year (<1 years / 1 to 5 years / >5 years) groups. Statistical significance was set at $p<0.05$.

Results

A total of 85 patients (107 amputations) were included in the study (Figure 2). All patients were male (100%). Forty-two neuromas were identified in total (39.3%). Neuroma was detected in 47.05% of the patients with RLP.

Patients with neuroma were aged between 22 and 53 years (mean±SD, 35.8±8.6 years). The mean time since amputation was 131.2±110.5 months (range, 4-360 months) and 60% of the patients had a duration of longer than 5 years. Neuroma was identified more frequently in patients with landmine injury (57.5%) than without (37.8%) but the difference did not reach statistical significance (p=0.070). The most common level of amputation was transtibial (below-the-knee, 61.9%). The VAS scores ranged from 2 to 10 points (mean±SD, 7.0±2.2). Demographic variables were not significantly different between patients with and without neuroma as shown in Table 1.

Neuroma formation was the most common in the posterior part of the amputation stump (53.1%) (Figure 3). The neuroma

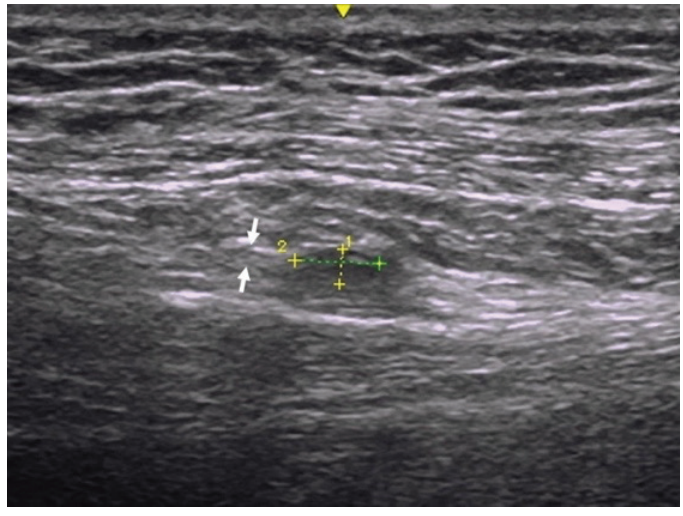

Figure 1. A longitudinal ultrasound image shows ovoid, hypoechoic lesion representing a neuroma in the amputation stump, directly continuous to femoral nerve (arrow)

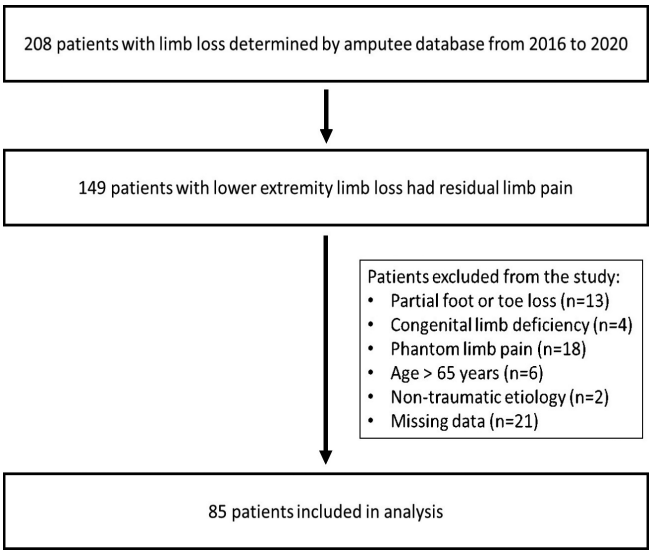

Figure 2. Flow chart of the study

size ranged from 9.4 mm² to 320.3 mm² (mean±SD, 76.8±64.3 mm²). When the neuroma size was compared according to the amputation year, a statistically significant difference was found

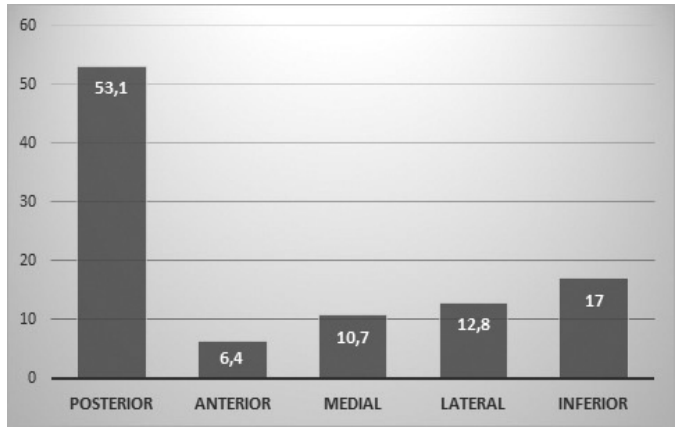

Figure 3. Distribution of neuroma sites in amputation stump

Table 1. Demographic variables of patients with and without neuroma

Variable	Neuroma (+) (n=40)	Neuroma (-) (n=45)	p
Age (years), mean±SD	35.8±8.6	34.3±8.5	0.460
BMI, mean±SD	26.0±4.1	25.0±3.5	0.270
Comorbidities, n (%)			
Hypertension	2 (5)	4 (8.9)	0.480
Diabetes mellitus	1 (2.5)	3 (6.7)	0.360
Time since amputation (months), mean±SD	131.2±110.5	106.2±102.1	0.420
Time since amputation (years), n (%)			0.110
<1 year	11 (27.5)	9 (20)	
1-5 years	5 (12.5)	14 (31.1)	
>5 years	24 (60)	22 (48.9)	
Etiology, n (%)			0.310
Mine	23 (57.5)	17 (37.8)	
Explosives	7 (17.5)	13 (28.9)	
Gunshot	7 (17.5)	6 (13.3)	
Rocket	2 (5)	4 (8.9)	
Electrical injury	1 (2.5)	4 (8.9)	
Car accident	0	1 (2.2)	
Amputation side, n (%)			0.530
Right	16 (40.0)	13 (28.9)	
Left	14 (35)	20 (44.4)	
Bilateral	10 (25)	12 (26.7)	
Amputation level, n (%)			0.180
Total	42 (39.3)	65 (60.7)	
Hip	0 (0.0)	1 (1.5)	
Above-the-knee	14 (33.3)	28 (43.1)	
Knee	2 (4.8)	2 (3.1)	
Below-the-knee	26 (61.9)	29 (44.6)	
Ankle (Syme)	0	5 (7.7)	

BMI: Body mass index, SD: Standard deviation

between the groups (>1 year, 1-5 years, >5 years) (p=0.010). The size of the neuroma was significantly larger in the group with amputation time over 5 years compared to the group under 1 year (p=0.030). There was no statistically significant difference in the size of the neuroma between the group with amputation time of 1-5 years and the groups with amputation time below 1 year and above 5 years (p=0.980, p=0.100, respectively) (Table 2).

A correlation was found between the time after amputation and the size of the neuroma (r=0.47, p=0.001). There was no correlation between VAS scores and neuroma size (r=-0.09, p=0.570) as shown in Table 3.

In patients with a neuroma, radiographic imaging revealed femoral spur in 35.7% of transfemoral amputations, tibial spur in 29.2%, and fibular spur in 37.5% of the transtibial amputations. In patients without neuroma, on the other hand, radiographic imaging revealed femoral spur in 35.7% of transfemoral amputations, tibial spur in 14.3%, and fibular spur in 28.6% of the transtibial amputations. There was no statistically significant difference in the frequency of bone spurs between patients with and without neuroma (p=0.930, p=0.190, p=0.490, respectively). There was no relationship between bone spurs and neuromas.

Discussion

The development of amputation stump neuromas is a frequent and common cause of stump pain that results from compression of the sensitive nerve endings by adjacent soft tissues (14), nerve traction by scar tissue surrounding and fixing the neuroma (15), or decreased blood supply to the neuroma with hypoxia of the nerve endings (16).

There is uncertainty about the actual prevalence rate of symptomatic neuroma in the literature, ranging from 4% to 49% (5). Neuroma was detected in 47.1% of the patients with RLP in our study. This relatively higher prevalence compared to most of the previous reports may be associated with the small sample size and retrospective design of the study.

The most common level of amputation was transtibial by 61.9% in patients with a neuroma in our study. A difference in terms of biomechanical load on the stump has been stated between transtibial amputees and others (17). Moreover, patients with transtibial amputations are more functional and mobile than individuals with upper amputation levels (18). Therefore, increased mechanical forces may affect the formation of neuroma in individuals with transtibial amputation (10).

RLP is an important problem in patients with landmine injury (19,20). We found that neuroma was identified in 57.5% of patients with landmine injury. Similarly, neuroma was detected in half of the patients with landmine injury in a study by Aydemir et al. (10). It has been reported that unshaped stump, non-elective sudden surgery, and contaminated blast-related extremity wound affect the development of stump neuromas in patients with landmine injury (4,21).

Neuromas develop within a 1-12-month period following a traumatic event or a nerve transection. The size of neuroma increases due to localized chronic irritation and is affected by the immediate environment, especially in areas where pressure is bearing. The slow growth of the neuroma is noticed over 2-3 years (13), after that growth ceases. However, neuromas remain *in situ* for the patient's lifetime. The enlargement of the neuroma is limited, and its final size is directly associated with the number of damaged axons (22) and the size of the main nerve (13). In our study, a correlation was also found between the time after amputation and the size of the neuroma; however, there was no correlation between pain scores and neuroma size. Similarly, there was no relationship between pain scores and neuroma volume in a study by O'Reilly et al. (11).

The time from the first injury to present neuromas is quite variable. Neuromas can be asymptomatic for a long time. In our study, neuroma after 5 years of amputation in 60% of the patients suggests that RLP caused by symptomatic neuromas may have a late-onset. Therefore, long-term follow-up is required for

Table 2. Time since amputation, amputation type, and mean area of neuromas

Time since amputation	Above-knee	Knee	Below-knee	Area of neuroma, mm² mean±SD
<1 year	2	1	7	41.32±30.45
1-5 years	3	0	4	46.65±27.35
>5 years	9	1	15	99.41±72.20

Table 3. Correlations between neuroma size and demographic and clinical parameters of patients

	Neuroma size (mm²)	
	r	p
Age, years	0.346	0.029*
Body mass index, kg/m²	0.758	0.062
Time since amputation, months	0.471	0.001*
Visual analogue scale	-0.091	0.574

patients with lower extremity amputation due to probable late-onset of RLP caused by neuromas (5).

Altered anatomy because of amputation can probably cause the development of many bone lesions including bone spurs (11). It has been declared that nerve trunk indentation of bone spurs can be associated with neuromas (23). In the US imaging study by O'Reilly et al. (11), it was reported that some symptomatic neuromas appear to be attached to the cut end of the bone or bony spur or the periosteum or the scar. Prompt shaving of bone surfaces is recommended during amputation surgery (23). There was no relationship between bone spurs and neuromas in our study. Further prospective studies are needed to investigate the relationship between the bone cutting technique and bony spurs and neuroma formation.

This study has several limitations. First, the sample size in the study is overall small. Second, the results of the study are limited to patients with lower limb amputations, not reflecting patients with upper limb amputations. Third, the morphology of the nerves has not been evaluated in the study. Since the evaluation of the morphology of the nerves may allow for a more detailed analysis of the formation of a neuroma. Last, it is stated in which part of the stump the neuroma is detected, but it is not specified in which nerve the neuroma is related.

Conclusion

In conclusion, this study found a high prevalence of symptomatic neuroma among lower limb amputees. The frequency of neuromas was higher in patients with transtibial amputation and landmine injury. There was no relationship between bone spurs and neuromas. The period after amputation for more than half of the patients with neuroma was a minimum of 5 years. Although there was a correlation between the amputation time and the neuroma size, there was no correlation between pain scores and neuroma size.

Ethics

Ethics Committee Approval: The study protocol was approved by the Committee on Human Research Ethics at Ankara City Hospital (no: E1-20-839, date: 25.06.2020).

Informed Consent: Retrospective and cross-sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ö.A., Design: M.Ö.A., Data Collection or Processing: M.Ö.A., G.K.K., Analysis or Interpretation: M.Ö.A., Y.D., K.A., Literature Search: S.G.A., Writing: M.Ö.A., Y.D., N.K., S.G.A., K.A.

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Clinical, surgical and histopathological characteristics of liver transplant recipients: An analysis of a large sample from Turkey

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ABSTRACT

Aims: Liver transplantation (LT) is the most effective treatment method for end-stage liver failure and acute liver failure, depending on all causes. This study aimed to examine the clinical, surgical, and histopathological characteristics of LT recipients in a referral center in Turkey.

Methods: In this single-center study, demographic, clinical, laboratory, radiological, surgical, and histopathological data of LT recipients aged 18 years or over between December 2017 and February 2021 were retrospectively analyzed. All subjects were transplanted from live donors and cadavers.

Results: The sample included 162 subjects [mean age: 50.1 (18-70) years; male: 64.8%. The proportion of live donor transplantation was 86.4% (n=140)]. The mean follow-up time was 20.5 months (1-39 months). The most common primary indication was hepatocellular carcinoma (n=43, 26.5%) and chronic hepatitis B virus infection-related cirrhosis (n=30, 18.5%). The most common postoperative complication was biliary complications (30.9%). One-year survival was 88.9%, two-year survival was 85.8%, and three-year survival was 83.3%. During the 3-year follow-up, the total graft loss rate was observed by 17.9%, and the mortality rate was 15.4%.

Conclusions: The main goal in LT is the long-term survival of the graft and the patient. The present study showed that demographic characteristics, etiological characteristics, postoperative complications, and mortality rates among LT recipients were consistent with the results of other centers around the world.

Introduction

Liver transplantation (LT) was performed first in 1963 in the United States by Thomas Starzl. Today, LT is the most effective treatment for end-stage liver failure and acute liver failure (ALF) (1). LT has been performed on more than 80000 patients with chronic liver failure in the world (2). Recently, survival rates after transplantation have increased considerably, with 96% in 1 year and 71% in 10 years after transplantation (3). The underlying reasons for this success are the introduction of new immunosuppressive agents, advances in surgical techniques, early diagnosis and treatment of complications after LT (4).

Generally, the most common LT indication is cirrhosis with end-stage liver failure, followed by hepatocellular carcinoma (HCC) and acute ALF (2). The most common indications of LT in Europe between 1988 and 2011 were reported as cirrhosis (57%), cancer (15%), cholestatic diseases (10%), ALF (8%), metabolic disease (6%) and other causes including Budd-Chiari syndrome, benign liver tumors, polycystic diseases, parasitic diseases (4). ALF requires immediate LT, and the most common underlying diseases are viruses (most commonly hepatitis A and B viruses), drugs (most commonly acetaminophen), and toxic agents (2). The priority of patients on the waiting list is determined by the Child (child turcotte pugh) score and, since

2002, the model of end-stage liver disease (MELD) scoring system (2). Patients with end-stage liver failure with a MELD score of 15 and above are recommended to be included in the transplantation list, while the risk of death of patients with a score above 30 and the risk of morbidity and mortality that will increase after transplantation should be taken into consideration (5,6).

In addition to numerous advances in surgical techniques, recipient selection and donor management, organ preservation, perioperative anesthesia, advances in postoperative care and effective immunosuppressive treatments increase long-term survival success after transplantation (7). The immunosuppressive treatment regimen typically consists of a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate), corticosteroids, sirolimus, and everolimus (8,9). Despite the effective immunosuppressive treatment and advances in surgical techniques in LT, postoperative complications are still an important issue. Infections, acute rejections, vascular and biliary tract pathologies continue to be the most important complications in the early postoperative period (10,11). Development of de novo malignancies, new cardiovascular events, and recurrence of primary disease are important causes of long-term graft loss and mortality (12,13).

The characteristics of LT recipients in Turkey have been reported in relatively small samples, and mostly from non-referral centers. Therefore, the current study aimed to examine the clinical, surgical, and histopathological findings of donor and cadaver-derived LT.

Methods

This was a single-center, retrospective study that included LT recipients who underwent surgery at Istanbul Yeni Yuzyil University, Faculty of Medicine, Gaziosmanpasa Hospital, department of general surgery and transplantation clinic between December 2017 and February 2021. Included patients were adults over the age of 18 who underwent LT for the first time from live donors or cadavers. Younger patients and those who were admitted for a repeat LT for any cause were excluded. The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Yeni Yuzyil University (protocol date and number: 13.08.2020/033).

Data were obtained using electronic medical records. Age, gender, height, weight, body mass index (BMI), blood type, child score, MELD (model of end-stage liver disease) score (calculated with a mathematical formula via internet application), medical history, and underlying diseases for transplantation indication were determined. The date, timing, and duration of surgery, blood products used, and perioperative complications were recorded. Early postoperative intensive care requirement, need for mechanical ventilation, and length of hospital stay was obtained. Follow-up data at the outpatient clinic that included laboratory, radiological, histopathological (biopsy performed before and after the operation, macroscopic and histopathological examination of hepatectomy materials), medical, and surgical treatments, complications, and mortality were recorded using the patient records.

The same surgery team performed the operations of the patients included in the current study, and the same gastroenterology team performed follow-up.

Statistical Analysis

The Statistical Package for the Social Sciences Statistics for Windows, version 25 (Armonk, NY: IBM Corp., 2017) and MedCalc statistics package program were used for data evaluation. Descriptive statistics of categorical variables are presented as numbers and percentages. Scale variables are presented as mean±standard deviation for normally distributed variables and as median (minimum-maximum) for non-normally distributed variables.

Results

The study sample included 162 subjects [mean age: 50.1 (18-70) years; male: 64.8%]. The mean age of men and women was 51.8 years and 47.1 years, respectively. The mean height measured before transplantation was 165.6 cm, the mean weight was 73.7 kg, and the mean BMI was 26.9 (Table 1). The blood type groups, Child score, MELD score, and other preoperative findings are summarized in Table 1.

The etiology of the transplantation was chronic Hepatitis B virus (HBV) infection-related cirrhosis in 30 patients (18.5 %), cryptogenic liver cirrhosis in 27 patients (16.7%), genetic-metabolic liver diseases (autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis, primary biliary cholangitis, hemochromatosis, sickle cell anemia) in 25 patients (15.4%), cirrhosis linked to non-alcoholic steatohepatitis (NASH) in 21 patients (13.0%), alcohol-related cirrhosis in 19 patients (11.7%), and ALF in 5 patients (3.0%) (Table 2). The number of patients transplanted with the diagnosis of HCC was 43 (26.5% of all transplants), and the most common underlying cause in these patients was chronic HBV infection (Table 3).

Living donor LT and cadaveric LT were performed in 140 (86.4%) and 22 (13.6%) patients, respectively. Four (9.3% of all HCC) of HCC patients underwent transarterial chemoembolization, 1 patient (2.3% of all HCC) underwent radiofrequency ablation, and 1 patient had liver resection preoperatively. Perioperative and early postoperative evaluation showed a mean operation time of 6 h and 7 min, 4 units of erythrocyte suspension, 2.5 units of frozen plasma suspension, and 0.3 units of platelet suspension requirement. The number of days of intensive care after the operation was 2.1 days, and the length of hospital stay was 17.3 days. Twenty (12.3%) needed

mechanical ventilation in the intensive care unit during a mean of 1.8 days.

The most common perioperatively postoperative surgical complications were bile duct complications [primarily bile leaks and strictures: 22 (13.6%) and 20 (12.4%), respectively, and vascular complications: primarily portal vein thrombosis, hepatic artery thrombosis; 6 (3.7%) and 4 (2.5%), respectively]. The most common late complications were intraabdominal bleeding and complications requiring intraabdominal surgery [ileus, colon perforation, duodenal perforation; 1 (0.6%), 1 (0.6%), 1 (0.6%), respectively]. Delirium in 11 (6.8%) and epileptic seizures in 3 (1.9%) were the other complications.

Following surgery, immunosuppressive treatment was started with corticosteroids, tacrolimus, and mycophenolate mofetil in all patients. Antithymocyte globulin therapy was administered to 3 (1.9%) patients with early signs of acute rejection. Perioperative/early postoperative and postoperative/late postoperative operational complications are summarized in Table 4.

The mean follow-up period (transplant age) was 20.49 months (1-39 months). Graft loss developed in 29 (17.9%) patients and mortality occurred in 25 (86.2%) of them. Time to graft loss was 207.9 (1-950) days, and time to mortality time was 195.56 (3-950) days. Two (6.9%) patients developed chronic

Table 1. Preoperative characteristics

Age, years, mean (min.-max.)		50.1 (18-70)
Gender, n (%)	Male	105 (64.8)
	Female	57 (35.2)
Donor, n (%)	Cadaver	140 (86.4)
	Living	22 (13.6)
Child classification, n (%)	Child A:	11 (7.1 %),
	Child B:	108 (70.1%)
	Child C:	35 (22.7%)
MELD score, mean (min.-max.)		16.3 (8-35)
Body mass index, mean (min.-max.)		26.9 (16.5-37.6)
Blood group, n (%)	A	66 (40.7)
	B	32 (19.8)
	AB	17 (10.5)
	O	47 (29.0)

Min.-max.: Minimum-maximum, SD: Standard deviation, MELD: Model of end-stage liver disease

Table 2. Primary etiological diseases

Chronic viral hepatitis, n (%)	Hepatitis B virus	30 (18.5)
	Hepatitis D virus	6 (3.7)
	Hepatitis C virus	4 (2.5)
Acute liver failure, n (%)	Toxic hepatitis	2 (1.2)
	Wilson's disease	2 (1.2)
	Hepatitis B virus	1 (0.6)
Genetics-metabolic liver diseases, n (%)	Autoimmune hepatitis	10 (6.2)
	Wilson's disease	7 (4.3)
	Primary sclerosing cholangitis	4 (2.5)
	Primary biliary cirrhosis	2 (1.2)
	Hemochromatosis	1 (0.6)
	Sickle cell anemia	1 (0.6)
Transplant due to rejection, n (%)	Acute rejection	3 (1.9)
	Chronic rejection	3 (1.9)
	Primer non function	2 (1.2)
Cryptogenic cirrhosis, n (%)		27 (16.7)
Nonalcoholic steatohepatitis, n (%)		21 (13.0)
Alcoholic cirrhosis, n (%)		19 (11.7)

rejection, 1 (3.5%) patient had primary non-function, 1 (3.5%) patient had delayed graft dysfunction who underwent a second LT (patients with repeat LT history were excluded, please see what you describe above!). Mortality developed in the first year after transplantation in 18 (11.1%), in the second year in 5 (3.1%), in the third year in 2 (1.2%) patients. One-year survival was 88.9%, two-year survival was 85.8%, and three-year survival was 83.3%. Mortality was linked to sepsis in 14 (48.3%) patients, pneumonia in 6 (20.7%) patients, acute myocardial infarction (AMI) in 2 (6.9%) patients, primary non-function in 2 (6.9%) patients, and 1 (3.5%) patient acute respiratory distress syndrome (ARDS) due to Severe acute respiratory syndrome Coronavirus-2 virus (COVID-19) infection that develops one year after transplantation.

COVID-19 infection was not observed in any patient preoperatively or early after the operation. Seven (4.3%) patients were diagnosed with COVID-19 infection at least 4 months after the operation. One (0.6%) of these patients died due to ARDS, and the other patients were discharged home (Table 5).

Discussion

LT is the most effective treatment method in ALF and end-stage liver failure. An earlier analysis showed approximately 64000 LTs were performed in Europe from 1988 to 2009, and the most common cause was cirrhosis due to alcoholic liver cirrhosis, HCC, and viral hepatitis (13). The 5-year and 10-year survival were reported as 72% and 62%, respectively (13). Transplants due to cirrhosis associated with viral hepatitis have also shown a gradual increase (13).

Today, with improved immunosuppressive treatments, surgical techniques, perioperative and intensive care management 1-year survival has exceeded 90% in more experienced transplantation centers (10,11,14-16). Survival after cadaveric LT was reported as 91.4%, 82.5%, and 74.7% at 1, 5, and 10 years, respectively, by different authors previously

Table 3. Underlying etiological diseases of liver transplant patients due to hepatocellular carcinoma

Chronic viral hepatitis, n (%)	Hepatitis B virus	19 (44.2)
	Hepatitis D virus	2 (4.7)
	Hepatitis C virus	1 (2.3)
Cryptogenic cirrhosis, n (%)		8 (18.6)
Alcoholic cirrhosis, n (%)		7 (16.3)
Nonalcoholic steatohepatitis, n (%)		6 (14.0)

Table 4. Perioperative/early postoperative and postoperative/late surgical complications

Perioperative/early postoperative complications, n (%)	Arterial complications	Hepatic artery thrombosis	4 (2.5)
		Hepatic artery dissection	2 (1.2)
	Venous complications	Portal vein thrombosis	6 (3.7)
		Vena cava stenosis	1 (0.6)
	Bile duct and anastomosis complications	Leakage	22 (13.6)
		Stenosis	20 (12.4)
		Leakage+stenosis	8 (4.9)
	Neurological complications	Brachial plexus injury	1 (0.6)
Postoperative/late complications, n (%)	Hepatobiliary bleeding		4 (2.5)
	Gastrointestinal system bleeding		4 (2.5)
	Intracranial bleeding		2 (1.2)
	Bile peritonitis		2 (1.2)
	Wound infection		1 (0.6)
	Intra-abdominal abscess		1 (0.6)
	Incisional hernia		1 (0.6)
	Pleural effusion		1 (0.6)
	Ileus		1 (0.6)
	Colon perforation		1 (0.6)
	Duodenal perforation		1 (0.6)
	Scrotal Fournier gangrene		1 (0.6)
	Acute appendicitis		1 (0.6)

Table 5. Causes of graft losses

Graft losses causing mortality, n (%)	Sepsis	14 (48.3)
	Pneumonia	6 (20.7)
	Acute myocardial infarction	2 (6.9)
	Primary non-function	2 (6.9)
	COVID-19 associated ARDS	1 (3.5)
Graft losses with retransplantation without mortality, n (%)	Chronic rejection	2 (6.9)
	Primary non-function	1 (3.5)
	Delayed graft dysfunction	1 (3.5)

ARDS: Acute respiratory distress syndrome, COVID-19: SARS-CoV-2 virus infection

(10). In our study, 1-year survival was 88.9%, 2-year survival was 85.8%, and 3-year survival was 83.3%, which is close to the literature. In a similar study in Turkey, the mortality rate was 25.5% during the follow-up period, more than half of mortality occurred in the first 3 months, and approximately 20% were lost during operation (16). In our study, no mortality developed during the operation, our mortality rate was 15.4% during the follow-up period.

In the literature, the most common etiological causes of LT are end-stage hepatic failure due to viral hepatitis, alcohol-induced cirrhosis, and HCC (2). Yaprak et al. (16) reported that the most common etiological causes in patients who underwent LT were chronic HBV/HDV, chronic HCV, primary biliary cholangitis/primary sclerosing cholangitis, and cryptogenic cirrhosis, respectively. In our study, the most common etiological causes were consistent with that earlier study.

