Familial and single cases of restless leg syndrome

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SUMMARY

Heredofamilial cases of restless leg syndrome are presented. In a family a father (50-year-old) and his daughter (19-year-old) were investigated. Moreover, his mother and sister gave the history of restless leg syndrome. The father complained of a disturbing feeling at his legs which urged him unwillingly to move his legs and arms, causing insomnia for 20 years. In order to prevent this impulsive feeling that forced him to move his legs, he wrapped his legs into nylons, towels, hit his legs with his hands, got up and walked around or snack. The patient who coped with these symptoms till late hours of the night could only fall asleep at dawn. He had no complaint during daytime. The sleep EEG investigations demonstrated that the patient had severe sleep disturbance and the sleep switched from second period to first period or from the first period to awakening. His daughter (19 years old) occasionally had a feeling that as if her feet did not belong to her during sleep for 2 years. This urged her to keep her feet in planter flexion. Sometimes she wrapped and squeezed her ankles with a rope, and only through the pain due to this squeezing she could avoid of this feeling. If she still could not get rid of this feeling she lied down on her abdomen and moved her legs up and down. After getting tired, she could go to sleep. Both father and daughter complained insomnia and this was confirmed by sleep EEG investigations. The severity of symptoms varied among the members of the family. In addition to familial cases presented above a single case with restless leg syndrome is presented. A 26-year-old male complained unusual feeling at his right leg, which caused movement or the right leg and hitting of the heel since he was 14. The symptoms not only occurred night, but also during the day. The patient needed to move his legs in order to get read of unpleasant feeling. The etiology, pathophysiology and the treatment of the restless leg syndrome are unknown. None of the treatment modalities used in the father gave satisfactory results.

Key words: Heredofamilial feature, restless leg, sleep disturbance, sleep EEG

Introduction

The syndrome was first investigated by Dr. Ekbom in 1945 (8). Dr. Critchley (5) has reported that Thomas Willis has denoted the syndrome as “the case of the person having restless in the arms and legs interfering sleep in the bed” in second edition of his textbook in 1695 (17). Ekbom (9) reported that the same expressions had taken place in the first edition of that book published in 1685 (17). In 1861, the same syndrome was described as “Anxietas Tibiarum” and classified in a form of hysteria by Wittmaack (18). George Beard examined the issue under the title of neurasthenia and he associated it with the spinal irritation (2). Oppenheim has referred it as a syndrome of hysterical or neurasthenic symptoms in his book (15). Ruwak and Mussio-Fournier called attention to the familial form of the syndrome (13). Complaints of the syndrome are usually paresthesia or pain in the legs. It is not easy to distinguish between the two forms. The form with paresthesia, which is more common can be diagnosed easily. Ekbom had called this form “asthenia crurum paresthetica” (7). Ekbom stated (9) that the most comprehensive review was ever published by Jolivet since 1945 (11). However, it is also important that Askupmark (1) and Nordlander (14) have reported that anemia may cause the restless leg syndrome. Moreover Ask-upmark underlined the causal effects of the venous system enlargement in the epidural space of spinal canal (1). Gorman et al., found anxiety and depression in 10 patients with the restless leg syndrome by using the MMPI test (10). The neurogenic origin of the syndrome has been mentioned by Callaghan (3) and Spillane (16) in patients with uremic syndrome and chronic pulmonary disease, respectively.

In this paper, the clinical signs, EEG in rest and sleep and treatment methods have been examined in the cases of the familial and single restless leg syndrome.
Material and Methods

Cases: Case 1. Ş.Ö. Male, 50-year-old. He was referred by a psychiatrist from Izmir with the following note: “the patient has some involuntary movement in his right side in the night. I think that he has the epilepsy but the other colleagues think that he has conversion. The patient had no relief after the treatment of Faraday’s induction. He had symptoms even in the deep sleep. His mother, sister and daughter have also the same condition. His wife reported that these movements were so severe. They had become miserable from this condition. Could we get the information about the seizure from EEG and sleep EEG? Could you please examine that whether the cause of the condition was psychologic or epileptic?”

Patient history: he complained from a disturbing feeling at his legs which urged him unwillingly to move his legs and arms, causing insomnia for 20 years. After getting tired from these movements he could sleep at the dawn. These movements were described as asynchrony and asymmetric global movements in arms and legs.

