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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

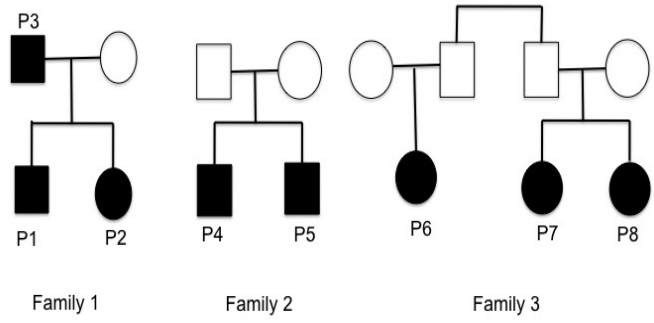

Figure 1. Flow-chart of the study participants

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.

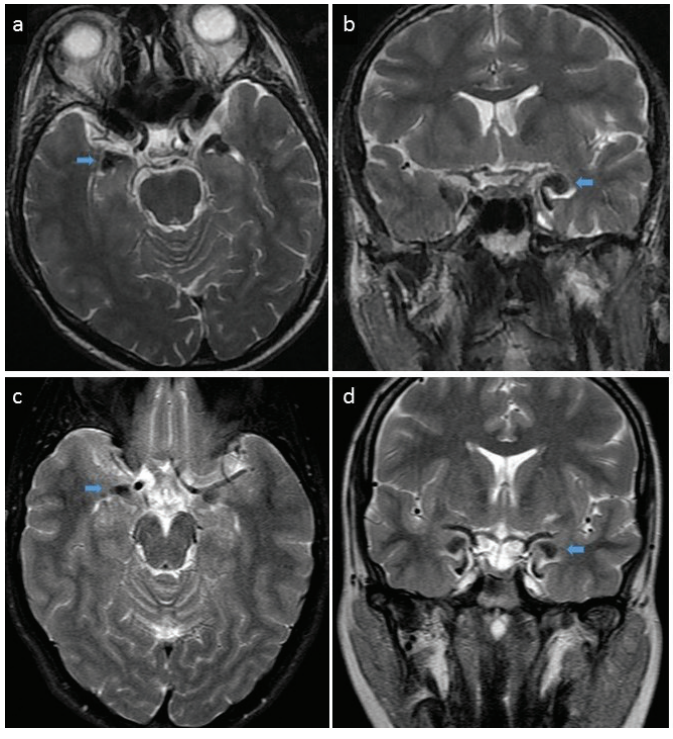

Figure 2. Magnetic resonance imaging images in two patients with lipoid proteinosis. Bilateral symmetric bean shaped (arrows in a and b) and oval (arrows in c and d) calcifications in the uncal part of temporal lobes involving both the hippocampi were seen signal-free in the axial and coronal T2-weighted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