Postoperative complications are still an important issue in LT recipients. Biliary complications are the most common, having been reported in 5-32% of recipients (17). Biliary complications are one of the most important causes of chronic graft rejection in the long term (18). Strictures and leaks in the bile ducts or anastomosis area are the most common issues (16-22). Some studies have suggested that the main risk factor is the type of biliary reconstruction, but the complication rate of the Roux-en-Y technique is similar to choledocholedocostomy (23). The duct-to-duct anastomosis of the common bile duct has the advantage of easy access to the bile system and preservation of the Oddi sphincter, which prevents reflux to the bile duct (23-25). In the current study, biliary complications were observed in 3 patients (21.4%) who underwent Roux-en-Y choledocojejunostomy, while 47 (31.8%) patients who underwent canal-to-duct had biliary complications. Pfitzmann et al. (10) reported the rate of postoperative biliary complication rate as 24.3%. Another large study reported 17.8% biliary complications, and the cumulative incidence after 1, 3, and 5 years after LT was 12.9%, 18.2%, and 20.2%, respectively (20). In the current study, the biliary complication rate was 30.9%, and bile duct leakage and stenosis in the biliary tract were the most common, consistent with the literature.

Postoperative vascular complications are frequently reported in the literature. While hepatic artery thrombosis, one of the early surgical complications after transplantation, is observed in 1-7% of the recipients, it may cause graft dysfunction by 27.4% within 5 years (26). Among the venous complications, portal vein thrombus has been reported at a rate of 2.1-26% and inferior vena cava anastomotic stenosis at a rate of 1-6% (27,28). The arterial complication rate was reported as 11.4% (10). In a sample from Turkey, hepatic artery thrombus was found in 1% and portal vein thrombus in 1.5% of the recipients (16). In the current study, the most common vascular pathologies were portal vein thrombus (3.70%) and hepatic artery thrombus (2.47%), slightly higher than the previous study. Bacterial pathogens are the most common causes of infection after liver transplantation, the highest incidence occurs during the first month after LT, viral infections are more common after 3 months, and fungal infections are less common following LT (29). At least one case of biopsy-proven acute rejection was reported in 16-27% of patients who underwent live donor LT (30-35). In our study, acute and chronic rejection was detected in 3 (1.8%) patients after LT, markedly lower than the previous reports.

The incidence of acute and chronic rejection has decreased with the improvement of immunosuppression regimens in LT recipients. Acute cellular rejection occurs in 15-25% of liver transplant recipients with tacrolimus-based immunosuppression regimens and is usually resolved with steroids in the majority (36). Another major issue after LT is the recurrence of the primary disease. While congenital anatomical diseases do not recur, other causes like HBV and HCV infection, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, hemochromatosis, NASH, alcohol-induced liver disease, and HCC can recur after LT and cause graft loss (37,38). In the current study, primary disease recurrence was roughly 10% in HCC patients with background HBV.

In a previous study from Turkey, sepsis, pneumonia, and acute renal failure were the main causes of mortality, whereas prolonged biliary complications, HCC recurrence, preoperative death, sepsis, early graft loss, and intraabdominal bleeding were linked to mortality in another country (16). The most common cause of mortality in the current study was sepsis, pneumonia,

AMI, and primary non-function, showing differences from other international centers.

The limitations of the current study are its retrospective design and single-center involvement. Nonetheless, the large sample size is a strength concerning the previous reports from Turkey.

Conclusion

This study showed a considerable number of LTs can be made from both living donors and cadavers, and age, gender, underlying diseases, follow-up periods, postoperative complications, and mortality rate were comparable to the studies conducted in Turkey and the world.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Istanbul Yeni Yuzyil University (protocol date and number: 13.08.2020/033).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: A.B., M.S., Analysis or Interpretation: A.B., M.S., Literature Search: A.B., M.S., Writing: A.B.

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The effects of urinary incontinence on quality of life and sexual function in women of reproductive age

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ABSTRACT

Aims: Urinary incontinence (UI) is a common condition in women and might affect women's physical and psychological health in different aspects. This study evaluated the effects of UI on the quality of life (QoL) and sexual function in women of reproductive age.

Methods: In this prospective case-control study, sexually active and premenopausal women who were admitted to the urogynecology outpatient clinic of our hospital with UI were included. Women without UI complaints were selected for the control group. All the women were asked to fill the Urogenital Distress Inventory-6 (UDI-6), the Incontinence Impact Questionnaire-7 (IIQ-7), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire-12 (PISQ-12).

Results: There were 64 women [median age: 42 (12)] in the UI group and 58 women [median age: 40 (11)] in the control group. Although the median age was similar in the two groups, the UI group had significantly more gravidas [3 (1) vs. 2 (1); p<0.00] and parity [2.5 (1) vs. 2 (1); p<0.001], body mass index [27.9 (7.2) vs. 24.9 (5.1); p=0.002], and Pelvic Organ Prolapse-Quantification [0 (0) vs. 0 (0); p=0.03] levels. The most common UI type was mixed UI (64.1%) followed by the stress (20.3%) and urge UI (15.6%). The UI group had significantly higher scores in both the subscale and total scores in IIQ-7 and UDI-6 questionnaires (p<0.001). For the PSIQ-12 questionnaire, the behavioral-emotive subscale did not differ between the two groups, while physical and partner subscales and the total score were significantly lower in the UI group (p<0.001).

Conclusions: This study showed that UI had a negative impact on QoL and sexual function in women of reproductive age. Sexual dysfunction occurs mainly on physical and partner-related issues.

Introduction

Urinary incontinence (UI), involuntary leakage of urine, is a common disorder observed in women. The incidence of UI in females increases by age and it is found in 12% in nulligravid women around the age of 20, and 45-78% in women living in nursing homes (1,2). Aging, obesity, parity, mode of delivery, and menopause are major risk factors for female UI (3-6). Apart from the disturbing physical effects of wetness, UI in women has various psychological negative effects such as anxiety, depression, social isolation, decreased quality of life (QoL), and sexual dysfunction (7-9).

UI is divided into three subheadings: stress incontinence, urge incontinence, and mixed incontinence (10). While stress incontinence is defined as involuntary UI with laughing, coughing, sneezing, or any similar efforts increasing intra-abdominal pressure, urge incontinence is defined as leakage of urine with a sudden desire for urination due to involuntary detrusor contractions. Mixed incontinence is involuntary urinary leakage associated with both conditions

Coital incontinence is defined as urinary leakage that occurs during sexual intercourse (10). It is generally accepted to occur in two different ways. Coital incontinence during penetration

or intercourse is associated with stress UI (11), while coital incontinence during orgasm is usually associated with detrusor overactivity (11,12). Coital incontinence has been reported in about 1 in 3 incontinent women (13). In a recent international study, the rate of coital incontinence was reported as 8% at penetration, 9% at orgasm, and 35% during intercourse (14). Intriguingly, nearly half of the patients reported a combination of them.

Regardless of the underlying mechanism, UI could lead to sexual dysfunction in women (15). In this study, we measured the effects of UI on QoL and sexual dysfunction, specifically in women of reproductive age without significant pelvic organ prolapse.

Methods

In this prospective case-control study, sexually active and premenopausal women who were admitted to Urogynecology Outpatient Clinic of Ankara Zekai Tahir Burak Women's Health Training and Research Hospital between August 2018 and March 2019 with the complaint of UI were included in the study. The study was approved by the Ethics Committee of the Ankara Zekai Tahir Burak Women's Health Training and Research Hospital (protocol number: 07/2018, date: 13.12.2018). For the control group, women who were admitted to the gynecology outpatient clinics of the hospital without any UI complaints were selected. The inclusion criteria were age 18 or older, being sexually active for the previous six months, and being in the premenopausal period. Women who had physical or psychiatric diseases that required a significant medical intervention in the previous year, a history of previous prolapse-incontinence surgery or current pelvic organ prolapse higher than stage 1, chronic pelvic pain, difficulties in reading and understanding the Turkish language, and women using hormonal contraception were excluded. All participants signed informed consent before participating in the study.

The women who were admitted to the urogynecology clinic with UI were evaluated according to the guidelines (16). The UI symptoms and as well as systemic symptoms for urinary tract infections, dysuria, and hematuria were questioned by the standard urogynecology application form of the hospital. Urinalysis and culture were obtained. The cough stress test, Q tip test, residual volume were assessed and the presence of pelvic organ prolapse was evaluated according to the Pelvic Organ Prolapse-Quantification (POP-Q) classification system. Urodynamic evaluation was done in complicated cases (16). Incontinent women were classified as stress UI, urge UI, or mixed UI according to the symptoms, clinical and urodynamic findings (if performed).

We used the Incontinence Impact Questionnaire-7 (IIQ-7) and the Urogenital Distress Inventory-6 (UDI-6) to evaluate the effects of UI on QoL, and Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire-12 (PISQ-12) to evaluate its effects on sexual dysfunction. The IIQ-7 and UDI-6 were developed and combined to assess the impact of UI on QoL (17). The IIQ-7 consists of seven questions with the subscales of physical, travel, social and emotional (17). The response to each question measures the severity of the symptoms by grading the responses from zero (not at all) to three (greatly) points. The total score and subscale scores are converted to a range between 0 and 100. Higher scores represent a greater negative impact on QoL. The UDI-6 consists of six questions with three subscales addressing irritation symptoms, stress symptoms, and obstructive/voiding difficulty symptoms (17). The scoring is similar to IIQ-7. Similarly, higher scores indicate more severe symptoms and increased symptom distress. Both IIQ-7 and UDI-6 have been validated for the Turkish female population (18).

The PISQ-12 is a Likert-type questionnaire with 12 questions. It is specifically designed to evaluate the effect of pelvic organ prolapse/UI on female sexual function (19). It consists of three subscales: behavioral/emotive, physical, and partner-related factors. The maximum total score that can be obtained is 48 and higher total and subscale scores are associated with better sexual functioning. Its validity and reliability in the Turkish version were demonstrated by Cam et al. (20).

Statistical Analysis

Statistical Package for Social Sciences Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp., 2013) was used for the analysis of the data. The suitability of the data to a normal distribution was examined by the Kolmogorov-Smirnov test. Parametric methods were used in the analysis of variables with normal distribution and non-parametric methods were used in the analysis of variables that did not have a normal distribution. Categorical data are expressed as numbers (n) and percentages (%). Normally distributed nominal data are shown in tables as mean±standard deviation, while non-normally distributed nominal data are expressed as the median±interquartile range (IQR: 25-75). Cross tables were created for the necessary questions. The chi-square test, Mann-Whitney U test, and independent sample test were used for comparative statistical analysis. Spearman correlation test was used to examine the correlations of variables with each other. The data were analyzed at a 95% confidence level and the p-value was accepted as significantly less than 0.05. Before the study was begun, the statistical program available on the British Colombia University Department of Statistics website was used to calculate the power analysis of the study (https://www.stat.ubc.ca/~rollin/stats/ssize/n2). With a two-sided test, it was found that 49 patients in each group were sufficient to reach an alpha=0.05 significance level and achieve a power of at least 95% (20).

Results

During the study period, there were 129 women who consented to participate in the study. Four women in the UI group and three women in the control group were excluded due to incomplete filling of the forms. Therefore, 64 women in the UI group and 58 women in the control group were included in the analysis (Figure 1). The median age of the total participants was 41 (IQR: 12). The comparison of the demographic characteristics of the two groups is given in Table 1. While there was not any statistical significance between the median ages of the groups, the UI group had a statistically significantly higher number of gravida and parity, body mass index (BMI), and POP-Q levels. Although the median and IQR values of the POP-Q levels were similar between the groups, there was a statistically significant difference due to the distribution within the groups (p=0.030). The most common UI type was mixed UI (64.1%) followed by stress UI (20.3%) and urge UI (15.6%).

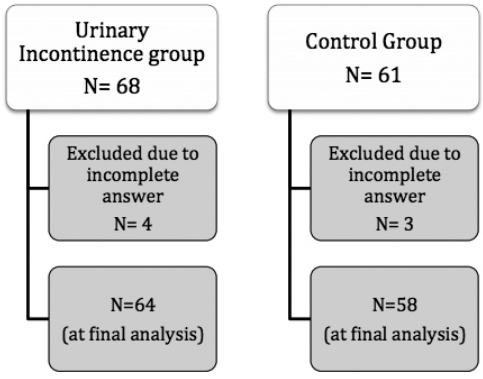

Figure 1. Flow-chart of the study participants

The comparison of the subscale and total scores of the IIQ-7, UDI-6, and PISQ-12 between the groups is shown in Table 2. The UI group had statistically significantly higher in both the subscale and total scores in IIQ-7 and UDI-6 questionnaires (p<0.001). For the PSIQ-12 questionnaire, the behavioral-emotive subscale did not differ between the two groups (p=0.31), while physical and partner subscales and the total scores were statistically significantly lower in the UI group (p<0.001).

The correlations between the total PISQ-12 score and the IIQ-7 and UDI-6 subscale and total scores, age, gravida, parity, BMI, and POP-Q stage were evaluated. The total PISQ-12 score was negatively correlated with all listed variables except age. The behavior-emotive subscale score was negatively correlated with only the number of gravidities (r=-0.270, p=0.005) and parity (r=-0.210, p=0.030).

Discussion

Our results showed that the UI has a significant effect on QoL and sexual function in women of reproductive age without pelvic organ prolapse. UI decreases QoL and sexual function in women due to its physical and psychological effects. While the damaging effects of UI were seen in the subscale and total scores of UDI-6 and IIQ-7, the PISQ-12 questionnaire results warrant further evaluation.

Table 1. The demographic characteristics of the study groups.

	Incontinence group (n=64)	Control group (n=58)	p
Age, median (IQR)	42 (12)	40 (11)	0.300
Gravidity, median (IQR)	3 (1)	2 (1)	<0.001
Parity, median (IQR)	2.5 (1)	2 (1)	<0.001
Delivery mode, n (%)			
Nil	1 (1.6)	1 (1.7)	
Vaginal	51 (79.7)	40 (69)	
C/S	10 (15.6)	15 (25.9)	0.560
Vaginal + C/S	2 (3.1)	2 (3.4)	
BMI	27.9 (7.2)	24.9 (5.1)	0.002
Medical diseases, n (%)			
None	39 (60.9)	47 (81.0)	
Hypertension	3 (4.6)	0 (0)	
Diabetes mellitus	11 (17.1)	4 (6.8)	
COPD	7 (10.9)	4 (6.8)	0.250
Other	4 (6.2)	3 (5.1)	
POP-Q	0 (0)	0 (0)	0.030
Type of UI, n (%)			
Stress	13 (20.3)		
Urge	10 (15.6)	NA	
Mixed	41 (64.1)		

C/S: Cesarean section, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, POP-Q: Pelvic Organ Prolapse-Quantification, UI: Urinary incontinence, IQR: Interquartile range

Table 2. The comparison of the subscale and total scores of the IIQ-7, the UDI-6, and PISQ-12 between groups. The values are given median (IQR) or mean±SD, as appropriate

	Incontinence group (n=64)	Control group (n=58)	p
IIQ-7, median (IQR)			
Physical	33.3 (66.7)	0 (0)	<0.001
Travel	16.7 (66.7)	0 (0)	<0.001
Social	33.3 (66.7)	0 (0)	<0.001
Emotional	33.3 (75)	0 (0)	<0.001
Total	33.3 (54.8)	0 (0)	<0.001
UDI-6, median (IQR)			
Irritative	66.7 (50)	16.7 (16.7)	<0.001
Stress	66.7 (50)	0 (8.3)	<0.001
Obstructive	33.3 (50)	0 (16.7)	<0.001
Total	33.3 (54.8)	0 (0)	<0.001
PISQ-12			
Behavioral-emotive, median (IQR)	7 (7)	9 (9)	0.310
Physical, median (IQR)	13.5 (8.8)	19 (2)	<0.001
Partner, median (IQR)	8 (3.75)	10 (1)	<0.001
Total, mean±SD	27.3±7.8	35.29±5.6	<0.001

IIQ-7: Incontinence Impact Questionnaire-7, UDI-6: Urogenital Distress Inventory-6, PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire-12, SD: Standard deviation

The behavioral and emotive subscale of the PISQ-12 measures women's desire, orgasm, sexual excitement, and satisfaction from sexual activity. According to our findings, this subscale did not differ between the continent and incontinent women. However, the physical subscale questioning dyspareunia, UI during sexual intercourse, restriction of sexual activity because of UI or pelvic organ prolapse, and execration, embarrassment, feeling guilty from sexual activity, were significantly lower in the incontinent women. The partner scale, which explores erection problems and premature ejaculation in the partner and intensity of orgasm degree in the last 6 months in women, was also significantly lower in the incontinent women. Thus, our results suggest that UI does not affect sexual arousal and orgasm among women of reproductive age. The low total PISQ-12 score was mainly due to the low physical and partner subscale scores. Although low physical subscale scores in incontinent women are an expected result, low partner subscale scores are difficult to explain. It is much more difficult for us to speculate whether it is due to urinary leakage of women during sexual intercourse. Indeed, Bekker et al. (21) investigated partners of incontinent women, and their results were in accordance with our study. Men who have partners with UI showed worse total sexual scores together with worse scores in frequency, satisfaction, and erectile dysfunction subscales.

Female sexuality is a complex condition that is influenced by cultural, religious, emotional, and physical factors and depends on the quality of the relationship rather than quantity. As obstetrics and gynecology professionals, we focus almost entirely on the female patient and try treating her. However, as can be seen in our study results, we may overlook that the partner indirectly affected using this process is also an important part of the problem. We can speculate that this problem may be more important in closed societies than in developed Western societies. Based on the results of the study, it would be an appropriate approach to at least include the partner in the treatment process and to provide counseling when necessary. With another study that can be planned in the future, it may be possible to examine the way the partner perceives this disease and the behavioral problems that occur as a result.

The reason we did not find a difference between behavioral-emotive subscale scores of those with and without UI might be the exclusion of menopausal women in our study. Female external genitalia, vagina, bladder trigone, and urethra exhibit estrogen receptors. The term "genitourinary syndrome of menopause" is currently used to define the effects of low estrogen levels on the genitourinary epithelium (22). The symptoms of the genitourinary syndrome of menopause are genital symptoms of vaginal dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (22,23). Besides, sexual desire and arousal are declined in postmenopausal women (24,25). Thus, this might explain the controversy between our results and others (20,26). However, various validated questionnaires are used to evaluate sexual function with different subscales. Although negative impacts of UI on sexual function are general findings, subscale

evaluations differ substantially due to the variability of the questionnaires (14,27-29). For instance, in a recent study from our country conducted in a similar cohort of women like our study, the frequency, satisfaction, avoidance, and anorgasmia sexual subdomains were significantly worse in the UI group compared to the control group (28). However, partner-related factors were not sought by this questionnaire. Consistent with the previously reported studies, our findings showed that incontinent women had higher gravidity, parity, BMI, and POP-Q stage compared to continent women. Besides, negative correlations were observed between sexual function and these factors.

Another important point to consider is that different subtypes of UI have varying effects on sexual function. The mixed UI subtype affects sexual function worse than other subtypes (28,30,31). Similarly, mixed UI has affected QoL negatively more than other subtypes (28,31,32). As most of our patients were in the mixed UI group, we could not investigate the effects of different types of UI on QoL and sexual function separately.

There are strengths and limitations of our study. Unlike other studies, we have specifically addressed women of reproductive age and underlined their most affected sexual dysfunction. However, our study was conducted in a single center with a relatively small number of participants. Furthermore, we did not assess the effects of different types of UI. Although we have evaluated pelvic organ prolapse, we did not specifically address anterior and posterior compartment defects.

Conclusion

In conclusion, UI has negative impacts on QoL and sexual function in women in the reproductive period. This negative effect is mainly observed in the physical and partner-related aspects of the sexual relationship. Accordingly, it is far most important for women's health to question women who apply to gynecology outpatient clinics and provide them with counseling about preventive and therapeutic approaches.

Ethics

Ethics Committee Approval: The study were approved by the Ankara Zekai Tahir Burak Women's Health Training and Research Hospital of Ethics Committee (protocol number: 07/2018, date: 13.12.2018).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., K.M., N.K., Concept: A.Y., Ş.Ö., Ö.E.B., Y.E.Ü., Design: A.Y., Ş.Ö., Ö.E.B., Y.E.Ü., Data Collection or Processing: A.Y., K.M., N.K., Analysis or Interpretation: A.Y., Literature Search: A.Y., K.M., N.K., Ş.Ö., Writing: A.Y., Ö.E.B.

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Fetal gender distribution in post-term pregnancy and intrauterine death: Maternal and neonatal outcomes by fetal sex

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ABSTRACT

Aims: Fetal sex plays an important role in pregnancy and its outcomes due to hormonal and chromosomal differences. The current study examines the effect of fetal sex on delivery time, intrauterine death and maternal-neonatal outcomes.

Methods: Pregnant women who gave birth in University of Health Sciences Turkey, Tepecik Training and Research Hospital Delivery Unit between 2014 and 2019 were screened retrospectively for the study. Pregnancies of ≥37 weeks (259 days) were included in the study, and pregnancies with ≥42 weeks (294 days) were classified as post-term (prolonged) pregnancy. Intrauterine death and maternal-neonatal outcomes were compared according to fetal gender.

Results: The prevalence of post-term pregnancy was 0.76%. A total of 45,147 pregnancies were found, including 22,788 (50.5%) males (M) and 22,359 (49.5%) females (F) who met our criteria for the study. In births between 37-40 0/6 weeks male sexes ratio was higher (M/F sex ratio: 37 0/6 weeks: 1.05; 38 0/6 weeks: 1.01; 39 0/6 weeks: 1.01). The female sex birth rate becames more prominent after the 40th week, 75% of the newborns at the 44th week were observed to be female (M/F sex ratio: 44 0/6 weeks: 0.33). However, although female sex ratio was higher in post-term pregnancies, contrary to the literature, this difference was not significant. Intrauterine fetal death was observed more frequent in post-term pregnancies than term pregnancies (0.93% vs 0.3%, p=0.017). The risk of intrauterine fetal death was approximately three times higher in post-term pregnancies than term pregnancies (Odds ratio: 3.16; 95% confidence interval: 1.16-8.58). In post-term pregnancies, birth weight (3458.7±462.9 g vs. 3338.5±416.5 g), head circumference (35.2±1.1 cm vs. 34.9±1 cm) and body length [50 (44-56) cm vs. 50 (40-55) cm] were higher in male sexes and all these results were statistically significant (p=0.049, p=0.004 and p=0.003, respectively).

Conclusions: Contrary to the literature, fetal sex is not a significant risk factor in post-term pregnancy. But intrauterine death increases about 3-fold in post-term fetuses compared to term fetuses.

Introduction

Pregnancies ≥42 weeks (294 days) from the last menstrual period are classified as post-term (prolonged) pregnancy (1,2). Its incidence ranges between 0.4% and 10% (average, 7%) (3-5). Although the etiology of post-term pregnancy is not fully known; genetic transition (6), anencephaly and placental sulfatase deficiency showing recessive passage linked to the X chromosome (7), nulliparity (8), post-term pregnancy history (9), and maternal obesity (10) are thought to be the effective factors in prolonging pregnancy. Another factor discussed in post-term pregnancy etiology is fetal sex (11,12).

Fetal sex is determined during fertilization, and accordingly, undifferentiated gonads differentiate into the ovarium or testicle. Although males carry one X and one Y chromosome, females contain two X chromosomes. Thus, only males can encode the genes on the Y chromosome. In females, genes from the two X chromosomes can be encoded until one X chromosome is inactivated. Inactivation is completed during the gastrulation

phase (13). This difference between male and female sex is thought to be associated with the spontaneous abortion of the male sex (14), stillbirth (15,16), neonatal morbidity, and mortality (17,18), high operative birth, and cesarean rates (18,19), pre-eclampsia (16,20), and gestational diabetes (16,21). Currently, preterm labor and premature rupture of membranes are considered common in male fetuses (17,22,23). However, fetal sex as an etiologic factor in post-term fetuses is still controversial (11,12,15).

Timing labor is important to achieve a good perinatal outcome. The objective of this study was to examine the association between fetal sex on delivery time and intrauterine fetal death. Additionally, we investigated the association of fetal sex and anthropometric measurements, APGAR score, and the need for neonatal intensive care unit (NICU) in post-term pregnancies.

Methods

Study design and participants

This single-center, retrospective study included pregnant women who delivered in the University of Health Sciences Turkey, Tepecik Training and Research Hospital Delivery Unit, Izmir, Turkey, between 2014 and 2019. Data were collected using electronic medical records and patient charts. The setting performs an average of 10,000 deliveries/year.

The last menstrual period (LMP) and crown-rump length (CRL) in the first 6-14 weeks were used to determine the gestational age of the pregnancy. Dating was performed according to both dates for each pregnancy, and if the difference was more than 14 days, the dating value calculated according to CRL was accepted as gestational age. However, for pregnant women with unknown LMP, the dating value calculated according to CRL was accepted as gestational age. Pregnancies between 37-38 0/6, 39-40 0/6, 41-41 0/6, and ≥42 weeks were defined and grouped as the early term, term, late-term, and post-term, respectively (2).

Multiple pregnancies, births before 37 weeks (259 days), pregnancies with chromosomal and/or major congenital anomalies, unavailable CRL measurement between the first 6-14 weeks, and those whose with missing information were excluded.

Pregnancies ≤19 years and ≥35 years were defined as adolescent pregnancies and advanced age pregnancies, respectively. Newborns weighing <2500 and ≥4000 grams (g) were considered to have low birth weight (LBW) and macrosomia, respectively. The Helsinki Declaration was followed and ethics committee approval was obtained from the Ethics Committee of Health Sciences University Turkey, Tepecik Training and Research Hospital, Izmir, Turkey (approval no: 2020/14-8, date: 23.12.2020).

Statistical Analysis

The Statistical Package for the Social Sciences 22.0 version (IBM Corporation, Armonk, New York, US) was used for data analyses. The normality of distribution of variables was evaluated by the Kolmogorov-Smirnov test and Q-Q plot. Student's t-test was used to compare normally distributed variables and the data were given as mean±standard deviation. Mann-Whitney U test was used to compare nonnormally distributed variables and the data were given as the median with minimum and maximum. Chi-square test was used to compare categorical variables and Odds ratio (OR) [95% confidence interval (CI)] calculations were made. $p<0.05$ was considered significant.

Results

A total of 45,147 pregnancies were identified, including 22,788 (50.5%) male fetuses and 22,359 (49.5%) female fetuses who met our criteria for the study. The prevalence of post-term pregnancy was 0.76%. Fetal sex ratios according to gestational age are shown in Table 1. Accordingly, in births between 37-39 0/6 weeks, the male sex ratio was higher. The female sex birth ratio became more prominent after the 40th week, and 75% of the newborns at the 44th week were female; however, although the female sex ratio was higher in post-term pregnancies, the difference was not significant (Table 1).