The patient described an unpleasant feeling causing compulsion to move his extremities. In order to prevent this impulsive feeling that forced him to move his legs, he wrapped his legs into nylons, towels, hit his legs with his hands, got up and walked around or snack. He had no complaint during daytime. To fall asleep the patient was trying to lie along in various places in the house by watching TV. When he reported that his mother, sister and daughter had the same condition, family history were taken and the pedigree was composed (Figure 1).

Case 2. G.Ö. Female, 19-year-old (Daughter of the patient). She had an occasional feeling that as if her feet did not belong to her during sleep for 2 years. This urged her to keep her feet in planter flexion. Sometimes she wrapped and squeezed her ankles with a rope, and only through the pain due to this squeezing she could avoid of this feeling. If she still could not get rid of this feeling she lied down on her abdomen and moved her legs up and down. After getting tired, she could go to sleep. Occasionally, the condition described by her as “leg numbness” had came after when she thought that it would occur. She said that she was uncomfortable when she was flat on the back. She said that the condition occured one a month and more frequent in summer. If she could prevent the condition, she could fall asleep. She described that the feeling migrated to the other leg. When she could not prevent it in 15-20 minutes, she could sleep only 2 hours for all night. These leg movements came from the inevitable impulse when she was conscious. She could sleep in a various position for example she let her legs hang down. She described that she had a tic of ankle movement. For that reason her boots were worn and twisted (Figure 2).

Case 3. N.S. Female, 47-year-old (Sister of the patient). She had given her history responding to the letter: Occasionally, she had an unpleasant feeling in her legs since she was 24-year-old. She mentioned that this condition occurred when she lost weight or at the warm air. She added that she had a treatment for this condition but she had taken the pills for her sleep disturbances.

Case 4. Female (1900-1956) (Mother of the patient). She had also an unpleasant feeling in her legs and she had sleep disturbances because of it. The patient described that every family member had migrated from one sleep corner to another.

It has been described that a woman from the fourth generation had restless leg in the daytime. Also a man (72-year-old) from the third generation had described that he had an unpleasant feeling in his left leg during falling asleep. However he had also added that this condition had no restriction for him and he had no treatment for this condition.

The single case (26-year-old) had some leg movements such as traction of the toes, contraction of the thigh at night preventing to fall asleep. He felt that he had to lift his leg and beat his foot on the ground. This impulse could not be prevented by the pressure of the other leg. Because of this condition he had sleep disturbance. The condition which occurred every-

Figure 1. The pedigree in a family with the restless leg syndrome. The patient and his sister and daughter had the syndrome as fourth ands fifth generations, respectively. The mentioned family is at the middle of the diagram. The family diagram has been taken from the male of 3rd generation who had the mild syndrome
day increased by stress and fatigue. He mentioned that he needed to move his leg in the daytime and he could not let his leg stable.

In addition, from time to time during the daytime he had some impulse of hitting or punching. He could cope with this feeling by buzzing from the environment. He had hit the trees. But he had never have this feeling during the struggle. For example, he had impulse to hit pointed iron fence.

In addition, the absent seizures, impaired consciousness with the growing and shrinking of the objects were described. He could not move his eyes at that moment. EEG examination revealed the focus of sharp wave on the right.

Methods

1. A. Clinical physical examination, neurological examination and EEG, fasting blood glucose, SGOT, alkaline phosphatase, peripheral blood and urine examination were performed.

B. The patient’s movements were monitored at night.

2. Tests of EEG:

A. Resting EEG: the Grass Model-6 16-channel EEG device was used for resting EEG in the patient, his daughter and in the single case. Resting EEG was recorded with monopolar links by using the reference electrodes placed according to 10-20 system to the vertex and the ears and bipolar links from the electrode to electrode. The eye movement and hyperventilation tests were performed.

B. Sleep EEG: the Grass Model-6 16-channel EEG device was used for sleep EEG. The patient slept in laboratory without electrodes at the first night (first adaptation day), in second night the patient slept in laboratory with electrodes (second adaptation day). Finally, the sleep EEG was recorded at the third night for average 8 hours. EEG was recorded by using vertex as a reference with electrodes placed in other cantuses of both eyes and upper/lower orbit of the left eye for horizontal and vertical eye movements, respectively. Bipolar electromyography (EMG) and electrocardiography (ECG) were recorded from submental and infraclavicular regions, respectively. The amplification was 7 mm=50 mcv and rate was 15 mm/s.

The sleep periods in EEG were classified according to Dement and Kleitman (6); first period (drowsiness) is described the waves with the low voltage and mix frequency (quick and slow); second period is described (mild sleep) with additional k-complex and sleep spindles, third period is described (moderate deep sleep) as <50% of EEG is composed of the waves with high voltage and forth period (deep sleep) is described as >50% of EEG is composed of the waves with high voltage. REM sleep (rapid eye movement sleep, paradoxal sleep (12)) EEG record is similar with the first period and additionally EMG activity disappears and REM appears with single or group bursts.