Term pregnancies were classified according to gestational week. The male sex ratio was higher in early-term (37-38 0/6

Table 1. Fetal sex ratios by gestational age

Gestational age at birth, week	Male	Female	Male/female ratio
37 0/6, n (%)	3226 (52)	2981 (48)	1.05
38 0/6, n (%)	6779 (50.8)	6561 (49.2)	1.01
39 0/6, n (%)	5991 (50.9)	5789 (49.1)	1.01
40 0/6, n (%)	5335 (49.7)	5392 (50.3)	0.96
41 0/6, n (%)	1261 (47.3)	1406 (52.7)	0.87
42 0/6, n (%)	183 (46.1)	214 (53.9)	0.82
43 0/6, n (%)	12 (48)	13 (52)	0.89
44 0/6	1 (25)	3 (75)	0.33
Total	22788 (50.5)	22359 (49.5)	1.02

weeks) and full-term (39-40 0/6 weeks) births, whereas the female sex ratio was higher in late-term (41-41 0/6 weeks) and post-term (≥42 weeks) births (Table 2).

Table 3 shows the intrauterine fetal mortality rates by gestational week and fetal sex. Intrauterine fetal death ratio (M/F) in the early term, full-term, late-term, post-term was 1.1, 0.85, 0.55, and 0.58, respectively, and the differences between male and female sex were not statistically significant. However, intrauterine fetal death was observed more frequently in post-term pregnancies than term pregnancies (0.93% vs. 0.3%, p=0.017). The risk of intrauterine death was approximately three times higher in post-term pregnancies than the term pregnancies (OR: 3.16; 95% CI: 1.16-8.58) (Table 3).

The comparison of demographic characteristics of singleton post-term pregnancies classified based on fetal sex is shown in Table 4. Although the adolescent pregnancy rate was 9% and 11.7% in pregnant women with male and female fetuses, respectively, and the advanced age pregnancy rate was 14.2% and 12.1% in pregnant women with male and female fetuses, respectively, the differences between the groups were not statistically significant. No difference was found between the groups concerning parity, delivery types, cesarean types (primary-repeated), and first-trimester maternal body mass index (Table 4).

Table 5 shows the neonatal outcomes of live-singleton post-term pregnancies by classifying them according to the sex of the newborn. Birth weight (3458.7±462.9 g vs. 3338.5±416.5

Table 2. Fetal sex ratios according to the classification of term pregnancies

Gestational age at birth	Male	Female	Male/female ratio
Early term (37-38 0/6 weeks), n (%)	10005 (51.2)	9544 (48.8)	1.04
Full term (39-40 0/6 weeks), n (%)	11326 (50.3)	11179 (49.7)	1.01
Late term (41-41 0/6 weeks), n (%)	1261 (47.3)	1406 (52.7)	0.89
Post-term (≥42 weeks), n (%)	196 (46)	230 (54)	0.85
Total, n (%)	22788 (50.5)	22359 (49.5)	1.02

Table 3. Intrauterin fetal death rates according to the gestational weeks and fetal sex

Gestational age at birth	Male	Female	Male/female ratio	95% CI	p
Early term (37-38 0/6 weeks), n (%)	49 (0.49)	43 (0.45)	1.1	0.72-1.64	0.689
Full term (39-40 0/6 weeks), n (%)	19 (0.16)	22 (0.19)	0.85	0.46-1.58	0.609
Late term (41-41 0/6 weeks), n (%)	1 (0.08)	2 (0.14)	0.55	0.05-6.15	0.628
Post-term (≥42 weeks), n (%)	1 (0.51)	3 (1.3)	0.58	0.05-6.50	0.397
Total, n (%)	70 (0.3)	70 (0.3)	1.0	0.85-1.90	0.247

CI: Confidence interval

Table 4. Demogaphic properties of singleton post-term pregnancies (≥42 weeks)

	Male (n=196)	Female (n=230)	p
Maternal age, years, median (min-max)	26 (15-41)	26 (14-43)	0.702
Adolescent pregnancy ≤19, n (%)	18 (9)	27 (11.7)	0.392
Advanced age pregnancy ≥35, n (%)	28 (14.2)	28 (12.1)	0.520
Parity, n (%)			0.656
Nulliparous	92 (46.9)	103 (44.7)	
Multiparous	104 (53.1)	127 (55.3)	
Gestational age, weeks, mean±SD	42.3±0.3	42.3±0.4	0.695
Delivery type (n,%)			0.458
Vaginal delivery	111 (56.6)	122 (53)	
Cesarean section	85 (43.4)	108 (47)	
C-section type (n,%)			0.829
Primary C-section prevalence	65 (76.5)	84 (77.8)	
Repeated C-section prevalence	20 (23.5)	24 (22.2)	
BMI in the first trimester, mean±SD	26.9±0.3	26.8±0.3	0.625

BMI: Body mass index, min: Minimum, max: Maximum, SD: Standard deviation

g), head circumference (35.2±1.1 cm vs. 34.9±1 cm), and body length [50 (44-56) cm vs. 50 (40-55) cm] were higher in male neonates, and these results were all statistically significant (p=0.049, p=0.004, and p=0.003, respectively). The prevalence of LBW and macrosomia was similar for both sexes. No significant difference was found between the groups concerning the number of newborns with 1st and 5th minute APGAR scores of <7 and the need for NICU (Table 5).

Discussion

In modern obstetrics, post-term pregnancy is considered a complex biological process closely related to factors, such as the chronological duration of pregnancy, onset mechanism of delivery, intrauterine fetal status and sex, and the fetoplacental system. Studies showed its prevalence as 0.4%, 0.6%, 2.3%, and 8.1% in Austria, Belgium, Germany, and Denmark, respectively (3). The rate varies between 1% and 2.5% in America and Canada and 1.16% in China (24). To the best of our knowledge, our study is the largest study of post-term pregnancy populations in Turkey, and the post-term prevalence was 0.76% over 6 years. These differences may be due to differences in the management of labor induction between countries.

In our study, although the female sex ratio was higher in post-term pregnancies, contrary to the literature, this difference was not significant. In addition to studies showing that male sex is more common in post-term pregnancies (11,25), some studies showed that female sex is more common (12,15). The different results between studies may be due to three reasons. The main reason is the differences in the diagnosis of post-term pregnancy. Post-term pregnancy is most commonly diagnosed based on the incorrect calculations of the patient's LMP (26). Many women have menstrual cycle irregularities or follicular phase duration, and ovulation times may differ. Therefore, accurate determination of gestational age is important in post-term diagnosis and pregnancy management. Dating with ultrasonography measurements instead of only deciding based on LMP for gestational age reduces the post-term incidence from 10-15% to 2-5%, and the best measurement method is the first-trimester CRL among other old ultrasonic measurements (27,28). Therefore, gestational age was confirmed by dating according to 14 weeks CRL in addition to LMP, and if a difference of 14 days with LMP was observed, we accepted the ultrasound date as the gestational age. This study applies double validation (according to LMP and CRL combination) to minimize errors. Another reason that may lead to different results in different studies is the occurrence of racial differences (29). Finally, the sex ratio may change due to wars and natural disasters, and environmental factors (24,30,31).

Post-term pregnancies cause a significant increase in perinatal morbidity and mortality (32,33). When the gestational age exceeds 42 weeks, perinatal mortality increases 2-3 times compared with the 40 weeks gestation (32,33). Our study showed similar results in which intrauterine death was observed approximately three times higher in post-term fetuses compared with term pregnant women (OR: 3.16; 95% CI: 1.16-8.58; p=0.017). The cause of intrauterine death was placental aging and uteroplacental insufficiency, meconium aspiration, and intrauterine infections (1). Especially, placental aging is speculated to be the cause of intrauterine death (34). Studies showed that placental mitochondria decreased, free oxygen radicals increased, and apoptosis increased in the placentas of post-term pregnant women (34). Additionally, amniotic fluid decreases as the pregnancy progresses. As gestation exceeds 40 weeks, the amount of AFI decreases by an average of 8% each week (35). Decreased AFI increases the risk of meconium aspiration.

When newborns of live-singleton post-term pregnancies were compared, birth weight, head circumference, and body length were higher in male newborns (p=0.049, p=0.004, and p=0.003, respectively). Similar to our study, previous studies showed that the weight, head circumference, and body length measurements of male newborns were higher than those of female newborns (36,37). Theoretically, the anthropometric difference between male and female newborns is due to different growth rates in the intrauterine period. Many theories have been proposed to explain this sex-specific growth pattern. The most

Table 5. Neonatal outcomes among live-singleton post-term births (≥42 weeks) according to sex

	Male (n=195)	Female (n=227)	p
Birth weight of newborns, g, mean±SD	3458.7±462.9	3338.5±416.5	0.049
Head circumference of newborns, cm, mean±SD	35.2±1.1	34.9±1	0.004
Body length of newborns, cm, median (min-max)	50 (44-56)	50 (40-55)	0.003
LBW (<2500 g), n (%)	5 (2.5)	3 (1.3)	0.350
Macrosomia (>4000 g), n (%)	21 (10.7)	16 (7)	0.177
APGAR score <7, 1st minute, n, (%)	3 (1.53)	1 (0.44)	0.245
APGAR score <7, 5th minute, n (%)	1 (0.51)	1 (0.44)	0.914
NICU hospitalization, n (%)	1 (0.51)	1 (0.44)	0.914

LBW: Low birth weight, NICU: Neonatal intensive care unit, min: Minimum, max: Maximum, SD: Standard deviation

supported theory is that the male sex triggers fetal growth due to androgen secretion (38).

Macrosomia, intrapartum fetal distress, lower 1st and 5th minute APGAR scores are thought to be higher in post-term fetuses compared with term deliveries (1,39,40). As far as we know, there is no study examining term pregnancies among themselves according to fetal sex. For the first time in the literature, perinatal results were compared based on fetal sex, but no statistically significant difference was observed between the male and female sexes. In contrast to the literature regarding term pregnancies (15,18), the male sex does not pose any additional risk in post-term fetuses. The different results in previous studies may be due to the calculation of gestational age without dating.

This study has several limitations, including the retrospective design and single-center observations. The exclusion of pregnant women without CRL measurement in the first trimester (6-14 weeks) is a strength, preventing mistakes in the post-term decision.

Conclusion

In conclusion, this study showed that, contrary to the literature, fetal sex is not a significant risk factor in post-term pregnancy. However, post-term pregnancy has a higher risk of intrauterine death compared with term pregnancies.

Ethics

Ethics Committee Approval: The study was obtained from the Ethics Committee of Health Sciences University Turkey, Tepecik Training and Research Hospital (approval number: 2020/14-8, date: 23.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.B., T.V., Design: B.B., C.G., H.G., M.G.B., Data Collection or Processing: B.B., T.V., Analysis or Interpretation: B.B., T.V., C.G., H.G., M.G.B., Literature Search: B.B., T.V., C.G., H.G., M.G.B., Writing: B.B., T.V., C.G., H.G., M.G.B.

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Nifedipine and indomethacin in preventing preterm labor under 32 gestational weeks

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ABSTRACT

Aims: This study compared nifedipine and indomethacin treatments, commonly used tocolytic agents, in terms of efficacy and maternal side effects.

Methods: This retrospective study included pregnant women spontaneous preterm labor between 24 and 32 weeks of gestation who were treated with indomethacin or nifedipine between January 2017 and June 2020. Subjects with polyhydramnios, multiple pregnancies, preterm premature rupture of membranes, and those with 4 cm or more cervical dilatation, and who required emergency cesarean delivery were excluded. Study endpoints were delivery within 48 h, prolongation of pregnancy up to 34 weeks and 37 weeks, and maternal side effects.

Results: A total of 307 pregnant women were analyzed. Nifedipine and indomethacin were administered to 205 and 102 patients, respectively. The median maternal age was 25 years in both groups. The rate of delivery within 48 h was significantly higher by 20.6% among subjects who received indomethacin compared with the 9.8% delivery rate among subjects who received nifedipine ($p=0.009$). However, delivery after gestational 34 weeks and 37 weeks were significantly higher in the nifedipine group ($p<0.001$ and $p=0.003$, respectively). No patients in the indomethacin group had side effects, but 6.8% of the nifedipine group required drug change due to side effects.

Conclusions: This study showed that nifedipine was superior to indomethacin in achieving a 48-hour delay in preterm labor, increasing the gestational age at birth, and decreasing the preterm delivery rates.

Introduction

Birth with a gestational age between 20 0/7 and 36 6/7 is called preterm (1). The prevalence of preterm birth is between 5% and 18% worldwide (2), and 15% occurs before the 32nd week of gestation (3). Spontaneous preterm deliveries are responsible for 70-80% of all preterm deliveries (4). About 30% of women with acute preterm labor recover without treatment (5), and only 50% of the patients hospitalized for preterm labor experience preterm delivery (6-8).

Tocolytics are used to reduce or stop uterine contractions and delay or prevent labor by preventing the cervical change process. With tocolytic therapy, delivery is delayed for a short time (48 h) to allow sufficient time for administrating antenatal corticosteroids and neuroprotective magnesium sulfate.

Magnesium sulfate, beta-agonists, non-steroidal anti-inflammatory drugs (NSAIDs), or calcium channel blockers (CCBs) are short-term tocolytic agents used to prevent preterm labor. NSAIDs and CCBs are the most effective agents in delaying labor and improving neonatal and maternal outcomes (9). The use of NSAIDs has been associated with premature closure of the ductus arteriosus and oligohydramnios (10). The use CCBs or NSAIDs between viability and 32 weeks or use CCBs at and after 32 weeks of gestation to stop preterm labor is recommended as a preventive measure (11). Hence, nifedipine from the CCB class and indomethacin from the NSAIDs class

are widely used. Studies comparing NSAIDs and CCB have obtained different results (12-15).

This study aimed to compare the efficacy and maternal side effects of commonly used tocolytic nifedipine and indomethacin as the first-line treatment.

Methods

The study was conducted retrospectively between January 2017 and June 2020 and approved by the Etlik Zubeyde Hanim Obstetrics and Gynecology Training and Research Hospital Institutional Review Board (decision no: 2020-14/08, date: 14.09.2020).

The study included pregnant women at a gestational age between 24 and 32 weeks (confirmed by the date of last menstruation and first-trimester ultrasound) who were admitted to the hospital with spontaneous preterm labor, and were treated with nifedipine or indomethacin. Patients with polyhydramnios, multiple pregnancies, preterm premature rupture of membranes, or 4 cm or more cervical dilatation were excluded.

Preterm labor diagnosis was defined in line with the recommendations of the American College of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins: Management of Preterm Labor: as “regular uterine contractions accompanied by changes in cervical dilatation and/or effacement or in the presence of signs of cervical dilatation of at least 2 cm in addition to regular contractions” (1).

In our center, nifedipine is administered orally at 10 mg (1 capsule) in 3 doses, 20 min apart, followed by 10 mg orally every 6 h for 48 h. Indomethacin is given rectal 100 mg (1 suppository) loading followed by 25 mg orally every 6 h for 48 h. A course of betamethasone (12 mg intramuscular 2 doses every 24 h) to accelerate fetal lung maturation and neuroprotective magnesium sulfate 6 g loading and 2 g/h maintenance therapy is given to women at high risk of delivery within 24 h. Maternal blood pressure is monitored every 15 min for the first 2 h, and every 4-6 hours thereafter. Medication changes due to maternal symptoms such as nausea, reflux, vomiting, flushing, headache, dizziness, palpitations, tachycardia, or maternal hypotension (systolic and diastolic blood pressure <90 mmHg and <50 mmHg, respectively) are recorded. Uterine contractions are constantly monitored.

Information such as uterine contractions, maternal side effects, and time of delivery after treatment was obtained from the patient records. Response to treatment was defined as cessation of uterine contractions within the first 2 h. Post-treatment birth information was recorded at three-time points (up to 48 h, 34 weeks, or 37 weeks). Subjects whose drugs were changed due to side effects or drug unresponsiveness, those who needed an emergency cesarean section for any reason during treatment, and those who did not give birth in our hospital were further excluded from the study.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp., 2015). Kolmogorov-Smirnov test was used to test the distribution of the variables. Mann-Whitney U test was used to compare the numerical data between the indomethacin and nifedipine groups if the variables were not normally distributed. The chi-square test was used to compare categorical variables between groups. Descriptive statistics were reported as median (interquartile range) for continuous variables and numbers (percentages) for categorical variables. $P<0.05$ was considered statistically significant.

Results

A total of 330 patients hospitalized for preterm labor between 24 and 32 weeks of gestational age and who needed tocolysis were included in this analysis.

As shown in Table 1, age, body mass index, parity, previous preterm birth history, gestational age at the time of tocolysis, initial cervical dilatation and effacement status, and history of tocolysis in the current pregnancy was not different between the two groups.

Table 2 shows the obstetric results of the drug responses of both groups. In the first two hours, 84 patients (82.4%) receiving indomethacin and 176 patients (85.9%) receiving nifedipine responded to the tocolytic agent, and uterine contractions stopped ($p=0.422$). Delivery occurred within 48 h in 20.6% and 9.8% of the patients receiving indomethacin and nifedipine, respectively ($p=0.009$). Delivery occurred after 34 weeks of gestation in 47.1% of the patients treated with indomethacin and 67.8% of the patients treated with nifedipine ($p<0.001$). Term delivery (>37 weeks) rates were 28.4% among the subjects treated with indomethacin and 45.9% among those who received nifedipine ($p=0.003$). Preterm birth rates were 71.6% and 54.1% in the indomethacin and nifedipine groups, respectively ($p=0.004$). The week of delivery was lower in those treated with indomethacin than those treated with nifedipine ($p<0.001$).

Maternal side effects (hypotension (n=8) and tachycardia (n=7) requiring a drug change developed in 15 (6.8%) of 220 patients using nifedipine. No patients receiving indomethacin was developed side effects. The rate of maternal side effects was significantly higher in the nifedipine group ($p=0.026$). Eight (7.3%) of 110 patients who received indomethacin were subject to drug change due to treatment unresponsiveness. These patients were excluded from the study due to medication changes. Of the remaining 307 patients, 205 were treated with nifedipine and 102 with indomethacin. Neuroprotective magnesium sulfate treatment was administered to 36 patients in the indomethacin and 19 patients in the nifedipine group, respectively.

Table 1. Maternal characteristics of the sample (n=307)

	Indomethacin (n=102)	Nifedipine (n=205)	p
Age[a]	25 (8)	25 (7)	0.541
Body mass index[a]	25 (4.7)	26 (4.3)	0.234
Nullipare[b]	62 (60.8)	125 (61.0)	0.974
Multipare[b]	40 (39.2)	80 (39.0)	
Prior preterm birth[b]	11 (10.7)	27 (13.1)	0.587
Gestational age[b]	29 (3.8)	29 (2.3)	0.641
Prior tocolytic history[b]			
Yes	11 (10.8)	24 (11.7)	0.811
No	91 (89.2)	181 (88.3)	
Cervical dilatation[b]			
<2 cm	71 (69.6)	136 (66.3)	0.565
>2 cm	31 (30.4)	69 (33.7)	
Cervical effacement[b]			
<50%	75 (73.5)	166 (81.0)	0.135
>50%	27 (26.5)	39 (19.0)	

[a]Median (interquartile range), [b]number (percentage)

Table 2. Obstetric outcomes (n=307)

	Indomethacin group (n=102)	Nifedipine group (n=205)	p value
Response in the first 2 hours[a]	84 (82.4)	176 (85.9)	0.422
Delivery in 48 hours[a]	21 (20.6)	20 (9.8)	0.009
Gestational age at delivery[a]			
≥34 week	48 (47.1)	139 (67.8)	<0.001
≥37 week	29 (28.4)	94 (45.9)	0.003
Preterm birth (<37 week)[a]	73 (71.6)	111 (54.1)	0.003
Birth week[b]	33 (7.5)	36 (5.6)	<0.001

[a]Number (percentage), [b]median (interquartile range)

Discussion

The response to the drug in the first 2 h was similar in both groups. Delayed labor for 48 h and delivery after 34 weeks of gestation and after 37 weeks were significantly higher in the pregnant women taking nifedipine. Gestational age at birth was significantly lower in the women given indomethacin. Whereas no patient in the indomethacin group produced any side effects, 6.81% of them in the nifedipine group required drug change due to the side effects.

NSAID, CCB, betamimetics, magnesium sulfate, and oxytocin receptor antagonists used as tocolytic agents are more effective than placebo in delaying labor for 48 h (9,16). However, the use of betamimetics and magnesium sulfate is no longer recommended for tocolysis due to high maternal and fetal side effects (11,17). Nifedipine and indomethacin are now more popular and widely used tocolytic agents. However, the choice of primary care treatment varies. The National Institute for Health and Care Excellence guideline (18), the French College of Gynecologists and Obstetricians guideline (19), and the World Health Organization (20) recommend nifedipine as a first-line treatment. Some authors recommend indomethacin as first-line tocolytic therapy for women between 24 and 32 weeks of gestation (12). In many studies, indomethacin treatment for tocolysis was compared with placebo with the result that indomethacin-prolonged pregnancy, but different results were shown in neonatal morbidity or mortality (14). A study by Haas et al. (21) concluded that indomethacin was effective in prolonging labor for 48 h compared to placebo, having low maternal side effects and good neonatal outcomes. A review article published in 2015 concluded that indomethacin was not different from placebo, magnesium sulfate, or CCB in terms of side effects, and it was associated with fewer maternal side effects than betamimetics (14). Kashanian et al. (13) reported that, among 79 preterm women, nifedipine was more successful than indomethacin in stopping contractions within 2 h of starting treatment. Additionally, when the contractions stopped within the first 2 h with indomethacin, the effect continued for up to 48 h. Different from previous studies, although the response to treatment was similar in the first 2 h, nifedipine was more effective than indomethacin in delaying delivery.

A recent Cochrane review concluded that indomethacin was a powerful tocolytic with low maternal side effects but remained suspicious for fetal complications (17). NSAIDs cross the placental barrier and inhibit fetal prostaglandin synthesis; thus, due to decreased renal blood flow and increased vasopressin effect, fetal kidney failure and oligohydramnios develop in 70% of the cases with their use beyond 72 hours (22). Additionally, indomethacin is recommended before the 32nd week of gestation and for a maximum of 48 h to prevent premature closure of the ductus arteriosus (23). Although the ACOG recommends indomethacin for treating preterm labor (1), indomethacin treatment is not recommended by some authors and organizations (14,20,24,25), or limited use is recommended due to controversial and insufficient data (26). Our study did not evaluate the effects of nifedipine and indomethacin on the fetus; on the other hand, it focused on the effectiveness of nifedipine and indomethacin in stopping preterm labor.

CCB causes relaxation of the myometrium by blocking the flow of calcium through the cell membranes. The commonly used agent in this group is nifedipine (11). Haas et al. (21) reported that CCBs could delay the delivery for 48 h in 66% of the preterm labor cases and seven days in 62% of them. In a review comparing tocolytic agents, the authors reported that nifedipine was superior to betamimetics in delaying delivery beyond 48 h, seven days, and 34 weeks of gestation (27). Additionally, nifedipine reduces adverse neonatal outcomes relative to betamimetics and NSAIDs. In a single-center, randomized clinical trial that compared magnesium sulfate, nifedipine, and indomethacin for efficacy and maternal side effects among women with acute preterm labor, no differences among the three drugs were observed in delaying delivery for more than 48 h or seven days. Additionally, there was no difference in terms of gestational age at birth (28). CCBs improved neonatal morbidity compared to NSAIDs (11). Nifedipine is one of the safe tocolytic agents first preferred in clinical practice in medical treatment in the threat of preterm labor due to its rarity of maternal and fetal side effects and its oral applicability (29). In our study, only 9.8% of the patients who received nifedipine delivered before 48 h. Unlike previous studies, nifedipine was more successful in delaying labor than indomethacin, and the gestational age at birth was longer. We suggest that the pregnancy with preterm labor, the first choice of drug should be nifedipine to prevent birth before 32 weeks of gestation, and indomethacin should be an option for those who cannot tolerate nifedipine.

Our study has some limitations. We did not record the newborn outcomes. Additionally, we could not evaluate the effects of combinations as the number of patients who received nifedipine plus magnesium sulfate therapy was small. However, the study includes a reliable analysis of the response to tocolytic therapy and maternal side effects among patients presenting with preterm labor.

Conclusion

In conclusion, the results of our study showed nifedipine was superior to indomethacin in delaying labor for 48 h, which is the goal of treatment in preterm labor. Thus, increasing the gestational age at birth and reducing preterm birth rates were more likely with nifedipine.

Ethics

Ethics Committee Approval: The study was approved by the Etlik Zubeyde Hanim Obstetrics and Gynecology Training and Research Hospital Institutional Review Board (decision no: 2020-14/08, date: 14.09.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., Concept: G.D., Design: G.D., Data Collection or Processing: M.A., Analysis or Interpretation: Ö.Y.Ç., A.K., Literature Search: G.D., Ş.Ç., A.T.Ç., Writing: G.D., A.T.Ç.

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Restless legs syndrome in migraine patients at an outpatient clinic

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ABSTRACT

Aims: The prevalence of Restless legs syndrome (RLS) in migraine patients is estimated to be 8.7-39.0%. In this study, we set out to compare the frequency of RLS in patients diagnosed with migraine with headache free participants.

Methods: We included 201 patients with migraine with or without aura and age and gender-matched 102 headache free group from outpatient setting in this cross-sectional study. None of the migraine patients were receiving prophylactic medications that could affect dopamine metabolism. Patients with comorbidities such as kidney disease, Parkinson's disease, rheumatoid arthritis, and polyneuropathy were excluded from this study. The headache free participants had no neurological or systemic disease, no addiction/and no medical treatment. The frequency and severity (with RLS Rating Scale) of RLS was examined in two groups.

Results: 40.3% (n=81) of the migraine patients met the diagnostic criteria for RLS than the headaches-free participants (15.7%, n=16) ($p<0.001$). The RLS (+) and RLS (-) migraine groups were similar in terms of age, gender, number of attacks per month, presence of aura, smoking, and family history for RLS. Disease duration was longer in the migraine patients with RLS and RLS severity was higher in patients with longer disease duration ($p<0.001$ and $p=0.05$). Five of six patients with hypertension and migraine patients had RLS (vs. 76 of 195 for patients without hypertension, $p=0.04$). Logistic regression analysis showed a significant association only between the disease duration and the presence of RLS [Odds ratio: 13.25, (95% confidence interval: 5.62-31.24), $p=0.001$].

Conclusions: This study found almost three times higher frequency of RLS in patients with migraine. RLS symptoms should be questioned during the management of patients with a migraine diagnosis, particularly in long-standing disease.

Introduction

Migraine is a chronic headache syndrome that lasts 4-72 hours, usually unilateral, throbbing, moderate or severe, and characterized by recurrent attacks that increases with routine physical activities associated with nausea and/or vomiting or photophobia, phonophobia (1). It is 2.5 times more likely in women than men, and its prevalence in Turkey is 16.4% (2).

Restless legs syndrome (RLS) is defined as the feeling of restlessness in the legs, rarely in the arms, or the desire to move the legs, which worsens in long-term inactivity especially at night, and improves with movement (3). In studies using different methods, the worldwide prevalence of RLS has been reported as 2.5-29% (4). In our country, this rate is between 5.52-9.7% according to the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria and it is seen twice as often in women (5-7). There are clinical and epidemiological studies show that there is a relationship between migraine and RLS (8). Both the frequency of RLS in patients with migraine and the frequency of migraine in patients with RLS is higher than

in controls (9). The prevalence of RLS in migraine patients is estimated to be 8.7-39.0% (3,10). This association is thought to be related to a common pathophysiological link rather than comorbidity (11). The most common reason for this association may be dopamine and iron metabolism disorders. However, the etiopathogenesis of RLS and its relationship and/or comorbidity with migraine has not been clarified yet.

To the best of our knowledge, only one study was published on the prevalence of RLS in Turkish migraineurs, and it was reported that the frequency of RLS was higher than controls (12). The authors observed association of RLS with the age of the patient and duration of the disease. To contribute the existing literature and improve the in the field, we aimed in this study to compare the frequency of RLS in patients diagnosed with migraine and

Headache-free controls. We also explored the clinical characteristics of migraine patients with RLS.

Methods

Migraine patients and headache-free participants

This cross-sectional study included patients admitted to the neurology outpatient clinic and were diagnosed with migraine with or without aura according to The International Classification of Headache Disorders-III. The control group included age and gender-mathced headache free volunteers (1). The headache free group did not have any neurological or systemic disease, addiction or medical treatment. The study group and headache-free controls were evaluated by two neurologists and detailed neurological were examined. None of the migraine patients were receiving prophylactic medications such as serotonin reuptake inhibitors or amitriptyline that could affect dopamine metabolism. Age, gender, average number of migraine attacks per month, length of disease, the presence of aura, a type of aura, coexistening of hypertension, smoking, family history for RLS were recorded. Patients with comorbidities such as kidney disease, Parkinson's disease, rheumatoid arthritis, and polyneuropathy were excluded. Hemoglobin (Hb) level above 13.0 g/dL for men and 12.0 g/dL for women, and serum ferritin level above 50 mL/ng were taken as reference values (13).

All procedures were performed in accordance with the Declaration of Helsinki, Erciyes University Clinical Research Local Ethics Committee (decision no: 2021/147, date: 03.03.2021), and informed written consent was obtained from all participants or their legal representatives.

Clinical evaluation

RLS was diagnosed using the IRLSSG criteria in migraine patients and headache-free participants by two neurologists using face-to-face interview. The IRLSSG diagnostic criteria include five-questions based on the patient's history (5). Subjects who met all RLS diagnostic criteria were accepted as RLS (+). Then, the Turkish version of "RLS Rating Scale" was applied to the patients diagnosed with RLS (14). This scale consists of 10 questions each graded between 0 and 4. While the first five questions are related to the severity of symptoms, and the last five questions are related to the effects of RLS on daily living activities or quality of life. The score obtained indicates the severity of the disease. The highest score in this tool is 40, and while scores between 1 and 10 are classified as mild, between 11 and 20 moderate, between 21 and 30 severe, and between 31 and 40 very severe.

Statistical Analysis

We performed statistical analyses using the IBM Statistical Package for Social Sciences statistics 21.0 (IBM.Corp., Armonk, NY, 2012). Descriptive statistics were displayed as mean±standard deviation for continuous variables; and as counts and proportions for categorical data. The distribution normality of the continuous variables was calculated using the Shapiro-Wilk test. We used independent samples t-test to compare continuous variable fort he normally distributed variables and the chi-square test for categorical variables. We analysed the two groups with the Mann-Whitney U test for the non-normally distributed variables. Logistic regression analysis was performed to explore the variables independently associated with the presence of RLS. $P<0.05$ was considered significant.

Results

The study included 201 patients [152 females (75.6%), 49 males (24.4%), with the mean age of 34.6 years±11.6] diagnosed with migraine with or without aura, and 102 headache-free participants [67 females (65.7%), 35 males) (34.3%), mean age 31.9 years±10.8] were included. There was no statistically significant difference between the two groups in terms of age and gender.

More patients (40.3%, n=81) in the migraine patients met the diagnostic criteria for RLS than the headache-free group (15.7%, n=16) ($p<0.001$).

The number of patients with RLS was 81 (40.3%) and those without RLS was 120 (59.7%). 77.8% of RLS (+) and 74.2% of RLS (-) migraine patients were female ($p=0.559$). The two groups were similar in terms of age, number of attacks per month, presence of aura, smoking, and family history for RLS. Length of disease was longer in the (+) migraine patients with RLS than RLS (-) group (mean 14.6±9.7 years and 4.6±5.0 years respectively, $p<0.001$). Five of six patients with both hypertension and migraine patients had RLS (76 of 195 for patients without hypertension, $p=0.041$) (Table 1). Serum ferritin levels were below 50 mL/ng in 74.2% of RLS (+) migraine patients and 79% of RLS (-) migraine patients and there was

no statistically significant difference (p=0.526). Serum Hb levels of the two groups were within normal laboratory values (83.3%, 90.1% of patients, respectively, p=0.173). Additionally, the migraine patients with severe/very severe RLS (n=20) had a longer disease duration than the patients with mild/moderate RLS (n=61) (18.3±9.7 years, 13.4±9.5 years; p=0.050).

Logistic regression analysis showed a significant association the disease duration and the presence of RLS (Odds ratio: 13.25, 95% confidence interval: 5.62-31.24), p=0.001). Other potential covariates age, gender, aura, the frequency of attacks, length of disease, family history, hypertention, smoking status, Hb and ferritin level showed no significant association with the presence of RLS in migraineurs (Table 2).

Discussion

This study showed that RLS was more common in patients with migraine than headache-free volunteers (40.3%/15.7%). Moreover, RLS was more frequent in migraine patients with hypertension, the frequency and severity of RLS was related to the disease duration.

The frequency of RLS in healthy populations has been reported to be approximately 10% (15). However, studies also showed that this rate is approximately two to three times higher in patients with migraine. First, headache and RLS comorbidity was reported by Young et al. (16) with higher prevalence of RLS in 50 patients with headache. Later, in a case-controlled study matched for age and gender, among 411 migraine patients the frequency of RLS was significantly higher compared with the controls (17.3%/5.6%) (17). In a population-based study from Taiwan, 23.641 migraine patients and 94.564 people without migraine were compared, and an increased risk of RLS was found in migraineurs regardless of the comorbidities and migraine type (18). The prevalence of RLS in migraine patients was 33% in a single case-control study from Turkey (12). Our observation of 40.3% RLS among migraine patients is in agreement with that study. Also consistent with the literature, we found that the presence of RLS in migraineurs was about three times higher than in headache-free controls (17).

Several hypotheses have been proposed regarding the higher prevalence of RLS in migraineurs The most important of these is the idea that dopamine and iron regulation disorders are mechanisms that can lead to both conditions (19,20). The reasons suggesting that the dopaminergic system affects the pathophysiology of both RLS and migraine are as

Table 1. Demographic and clinical characteristics of migraine patients with and without RLS

	RLS (+) (n=81)	RLS (-) (n=120)	p value
Age (year), mean±SD	36.1±12.5	33.5±10.9	0.128*
Female, n (%)	63 (77.8)	89 (74.2)	0.559**
Length of disease (year), mean±SD	14.6±9.7	4.6±5.0	0.001*
Presence of aura, n (%)	9 (11.1)	14 (11.7)	0.903**
Smoking, n (%)	26 (32.1)	28 (23.3)	0.281**
Hypertension, n (%)	5 (6.2)	1 (0.8)	0.040**
Frequency of attacks			0.442**
Episodic, n (%)	76 (93.8)	109 (90.8)	-
Chronic, n (%)	5 (6.2)	11 (9.2)	-

*The independent samples t-test was used for analyses.
**The chi-square test was used for analyses.
SD: Standart deviation, RLS: Restless legs syndrome

Table 2. Regression coefficients of logistic regression of migraine patients with RLS

	OR	95% CI	p value
Age	1.02	0.99-1.04	0.11
Gender	0.89	0.38-2.06	0.79
Presence of aura	0.74	0.28-1.95	0.55
Length of disease	6.19	3.40-11.26	0.000
Headache frequency	0.75	0.42-1.32	0.32
Family history	1.75	0.46-6.58	0.40
Hypertension	7.89	0.89-68.31	0.06
Hb level	1.99	0.78-5.03	0.51
Ferritin level	0.70	0.30-1.58	0.39
Smoking status	1.51	0.77-2.98	0.22

OR: Odds ratio, CI: Confidence interval, RLS: Restless legs syndrome, Hb: Hemoglobin

follows: Dopamine-mediated symptoms (like yawning and gastrointestinal symptoms) before migraine attacks, dopamine agonists increase migraine symptoms, animal studies showed that dopaminergic pathways are involved in both RLS and migraine, and dopamine agonists are effective for treating RLS (21-23).

Concerning the iron metabolism hypothesis; it has been reported that iron deposits are observed in the deep brain nuclei in patients with migraine and that recurrent migraine attacks are related to these iron stores (24). Iron deficiency affects RLS etiology (25). Based on this information, it is thought that iron storage and therefore usable iron deficiency may be one of the common pathophysiological mechanisms of these two diseases. Besides, since iron is the cofactor of tyrosine hydroxylase, a enzyme required in the synthesis of dopamine, it may be that striatal dopamine neurotransmission is impaired in brain iron metabolism disorders and this situation leads to RLS (26). Unlike previous studies that indicated a common mechanism regarding iron metabolism, serum Hb and ferritin levels were similar in migraine patients with and without RLS in our study.

Various studies have reported the presence of RLS in migraine sufferers was related to the characteristics of the patient and disease (11). Age, family history for RLS, length of disease, comorbidities, frequency, and severity of headache can predict RLS occurrence (17,18,27,28).

It has been concluded in some studies that migraineurs with a longer disease duration are more likely to have RLS (12,18,27). Similar to the previous studies, long migraine duration was associated with increased frequency of RLS in our study, some authors consider that this association occurs due to central sensitization. In central sensitization, due to the plasticity of the somatosensory nervous system in response to chronic pain, the activity of neurons and nociceptive pathways increases and this causes pain, allodynia or hypersensitivity (29). This may also be one reason why the severity of RLS, which is another significant finding, increases as the duration of the disease increases (30).

Hypertension was significantly higher in migraine patients with RLS in our study. Previous studies also showed that hypertension is more common in patients with RLS (31). It was suggested that the presence of periodic leg movements during polysomnography increases blood pressure transiently (32). Additionally, in a study-separated patients as primary and secondary RLS, patients with primary RLS were younger and the prevalence of hypertension did not increase, whereas the rate of hypertension diagnosis was more common in patients with secondary RLS (33).

This study has some limitations. Since it was conducted a cross-sectional study the temporal relationship between the diagnosis of migraine and the presence of RLS symptoms could not be evaluated. Whether the symptoms are improved after migraine treatment was also not evaluated. The number of participants in both the patient and headache-free groups were also low.

Conclusion

In conclusion, we observed a higher frequency of RLS in patients with migraine than controls. We also observed a positive association between the frequency and severity of RLS and the duration of migraine. Since both diseases negatively affect the quality of life, RLS symptoms should be screened especially when migraine is diagnosed.

Ethics

Ethics Committee Approval: The study were approved by the Erciyes University Clinical Research Local Ethics Committee (decision no: 2021/147, date: 03.03.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç.S., B.S.A.P., N.K., Concept: M.C.A., Design: B.S.A.P., M.C.A., Data Collection or Processing: A.Ç.S., B.S.A.P., N.K., Analysis or Interpretation: A.Ç.S., B.S.A.P., M.C.A., Literature Search: A.Ç.S., B.S.A.P., N.K., Writing: A.Ç.S., B.S.A.P., M.C.A.

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Neurogenic dysphagia experiences/characteristics at a tertiary center-retrospective analysis

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ABSTRACT

Aims: To compare demographic and clinical features and their relation to rehabilitation outcomes in patients impaired swallowing after stroke or traumatic brain injury (TBI), anoxic brain injury, encephalitis and glioma.

Methods: This retrospective study evaluated the medical records of patients with brain injury in our university rehabilitation. Patients who received swallowing therapy for 24 sessions (3 days a week for 8 weeks) were included. Swallowing was evaluated with a functional oral intake scale (FOIS) and videofluoroscopic swallowing study before and after rehabilitation. Videofluoroscopy images were scored using the Penetration Aspiration Scale (PAS). Functional status was assessed with the Functional Independence Measure.

Results: The study included 271 patients [stroke: 175 (64.6%); TBI: 58 (21.4%); anoxic brain injury: 13 (4.8%); glioma: 18 (6.6%); and encephalitis 7 (2.6%)]. Significant improvement was observed on the FOIS in stroke (pretreatment: 5.9±1.9 vs. posttreatment: 6.1±1.9, p=0.011) and TBI groups (pretreatment: 5.3±2.4 vs. posttreatment: 5.9±7.0, p=0.007). In both groups, significant improvements were observed in all three consistencies (solid, pudding, and liquid) according to PAS after treatment ($p<0.05$). Stroke patients with the middle cerebral artery (MCA) and posterior cerebral artery syndromes showed statistically significant improvement on FOIS. Patients with the MCA syndrome also showed significant improvement in the liquid score of the PAS.

Conclusions: Swallowing therapy was found effective in improving swallowing functions in patients with stroke and TBI. In particular, stroke patients with MCA involvement gained more benefit from treatment.

Introduction

Swallowing is a complex sensorimotor event that involves both voluntary and involuntary processes. Structures at many levels from the cerebral cortex to the bulbus within the central nervous system are involved in swallowing (1). Dysphagia, which is the medical term for having difficulty swallowing, is common in patients with a number of neurological disorders. Dysphagia may even occur secondary to peripheral nervous system lesions, muscle disorders, and neuromuscular junction disorders (2). Neurogenic dysphagia is usually caused by brain damage. It may lead to lethal complications such as aspiration, pneumonia, malnutrition, and dehydration (3). The incidence of post-stroke dysphagia is 30-50% (4). Approximately 27-61% of patients after traumatic brain injury (TBI) have swallowing disorders due to cognitive and behavioral problems, loss of neuromuscular control, intubation, and tracheostomy history (5,6). Patients with a history of high-grade glioma or encephalitis may also have neurogenic dysphagia with progressive neurological and cognitive deficits.

Before recommending any specific treatment, experienced physical medicine and rehabilitation specialists and swallowing therapists should locate and identify the mechanism underlying the swallowing problem with a comprehensive evaluation. Various tests can help diagnose swallowing problems. Videofluoroscopy is the gold-standard method in assessing swallowing disorders. Fiberoptic endoscopic examination, ultrasonography, scintigraphy, and pharyngeal manometry can also be used. Diet modifications, postural maintenance, compensatory strategies, swallowing maneuvers, exercises, electrical stimulation, botulinum toxin administration, or surgical methods are the most common treatment methods of neurogenic dysphagia (7).

Neurogenic dysphagia rehabilitation is of vital importance in patients with neurological diseases to provide proper nutrition and prevent secondary complications. However, there is no consensus on how treatment will be administered in which patient group. Although most interventional treatment studies have been conducted in patients with stroke, rehabilitation studies of patient groups such as TBI, anoxic brain injury, glioma, and encephalitis are still not sufficient. The present study documents the clinical functioning outcomes of patients with neurogenic dysphagia who have been treated in a tertiary rehabilitation hospital in Turkey. The aims of this study were 1) to compare rehabilitation outcomes in patients with stroke and other acquired brain injuries; 2) to determine the features of dysphagia according to the vascular area involvement in stroke.

Methods

Study design and participants

In this single-center, retrospective study, we reviewed the electronic medical records of the patients with acquired brain injury (ABI) who were admitted to a university rehabilitation hospital between January 2010-December 2014. All cases between these dates were examined for inclusion in the study and patients who had a history of swallowing problems after brain damage was included. The study protocol was approved by the Local Ethics Committee (Gülhane Military Medical Academy, decision no: 1642-63250, date: 04.11.2014).

Demographic data including etiology of brain injury, age at the time of injury, sex, time since injury, history of aspiration pneumonia, and history of tracheostomy were collected. Arterial involvement in patients with stroke was determined using MRI findings.

Clinical assessment

Functional status was assessed with the Functional Independence Measure (FIM). The validity and reliability of the FIM for Turkish stroke survivors was performed by Küçükdeveci et al. (8). Patients were evaluated with a videofluoroscopic swallowing study and the functional oral intake scale (FOIS) at baseline and after completing the rehabilitation program. For the videofluoroscopic swallowing study, radiopaque was used as a contrast agent to visualize the bolus. Imaging shots were taken during the swallow. Swallowing functions were evaluated in three different consistencies as defined previously by Luchesi et al. (9) study: liquid, pudding, and solid. The pudding consistency was prepared according to the recommendation of the manufacturer of the food thickener used (Nestle thicken-up®). Liquid and solid consistencies consisted of water and a standard cracker, respectively. While the patient was sitting in a wheelchair between the C-arm of the device (Ziehm Imaging, Vario DDD, Nürnberg, Germany) the patient's head was positioned on the midline, facing up. Images were adjusted to include the lips at the front, the cervical vertebra at the back, the soft palate at the top, and the C7 vertebra at the bottom. The presence of penetration-aspiration, degree of penetration-aspiration, and presence of pharyngeal residue were recorded.

Penetration Aspiration Scale (PAS) was used to determine the penetration-aspiration severity. The validity and reliability study of the PAS was conducted for the Turkish population (10). Obtained images from the video-fluoroscopy were scored using this scale. The presence of penetration-aspiration, degree of penetration-aspiration, and presence of pharyngeal residue were recorded. Material entering the airway and contacting the vocal folds was defined as penetration; material passing below the vocal folds was defined as aspiration. In the video-fluoroscopic swallowing study, aspiration is observed when the bolus passes through the glottis. Scores on the PAS were evaluated separately and graded between 1 and 8 (9). The PAS results were divided into 3 categories: no penetration or aspiration (PAS 1), penetration (PAS 2-5), and aspiration (PAS 6-8). A team including a physical medicine and rehabilitation specialist and a swallowing therapist assessed the videofluoroscopic swallowing study.

The FOIS was used to determine the patient's functional oral intake status at 7 levels; level 1 to 3 indicate varying degrees of non-oral feeding (tube dependency); level 4 or 5 indicates total oral intake with special preparations, and level 6 or 7 indicate total oral intake without special preparations (11).

Treatment protocol

All patients received an 8-week swallowing rehabilitation as part of an inpatient rehabilitation program that was a standard procedure after brain injury. The therapy was planned 3 days a week and each session was completed in 45 min. The following order was followed in line with the patient's needs and video-fluoroscopic study results:

1. Bolus size and consistency modifications,

2. Postural maintenance (informing the patient and family/caregiver about the importance of optimal posture in terms of swallowing function),

3. Compensatory strategies (e.g., chin tuck, head tilt),

4. Exercise (e.g., range of motion of the lips, jaw, tongue, hyolaryngeal mobilization, chewing training, thermal tactile stimulation),

5. Swallowing maneuver (e.g., effortful swallow, Mendelsohn maneuver).

Statistical Analysis

All statistical tests were performed using Statistical Package for the Social Sciences Statistics for Mac version 20.0 (Armonk, NY: IBM Corp., 2011). The distributions of continuous variables were determined using a Kolmogorov-Smirnov test. Nominal data were displayed as the frequency and percentage. Continuous data were reported as mean±standard deviation, median and interquartile range where appropriate. Categorical data were compared with the chi-square test. Within-group comparisons were performed using a paired t-test or Wilcoxon signed-rank test as appropriate. $p<0.05$ was considered statistically significant.

Results

The study included 271 patients [mean age: 50.0±20.1 years; male sex: 179 (66.1%); stroke: 175 (64.6%), TBI: 58 (21.4%); ABI: 13 (4.8%); glioma: 18 (6.6%) and encephalitis: 7 (2.6%)]. The demographic characteristics of the patients are shown in Table 1. Patients with stroke were older [age, median: 61.0 (50.0-71.0) years], and the patients with TBI were younger [age, median: 24.0 (15.0-38.0) years] compared with the other patients with other etiologies. Patients with ABI and encephalitis seemed to have more risk of aspiration pneumonia compared to stroke patients. Sixty-three of the patients had a history of aspiration pneumonia, while 28.6% (n=18) of them were tube dependent, and 30.2% (n=19) showed improvement in FOIS outcomes after the rehabilitation program. Encephalitis was the leading etiology associated with a history of aspiration pneumonia (57.1%) and tracheostomy (71.4%). Patients with ABI had the highest rate of tracheostomy history (84.6%), and more than half of the patients with ABI had experienced aspiration pneumonia (53.8%). Although 35.6% (n=31) of the patients had normal feeding, 33.3% (n=29) of 87 patients with a history of tracheostomy use were tube dependent.

Table 2 displays changes in FOIS level of the patients after a rehabilitation program compared to baseline. Significant improvement was observed on the FOIS in patients with stroke (pretreatment: 5.9±1.9

Table 1. Demographic features of the patients according to brain injury etiology (n=271)

Etiology of brain injury	n	%	Age [median (Q1-Q3)]	Sex (female/male), n (%)	Time since injury (months) [median (Q1-Q3)]	History of aspiration pneumonia, n (%)	History of tracheostomy, n (%)	Total FIM score [median (Q1-Q3)]
Stroke	175	64.6	61.0 (50-71)	70 (40.0)/105 (60.0)	6.0 (2-11.2)	28 (16.0)	30 (17.1)	63.0 (43-91)
TBI	58	21.4	24.0 (15-38)	12 (20.7)/46 (79.3)	6.5 (3-23.2)	20 (34.5)	40 (69.0)	46 (30-80)
ABI	13	4.8	42.0 (32-60)	4 (30.8)/9 (69.2)	6 (4-41)	7 (53.8)	11 (84.6)	38 (28-75)
Glioma	18	6.6	40.0 (28-54)	5 (27.8)/13 (72.2)	8 (3-30)	4 (22.2)	1 (5.6)	63 (42-72)
Encephalitis	7	2.6	42.0 (29-52)	1 (14.3)/6 (85.7)	7 (4-30)	4 (57.1)	5 (71.4)	54 (31-71)

Q1-Q3: 1st and 3rd quartile, TBI: Traumatic brain injury, ABI: Anoxic brain injury, FIM: Functional Independence Measure

Table 2. Improvements and comparison of the FOIS according to etiology of brain injury (n=271)

FOIS levels of the patients									
	Tube dependent (1-3)		Oral intake (4-5)		Oral intake (6-7)		Total FOIS changes		
Etiology of brain injury	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy mean±SD [median (Q1-Q3)]	Post-therapy mean±SD [median (Q1-Q3)]	p
Stroke	26 (14.6)	11 (6.3)	10 (5.7)	11 (6.3)	139 (79.5)	153 (87.5)	5.9±1.9 [7 (6-7)]	6.1±1.9 [7 (6-7)]	**0.011**
TBI	16 (27.6)	7 (12.1)	7 (12.1)	3 (5.2)	35 (60.4)	48 (82.7)	5.3±2.4 [7 (5-7)]	5.9±7.0 [7 (6-7)]	**0.007**
ABI	5 (38.5)	3 (23.1)	1 (7.7)	0	7 (53.9)	10 (76.9)	4.5±2.9 [7 (5-7)]	5.0±2.7 [7 (5-7)]	0.180
Glioma	2 (11.1)	1 (5.6)	1 (5.6)	1 (5.6)	15 (83.3)	16 (88.9)	6.3±1.4 [7 (6-7)]	6.5±1.4 [7 (6-7)]	0.317
Encephalitis	2 (28.6)	1 (14.3)	2 (28.6)	0	3 (42.9)	6 (85.8)	3.4±3.0 [7 (4-7)]	6.0±2.2 [7 (5-7)]	0.083

FOIS: Functional oral intake status, TBI: Traumatic brain injury, ABI: Anoxic brain injury, SD: Standard deviation

vs. posttreatment: 6.1±1.9, p=0.011) and TBI (pretreatment: 5.3±2.4 vs. posttreatment: 5.9±7.0, p=0.007). However, there were no significant changes in the FOIS in patients with ABI (pretreatment: 6.3±1.4 vs. posttreatment: 6.5±1.4, p=0.317), glioma (pretreatment: 4.5±2.9 vs. posttreatment: 5.0±2.7, p=0180, and encephalitis (pretreatment: 3.4±3.0 vs. posttreatment: 6.0±2.2, p=0.083).

Comparison of the patients who had improvement in FOIS and those who did not were compared. Patients who showed an improvement were significantly younger (43.0±19.9 years of age) than the patients who did not improve (51.7±19.9 years of age) (p<0.05).

PAS scores of the patients are shown in Table 3. In the stroke and TBI groups, significant improvements were observed in all three consistencies (solid-pudding-liquid) after treatment. In the encephalitis group, a significant increase was observed only in the solid consistency after treatment.

A hundred seventy-five patients with stroke were grouped according to the artery involvement: 128 (73.1%) with the middle cerebral artery (MCA), 27 (15.4%) with the posterior cerebral artery (PCA), 14 (8.0%) with the anterior cerebral artery (ACA), and 6 (3.4%) with internal carotid artery (ICA) involvement. Patients with MCA and PCA syndromes showed statistically significant improvement on the FOIS; however, the patients with ICA and ACA syndromes did not (Table 4). The only significant improvement on the PAS was observed in the liquid scores of patients with MCA syndrome (Table 5).

Discussion

In this study, data on the change in oral intake and swallowing dysfunction after swallowing therapy in patients with acquired brain damage in a tertiary rehabilitation center were examined. It was concluded that there were significant improvements in oral intake and aspiration-penetration rates in patients with stroke and TBI after swallowing therapy, but the changes in ABI, glioma, and encephalitis groups were not significant. When the patients with stroke were examined according to their vascular involvement, it was determined that MCA and PCA syndromes gave a significant response to the treatment. The results are valuable because it examines the response to treatment of different groups of patients with neurological swallowing disorders and different vascular involvement.