The sleep EEG records lasting 7-8 hours were examined visually and the percentage of REM and NREM sleep were calculated.

C. EEG technicians examined the extremity movements in the patient and his daughter and tried to clarify the connection between the movements and the sleep period.

3. Electromyographical examination was performed only in the patient. Muscles were examined by concentric needle electrode for spontaneous and maximum contractions and nerve conduction rates were recorded.

4. Treatment: pimozide (Norofren) 1x2 in the first week and 1x3 in the second week, clordiazepoxide 10 mg for 1 week and 25 mg for 1 week, nitrazepam 1/2 and then 1 tablet, phenobarbital 1/2 tablet at the first
week and then 1 tablet, diazepam (Nervium), 5 mg/day at the first week and then 10 mg/day. Clonazepam (Rivotril) 2 mg/day at the first week and then twice a week were administrated. And then hexanicite (peripheral vasodilator 0.20 g) was administrated three times a day for 15 days.

Results

1. A. Clinical, physical and neurological examinations and laboratory results except EEG were normal in the patients. No anemia was found in both patients.

B. The patients were monitored along with 2 adaptation nights and 2 EEG recording until the morning. His daughter were monitored along with one adaptation and one EEG recording nights. The single case was evaluated by the history. Observation results of the patient: “The patient went to bed at 23.30. His wife informed us that he slept. He did not have a sleeping posture. He looked anxious. He was turning from one side to the other rapidly. At the same time he was throwing his extremities out of the bed. He was crying as if he was suffering. At 24.20 he was awaken suddenly and he hit to his extremities by hands. He said that he had to go around. At 1.15 he went to bed again and slept in 10 minutes. He repeated the same movements and additionally he grasped the bedpost with his hand. He was restless and one of his leg was extended. He pressed his feet and hands with the sharp edge of the bed. After 15-20 minutes he awoke and got up suddenly extending his arm and hit proximal part of his arm with other hand.

Observation results of the patient’s daughter at the adaptation night: “The patient slept at 2.00. 2 hours later she turned from one side to the other. At 4.00, she had global contraction and there was no movement at her extremities. At 4.15, fingers of the both hands jerked. At 5.25 she had normal posture. At 5.50 she had jerks at her right leg, she awaken and asked the time and then she fell asleep. At 6.00, she awoke.

2. EEG results:

a. Daytime resting: The resting and activation EEG of the patient ((20.12.1977/1730) and his daughter 1.12.1977/1674 were found normal. The patient had short term drowsiness periods in his EEG.

b. Sleep EEG: the percentage of the periods, REM cycles and number of REM in the sleep EEG of the patient (9.12.1977; 15.12.1977) and her daughter (1.12.1977) are presented in Table I, the number of extremity movements is presented in Tables II and III.

EEG records of the patient showed that he was awake most of the time or at the first period sleep. Also he had passed between the periods for 20-40 s. Bilateral diffuse delta bursts which were synchrony and 4-6 seconds were observed at the time of between the periods in both the patient and his daughter. His daughter had also the same bursts in REM period.

3. EMG. No spontaneous activity was observed in left brachial biceps, left abductor pollicis brevis, left extensor digitorum brevis, left anterior tibial, left and right vastus medialis. The conduction rate, distal motor latency and amplitude and shapes of the evoked muscles responses in the left median and left peroneal nerves were normal.

<table>
<thead>
<tr>
<th>Name (age) and date</th>
<th>Periods of sleep</th>
<th>1</th>
<th>REM</th>
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<tbody>
<tr>
<td>Movement</td>
<td>Awake</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rounding and body movement</td>
<td>41</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Foot movement</td>
<td>7</td>
<td>10</td>
<td>-</td>
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<tr>
<td>Arm movement</td>
<td>9</td>
<td>4</td>
<td>-</td>
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<tr>
<td>Shooting left leg with left arm</td>
<td>1</td>
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<tr>
<td>Shooting left leg with right arm</td>
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*: Numbers indicate the number of movement
Restless leg syndrome is one of the important cause of sleep disturbance. Observations showed that these patients had no healthy sleep. Our case (the father) is an example. They were afraid of sleeping.

There is no continuous effects of the warm or cold. But most of the patients do not like the warm environment. For example, in soldiers who have to go to bed with their clothes, it disturbs. These patients do not want to cover their legs in the bed. Some of them walk on the snow. Others like the warm. They go to bed with their socks or warm their foot. Some of them reported that the restlessness disappeared when they had fever. They prefer to lie on their stomach. It was the case in our female patient.

The psychological factors are important. In some cases, the syndrome appears after the unpleasant daily activities. Ekbom reported that his patients were calm, balanced and they had no mental problems (9). According to him, the signs of the syndrome are misinterpreted as nervousness. The patients do not want to tell their problem because of shyness. But they like to be interested. There is no physical signs in the patients.

The course and severity of the disease vary from mild to severe. In mild cases, the signs of the disease are short term, and they have the nights with normal sleep. In severe cases, the long term leg movements and sleep disturbance are available. As a rule, it is a chronic condition which has intervals between the mild and severe periods. The long term asymptomatic intervals may be observed. In pregnancy, the syndrome may be increased. This syndrome may be observed in all ages. The mild cases are more than the others. The prevalence has been found as 5% in 500 healthy people. There is no gender difference. Moderate cases are less than the mild cases. Ekbom reported that 72 males and 103 females in his 175 severe cases (9).

Jolivet suggested that the diagnosis of the restless leg should be based on the deep feeling between the knee and the ankle during the sitting or lying position (11). According to Gorman, these were the criteria which were observed in rare patients (10). Most of the patients do not report whether the feeling was superficial or deep. They report that they have restless on their thigh. Some of them have the feeling when they are standing. Ekbom (9) and Jolivet (11) suggested that there were asymptomatic “frust” and “parcial” forms which could be detected by the investigation. Jolivet suggested that these forms cause little symptoms such as mild paresthesia and restless in stabile positions (11). With the frust and parcial forms, the prevalence of the restless leg syndrome reaches to 5%.

Goormen et al., reported 27 patients (mean age: 53; 31-73) with restless leg syndrome for 5-20 years (10). In study population, 9 patients had pain and unpleasant feeling in their legs; 5 patients had prickling, tingling and paresthesia, 3 patients had prickling and the others had hitting legs.

The feeling was mentioned as deep and superficial by 8 and 2 patients, respectively. The symptoms were bilateral in all patients but half of the patients had more severe symptoms unilaterally. The localization of the symptoms varied from legs to foot.

4. Treatment. The patients showed no improvement with pimozid treatment (15 days). Moreover his complains increased. He had no sleep. He awaked frequently and developed fear. The patient reported that there was no improvement with librium, magodon and phenobarbital. He reported that he awaked rarely when he took Rivotril 2 mg 1 hour before sleeping. But he told that 4 mg dose caused ataxia. The patient continued Hexanicite 0.20 gr x 3 treatment. However, no expected benefit was observed. The patient preferred to use clordiazepoxide 25 mg once a day.

**Discussion**

Familial and single “restless leg” syndrome in our cases showed similar clinical symptoms to 179 cases reported by Ekbom (8,9) who described the syndrome for the first time in 1945 (8). Ekbom describes the syndrome: unpleasant feeling, such as insect feeling in the legs between knee and ankle, sometimes in
thigh and foot. Usually it occurs unilateral but may also occur bilaterally. The same case can have it in the right and sometimes in the left leg. It occurs in hands and arms rarely. This strange feeling is felt deeply in “muscles or bones”. The patient describes this feeling as a withdrawal or a stress in his feet. The patient needs to move to get rid of it. He mentions this feeling as “young wolves in my legs”, “itching in my legs”. Patients describe it with difficulty, unlike the well-known symptoms. They say that they could sleep when this feeling disappears. Also they describe it as a very bad feeling: “This is the worst simple disease so that I do not want nobody to have it. Acroparesthesia arms may be confused with the same feeling. In the form of the painful syndrome, an annoying pain occurs. There is mild to moderate dull pain. Pain is a simple stubborn pain and rarely severe. The patients with the restless leg syndrome can be divided into two groups: having complains of unpleasant feeling or pain. The first group is more common. Sometimes it may be associated with paresthesia and pain.

Symptom characteristics are the emergence of symptom in the legs at rest, relief with moving and the deterioration at night. In the daytime symptoms disappears completely but it may begin at the long term immobilization and fatigue. This is more uncomfortable in the train trips, conferences, theaters and cinemas. Some patients say that they have never get peace and relax. It forces the patient to move. Duration varies according to the severity of cases, sometimes it takes all night allowing only 1-2 hours sleep.