Neurogenic dysphagia is a common cause of mortality in neurological disorders. However, most studies into neurogenic dysphagia have focused on patients with stroke (12-15). However, there is a paucity of evidence indicating the effectiveness the dysphagia rehabilitation in TBI. Most of the studies involving patients with TBI consist of heterogeneous patient groups (16,17). However, patients with stroke and TBI have different

Table 3. PAS assessments of the patients by the videofluoroscopic swallowing study (n=271)

PAS levels of the patients	Liquid		Pudding		Solid	
Etiology of brain injury	**Pre-therapy, n (%)**	**Post-therapy, n (%)**	**Pre-therapy, n (%)**	**Post-therapy, n (%)**	**Pre-therapy, n (%)**	**Post-therapy, n (%)**
Stroke*						
No penetration	113 (64.6)	120 (68.6)	155 (88.6)	155 (88.6)	146 (83.4)	147 (84.0)
Penetration	-	9 (5.1)	20 (11.4)	20 (11.4)	-	3 (1.7)
Aspiration	62 (35.4)	46 (26.3)	-	-	29 (16.6)	25 (14.3)
TBI*						
No penetration	29 (50.0)	35 (60.3)	47 (81.0)	51 (87.9)	45 (77.6)	49 (84.5)
Penetration	-	6 (10.3)	11 (19.0)	7 (12.1)	-	2 (3.4)
Aspiration	29 (50.0)	17 (29.3)	-	-	13 (22.4)	7 (12.1)
ABI						
No penetration	7 (53.8)	7 (53.8)	8 (61.5)	9 (69.2)	7 (53.8)	7 (53.8)
Penetration	-	1 (7.7)	5 (38.5)	4 (30.8)	-	2 (15.4)
Aspiration	6 (46.2)	5 (38.5)	-	-	6 (46.2)	4 (30.8)
Glioma						
No PA	11 (61.1)	12 (66.7)	17 (94.4)	17 (94.4)	17 (94.4)	17 (94.4)
Penetration	-	-	1 (5.6)	1 (5.6)	-	-
Aspiration	7 (38.9)	6 (33.4)	-	-	1 (5.6)	1 (5.6)
Encephalitis**						
No PA	2 (28.6)	2 (28.6)	7 (100)	7 (100)	3 (42.9)	6 (85.7)
Penetration	1 (14.3)	4 (57.1)	-	-	-	1 (14.3)
Aspiration	4 (57.1)	1 (14.3)	-	-	4 (57.1)	-

*p<0.05 in PAS-liquid, PAS-pudding, and PAS-solid with chi-square test.
**p<0.05 only in PAS-solid with chi-square test.
PAS: Penetration Aspiration Scale, TBI: Traumatic brain injury, ABI: Anoxic brain injury

characteristics. Stroke survivors are seen at older ages than patients with TBI, which may explain the FIM scores similar to the others. While vascular damage due to stroke most often affects focal areas unilaterally, brain damage in TBI is usually bilateral and diffuse. Cognitive impairment is more common in patients with TBI (18). With regard to oropharyngeal damage, speech problems are more frequent in stroke patients, whereas delay in pharyngeal peristalsis is more frequent and severe in patients with TBI (19). In the present study, improvements were observed in the oral intake and penetration-aspirating rates of patients with TBI during dysphagia rehabilitation, similar to patients with stroke. According to our FOIS data, 27.6% of the patients with TBI were tube dependent, while only 14.6% of the patients with stroke were tube dependent. Improvement in functional oral intake was seen in 16.6% of the patients with stroke and 27.6% of the patients with TBI.

Dysphagia is observed in approximately 26% of patients with brain tumors (20). The most important factors determining the frequency and severity of dysphagia are tumor location and size (21). In the study where Park et al. (22) compared the dysphagia characteristics of patients with stroke and brain tumors, it was concluded that patients with brain tumors were not different from stroke patients in terms of age, lesion location, and degree of swallowing dysfunction. However, they also reported that whether the tumor is malignant or benign does not affect the degree of swallowing dysfunction. In a study comparing the functional gains in brain tumor and stroke patients after inpatient rehabilitation, the authors concluded that patients with brain tumors benefit from treatment similar to stroke patients (23). Similarly, in the study by Wesling et al. (21), in which changes in swallowing dysfunction after inpatient rehabilitation between the

Table 4. Improvement and comparison of the FOIS according to vascular area involvement in patients with stroke (n=175)

Vascular area involvement		Tube dependent (1-3)		Oral intake (4-5)		Oral intake (6-7)		Total FOIS changes		
	n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy mean±SD [median (Q1-Q3)]	Post-therapy mean±SD [median (Q1-Q3)]	p
ICA	6 (3.4)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	4.5±2.7 [6 (1-7)]	4.6±2.8 [6 (1-7)]	0.317
MCA	128 (73.1)	14 (11)	6 (4.7)	2 (1.6)	2 (1.6)	112 (87.5)	120 (93.8)	6.2±1.6 [7 (1-7)]	6.4±1.4 [7 (1-7)]	**0.014**
ACA	14 (8.0)	3 (21.4)	2 (14.3)	2 (14.3)	2 (14.3)	9 (64.3)	10 (71.4)	5.0±2.6 [6 (1-7)]	5.0±2.7 [6 (1-7)]	0.317
PCA	27 (15.4)	8 (29.6)	2 (7.4)	4 (14.8)	5 (18.5)	15 (55.6)	20 (74.1)	5.2±2.6 [7 (1-7)]	5.4±2.6 [7 (1-7)]	**0.046**

FOIS: Functional oral intake status. ICA: Internal carotis artery, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, PCA: Posterior cerebral artery, TBI: Traumatic brain injury, ABI: Anoxic brain injury

Table 5. PAS assessments of the patients with stroke according to vascular area involvement (n=175)

	PAS					
	Liquid		Pudding		Solid	
	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)	Pre-therapy, n (%)	Post-therapy, n (%)
ICA						
No penetration	2 (33.3)	2 (33.3)	4 (66.7)	4 (66.7)	3 (50.0)	4 (66.7)
Penetration	-	-	2 (33.3)	2 (33.3)	-	-
Aspiration	4 (66.6)	4 (66.6)	-	-	3 (50.0)	2 (33.3)
MCA*						
No penetration	89 (69.5)	100 (78.2)	120 (93.8)	120 (93.8)	112 (87.5)	115 (89.8)
Penetration	-	-	8 (6.3)	8 (6.3)	-	-
Aspiration	39 (30.5)	28 (21.8)	-	-	16 (12.5)	13 (10.2)
ACA						
No penetration	6 (42.9)	7 (50.0)	10 (71.4)	10 (71.4)	10 (71.4)	10 (71.4)
Penetration	-	-	4 (28.6)	4 (28.6)	-	-
Aspiration	8 (57.2)	7 (50.0)	-	-	4 (28.6)	4 (28.6)
PCA						
No penetration	16 (59.3)	20 (74.1)	21 (77.8)	21 (77.8)	21 (77.8)	21 (77.8)
Penetration	-	-	6 (22.2)	6 (22.2)	-	-
Aspiration	11 (40.7)	7 (25.9)	-	-	6 (22.2)	6 (22.2)

*p<0.05 only in PAS-liquid with chi-square test.
ICA: Internal carotis artery, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, PCA: Posterior cerebral artery, TBI: Traumatic brain injury, ABI: Anoxic brain injury, PAS: Penetration Aspiration Scale, PAS: Penetration Aspiration Scale

two groups were analyzed, no difference was found between the two groups. In the present study, contrasting with the previous studies, desired gains could not be obtained after treatment in patients with brain tumors. The reason for this finding may be that the cognitive functions of the patients in our study were worse, or the lesion location and size were different compared to other studies.

Dysphagia is common in patients with encephalitis, especially in the presence of brainstem involvement (24). Dysphagia causes both deteriorations in quality of life and vital complications such as aspiration pneumonia. There are not enough studies on the importance of swallowing therapy for treating dysphagia in patients with encephalitis (25). In this study, only the change in PAS-fluid values was found to be significant after swallowing therapy.

Although there are different types of dysphagia treatment in the literature, swallowing rehabilitation is an effective method for patients with neurogenic dysphagia. Since swallowing has a complex physiology, only a single exercise or maneuver is not sufficient to rehabilitate the swallowing dysfunction (26). For this, it is necessary to understand patients' swallowing dysfunction correctly and to determine appropriate strategies. In the present study, swallowing therapy (3 days a week, 8 weeks, 24 sessions) was implemented in line with the patient's needs and video-fluoroscopic study results. Bolus size and consistency modifications, postural maintenance, compensatory strategies (e.g., chin tuck, head tilt), exercises (e.g., range of motion of the lips, jaw, tongue, hyolaryngeal mobilization, chewing training), and swallowing maneuver (effortful swallow, Mendelsohn maneuver) were applied in treatment. Our outcomes showed that the tube dependency and oral feeding restrictions decreased after therapy in all patients, but improvement rates in patients with stroke and TBI were most pronounced.

Different central nervous system regions from the cerebral cortex to the medulla oblongata affect swallowing physiology. The cerebrum is responsible for cognition and coordination as well as oral chewing and peristalsis. The brain stem is responsible for pharyngeal swallowing, laryngeal elevation, glottic closure, and cricopharyngeal relaxation. Within the cortex, lesions of the insula, the frontal operculum, and the primary sensorimotor cortex are most commonly associated with swallowing dysfunction. Kim et al. (27) investigated the patterns of post-stroke swallowing difficulties according to the vascular territories involved in the stroke and found that territorial anterior infarcts are more related to oral phase dysfunction whereas territorial posterior infarcts are more related to pharyngeal dysfunction. In the present study when the patients with stroke were examined separately according to the vascular area involvement, videoflouroscopic examinations showed that aspiration levels were higher in the patients with ICA and ACA involvement compared to patients with MCA and PCA involvement. As expected, the aspiration of liquids was evident in all stroke patients. However, the most tolerable consistency was pudding for all post-stroke examinations. There was a significant gain after swallowing rehabilitation in patients with MCA or PCA involvement according to the functional oral outcomes due to the major artery of swallowing areas nourished by these vessels.

There were several limitations in this study. Firstly, the study was in a retrospective design and lacked a control group that did not receive swallowing therapy. Therefore, the potential influence of spontaneous recovery on results could not be measured. However, it is unethical to leave patients without treatment while swallowing treatment is available. Secondly, the number of patients with ABI, encephalitis, and brain tumors was small compared with the group of stroke patients. Also, the lack of data on cognitive performance which is associated with the swallowing function is considered another limitation. Among the notable strengths are the large number of patients overall and the inclusion of different etiologies of brain injury.

Conclusion

Swallowing therapy is an important part of rehabilitation in patients with neurogenic dysphagia after ABI. To our knowledge, this is the first study among Turkish patients who showed the efficacy of swallowing therapy in different etiologies of ABI. The outcomes were overall better for patients with TBI and stroke, and the patients with stroke with MCA and PCA involvement gained more benefit from the treatment.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee (Gülhane Military Medical Academy, decision no: 1642-63250, date: 04.11.2014).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.İ., Design: S.K., E.Y., Data Collection or Processing: R.A., Ö.İ., Analysis or Interpretation: B.A., S.K., Literature Search: B.A., Ö.İ., E.Y., Writing: B.A., S.K.

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Cranial magnetic resonance imaging findings and their relationship with neuropsychiatric findings in adult patients with lipoid proteinosis

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ABSTRACT

Aims: Lipoid proteinosis (LP) is a rare genodermatosis with relatively increased prevalence in Turkey. Dermatologists commonly recognize the disease due to the prominent mucocutaneous findings. Neuropsychiatric involvement is common, and the findings are heterogeneous. This study aimed to examine the cranial magnetic resonance imaging (MRI) findings of LP patients along with their neuropsychiatric involvement.

Methods: This single-center, retrospective study included patients diagnosed with LP from March 2017 through March 2020. Demographics, neuropsychiatric complaints, and physical examination findings were retrieved from the medical records. The same radiologist evaluated all cranial MRI images to search for the calcifications within the temporal lobe, the mesolimbic region, and particularly the amygdala. The secondary end-points were the presence of additional radiological findings localized to other areas of the brain.

Results: Eight patients [age, mean±standard deviation: 30.2±9.0 years (range 23-51), female: 50%] were eligible. Two (25%) patients had clear neuropsychiatric involvement. One patient had mental retardation and history of intractable epilepsy during childhood. Another patient had complaints of severe amnesia and difficulties in concentrating. Five patients (62.5%) showed the typical symmetric bean-shaped or oval calcifications in the uncal part of the temporal lobes involving the amygdala nuclei of hippocampi. In addition to the calcifications, one patient had arachnoid cysts. Cranial MRI findings were normal in the remaining three patients. MRI findings were normal in the patient with mental retardation

Conclusions: In this study, complaints and neuropsychiatric evaluation were inconsistent with the findings on cranial MRI among patients with LP.

Introduction

Lipoid proteinosis (LP), also known as Urban Wiethe disease, is a rare autosomal recessive genodermatosis related to the *loss-of-function* mutations of the extracellular matrix protein 1 (ECM-1) gene (1). Due to the widespread action of ECM-1, LP is a conspicuous disease regarded as a human disease model for skin aging and basolateral amygdala lesions (2-6). The affected sites are mostly the skin, oral, nasal, laryngeal mucosa, and the central nervous system (CNS), particularly the mesolimbic region (7). The manifestations of the disease are heterogeneous, and the involvement of different organ systems varies among patients.

LP is more common in some regions, with most reports from South Africa (8,9). In addition to individual case reports, several case series of Turkish patients with LP have highlighted the relatively increased prevalence in Turkey, probably related to the high ratio of consanguineous marriages (10-12).

LP can be diagnosed easily by the stigmatizing features, including the typical voice hoarseness and facial, periocular, and mucosal deposits. Although the clinical manifestations

commonly start during infancy, significant diagnostic delays may occur, and a substantial proportion of patients with LP are diagnosed in adulthood (7).

All patients with LP should undergo CNS imaging. Clinicians may prefer different cranial imaging methods like direct radiography, CT scans, or magnetic resonance imaging (MRI) to search for CNS calcifications (7,13). The onset of neurological findings demonstrates variability among LP cases (7). A slowly progressive pattern has been purported; thus, the patients without neuroradiological involvement also warrant long-term follow-up for the emergence of neuropsychiatric complaints (7). The pathognomonic cranial radiological finding of LP is the symmetrical bean-shaped calcifications within the temporal lobe. They can be detected either by direct radiography, computed tomography (CT) scanning, or MRI (14). Brain calcifications most commonly involve the amygdala but may extend to the hippocampus, parahippocampal gyrus, and striatum (8,13). The pattern of neurological involvement is commonly slowly progressive.

Recently, typical intracranial calcifications were linked to seizures in a case series from Turkey (15). However, the authors excluded patients without intracranial calcifications. Some patients with LP do not show neuropsychiatric symptoms. However, in addition to epilepsy, LP can manifest with highly variable neuropsychiatric findings, including migraine, schizophrenia, anxiety, abnormalities in mediating emotional responses, dizziness, ataxia, slight psychomotor retardation, and amnesic impairment (8).

Dermatologists are familiar with the manifestations of LP. Since the condition is underrecognized in other disciplines, the dermatologist frequently plays a central role in the diagnosis and multidisciplinary management of LP (7). We have published our experiences in treating the cutaneous and mucosal lesions in adult LP patients with erbium: YAG laser (16,17). Physician-to-patient interactions may help identify additional characteristics of this rare genodermatosis with an inherent diverse nature. Indeed, we have observed potential discordance between intracranial calcifications and neuropsychiatric involvement. Although some patients with massive CNS calcifications showed no neuropsychiatric symptoms, pathognomonic radiological CNS findings were not observed in some patients with severe neuropsychiatric symptoms. Besides, most of the patients did not experience difficulties in social interactions. They mentioned that the stigmatizing features of LP were the leading cause of the disease interfering with their social life. Thus, the patients actively sought treatment to eliminate the mucocutaneous and laryngeal lesions to restore the overall facial appearance and voice hoarseness. Finally, a recent case report of LP defined completely different brain MRI findings, including hydrocephalus, subependymal heterotopia, and absent splenium of corpus callosum without temporal lobe calcification, revealing the possibility of additional radiological findings (18).

Therefore, the current study examined patients with LP for their MRI findings, along with the neuropsychiatric complaints and findings.

Methods

This single-center, retrospective study included eight patients diagnosed with LP between March 2017 through March 2020 in a tertiary hospital setting. The study protocol was approved by the University of Health Sciences Turkey, Gülhane Institutional Review Board (no: 2020-462, date: 30.11.2020).

LP is suspected based on the clinical findings of larynx, skin, and CNS involvement; imaging findings of CNS involvement; a positive history of LP; or parental consanguinity. The clinicians searched for the presence of typical mucocutaneous signs, including beaded papules on the eyelid margin, acneiform scars on the facial skin, an enlarged, crenated tongue, mucosal deposits, and verrucous plaques over friction areas. Patients with LP were included in the study only if the diagnosis was confirmed by genetic analysis or pathology. Regardless of signs and symptoms specifying neuropsychiatric involvement, all patients with LP underwent cranial imaging. The patients who had undergone cranial MRI were eligible for inclusion. There were no specific exclusion criteria. Available data were collected using the patient charts and electronic medical records. Information on age, gender, comorbidities were recorded.

The presence of seizures or an established diagnosis of a psychiatric disorder was recorded for each patient. As part of the routine patient evaluation on admission, the patient interview includes questions about involvement in everyday activities. Then, specific aspects related to affective (difficulties in personal interactions, sadness, irritability, anhedonia) and cognitive (amnesia, concentration difficulty) functions are recorded, with the involvement of the family members or caregivers. Patients with suspected neuropsychiatric involvement are also referred to a psychiatrist. The patients referred to the psychiatry deparment underwent a cognitive evaluation with the Montreal Cognitive Assessment (MOCA) test, a fast screening tool to detect mild cognitive impairment. The MOCA test evaluates cognition aspects, including attention, concentration, executive functions, and memory. The threshold score to detect mild cognitive impairment is 21 among Turkish persons (19).

Cranial MRI orders identified were purposefully evaluated by a single, eleven-year-experienced radiologist. Axial T1 weighted, axial T2 weighted, axial fluid-attenuated inversion recovery sequence, coronal T2 weighted, and sagittal T1 weighted images were obtained in all participants. Post-contrast axial and coronal T1 weighted images were evaluated further, to identify other abnormalities. Pathognomonic findings, including

symmetric calcification in the uncal part of temporal lobes, were assessed with other unconventional features. Symmetrical calcifications were also classified as complete (bean-shaped) or focal (oval) according to the involvement of the nuclei in the region.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp., 2013). Numerical variables were shown as mean±standard deviation (SD) or median (minimum-maximum). Categorical variables were displayed as numbers and percentages.

Results

The study included eight patients with LP from three families (age, mean±SD: 30.2±9.0 years; range 23-51, female, n=4). Figure 1 shows the family tree of the study population. All patients had a long-standing diagnosis. Table 1 displays the demographic characteristics, neuropsychiatric involvement, and cranial MRI findings.

Neuropsychiatric findings

Only one patient (12.5%) reported a history of seizures. None of the patients had records of a psychiatric disorder diagnosed by the specialist or any related medication. Four patients had undergone neuropsychological testing, of whom three (75%) had scores above 21 points, and only one (25%) had a score consistent with mild cognitive impairment.

Two (25%) (P1 and P4) out of 8 patients had typical symptoms and signs of neuropsychiatric involvement. The first patient (P1), a 21-year-old male, had an intractable course of epilepsy during childhood and mental retardation. This patient had no history of epileptic seizures in ten years past. As he had mental retardation, further cognitive evaluation was not available. However, his 24-year-old sister (P2) and 51-year-old father (P3) also had LP diagnosis. They also showed no calcification on cranial MRI. MOCA test was normal in P2 but showed slight impairment in P3.

The second patient (P4), a male 21-year-old college student, had neuropsychiatric complaints but no mood disturbances. Concentration difficulty and amnesia interfering with his academic success were recorded in his chart. The onset of his symptoms was within the last 12 months, with a progressive course. Video-electroencephalography detected significant bilateral slow-wave activity in the right frontal lobe and sharp wave activity in the left frontotemporal lobes. However, his MOCA score was within the normal range. P5, 26-year-old brother of P4, was reported by his family members to show inappropriate affection and

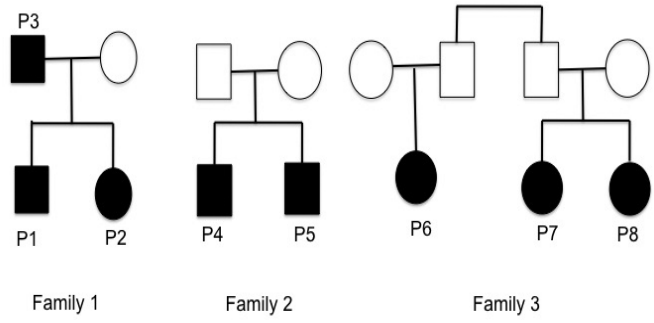

Figure 1. Flow-chart of the study participants

Table 1. Demographics, cranial magnetic resonance imaging findings and neuropsychiatric evaluation of the study population

Nr.	Age	Gender	Cranial MRI	Neuropsychiatric complaint, findings	Montreal Cognitive Assessment Score
1	21	M	Normal	Intractable epilepsy during childhood, MRI	Ineligible
2	24	F	Normal	None	22
3	51	M	Normal	None	19*
4	21	M	Bilateral perihipocampal calcifications, left temporal arachnoid cyst	Severe amnesia, described difficulty for concentration, EEG abnormalitis	26
5	26	M	Bilateral perihipocampal calcifications	None	-
6	24	F	Bilateral perihipocampal calcifications	None	27
7	31	F	Bilateral perihipocampal calcifications	None	-
8	33	F	Bilateral perihipocampal calcifications	None	-

*According to the mentioned score, this patient was reported to have mild cognitive impairment.
EEG: Electroencephalogram, MRI: Magnetic resonance imaging, M: Male, F: Female

frequent mood changes; however, he declined the psychiatric and neurologic evaluation.

MRI findings

Five patients (62.5%) showed pathognomonic symmetric calcifications in the uncal part of both temporal lobes involving the amygdala nuclei of both hippocampi. Of these five calcifications, three were bean-shaped (complete) (P4, P5, P6), and the remaining two (P7, P8) were oval (focal). The calcifications were detected as signal-free on T1 and T2 weighted images without involvement in post-contrast scans (Figure 2). In addition to the pathognomonic finding, a Galassi type-1 arachnoid cyst was detected adjacent to the left temporal lobe in one case (%12.5). No contrast involvement or accompanying vascular anomaly was observed in any patient following the administration of contrast material.

The relation of neuropsychiatric and MRI findings

Of the two patients (P1, P4) with symptoms and signs mentioning neuropsychiatric involvement, P1 showed no calcifications or other pathological findings on cranial MRI. Similarly, his sister (P2) and father (P3) also showed no pathological findings on cranial MRI.

In addition to periuncal calcifications, P4 had arachnoid cysts on MRI. Video-electroencephalography detected significant bilateral slow-wave activity in the right frontal lobe and sharp wave activity in the left frontotemporal lobes.

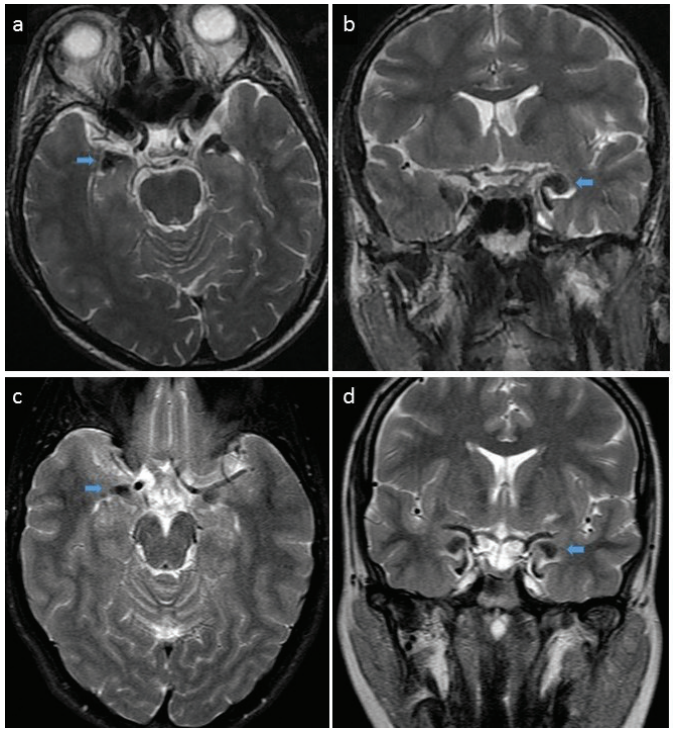

Figure 2. Magnetic resonance imaging images in two patients with lipoid proteinosis. Bilateral symmetric bean shaped (arrows in a and b) and oval (arrows in c and d) calcifications in the uncal part of temporal lobes involving both the hippocampi were seen signal-free in the axial and coronal T2-weighted images which are pathognomonic radiological findings for this disease

Of the three remaining patients, P7, a 31-year-old female, and P8, a 33-year-old female, were siblings. P6, a 24-year-old female, was their cousin. All three patients showed parahippocampal calcifications. P6 had the most severe calcifications. She was referred to the psychiatry department for cognitive evaluation, and her MOCA score was within normal ranges. All three patients reported no complaints suggestive of psychiatric and neurologic involvement; thus, P7 and P8 declined psychiatric and neurological evaluation.

From another perspective to evaluate resilience in coping with life, two female patients (P2, P7) had healthy children. A patient (P7) showed bilateral hippocampal calcifications. She was referred for cognitive assessment with average results on the MOCA test. Additionally, P3 was the father of P1 and P2. These patients did not define a neuropsychiatric complaint or a problem consistent with the additional burden of parenting.

Discussion

The foci of calcifications within the CNS are the best acknowledged causal factor for the neuropsychiatric involvement of LP (7). In this study, only three patients from the same family had no calcifications. Thus, the pathognomonic bilateral calcification pattern localized to the amygdaloid complex of LP has been detected in 62.5% of cases. Similar to our study, radiological CNS involvement has been reported in 50-75% of patients with LP (20,21). Autopsy findings of patients with LP revealed that these calcifications were due to pericapillary degenerative changes with calcification in the anterior choroidal artery territory, particularly the mesolimbic region. However, the calcifications may extend beyond the amygdala (22). Besides, these calcifications may be focal or involve the complete portion of the amygdaloid complex (21). In our study, all calcifications were confined within the amygdala. Both focal (P7, P8) and complete (P6) calcifications of the amygdala have been detected in the same family.

The radiological findings of LP have been observed only in isolated case findings (13,20,23). Although CT can provide superior results in delineating calcifications, MRI may detect additional findings in patients with LP (18). Due to the recent reports describing the extraordinary features of LP on MRI, cranial MRI is preferred for CNS imaging of patients with LP (18). In this study, additional pathological findings that could be detected on MRI were sought in a relatively large number of patients. As an unusual finding, only one case revealed arachnoid cysts, and none of the patients had a vascular abnormality.

The human amygdala plays a crucial role in executive functions and social signal processing (5). Amygdala pathologies

are strongly related to neuropsychiatric disorders (5). The investigations on LP cases with selective amygdala damage complemented the animal data on amygdala functioning (8). The patients with focal bilateral amygdala lesions typically show impaired recognition of fearful faces. However, this deficit is variable, possibly related to the compensation of social signal processing by other brain regions (5). Besides, different LP studies have defined considerable variations for neuropsychiatric involvement. Some studies reported the complete absence of psychiatric symptomatology. However, LP has been associated with intact intelligence and mental retardation (8).

In this study, two patients had typical neuropsychiatric involvement. One patient's family reported difficulty in social interactions. However, the patient declined psychiatric examination and, thus, could not be evaluated further. McGrath implicated patients with LP to have an impoverished emotional landscape related to the significantly reduced expression of negative emotions and overly trusting on others without a thorough character analysis (7). This preference for reduced expression of negative emotions might also explain the diminished requirement of patients with LP to apply for psychiatric treatment.

As a conspicuous finding, the patient with a history of intractable epileptic seizures and mental retardation showed no periuncal calcifications. The discordance between the radiological and neuropsychological findings in this patient can be explained through different hypotheses. First, the literature suggests diversity in features of LP, and to the periuncal calcifications, alternative mechanisms may be responsible for developing epileptic seizures. The interactions of ECM-1 protein with various extracellular matrix components and enzymes were hypothesized to contribute to the emergence of neurologic manifestations (7). Siebert et al. (21) investigated the neuroradiological findings of nine patients with LP with confirmed bilateral amygdala damage. They evaluated both static (cranial CT) and functional (single-photon emission CT and positron emission tomography) imaging results. Upon the analysis of the findings, six cases had bilateral calcification of the amygdaloid complex with full-blown degeneration in all portions. For the remaining three patients without calcifications on cranial CT scans, the functional imaging results confirmed a bilateral decreased perfusion in the temporal lobes (21). The reason for the absence of calcification in these patients is unknown.

As a minor possibility, the seizures of P1 might be related to another disorder. His 51-year old father and 24-year old sister with LP did not report signs or complaints of neuropsychiatric involvement. However, his father had mild cognitive impairment detected by the MOCA test. He was the oldest member of the series, and this finding is important as the brain involvement of LP is a slowly progressive degenerative process.

The other case (P4) with typical complaints revealed amygdala calcifications along with arachnoid cysts on MRI. The onset of neuropsychiatric symptoms was different for P1 and P4. The epileptic seizures ended in P1 during adolescence. However, the beginning of P4's complaints was later during early adulthood, emphasizing the requirement of long-term follow-up for the emergence of neuropsychiatric complaints.

Salih et al. (24) reported three Saudi families with LP. Two patients from the same family had modest mental retardation. However, only one of them had tiny calcifications of the amygdala on the CT scan. The CT scans of the other patient without calcification revealed a watershed ischemic injury involving the right hemisphere with periventricular white matter loss and thickening of the overlying skull. The authors mentioned that neither had developed seizures or obvious emotional problems on long-term follow-up (24).

Becker et al. (25) reported an intriguing discrepancy between the neuropsychological findings of German twins with LP. Although a twin had difficulty recognizing fearful expressions, modulating acoustic startle responses by fear-eliciting scenes, the other was not affected. The authors mentioned that the unaffected case showed potentiated response to fearful faces in her left premotor cortex face area and bilaterally in the inferior parietal lobule on the functional MRI study. As both regions have been implicated in the cortical mirror-neuron system, which mediates learning of the observed actions, the authors suggested that neuroplasticity in the mirror neuron system compensates for amygdala processing (25). Thus, only the macroscopic and radiological findings of LP cases may not entirely delineate the degree of neuropsychiatric involvement. The initial studies of patients with LP suggested a significant effect on the daily functioning of the affected cases related to CNS involvement. However, functional radiological studies provided an integral perspective to suggest correlations between radiological and functional impairments (8,23). According to the available data, Siebert et al. (21) mentioned that even patients with full-blown amygdala degeneration could perform normally in most everyday functions and may have subtle memory impairments.

In a recent review, hippocampal calcifications were reported as an incidentally detected but common feature in patients older than 50 years (26). In the current series, the mean age was 30.2 years, and 62.5% showed calcifications. However, the only 50-year-old patient (P3) had no calcifications. Thus, the pathophysiology of calcification in LP may be unrelated to typical senescence.

The current study has some limitations. First, although it was predictable, the sample size remained low, limiting further comparisons among different disease phenotypes. Second, selection bias cannot be neglected as the study population was predominantly composed of LP cases actively seeking treatment for better cosmesis; thus, the study might have selectively

included patients with a mild neuropsychiatric involvement. However, neuroradiological findings were detected in most cases included. Finally, the study design was retrospective, making the analyses prone to errors due to underreporting of some study variables.

Conclusion

The current study identified typical cranial radiological findings 62.5% in patients with LP. However, only 25% of the study population reported major complaints or had mental retardation. Upon detailed evaluation, another two had minor findings suggesting neuropsychological involvement. The association between the radiological findings and neuropsychiatric involvement was not straightforward. This rare disorder with considerable clinical variability warrants a thorough evaluation of the clinical and radiological findings.

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Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Gülhane Institutional Review Board (no: 2020-462, date: 30.11.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: A.B., A.A., E.Ç., Design: A.B., E.Ç., Data Collection or Processing: A.A., Analysis or Interpretation: A.B., A.A., E.Ç., Literature Search: A.B., E.Ç., Writing: A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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The assessment of rheumatologic immune-related adverse events with immune checkpoint inhibitors

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ABSTRACT

Aims: Immune-related adverse events (irAEs) may be observed due to the mechanism of action of immune checkpoint inhibitors (ICIs). This study investigated the frequency of rheumatologic irAEs and characteristics of the patients who developed rheumatologic irAEs due to ICIs.

Methods: This single-center, prospective, and observational study was conducted with the patients who received ICIs due to malignancy between December 2018 and November 2019. The demographic characteristics, clinical characteristics, and inflammatory and non-inflammatory irAEs were evaluated.

Results: The study included 38 patients (mean age: 54.5±19.2 years, male: 65.8%). Thirty-one (86.1%) patients received nivolumab, 4 (11.1%) patients received atezolizumab, and one (2.8%) patient received pembrolizumab. The median number of treatment cycles with ICIs was 11.5. Rheumatologic irAEs were observed in 20 (55.6%) patients. Four (11.2%) patients had inflammatory and 16 (44.5%) patients had non-inflammatory rheumatologic irAEs. The median time from the initiation of ICI treatment to the development of rheumatologic irAEs was 3 months. All patients with inflammatory rheumatologic irAEs were on treatment with a programmed cell death protein 1 inhibitor. Prednisolone and methotrexate were the drugs used to improve inflammatory musculoskeletal symptoms.

Conclusions: Inflammatory rheumatological irAEs due to ICIs were mostly polymyalgia rheumatica and rheumatoid arthritis-like symptoms. Low-dose corticosteroid therapy may be the appropriate choice of treatment of inflammatory rheumatologic irAEs.

Introduction

Antibodies against cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), the programmed cell death protein 1 (PD1), and its ligand (PD-L1) that act as checkpoints in immune response pathways, are named as immune checkpoint inhibitors (ICIs) and have begun used widely for treating hematologic malignancies, malignant melanoma, and solid cancers (1,2). CTLA-4 on T cells binds CD80/86, and PD1 on T cells binds its ligands, PD-L1, and PD-L2, on antigen-presenting cells, which cause T cell inhibition (3). Immune checkpoint molecules provide self-regulation of immune tolerance, while these engagements also lead to cancer cells escaping from cytotoxic T-lymphocytes. As a result, cancer cell invasion becomes easier (4). ICIs' anti-tumor effect emerges from the inhibition of the immune checkpoints that preserve the immunotolerance in T cells and the stimulation of the immune response of T cells to tumor cells (5). However, due to their effects on immune response, a higher prevalence of immune-related adverse events (irAEs) may be observed due to uncontrolled T cell activation (1).

Although irAEs may affect any organ system, cutaneous, gastrointestinal, pulmonary, and endocrine involvement may be more frequent. Rarely the patients may experience musculoskeletal, cardiovascular, hematologic, and neurologic irAEs (6,7). IrAEs are usually low-grade, show a mild or moderate course, and regress without treatment; however, a multidisciplinary approach may be necessary for high-grade irAEs (1,7).

IrAEs are more frequent with PD1 and PD-L1 inhibitors compared with CTLA-4 inhibitors due to their actions in different steps of immune regulation (1). It was shown that rheumatologic irAEs are more common in patients who receive PD1 and PD-L1 blockers or a combination of these agents compared with CTLA-4 inhibitors (8). This study evaluated the frequency of rheumatologic irAEs among patients who received ICIs and the characteristics of these patients.

Methods

Study design and sample

This single-center, observational study with prospective enrollment included patients on treatment with PD1 and PD-L1 inhibitors. The participants were enrolled at Gülhane Training and Research Hospital, Ankara, Turkey, from December 2018 through November 2019. The inclusion criteria were (a) having received at least one dose of ICI due to malignancy, (b) no prior rheumatologic disease, (c) age 18 of age or older, and (d) agreeing to participate in the study. Exclusion criteria were pregnancy and breastfeeding. All patients provided written informed consent. The study protocol was approved by the Local Ethics Committee of Gülhane Training and Research Hospital (approval no: 18/282, November 21, 2018).

The treatment response to malignancy was evaluated by clinical, laboratory and radiological assessments. The development of rheumatologic and non-rheumatologic irAEs related to ICI use was evaluated.

Evaluation of rheumatologic irAEs

The patients were referred to the rheumatology outpatient clinic from the oncology outpatient clinic and evaluated by two rheumatologists for a history of rheumatologic disease, family history of rheumatologic disease, and new-onset rheumatologic symptoms. Clinical and demographic data were obtained from face-to-face interviews with patients and using the patient charts. Previously diagnosed rheumatologic diseases, family history of rheumatologic diseases, type of malignancy, duration of malignancy, ICI type, and the number of ICI cycles were recorded. If necessary, imaging methods (radiography, ultrasound, or magnetic resonance imaging) were performed in patients with rheumatologic irAEs. Depending on the type of manifestation, serum autoantibodies, human leukocyte antigen (HLA) B27, C-reactive protein, and erythrocyte sedimentation rate were measured. After the first assessment, the patients were re-evaluated for new-onset rheumatologic irAEs every 3 months for one year or in case of a musculoskeletal symptom.

Rheumatologic irAEs were determined as non-inflammatory and inflammatory manifestations. Arthralgia and myalgia without morning stiffness worsened with physical activity and lessened with rest, also, xerostomia, xerophthalmia, photosensitivity without proven connective tissue disease was considered non-inflammatory rheumatologic adverse events. Inflammatory rheumatologic adverse events were defined as arthritis, bursitis, myositis, tenosynovitis, vasculitis, and connective tissue diseases and confirmed by examination, laboratory, and imaging methods (3,9,10).

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 11.5, SPSS Inc., Chicago. The normality assumption was assessed by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean±standard deviation, while non-normally distributed continuous variables were expressed as median (Q1-Q3). Categorical variables were summarized as counts (percentages).

Results

Basic characteristics

The study included 36 patients (25 male, 65.8%) with a mean age of 54.5±19.2 years. The median duration of malignancy was 26.5 (14-48) months. Eleven (30.6%) patients had Hodgkin's lymphoma, 10 (27.8%) patients had malign melanoma, 9 (25.0%) patients had renal cell cancer, 4 (11.1%) patients had small cell lung cancer, 1 (2.8%) patient had non-small cell lung cancer, and 1 (2.8%) hepatocellular cancer. Seventeen (47.2%) patients had metastatic disease. Thirty-two (88.9%) patients received PD1 inhibitors (nivolumab and pembrolizumab), and 4 (11.1%) patients received PD-L1 inhibitors (atezolizumab). Nivolumab was used in 31 (86.1%), atezolizumab in 4 (11.1%) patients, and pembrolizumab in 1 (2.8%) patient. The median number of ICI cycles was 11.5 (8-23). All patients received chemotherapy, and 12 (33.3%) patients received radiotherapy before initiation of ICI therapy.

Ten (27.8%) patients achieved complete response, 11 (30.6%) patients had partial regression, and 8 (22.2%) patients had stable disease with ICIs. Progression was recorded in 7 (19.4%) patients and 4 (11.1%) patients who died during the follow-up period (Table 1).

Rheumatologic evaluation

Rheumatologic irAEs were recorded in 20 (55.6%) patients. The median time to the occurrence of rheumatologic adverse events after initiation of ICI was 3 (1.5-7) months. The most

common musculoskeletal manifestation was arthralgia in 15 (41.7%) patients. The other irAEs were xerostomia in 5 (13.9%) patients, xerophthalmia in 3 (8.3%) patients, photosensitivity in 3 (8.3%) patients, arthritis in 2 (5.6%) patients, bursitis in 2 (5.6%) patients, polymyalgia rheumatica (PMR) like syndrome in 2 (5.6%) patients, tendinitis in 1 (2.8%) patient and myalgia in 1 (2.8%) patient (Table 2). Among patients with inflammatory rheumatologic irAEs, 2 (5.6%) patients had PMR-like symptoms, and 2 (5.6%) patients had rheumatoid arthritis (RA) like symptoms. The mean time of the initiation of PMR-like symptoms was 2.5 months, and it was 4 months for RA-like symptoms. Sixteen (44.5%) patients had non-inflammatory rheumatologic irAEs. All patients with inflammatory rheumatologic irAEs were onPD1 inhibitor treatment (Figure 1). Rheumatoid factor, anti-cyclic citrullinated peptide, antinuclear antibody, and HLA B27 were negative in all patients.

Arthralgia was common in the shoulders, elbows, and knees. Two patients had arthritis in the wrists. Bursitis in two patients was in the subacromial and subdeltoid bursa. Tenosynovitis of musculus extensor carpi ulnaris was recorded in two patients. Four (11.1%) patients with arthritis, bursitis and tenosynovitis received prednisolone therapy, and one (2.8%) patient who had corticosteroid-resistant arthritis received methotrexate. Prednisolone doses of 10 mg/day were sufficient for healing musculoskeletal manifestations. Seven (19.4%) patients with non-inflammatory rheumatologic irAE were treated with nonsteroid anti-inflammatory drugs. Ten (27.8%) patients had non-rheumatologic irAEs (Table 2). The patients with xerophthalmia and xerostomia had no radiotherapy to the gland localization.

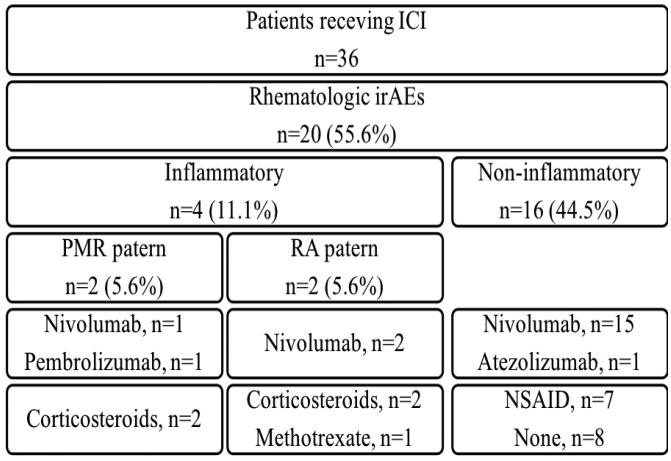

Figure 1. The immune-related rheumatologic adverse events of the study group

ICI: Immune checkpoint inhibitor, irAEs: Immune-related adverse events, RA: Rheumatoid arthritis, PMR: Polymyalgia rheumatica, NSAID: Non-steroidal anti-inflammatory drug

Table 1. Demographic and clinical characteristics of the study group

		Patients (n=36)
Gender, n (%)	Female	11 (30.6)
	Male	25 (69.4)
Age, years, mean±SD		54.5±19.2
Disease duration for malignancies (months), median (Q1-Q3)		26.5 (14-48)
Types of malignancy, n (%)	Hodgkin's lymphoma	11 (30.6)
	Malignant melanoma	10 (27.8)
	Renal cell cancer	9 (25.0)
	Small cell lung cancer	4 (11.1)
	Non-small cell lung cancer	1 (2.8)
	Hepatocellular cancer	1 (2.8)
Patients with metastatic disease, n (%)		17 (47.2)
Type of ICI, n (%)	Nivolumab	31 (86.1)
	Atezolizumab	4 (11.1)
	Pembrolizumab	1 (2.8)
Number of ICI cycle, median (Q1-Q3)		11.5 (8-23)
Patients received previous chemotherapy, n (%)		36 (100)
Patients received previous radiotherapy, n (%)		12 (33.3)
Response of the malignancy, n (%)	Complete response	10 (27.8)
	Partial regression	11 (30.6)
	Stable disease	8 (22.2)
	Progression	7 (19.4)

ICI: Immune checkpoint inhibitor, SD: Standard deviation, n: Number, Q: Quarter

Table 2. Rheumatologic and other immune-related adverse events of the study group

		Patients (n=36)
The time between initiation of ICI treatment and the occurrence of rheumatologic irAEs, months, median (Q1-Q3)		3 (1.5-7)
The number of patients with rheumatologic irAEs, n (%)		20 (55.6)
Rheumatologic irAEs, n (%)	Arthralgia	15 (41.7)
	Xerostomia	5 (13.9)
	Xerophthalmia	3 (8.3)
	Photosensitivity	3 (8.3)
	Arthritis	2 (5.6)
	Bursitis	2 (5.6)
	Polymyalgia rheumatica like syndrome	2 (5.6)
	Tendinitis	1 (2.8)
	Myalgia	1 (2.8)
The number of patients with non-rheumatologic irAEs, n (%)		10 (27.8)
Non-rheumatologic irAEs, n (%)	Rash	6 (16.7)
	Xerosis cutis, pruritus	2 (5.6)
	Alopecia	1 (2.8)
	Thyroiditis	1 (2.8)
	Seborrheic dermatitis	1 (2.8)
Treatment of the rheumatologic irAEs, n (%)	NSAID	7 (19.4)
	Corticosteroid	4 (11.1)
	Methotrexate	1 (2.8)

ICI: Immune checkpoint inhibitor, irAE: Immune-related adverse event, NSAID: Nonsteroidal anti-inflammatory drug

Discussion

ICIs, different from classical chemotherapeutic agents, show their anti-tumor effect by activating the immune system and attain widespread benefit for treating oncology patients. ICIs prevent the immune pathways that inhibit the autoactivation and overreaction of the immune system. Due to the activation mechanism of these drugs, irAEs may appear during the treatment (1,2). According to the current study, which evaluated the rheumatologic irAEs in patients using ICIs, the findings requiring treatment were particularly in patients who had similar symptoms with RA and PMR.

Monoclonal antibodies that blockade immune checkpoints to treat various types of malignancies in different stages are used widely. CTLA-4, PD1, and PD-L1 provide the balance between activation and inhibition of T cells (11). The main goal of ICIs is to increase the immune response to tumor cells by inhibiting immune checkpoints that prevent the inhibition of cytotoxic T-lymphocytes (12). In the central lymphoid tissues, to inhibit T cell activation, CTLA-4 prevents the engagement between CD80/86 on antigen-presenting cells and CD28 on T cells. Thus, the antibodies that inhibit CTLA-4 activate T cells, leading to an increase in peripheral T cell migration and attack on tumor cells. PD1 commonly exists in peripheral T cells. When PD1 binds to its ligands, PD-L1, and PD-L2, cancer cells proliferate due to T cell inhibition. The antibodies that inhibit PD1 and PD-L1 increase the T cell response against cancer cells (13). The accomplishment of ICIs in achieving remission or preventing disease progression in resistant or metastatic malignant melanoma, lung cancer, renal cell cancer, and Hodgkin's lymphoma provide their widespread use in oncology. In this study, ICIs were used frequently in patients with Hodgkin's lymphoma, malignant melanoma, and renal cell cancer consistent with the recommendations.

However, inhibition of immune checkpoints with ICIs with excessive activation of the immune system may lead to undesirable immune and inflammatory events. These irAE affect many organ systems and may lead to complications even may be fatal (13). The irAE rate with PD 1 and PD-L1 inhibitors was reported as 70%, whereas it may be up to 95% among patients using combination therapy (PD 1, PD-L1, and CTLA 4) (14-16). Hofmann et al. (17) investigated the irAEs in 496 patients with malignant melanoma receiving nivolumab and pembrolizumab. According to their study, there were 242 irAEs in 138 patients in the skin, endocrine, renal and gastrointestinal systems, but no rheumatologic irAE existed. However, differing from this study, we found that rheumatologic irAEs were more frequent than other irAEs. The second most frequent irAE was related to the skin with a similar frequency of rash, pruritus, and alopecia to the literature (17).

The rheumatological side effects that may develop due to an ICI treatment have not been recorded in most studies

so far and presented as case series. Arthralgia and myalgia can be considered paraneoplastic or related to conventional chemotherapeutic agents; oral dryness and ocular dryness can be attributed to radiotherapy, which may prevent the true frequency assessment regarding the rate of rheumatologic irAEs related to ICIs. The rate of rheumatologic irAEs was reported to be 1.5-22% in the literature (2,18). The current study found a higher rate of rheumatologic irAEs than the previous studies in the literature. Higher rates of rheumatologic irAEs may be related to the assessment of the patients periodically during the study period by rheumatologists in terms of the presence of any rheumatologic symptoms.

Whereas arthralgia and myalgia are the most frequently reported adverse events due to ICI, recent studies determined two groups of rheumatologic irAEs, PMR-like syndrome, and inflammatory arthritis. PMR-like syndrome and inflammatory arthritis are more frequent and comprise a higher rate among systemic symptoms (3,10,19-21). According to a prospective study conducted by Kostine et al. (19) rheumatologic irAEs were characterized as inflammatory and non-inflammatory, and arthralgia was accepted as a non-inflammatory irAE. In the same study, inflammatory rheumatologic irAEs were frequently seen as PMR and RA patterns. A review showed that rheumatologic irAEs are usually detected as PMR-like symptoms, tenosynovitis, and arthritis of hand joints, and with decreasing frequency asymmetric oligoarthritis, reactive arthritis, and psoriatic arthritis (13). Inflammatory arthritis as RA and PMR-like patterns was frequent in the current study, especially among patients who received PD1 inhibitors. The association between PD1 and PD-L1 receptors affects the pathophysiology of RA and PMR. PD1 polymorphism is associated with increased susceptibility to RA. Also, soluble and transmembrane PD1 expression decreases in patients with RA (22,23).

Rheumatologic irAEs such as inflammatory arthritis may occur as early as in the first month of the ICI therapy, while they may also arise after two years of treatment (13). According to the literature, PMR-like symptoms may develop earlier than RA-like symptoms related to ICI use (9). Similar to the literature, in the current study, we found that PMR-like symptoms have developed earlier than RA-like symptoms. According to the literature, autoantibody positivity was usually absent in patients with rheumatologic irAEs (9). Rheumatoid factor and anti-cyclic citrullinated peptide may be found positive in a few patients (24). A positive antinuclear antibody can rarely be found at low titers (9). No patient had a positive rheumatoid factor, anti-cyclic citrullinated peptide, or antinuclear antibody in the current study. Minor salivary gland biopsy was not performed in patients with sicca symptoms due to negative antinuclear antibodies and no other system findings associated with connective tissue disease. Recent studies showed that Sjogren's syndrome may develop during ICI therapy. However, in contrast with classical Sjogren's syndrome, antinuclear, anti-Ro, and anti-La antibody positivity may be seen in rare cases, and pathological evaluation may show differences due to acinar ductal destruction caused by T-lymphocyte infiltration (25,26).

The main concern about the management of inflammatory rheumatologic irAEs, especially using glucocorticoids, is the consideration of decreasing the effect of ICI treatment. Glucocorticoids may diminish the efficiency and strength of lymphocytes that infiltrate tumor tissue (27). Thus, high-dose glucocorticoid usage is recommended only for life-threatening organ manifestations. Besides, using 10 mg/day prednisolone for up to six weeks was found safe and did not decrease the efficacy of the ICI treatment in patients receiving PD1 and PD-L1 inhibitors (9,28). European League Against Rheumatism (EULAR) recommended methotrexate as the corticosteroid tapering agent for patients with continuing symptoms under 10 mg/day prednisolone treatment (9,29). According to the EULAR recommendations, we treated rheumatologic inflammatory irAEs with 10 mg/day prednisolone. This treatment was sufficient for providing and maintaining remission. Only one patient received methotrexate due to ongoing symptoms despite corticosteroid therapy.

There are some limitations of the current study. First, our study had a small sample from a single center. Further studies with larger samples and longer follow-up times may provide more data regarding rheumatologic irAEs. Two patients with sicca symptoms had no autoantibodies for Sjogren's syndrome, therefore, a minor salivary gland biopsy had not been performed.

Conclusion

In conclusion, immune checkpoint receptors help balance the immune system by a downregulation mechanism to ensure while the immune system acts against foreign, non-self, and infectious agents. This mechanism is the essential protector mechanism for preventing the development of autoimmunity and autoimmunity-related diseases. The central aim of ICI therapy is to impede the immune inhibitory pathways for providing T cell attacks against cancer cells that hide from the immune system. Consequently, the inhibition of immune checkpoints may cause rheumatologic irAEs. Physicians should be cautious about potential inflammatory rheumatologic irAEs that are not rare and can be overlooked or misdiagnosed, particularly the PMR-like and RA-like symptoms.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of Gülhane Training and Research Hospital with approval number 18/282 on November 21st of 2018.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.T., S.Ç., R.A., İ.E., M.B.A., B.Y., N.K., M.Ç., S.Y., Concept: E.T., S.Ç., M.Ç., S.Y., Design: E.T., S.Ç., M.Ç., S.Y., Data Collection or Processing: E.T., S.Ç., R.A., İ.E., M.B.A., B.Y., N.K., M.Ç., S.Y., Analysis or Interpretation: E.T., S.Ç., R.A., İ.E., M.B.A., B.Y., N.K., M.Ç., S.Y., Literature Search: E.T., S.Ç., Writing: E.T., S.Ç., R.A., İ.E., M.B.A., B.Y., N.K., M.Ç., S.Y.

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Analysis of the use of emergency medical services by Syrians under temporary protection in Ankara, Turkey

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ABSTRACT

Aims: This study aims to determine how Syrians who must live in a country other than their homeland use emergency medical systems (EMS) in that unfamiliar health system.

Methods: We retrospectively evaluated the data of Syrians who called on EMS between January 2017 and December 2020. Patient data were routinely recorded by ambulance personnel after each patient's intervention in the Emergency Health Automation System Database, created by the Ministry of Health of Turkey. International Classification of Diseases Version 10 codes were used to identify diseases.

Results: Of the total of 1,790,356 emergency patients, 24,266 (1.2%) were Syrian refugees. The most common ambulance requests frm the Syrians were due to birth and birth-related events (19.3%). The most common reason for ambulance assignment among females was birth (33.4%), and car accidents (10.0%) among males. Among patients <18 years of age, the most common reason for ambulance assignment was falls (15.0%). Among patients between 18 and 44 years of age, the most common reason was birth (32.1%). The most common reason for ambulance assignment between 45 and 65 years of age was chest pain (12.6%). Among patients aged 65 years or older, chest pain was the most common reason for ambulance assignment (11.6%).

Conclusions: Improving the training of ambulance teams in districts with large Syrian populations, especially for common medical issues such as birth and trauma, will increase the quality of care for these patients.

Introduction

Since the Syrian civil war began in 2011, 6.6 million Syrians have had to leave their country (1) and more than 5 million Syrians have immigrated to different countries in search of safety (2). They have immigrated to Lebanon, Jordan, Iraq, and Egypt, but mostly to Turkey. As of 2019, 3.5 million (64.3%) displaced Syrians have immigrated to Turkey, a neighboring country of Syria (2).

Although it is far from the Turkish-Syrian border, Istanbul, the country's most populous city, has become home to many Syrians (429,000). Other cities in which Syrian refugees settled are Gaziantep (459,000), Hatay (439,000), and Şanlıurfa (427,000), which are located on the Syrian border. In Turkey's capital city of Ankara there are currently 99,000 Syrians, accounting for 1.77% of the city's total population (3).

Emergency medical services (EMS) are among the most important parts of healthcare systems and the first point of contact for many people. Every day in the world, people die or become disabled due to various acute illnesses and injuries. Therefore, all people should have easy access to EMS (4). Access to health services has been identified as a human right in the Constitution of the Republic of Turkey. Therefore, The Republic of Turkey offers free healthcare services to everyone living within its borders. The Ministry of Health (MoH) of Turkey has issued a circular for those under temporary protection, saying that they have free access to all health services (5). In

this context, like other health services, EMS are offered free of charge to Syrians.

Studies on Syrians have largely focused on costs and access to health care. Karakuş et al. (6) and Gulacti et al. (7) evaluated the cost of Syrian patients to the healthcare system. However, few studies have focused on the use of EMS by Syrians, such as Altıner and Yeşil (8). This study aimed to examine how Syrians living under temporary protection in Ankara, Turkey use EMS.

Methods

Procedures

We retrospectively evaluated the data of Syrians who called on EMS for emergency assistance between January 2017 and December 2020. Also, provide the territory/region/hospital (s) where the patients are referred to in the database evaluated for this study. Ethics approval of the study was obtained from the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Oncology Health Application and Research Center Non-Invasive Ethics Committee (ref. no.: 2020-92; date: October 06, 2021).

The patients were routinely recorded by ambulance personnel (doctors, paramedics and emergency medical technicians) in the Emergency Medicine Automation System (ASOS) Database, created by the MoH of Turkey. International Classification of Diseases Version 10 codes are used to identify diseases. The data recorded in the ASOS Database by the ambulance personnel are also checked for possible errors by the Ankara EMS Command and Control Center.

To identify each patient in the ASOS Database, it is necessary to enter a name and surname as well as an ID number. For Turkish citizens, this ID number is the Identity Number of The Republic of Turkey, which is unique to each citizen. Non-citizens of Turkey are given a separate ID number by the Directorate General of Migration Management. In order to filter Syrians from the database among all other non-citizen patients, unique ID numbers of Syrians were obtained from the Directorate General of Migration Management. The data of the patients with these ID numbers were then exported from the ASOS Database.

Endpoints

In the study, the records of ambulance assignments made because of an emergency call to the 1-1-2 Emergency Call Center between 2017 and 2020 was retrieved from the ASOS database. From these data, age, gender, and nationality of the patients, reasons for the emergency calls, case diagnoses, hospitals where the cases were transferred, and the districts of the case variables were included in the study. Data were categorized according to the nationality of the patients as Turkish citizens, Syrians, and others. It was evaluated whether there was a difference between Turkish citizens and Syrians in terms of age, gender, and nationality of the patients, the reasons for the emergency calls, case diagnoses, the hospitals where the cases were transferred, and the districts of the cases.

Statistical Analysis

Data were extracted from ASOS in Excel format (Microsoft Excel 2016-Microsoft Corp., Redmond, WA, USA). The extracted data were then exported to IBM Statistical Package for the Social Sciences 25.0 (IBM Corp., Armonk, NY, USA) and analyzed statistically. Descriptive statistical methods (frequency, percentage, mean, standard deviation) were used to evaluate the study data.

Results

In the 4 years between January 1, 2017, and December 31, 2020, Ankara EMS had a total of 1,790,356 emergency patients, of whom 24,266 were Syrians. The ratio of Syrian patients to the total was 1.2%. The number of cases of Turkish citizens was 1,368,860 (76.5%). The number of patients other than Turkish citizens and Syrians was 397,230 (Table 1). The mean age of Syrian patients was 28.5±18.2 years and 56.5% of them were women. The mean age of Turkish citizens was 50.5±24.8 years and 49.6% of them were women.

Reasons for ambulance calls

The most common ambulance calls of Syrians were due to labor and pregnancy emergencies (19.3%). Other reasons were falls (6.3%), abdominal pain (6.3%), traffic accidents (6.1%), and anxiety (4.9%), respectively. In 2020, 915 Syrian patients with a

Table 1. Total number of cases of the Ankara EMS*

Year	Population (Ankara)	Total number of cases	Turkish citizens		Syrians		Others	
			Number of cases	% in total cases	Number of cases	% in total cases	Number of cases	% in total cases
2017	5,445,026	417,153	320,819	76.9	6,045	1.4	90,289	21.7
2018	5,503,985	436,762	336,539	77.1	5,937	1.4	94,286	21.5
2019	5,639,076	458,369	345,129	75.3	6,160	1.3	107,080	23.4
2020	5,663,322	478,072	366,373	76.6	6,124	1.3	105,575	22.1
Total		**1,790,356**	**1,368,860**	**76.5**	**24,266**	**1.4**	**397,230**	**22.1**

*EMS: Emergency medical services

pre-diagnosis of Coronavirus disease-2019 were assigned an ambulance.

Turkish patients called for an ambulance most frequently because of chest pain (7.3%). Other reasons were falls (6.6%), traffic accidents (6.6%), anxiety (5.7%), and nausea-vomiting (4.3%), respectively. The most common reasons for ambulance assignment of patients by years are given in Table 2.

EMS diagnoses

The most common reason for ambulance assignment among Syrian female patients was labor and pregnancy emergencies (33.4%), while it was car accidents (10.0%) among Syrian male patients. In Syrian patients <18 years of age, the most common reason for ambulance assignment was falls (15.0%). The most common reason for ambulance assignment among <18-year-old Syrian female patients was again labor and pregnancy emergencies (16.2%), while it was falls (19.2%) among <18-year-old Syrian male patients. Among the Syrian patients aged 18-44 years, the most common reason for ambulance assignment was labor and pregnancy emergencies female patients (49.7%), while it was traffic accidents among male patients (12.6%). The most common reason for ambulance assignment among Syrian patients aged 45-65 years was chest pain (12.6%), which was also the most common reason for ambulance assignment among male and female patients in this age group when considered separately (8.6% among women, 17.3% among men). Among Syrian patients >65 years of age, chest pain was the most common reason for ambulance assignment both among all patients (11.6%) and for each gender (10.2% among women, 13.0% among men) (Table 3).

In Turkish patients, the most common diagnosis was anxiety (7.9%) in female patients, while it was chest pain in male patients (9.2%). In Turkish patients under 18 years of age, the most common diagnosis was falls in both men and women (16.1% vs 11.1%). Turkish female patients in the 18-44 age group called an ambulance most frequently because of anxiety (14.7%), while male patients called because of traffic accidents (17.0%). Among Turkish patients aged 45-65 years, the most common diagnosis was anxiety in females (9.3%) and chest pain in males (14.9%). Among Turkish patients aged more than 65 years, women most frequently called for an ambulance because of falls (7.7%), while men called because of chest pain (10.0%).

Transfer to facilities

Of all Syrian patients, 85.1% were transferred to a hospital. Since 13.6% of these patients refused to be transferred to a hospital, the ambulance teams did not perform such interventions. Of these patients, 0.7% were diagnosed as dead at the scene and 0.6% were not transferred to a hospital because they were treated at the scene. Most of the Syrian patients (79.7%) were transferred to training and research hospitals and 19.0% were transferred to secondary care hospitals. In total, only 1.2% of these patients were transferred to university or private hospitals.

Turkish patients were mostly transferred to training and research hospitals (59.0%). Of them, 23.1% were transferred to secondary care hospitals. Those transferred to a university

Table 2. Reasons for ambulance calls by Turkish citizens and Syrians over the years

		2017	2018	2019	2020	Total
Turkish citizens	Chest pain, n (%)	22,292 (6.9)	24,660 (7.3)	27,918 (8.1)	24,599 (6.7)	99,469 (7.3)
	Falls, n (%)	20,193 (6.3)	24,724 (7.3)	26,046 (7.5)	19,918 (5.4)	90,881 (6.6)
	Traffic accidents, n (%)	20,911 (6.5)	26,686 (7.9)	24,515 (7.1)	18,631 (5.1)	90,743 (6.6)
	Anxiety, n (%)	20,085 (6.3)	21,196 (6.3)	21,545 (6.2)	15,466 (4.2)	78,292 (5.7)
	Nausea and vomiting, n (%)	14,257 (4.4)	15,539 (4.6)	16,674 (4.8)	12,925 (3.5)	59,395 (4.3)
	Other causes, n (%)	223,081 (69.5)	223,734 (66.5)	228,431 (66.2)	274,834 (75.0)	950,080 (69.4)
	Total, n (%)	**320,819 (100.0)**	**336,539 (100.0)**	**345,129 (100.0)**	**366,373 (100.0)**	**1,368,860 (100.0)**
Syrians	Birth, n (%)	1,230 (20.3)	1,140 (19.2)	1,092 (17.7)	1,215 (19.8)	4,677 (19.3)
	Falls, n (%)	382 (6.3)	426 (7.2)	369 (6.0)	348 (5.7)	1.525 (6.3)
	Acute abdomen, n (%)	397 (6.6)	366 (6.2)	392 (6.4)	369 (6.0)	1.524 (6.3)
	Traffic accidents, n (%)	390 (6.5)	437 (7.4)	348 (5.6)	300 (4.9)	1.475 (6.1)
	Anxiety, n (%)	301 (5.0)	298 (5.0)	336 (5.5)	261 (4.3)	1.196 (4.9)
	Other causes, n (%)	3.345 (55.3)	3.270 (55.1)	3.623 (58.8)	3.631 (59.3)	13.869 (57.2)
	Total, n (%)	**6,045 (100.0)**	**5,937 (100.0)**	**6,160 (100.0)**	**6,124 (100.0)**	**24,266 (100.0)**

hospitals were 10.0% of all Turkish patients. Among Turkish patients, 7.5% were transferred to private hospitals (Table 4).

Distribution of Syrian patients by case scene districts

The EMS demands of Syrian patients were most frequent in the central districts of the city (76.4%). The 5 districts in which Syrians requested EMS most often were Altındağ (29.5%), Mamak (15.5%), Keçiören (11.5%), Polatlı (9.2%), and Yenimahalle (7.4%). Of these districts, only Polatlı is not a central district (Table 5).

Discussion

In our study, the most common cause of ambulance calls in Syrian patients was labor and pregnancy emergencies, while Turkish patients made ambulance calls most frequently due to chest pain. The most common reason for ambulance assignment among Syrian female patients was labor and pregnancy emergencies, while it was traffic accidents among Syrian male patients. While the most common diagnosis in Turkish female patients was anxiety, it was chest pain in male patients. Both Syrian and Turkish patients were most frequently transferred to the training and research hospitals.

Considering the number of EMS cases in Ankara, we found that the rate of ambulance use by Syrians in 4 years constituted 1.4% of all cases. This rate did not change annually. Ninety-nine thousand Syrians live in Ankara, the capital city of Turkey, and their percentage within the city's total population is 1.77% (3). The percentage of Syrians in the city's total EMS cases is close to the percentage of Syrians in the city's total population.

Table 3. The most common reasons for assigning ambulance for Turkish citizens and Syrians

Diagnoses		<18 years of age		18-44 years of age		45-65 years of age		>65 years of age		Total	
		%	Diagnoses	%	Diagnoses	%	Diagnoses	%	Diagnoses	%	
Turkish Citizens	Women	Falls	11.1	Anxiety	14.7	Anxiety	9.3	Falls	7.7	Anxiety	7.9
		Traffic accidents	8.4	Traffic accidents	7.9	Chest pain	8.0	Cardiac arrest	7.3	Falls	6.6
		Anxiety	7.4	Birth	6.9	Nausea and vomiting	5.9	Chest pain	7.3	Chest pain	5.6
	Men	Falls	16.1	Traffic accidents	17.0	Chest pain	14.9	Chest pain	10.0	Chest pain	9.2
		Traffic accidents	11.5	Anxiety	6.4	Traffic accidents	6.3	Cardiac arrest	8.7	Traffic accidents	8.9
		Fever	7.9	Falls	5.9	Falls	5.1	Falls	6.1	Falls	7.0
	All	Falls	13.8	Traffic accidents	12.7	Chest pain	11.7	Chest pain	8.5	Chest pain	7.3
		Traffic accidents	10.1	Anxiety	10.4	Anxiety	5.7	Cardiac arrest	7.9	Falls	6.6
		Fever	7.7	Falls	5.3	Traffic accidents	5.5	Falls	6.9	Traffic accidents	6.6
Syrians	Women	Birth	16.2	Birth	49.7	Chest pain	8.6	Chest pain	13.0	Birth	33.4
		Falls	10.2	Anxiety	6.6	Anxiety	8.5	Cardiac arrest	6.5	Acute abdomen	6.3
		Traffic accidents	7.7	Acute abdomen	6.4	Acute abdomen	7.2	Acute abdomen	5.4	Anxiety	5.8
	Men	Falls	19.2	Traffic accidents	12.6	Chest pain	17.3	Chest pain	10.2	Traffic accidents	10.0
		Traffic accidents	13.4	Acute abdomen	8.2	Acute abdomen	5.3	Cardiac arrest	8.9	Falls	9.1
		Fever	8.3	Anxiety	6.5	Traffic accidents	4.3	Falls	5.1	Acute abdomen	6.2
	All	Falls	15.0	Birth	32.1	Chest pain	12.6	Chest pain	11.6	Birth	19.3
		Traffic accidents	10.8	Acute abdomen	7.1	Acute abdomen	6.3	Cardiac arrest	7.7	Falls	6.3
		Fever	7.9	Anxiety	6.6	Anxiety	6.2	Acute abdomen	5.1	Acute abdomen	6.3

Table 4. Types of transfer hospitals for Turkish citizens and Syrians

		2017	2018	2019	2020	Total
Turkish Citizens	Training and research hospitals, n (%)	71,828 (58.9)	74,625 (57.8)	78,687 (58.3)	88,259 (60.7)	241,690 (59.0)
	Secondary care hospitals, n (%)	28,731 (23.6)	29,504 (22.8)	30,780 (22.8)	36,244 (24.9)	96,596 (23.6)
	University hospitals, n (%)	12,174 (10.0)	13,868 (10.7)	14,920 (11.0)	11,986 (8.2)	40,802 (10.0)
	Private hospitals, n (%)	9,131 (7.5)	11,202 (8.7)	10,641 (7.9)	8,954 (6.2)	30,815 (7.5)
	Total, n (%)	**121,864 (100.0)**	**129,199 (100.0)**	**135,028 (100.0)**	**145,443 (100.0)**	**409,903 (100.0)**
Syrians	Training and research hospitals, n (%)	4,146 (80.9)	4,017 (79.4)	4,079 (79.5)	4,214 (79.1)	16,456 (79.7)
	Secondary care hospitals, n (%)	921 (18.0)	978 (19.3)	984 (19.2)	1.050 (19.7)	3.933 (19.0)
	University hospitals, n (%)	46 (0.9)	38 (0.8)	53 (1.0)	53 (1.0)	190 (0.9)
	Private hospitals, n (%)	14 (0.3)	24 (0.5)	18 (0.4)	13 (0.2)	69 (0.3)
	Total, n (%)	**5,127 (100.0)**	**5,057 (100.0)**	**5,134 (100.0)**	**5,330 (100.0)**	**20,648 (100.0)**

Table 5. Distribution of EMS cases of Syrians under temporary protection in Ankara by districts and years

	Population (2020)	2017	2018	2019	2020	Total
Akyurt, n (%)	37,456 (0.7)	45 (0.7)	61 (1.0)	86 (1.4)	75 (1.2)	267 (1.1)
Altındağ, n (%)	396,165 (7.0)	1,704 (28.2)	1,738 (29.3)	1,993 (32.4)	1,715 (28.0)	7,150 (29.5)
Ayaş, n (%)	13,686 (0.2)	28 (0.5)	32 (0.5)	38 (0.6)	19 (0.3)	117 (0.5)
Bala, n (%)	25,780 (0.5)	8 (0.1)	6 (0.1)	5 (0.1)	5 (0.1)	24 (0.1)
Beypazarı, n (%)	48,732 (0.9)	138 (2.3)	167 (2.8)	166 (2.7)	163 (2.7)	634 (2.6)
Çamlıdere, n (%)	888 (0.2)	5 (0.1)	9 (0.2)	10 (0.2)	4 (0.1)	28 (0.1)
Çankaya, n (%)	925,828 (16.3)	363 (6.0)	303 (5.1)	390 (6.3)	539 (8.8)	1.595 (6.6)
Çubuk, n (%)	91,142 (1.6)	156 (2.6)	155 (2.6)	189 (3.1)	165 (2.7)	665 (2.7)
Elmadağ, n (%)	45,122 (0.8)	40 (0.7)	18 (0.3)	14 (0.2)	27 (0.4)	99 (0.4)
Etimesgut, n (%)	595,305 (10.5)	111 (1.8)	132 (2.2)	145 (2.4)	131 (2.1)	519 (2.1)
Evren, n (%)	3,045 (0.1)	5 (0.1)	5 (0.1)	1 (0.0)	0 (0.0)	11 (0.0)
Gölbaşı, n (%)	140,649 (2.5)	77 (1.3)	48 (0.8)	34 (0.6)	69 (1.1)	228 (0.9)
Güdül, n (%)	8,438 (0.1)	2 (0.0)	1 (0.0)	3 (0.0)	0 (0.0)	6 (0.0)
Haymana, n (%)	28,922 (0.5)	46 (0.8)	61 (1.0)	62 (1.0)	72 (1.2)	241 (1.0)
Kalecik, n (%)	56,736 (1.0)	22 (0.4)	23 (0.4)	14 (0.2)	15 (0.2)	74 (0.3)
Kahramankazan, n (%)	12,941 (0.2)	81 (1.3)	109 (1.8)	104 (1.7)	100 (1.6)	394 (1.6)
Keçiören, n (%)	938,568 (16.6)	688 (11.4)	680 (11.5)	695 (11.3)	723 (11.8)	2,786 (11.5)
Kızılcahamam, n (%)	27,507 (0.5)	17 (0.3)	32 (0.5)	35 (0.6)	23 (0.4)	107 (0.4)
Mamak, n (%)	669,465 (11.8)	1,117 (18.5)	978 (16.5)	764 (12.4)	907 (14.8)	3,766 (15.5)
Nallıhan, n (%)	27,434 (0.5)	9 (0.1)	6 (0.1)	8 (0.1)	2 (0.0)	25 (0.1)
Polatlı, n (%)	126,623 (2.2)	515 (8.5)	580 (9.8)	580 (9.4)	559 (9.1)	2,234 (9.2)
Pursaklar, n (%)	157,082 (2.8)	161 (2.7)	123 (2.1)	160 (2.6)	93 (1.5)	537 (2.2)
Sincan, n (%)	549,108 (9.7)	150 (2.5)	195 (3.3)	197 (3.2)	173 (2.8)	715 (2.9)
Şereflikoçhisar, n (%)	33,310 (0.6)	80 (1.3)	67 (1.1)	55 (0.9)	50 (0.8)	252 (1.0)
Yenimahalle, n (%)	695,395 (12.3)	477 (7.9)	408 (6.9)	412 (6.7)	495 (8.1)	1,792 (7.4)
Total	**5,663,322 (100.0)**	**6,045 (100.0)**	**5,937 (100.0)**	**6,160 (100.0)**	**6,124 (100.0)**	**24,266 (100.0)**

EMS: Emergency medical services

Karakuş et al. (6) found that 88.8% of Syrian patients who applied for emergency department in a Turkish city closer to the Syrian border were men. In our study, unlike the findings in the literature, most of the patients were women. We suggest that the reason why the number of male patients in this study was higher than ours was that this study was conducted in a war zone and that those affected in the war were mostly men. In another study evaluating the EMS use of Syrians, 55.2% of Syrian patients were women (7). The findings of this study are similar to ours. We suggest that this is because it was conducted in a city like ours, far from the war zone of the Syrian border. Syrian children aged 0-18 years and Syrian women constitute 70.5% of all Syrian migrants (9). Because these Syrian immigrants live in a foreign country and culture, they have difficulty accessing healthcare services of hospitals. Therefore, they frequently use the ambulance service even in non-emergency events to easily reach the health services of the hospitals by ambulance transport.

In a study on Syrians in Turkey, it was found that they mostly presented emergency departments due to soft tissue disorders (10). In the same study, labor and pregnancy emergency events were not among the most common reasons for the presentation (10). In that study, by Kaya et al. (10), the fact that most patients (58.2%) who applied to the emergency department were men may have led to that result. In a study by Baykan and Aslaner (11) it was found that Syrian patients applied to gynecology and obstetrics clinics three times more often than Turkish citizens. We found in our study that the most common reason for ambulance calls was labor and pregnancy emergencies. In our study, the fact that most patients were female, their mean age was lower contributed to labor and pregnancy emergency disorders being the most common reason for them to call on EMS.

In a study by Vural et al. (12), Syrian female migrants conceived at earlier ages, their antenatal care was insufficient, and they were at risk of adverse pregnancy outcomes. We found that, in our study, the most common reason for assigning ambulances to early-aged patients was labor and pregnancy emergencies. The reason why ambulances were most frequently assigned to Syrian patients due to labor is that most of the Syrian patients in our study, similar to the literature, were women of childbearing age.

In a study examining EMS data from the United States, it was found that the most common reason for ambulance use among young patients was trauma, while it was cardiac issues among others (13). In our study, we found that the reasons for assigning ambulances to patients were trauma in young patients and cardiac causes in other than young patients, in line with the literature.

In a study by Altıner and Yeşil (8) evaluating the use of EMS among Syrian patients, most of the patients (69.4%) were transferred to training and research hospitals. In the same study, it was found that only 3% of patients were transferred to university and private hospitals (8). In our study, we found that the hospitals where patients were transferred most frequently were training and research hospitals, in line with the literature. We think that most patients are transferred to the hospitals owned by the MoH because Syrian immigrants under temporary protection in Turkey benefit from these hospitals free of charge in accordance with the health policies in the country.

In another study conducted in Turkey, it was found that emergency calls of Syrian patients were most frequently from the districts of the city center (8). Similarly, in our study, emergency calls of Syrian patients were most frequently from the districts of the city center (76.4%). The 5 districts of the Ankara EMS with the highest number of Syrian patients were Altındağ, Mamak, Keçiören, Polatlı, and Yenimahalle. Of these districts, only Polatlı is not in the city center.

The most important limitation of our study was that markers that would illustrate the disease severity, such as vital signs and triage codes, were not evaluated because they were not available in the ASOS database. If these markers could be obtained, the severity of the patients and unnecessary ambulance calls could be evaluated. Additionally, since we could not reach more details about the diagnoses such as falls and traffic accidents, we could not analyze them in detail. We suggest that future studies can evaluate the severity of the disease and detailed diagnosis of Syrian patients by analyzing these issues as well.

Conclusion

Due to the migration from Syria to Turkey because of the civil war in Syria, Turkish EMS teams began treating Syrian patients, especially in certain regions. Most of the Syrian patients treated by the ambulance teams consisted of women and young patients. The most common reason for the ambulance call of the Syrian patients was labor and pregnancy emergencies, and the most common diagnosis recorded by the teams after the EMS intervention was labor and pregnancy emergencies. Turkish patients most frequently called for an ambulance due to chest pain. Additionally, there was a statistically significant difference between Turkish and Syrian patients in terms of reasons for calls, and diagnoses.

Ethics

Ethics Committee Approval: Ethics approval of the study was obtained from the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Oncology Health Application and Research Center Non-Invasive Ethics Committee (ref. no.: 2020-92; date: October 06, 2021).

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Authorship Contributions

Concept: B.B., Design: B.B., Data Collection or Processing: E.U., Analysis or Interpretation: İ.Ş., E.U., Literature Search: İ.Ş., Writing: B.B.

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A case report on bullous cellulitis due to *Roseomonas gilardii* infection

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Keywords: Bullous cellulitis, *Roseomonas gilardii*, skin lesions, bacteremia

ABSTRACT

Bullous cellulitis is most often caused by beta-hemolytic streptococci and rarely by other bacteria such as *Roseomonas gilardii*. We described a case of a 75-year-old female who acquired bullous cellulitis secondary to *R. gilardii* bacteremia. She presented with multiple, raised skin lesions all over her body. She was afebrile. Her physical examination revealed leucocytosis predominant granulocytes count. She also had anemia (9.4 g/dL) and raised C-reactive protein. During admission, she was treated with intravenous ampicillin/sulbactam and subsequently changed to oral ciprofloxacin following discharge. She fully recovered in two weeks.

Introduction

Bullous cellulitis is initially characterized by erythema and rapid development of bullae, which can become hemorrhagic and cause skin necrosis (1). It is a soft tissue infection most often caused by beta-hemolytic streptococci (2). *Roseomonas gilardii,* a Gram-negative pink-pigmented coccobacillus belonging to species of genus *Roseomonas* is associated with low human pathogenicity (3). Thus, the clinical experience with *Roseomonas* infection, particularly *R. gilardii,* is relatively limited (4). Only a few case reports and case series have been published on this infection. Moreover, most of them were from western countries, dating back to the 1990s and early 2000s (3,5-7). We here described a patient who developed bullous cellulitis linked to *R. gilardii* bacteremia. Written informed consent was obtained from the patient to publish this case report anonymously.

Case Presentation

A 75-year-old Malay female presented with nonitchy, multiple, raised skin lesions all over her body for one week. She did not remember being bitten before the onset of the lesions. Her medical history was positive for hypertension and ischemic heart disease. She reported a right, below-knee amputation ten years ago due to necrotizing fasciitis. Her medication list included antihypertensives and cardiovascular agents but no antibiotics on admission.

The patient was conscious and afebrile on physical examination. There were multiple, raised skin lesions involving

bilateral lower land upper limbs and the back of her torso. One large hemorrhagic blister was noticed over the left anterior knee (Figures 1, 2). The next day, she complained of increased swelling in the right leg with the blister. Extensive erythema was observed on her leg.

Blood tests showed leucocytosis (17.2x109/L) with a predominant granulocyte count (78%). She also had anemia (9.4 g/dL) and elevated C-reactive protein (>200 mg/L). On admission blood culture was positive for *R. gilardii,* while swab culture from the skin lesion was negative. Her renal profile and liver function test came back as unremarkable.

She was diagnosed with bullous cellulitis due to *R. gilardii* bacteremia. Treatment with intravenous ampicillin/sulbactam was started and the clinical improvement was obtained by the sixth day. The treatment was subsequently switched to oral ciprofloxacin after antibiotic sensitivity testing. The patient was discharged home after seven days of hospitalization. After two weeks, she was fully recovered and her laboratory tests returned to normal during the follow-up.

Discussion

Roseomonas species are found in the environment, including soil, water, and air. However, the mechanism of infection and the clinical significance is not well understood (8). They are known opportunistic, whereby only 60% of isolates cause significant infection in humans (4). The infection can occur in immunocompromised states, such as acquired immunodeficiency syndrome, chronic renal disease on dialysis, diabetes mellitus, or malignancy (5,9). Comorbidities of hypertension and ischemic heart disease might have made vulnerable our geriatric patient to *R. gilardii* infection, similar to the case reported by Shokar et al. (3). Furthermore, necrotizing fasciitis history may also be associated with the increased risk of acquiring such infections.

Published cases of *R. gilardii* infection in the literature suggest episodic fever as the initial symptom (3,5). Interestingly, our patient remained afebrile throughout the course of the illness. Although rare, Dé et al. (5) reported one case of multiple episodes of *R. gilardii* bacteremia with no documented fever at any time. Additionally, Lewis et al. (7) noted that two of their seven patients did not experience fever. However, we were unable to compare the findings of the blood tests since there were no details of the whole blood count in previous publications.

Roseomonas spp. are slow-growing bacteria, which often takes up to 5 days for any growth in the culture. As in our patient, the organism is isolated from the blood. Wounds are rare sites of isolation apart from the respiratory tract and peritoneum (3). The slow growth of the organism could explain why antibiotic sensitivity testing was unavailable during the hospitalization of our patient.

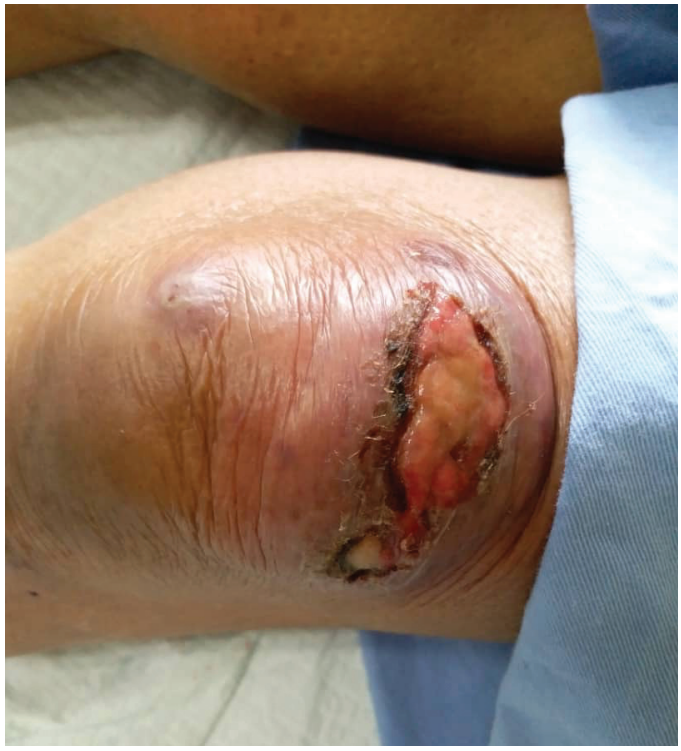

Figure 1. Haemorrhagic blister over left anterior knee

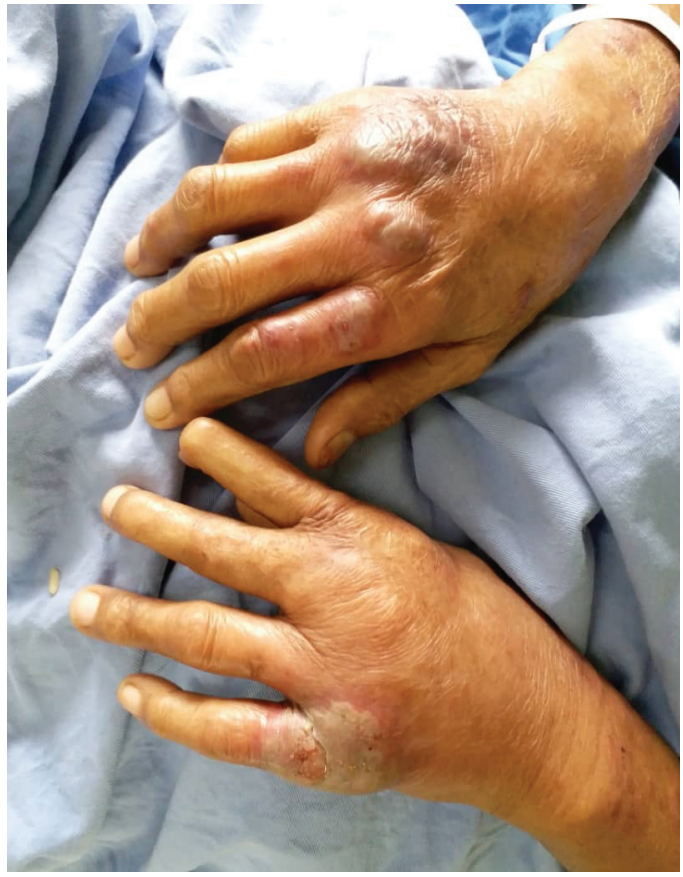

Figure 2. Multiple raised skin lesions over hands

Roseomonas spp. are susceptible to amikacin, followed by imipenem and ciprofloxacin, which explain the recovery of our patient (5,9). However, these organisms are resistant to several antibiotic classes, particularly beta-lactam antibiotics, extended-spectrum cephalosporins, and colistin (10). While waiting for the blood culture result in our patient, our patient was treated empirically with intravenous ampicillin/sulbactam. The isolate was susceptible to ciprofloxacin. Although treatment with intravenous ampicillin/sulbactam was found successful previously (7), later studies showed that *Roseomonas* spp. were probably resistant to this option (4,11). Nonetheless, there were reported cases of *Roseomonas* spp. infection in the pediatric population, which recovered following treatment with ampicillin/sulbactam (12).

Conclusion

The diagnostic differential of bullous cellulitis may be challenging. Apart from the time course, past drug exposure, and systemic features, blood culture is indispensable to delineate the cause. Although uncommon, *R. gilardii* infection should be remembered in patients with underlying debility. To the best of our knowledge, the current patient represents the first case of bullous cellulitis due to *R. gilardii* in Asia. Empirical therapy during hospitalization with intravenous ampicillin/sulbactam, followed by oral ciprofloxacin resulted in the resolution of the bullous cellulitis. Relevant phenotype and genotype should be explored in future studies to further characterize the *Roseomonas* reservoir, as the infection could be due to the patient's skin microbiota.

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Ethics

Informed Consent: A written informed consent was obtained from the patient to publish this case report anonymously.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: W.N.A.Ar-M.W.J., Concept: W.N.A.Ar-M.W.J., Design: W.N.A.Ar-M.W.J., N.L.A., Data Collection or Processing: W.N.A.Ar-M.W.J., Analysis or Interpretation: W.N.A.Ar-M.W.J., N.L.A., Literature Search: N.L.A., Writing: N.L.A.

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Minimally invasive management of white spot lesion using resin infiltration technique: A case report

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ABSTRACT

The resin infiltration technique is a non-invasive conservative method to manage initial carious lesions that appear as white spots on the enamel surface. The penetration of low viscosity resin into the enamel diminishes the white spot lesion immediately. The resin infiltration technique can be considered an alternative to micro-abrasion, macro-abrasion, and restorative treatment to treat the white spot lesions. This case report describes a technique used to arrest and mask the white spot lesions.

Introduction

Dental caries is considered one of the most prevalent chronic diseases worldwide (1). The first sign of dental caries is usually a white spot on the enamel surface when the tooth is dry. These post-eruptive white spots occur due to the demineralization of the enamel. Subsurface demineralization occurs beneath the intact enamel surface, creating an illusion of an opaque white spot. The appearance of the milky white lesion on the enamel surface is associated with the differences in the refraction of light on the lesion compared to sound enamel (2). Etiological factors for the white spots include early caries because of plaque accumulation around orthodontic brackets or poor oral hygiene, fluorosis, medication, molar incisal hypo-mineralization, and traumatic hypo-mineralization (3). These lesions can be detected using fiber-optic transillumination and dyes such as rhodamine and fluorescein (4).

In the oral cavity, the cycle of demineralization and remineralization of the enamel occurs. The demineralization process occurs when the pH falls below 5.5 (critical pH) and leads to the formation of a white spot. The remineralization process can halt the progression of these white spot lesions. Remineralization depends on factors such as pH and mineral bioavailability. Several remineralizing agents have been used to treat the white spot lesions. Casein phosphopeptide-amorphous calcium phosphate, bioglass, xylitol, nanohydroxyapatite, sodium tri-metaphosphate, dicalcium phosphate dehydrate, and argon laser are widely used for the remineralization of such lesions. Ozone can also be used for remineralizing white

spot lesions (5,6). However, a new concept of resin infiltration technique has also been introduced to eliminate the white spot lesions to enhance aesthetics.

This case report explains the ultraconservative approach of treating white spots using resin material-ICON (Table 1). The technique relies on the infiltration concept and helps treat white spot lesions on proximal regions and smooth surfaces.

Case Presentation

A 33-year old female patient reported to the Department of Conservative Dentistry and Endodontics complaining of a white spot on the upper front tooth region for two months. She had undergone oral prophylaxis previously. The intraoral examination revealed a white spot lesion on the maxillary right canine (Figure 1a). The patient was informed about various treatment options, and the most conservative approach, resin infiltration technique, was chosen.

After obtaining the informed consent from the patient, oral prophylaxis was performed, followed by polishing using rubber cups (Enhance Finishing System, Dentsply Sirona, North Carolina) and prophylaxis paste (Prisma GlossTM, Dentsply Sirona, North Carolina). Isolation was achieved using a rubber dam (Dental Dam, Coltene, USA) (Figure 1b).

Icon-Etch HCl 15% (Icon, Dental Milestones Guaranteed) was placed on the white spot lesion using an applicator tip for 2 min. The tooth surface was rinsed for 30 seconds to remove the acid, followed by drying with oil- and water-free air. The lesion was desiccated using Icon-dry (99% ethanol) for 30 seconds, which helped remove water from the pores of the lesion. On visual examination, the white spot was still visible, hence, Icon-Etch and Icon-Dry were reapplied. Whitish opaque lesion diminished significantly after the reapplication, following which Icon-resin was applied on the lesion for three minutes. The excess resin was removed from the facial surface using an applicator tip followed by interdental flossing (7,8). It was then light-cured (3MTM ESPETM Dental: EiparTM 2500 Curing Light, Australia) for 40 seconds. Icon resin was reapplied on the surface for one minute. Excess material was removed and light-cured for 40 seconds. Polishing was carried out using rubber cups and polishing paste (Prisma GlossTM, Dentsply Sirona, North Carolina). The surface of the lesion was then covered with a layer of nanohybrid composite (Filtek Z 350, 3M ESPE, USA) and light-cured for 20 seconds. Polishing was carried out using Sof-Lex polishing discs (3M ESPE, USA) (Figure 1c).

Discussion

White spots occur due to subsurface demineralization of enamel beneath the hyper-mineralized superficial enamel surface (9). Because of differences in refractive indices of enamel, water, and air, white spot lesions appear more prominent when the tooth is dried. The refractive index of sound enamel is 1.62. When enamel is demineralized, it becomes more porous. When the tooth is desiccated, water from these porosities is replaced by air (refractive index 1.0) and becomes more opaque compared to the sound enamel. These white spots become less visible when these micro-porosities get filled with water (refractive index: 1.33). However, when these micro-porosities get filled with resin infiltrant, their refractive index becomes 1.52. Hence, the difference between the refractive indices of infiltrated lesion and enamel becomes negligible, and the lesions appear similar to the surrounding sound enamel (2).

Infiltration with resin helps mask the spot, even in the deeper regions of the lesion. The resin infiltration technique diminishes the white spots immediately compared to remineralizing agents. This technique is a more conservative approach, as it is less invasive than micro-abrasion, macro-abrasion, or restorations (9). Instead of removing the lesion, this technique helps to arrest incipient lesions by blocking the diffusion of acid into the enamel. Enamel also gets mechanically strengthened with the help of this resin infiltration.

Etching helps to erode the superficial hyper mineralized enamel layer and expose the body of the lesion. The hyper-mineralized enamel on the surface is removed by the etchant which helps the resin infiltrate to the ceiling of the lesion. According to Meyer-Lueckel et al. (10,11), 15% HCl is considered suitable for removing the hyper-mineralized surface layer (approximately

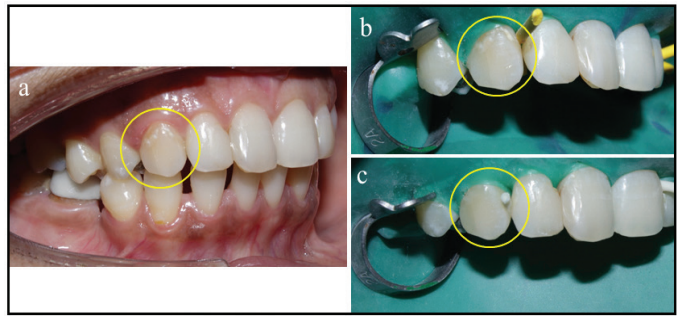

Figure 1. a) Initial situation. b) Preoperative picture (after rubber dam placement), c) Postoperative picture

Table 1. Composition of resin infiltration kit (Icon)

Commercial name (manufacturer)	Composition	Quantity
Icon-etch (dental milestones guaranteed)	15% hydrochloric acid, water, pyrogenic silica, surfactant, pigments	1 syringe (0.45 mL)
Icon-dry (dental milestones guaranteed)	99% ethanol	1 syringe (0.45 mL)
Icon-infiltrant (dental milestones guaranteed)	TEGDMA-based resin, initiators and stabilizers	1 syringe (0.45 mL)

TEGDMA: Tetraethylene glycol dimethacrylate

40 µm). Water present in the lesion's porosities is removed with the help of 99% ethanol, which permits the infiltrant to penetrate the pores driven by capillary forces (11).

Low viscosity, high surface tension, and low-contact angle enable the Icon Infiltrant to penetrate easily into the enamel (12). Compared with the other infiltrants, the Triethylene-glycol-dimethacrylate-resin infiltrant has shown deeper penetration. After applying for three minutes, tetraethylene glycol dimethacrylate-based infiltrant has shown to penetrate 414 microns into non-cavitated caries lesions. Resin is applied twice as there is a chance of shrinkage of the material after the first application, leading to the formation of spaces.The second application of resin helps to completely occlude these spaces (13). A thin layer of nanohybrid composite must be applied over the infiltrated tooth surface as the resin has a high staining potential (14,15). The resin infiltration technique is especially advantageous in the management of aesthetics of mild white spot lesions present post-orthodontic treatment. It can be used as an adjunctive therapeutic measure in the management of early caries lesions.

Conclusion

Resin infiltration is a micro-invasive approach for aesthetic treatment of white spots since no healthy tooth structure is removed. The enamel's resistance is increased by hampering the demineralization process by sealing the micropores, and it is also a suitable method to arrest further caries. This technique is easy to perform and painless.

Ethics

Informed Consent: Consent form was filled out by all participants.

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Authorship Contributions

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Ultrasound-guided hydrodissection to entrapped median nerve after electric shock: A case report

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ABSTRACT

A complication of electrical burns that increase the dysfunction is the peripheral nerve compression syndrome. Here, we presented a seventeen-year-old male patient who had an above-elbow amputation on the left and developed burns and severe median nerve entrapment in the right upper extremity after an electrical shock and underwent ultrasound-guided hydrodissection treatment. After the treatment, the edema detected ultrasonographically in the median nerve regressed, pain decreased and hand functions improved in the right upper extremity.

Introduction

Peripheral nerve compression and neuropathies are among the neurological consequences of electrical burns. The heat generated by the electrical current can cause direct peripheral nerve injury and neuropathy caused by edema and scar formation in tissues surrounding nerves. Although peripheral nerve compression due to scar formation following electrical burn exists in the literature, it has also been reported to occur through perineural fibrosis and nerve necrosis (1-3). The most common region of peripheral nerve involvement is the upper extremities, and the median and ulnar nerves are most commonly injured (2). Various conservative or surgical treatment methods are used to eliminate the pressure on the peripheral nerve. However, as these methods may be insufficient, additional interventions are necessary to alleviate peripheral nerve compression (2,4).

The ultrasound-guided hydrodissection technique of peripheral nerves has recently attracted the attention of physicians, especially in the fields of pain and musculoskeletal

medicine, but there is no information about its use in nerve entrapment complications due to electrical burns. The hydrodissection method eliminates the pressure on the nerve by injecting a non-irritating solution between the nerve and the surrounding tissues (5).

In this case report, we presented the treatment results of a 17-year-old patient who developed severe right median nerve entrapment due to electrical shock burn and underwent ultrasound-guided hydrodissection of the median nerve.

Case Presentation

A 17-year-old male patient was admitted to our hospital with complaints of pain in his right arm, weakness in his right hand, and limitation in range of motion (ROM) in his right wrist and fingers. The patient had undergone amputation above the left elbow eight months ago following electrical shock. The wound was repaired with a flap on the right axilla and with a graft placed on the anterior aspect of the right wrist and palm. Despite a 2-month physical therapy program including joint ROM, stretching, and strengthening exercises, no significant improvement was noted in his complaints.

In the physical examination of the patient after the first physical therapy program, the pain in the right arm was 8 according to the visual analog scale (VAS, 1-10), the wrist passive extension was 50°, and the proximal interphalangeal (PIP) joint passive extension of 3rd and 4th fingers was -30. There was no limitation in other passive ROM measurements of the extremity. Extensor and flexor muscle strengths of the wrist were 3/5, and flexor, extensor, abductor, and adductor muscle strengths of the fingers were 2/5. Complete loss of sensation was noted in the palm and fingers. The handgrip strength was 12 kg with a dynamometer, and the key pinch strength was 0.6 kg with a pinchmeter. Electromyographic (EMG) examination performed on admission showed that the right median nerve was denervated after giving a branch to the pronator teres muscle and right ulnar nerve after giving a branch to the flexor carpi ulnaris muscle. There were signs of moderate partial axonal degeneration in the right radial nerve. On ultrasonographic imaging, the median nerve was edematous in the proximal third of the forearm (cross-sectional area 0.13 cm²).

Hydrodissection procedure was performed using 5-12 MHz linear array transducer ultrasound (Logiq-e portable; GE Healthcare, China) in the proximal third of the forearm. After appropriate skin sterilization with chlorhexidine, the injection was performed with 1 mL of 2% lidocaine and 2 mL saline using a suitable needle tip (Figure 1). The procedure was applied 2 times with 1-month intervals. During this interval, the patient was allowed to continue daily therapeutic exercises.

After the treatment, the patient's pain regressed to VAS 2. The wrist extension improved up to 60°, and the 3rd and 4th PIP joint extension up to -10°. The extensor and flexor muscle strength increased to 4/5 in the wrist, and 4/5 in the fingers. The abductor and adductor muscle strengths of the fingers increased to 2/5. The handgrip strength rose to 17.3 kg and key pinch strength to 1.3 kg. Although EMG showed some improvements, some pathological findings consistent with the total axonal degeneration of median nerve distal to the lesion, and moderate to severe partial axonal degeneration of ulnar and radial nerves persisted. Post-treatment ultrasonographic imaging showed regression of edema in the median nerve (cross-sectional area 0.10 cm²).

Figure 2 displays the view of the right hand after treatment.

Discussion

Although there is no adequate treatment for median nerve entrapment, different treatments have been applied depending on the severity of the compression. It has been reported that conservative treatment is often beneficial in mild and moderate

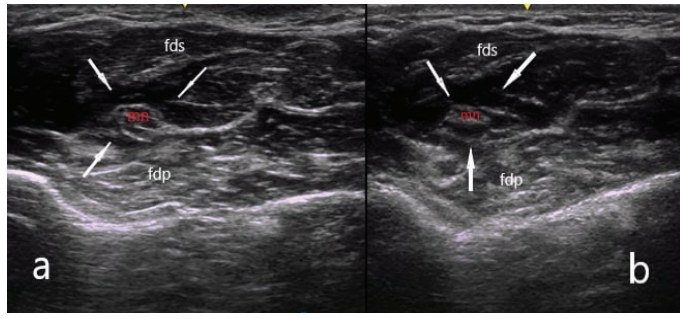

Figure 1. Axial ultrasound image of the median nerve during hydrodissection in proximal third of the forearm at first application (a) and second application (b). The space created by hydrodissection around the nerve (anechoic area, arrows) is seen. The change in the median nerve cross-sectional area in the month between the two applications is remarkable

mn: Median nerve, fds: Flexor digitorum superficialis, fdp: Flexor digitorum profundus

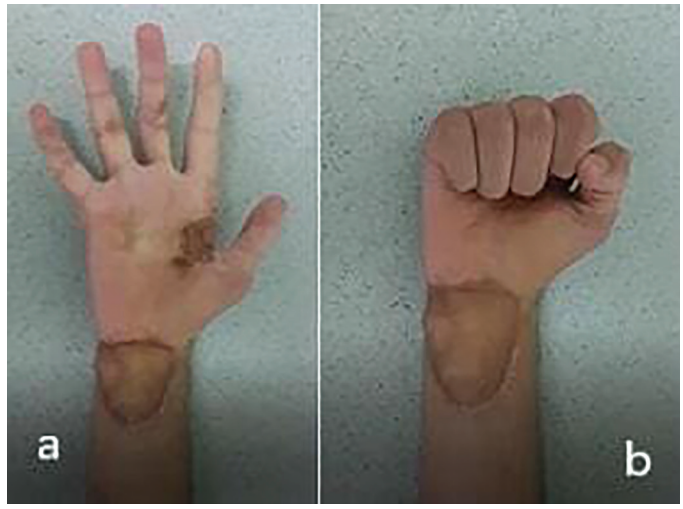

Figure 2. View of the right hand in active extension (a) and flexion (b) after treatment

cases, but the effect may be short and limited. Surgical treatment is used in cases with severe and insufficient response to conservative treatment. However, a significant number of patients experienced postoperative complications or recurrence (4,6).

Hydrodissection is a minimally invasive method used to separate normal tissues and fibrotic adhesions with a solution such as saline, steroid, local anesthetic, dextrose, or platelet-rich plasma (7-11). Several studies have reported that hydrodissection was effective in the treatment of peripheral nerve compressions such as piriformis syndrome (12) and carpal tunnel syndrome (8). Although it has been reported in the literature that dextrose may be preferred due to its analgesic effect, the ability used for multiple nerves, and higher doses, we used a more conventional fluid (i.e., normal saline) as an injection into a single nerve (7).

In the current case, although the ulnar and radial nerves were involved in clinical and electrophysiological evaluations, hydrodissection was applied only to the median nerve. Hydrodissection of the ulnar nerve has previously been performed only in a cadaver study and a few case reports (13,14). It was applied to the radial nerve only in one study where two cases were presented (15). We chose the median nerve as there was more scientific evidence for hydrodissection of this nerve (5,7,8). However, data on the risks and benefits of this new treatment method are limited (5). In this case report, we observed that ultrasound-guided hydrodissection to severely entrapped median nerve improved pain and functions without any complications in a patient who had multiple operations due to electrical burns.

Conclusion

Ultrasound-guided hydrodissection was found effective and safe in reducing pain and improving hand dysfunctions due to median nerve compression. Hydrodissection can be considered as an alternative treatment method before surgery.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: E.Y., E.G., Concept: E.Y., E.G., N.K., Design: E.G., N.K., Data Collection, or Processing: N.K., S.G.A., Analysis, or Interpretation: N.K., Literature Search: N.K., S.G.A., Writing: N.K.

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Coronavirus disease-2019: Infection control and prevention measures in dental radiology

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Dear Editor,

A public health emergency of international concern (PHEIC) was declared over Coronavirus disease-2019 (COVID-19), which is the sixth time World Health Organization (WHO) has declared a PHEIC since the International Health Regulations took effect in 2005 (1). Hegde and Ajila (2), described the situation of Indian dentists during the pandemic, however, adding a note on infection control protocol is of highest importance. Dentists were unaware of which guidelines to follow. The dental clinics were advised to remain closed in the containment zone and to continue with teledentistry. A survey found that only 40% of radiology department professional staff have enough knowledge of infection control practice (3). The Centers for Disease Control and Prevention have recommended that the dental healthcare personnel (DHCP) should be provided with education and training to prevent transmission of infectious agents, including refresher training. The main goal is safe care for the community through educating and training the DHCP to properly use the protective equipment before approaching a patient. In the absence of specific drugs, the protective measures in the dental radiology departments primarily target controlling the transmission routes such as droplets, contact surfaces, and aerosols (4).

Healthcare workers, including medical and dental radiologists, have been the frontline in the COVID-19 pandemic, hence, reinforcement of infection control protocols becomes crucial. The oral radiologists and technicians must use the personnel protective equipment, including eye protection, a filtering facepiece respirator (N95), a surgical cap, gloves, a fluid-resistant gown, and shoe cover (5).

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) virus has been identified in both blood and saliva samples of COVID-19 patients, which necessitates reviewing our current practice to prevent infections. Hand hygiene is the most critical measure to reduce the risk of transmitting microorganisms between individuals. SARS-CoV-2 can persist on surfaces from a few hours or to several days, depending on the type of surface, temperature, or humidity of the environment. Thus, the need for hand hygiene and thorough disinfection of all surfaces within the radiology department is of high priority (6).

The use of autoclaved or disposable film/receptor holders is recommended to reduce the clinician's contact with saliva while placing the film/receptor. Switching off the X-ray unit before cleaning and disinfection, remembering to wear protective gloves before touching the surfaces, and cleaning the surface using approved cleaning agents and surface disinfectants are essential. Disinfectants can be used in the form of wipes, and 0.5% hydrogen peroxide wipes can be used like Optim Blue wipes (7). The client green, a boxed wipe is designed for universal cleaning and is a licensed cleaning agent for medical equipment. It contains 2% chlorhexidine and 70% ethanol-based alcohol (8). The use of gloves for touching the radiology unit is also mandatory.

Radiology departments should contact their equipment vendors to find the safest disinfectant for each piece of equipment in use (9). The use of sprays, liquids, or foams directly on any surface of the extraoral unit is not suggested by most equipment providers. The use of clean, damp cloth is preferred by most manufacturers (10). According to Spaulding's Classification of Medical Equipment/Devices, surfaces of a radiology unit need to be either washed with soap and water or decontaminated using low-level or intermediate-level disinfectants, such as iodophor germicidal detergent solution, ethyl alcohol, or isopropyl alcohol (10). Changing the bite stick for each patient or using a disposable protective shield should be preferred. Wiping all the parts after exposure of each patient, by using surface disinfectant approved by the equipment provider should not be avoided. Some parts can be autoclaved at 134 °C (273 °F): A 3-4-minute cycle.

Cone-beam computed tomography (CBCT) units can be disinfected using the above modes of disinfection; however, other parts of CBCT units that are non-critical like a remote switch, control panel, chin rest, handgrips, head stabilizers, patient table, and patient chair should be handled as described above, and disposable bite guides must be used if barrier-protection or sterilization is not possible.

In conclusion, the DHCP must provide the best available standards of safe operating procedures for their patients and themselves.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.N., U.S., Concept: V.N., P.K.R., Design: V.N., R.K., Data Collection or Processing: V.N., U.S., Analysis or Interpretation: R.K., P.K.R., Literature Search: U.S., R.K., Writing: P.K.R., V.N.

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