Following to unpleasant feelings it is not possible to keep the legs immobile. In mild cases, people can sleep. Otherwise, he/she hits, move or massage to the legs. Frequently he/she walks up and acts like a bear in a cage. They get up and eat something. Some people smoke, read, kicking. One of the patients of Ekbom used to do Charleston dance (9).

This situation lasts from a few minutes to the hours and then the patient goes to bed and sleeps. After a while it starts again and the patient gets up. A 70-year-old pastor had symptoms at his hands in addition to the symptoms of restless leg.

The idea of doing something such as foot massage, waving in the air, lying on back with pedaling motion are common in the patients.

It is easy to diagnose if the syndrome is known and the patient describes the symptoms. The following criteria should be considered: an unpleasant feeling which occurs only at the early in the night when the patient gets rest and provokes to move the legs. It is not a skin sensation but it is felt in legs deeply.

In differential diagnosis, the restless leg syndrome is sometimes misinterpreted as Meralgia paresthetica but there is no similarity between them. It has been suggested that the cause of the restless leg was myokemi. It has been associated with the fasciculation of amyotrophic lateral sclerosis but it is more disturbing and it has no association with ALS or acroparesthesia.

The restless leg syndrome may have atypical forms. For example, it may occur completely one-sided and is felt throughout the day, especially in the form of cases with pain.

The etiology is unclear. It is thought to be hereditary. Dominant families are seen (8,13,15). Our familial cases had dominant heredity as it was seen in the examination of the pedigree. The emergence of various degrees of symptoms and the possibility of the disease ignorance might have limited our ability to show the dominant trait in all generations. The mild restless syndrome in a twin has been reported. Their mother also have shown signs of severe syndrome. This syndrome may be seen with poliomyelitis, infection, avitaminosis (the foot burning syndrome in Japanese camps at the World War 2), anemia, diabetes, long-term cold, drugs (Promethazine), abrupt discontinuation of barbiturates and prostatitis. It may also occur in the last half of pregnancy or the last 3 months. As a rule, it disappears after birth. The incidence of the syndrome during pregnancy is 11%. Iron deficiency (<60 mg/100 ml) was found in 24% of the patients. In most cases, symptoms are mild. Three cases of carcinoma with restless leg have been reported (9).

It is unknown how this unpleasant feeling occurs. Some authors suggest that it originates from the spinal cord and others think that the cause is the limb dysfunction.

According to Ask-Upmark, the patient wakes up with pain and pressures at the bottom of the chest in midnight or in the morning (1). The patient has no lung and heart problem. This condition is seen at night and improves after getting up and walking around the room. This situation is similar to restless leg syndrome. In restless leg syndrome the developmental deficit in venous system of epidural space at the level of the Th6 of spinal canal has been considered. At Th6 level, diameter of the spinal cord is narrow. If it is the case, it is easy to understand the relieving effect of lying on the stomach. Positive effects of 10% dextran administration suggest that the etiology of the syndrome is multifactorial.

Wittmaack has defined the syndrome as “anxietas tibiaram” and classified as a common symptom of hysteria in 1861. Cameron has described “leg with-
drawal and limbs jerk” in patients with anxiety during falling asleep (4). According to Ekbom, the pathogenesis of the syndrome is unknown (9). However, he has considered that the syndrome has no psychogenic origin because it occurs in healthy subjects and lasts for years. While Jollvet et al. have suggested that the syndrome occurs in patients with unstable but they have performed no psychological examination (11).

Gorman has demonstrated in his series that the syndrome occurs especially in tense or depressed patients or normal people under the stress (10). MMPI test was applied in 27 patients and 17 patients had depression and anxiety. Patients without any symptoms of depression or anxiety should be examined for the masked depression or organic neurological disease. It is not clear whether the restless leg is an etiological factor or chronic unrest in depressed patients. However it should be considered that emotional factors may lead to restless leg syndrome such as diarrhea or tension headaches. While the parasitic infection or colon spasm may cause diarrhea, or increased intracranial pressure may cause headache, sometimes the restless leg syndrome is caused by peripheral neuropathy or other neurological diseases. Even if there is no direct evidence, the real physiological mechanism of the symptoms may be due to the prolonged contraction of skeletal muscles because of the anxiety.

Callaghan has reported the restless leg syndrome in uremic neuropathy (3). The emergence of the restless leg syndrome in 5 uremic patients is considered that the irritation and injury of peripheral nerves as a result of uremia may cause the symptoms. The restless leg symptoms are considered as peripheral nerve symptoms due to the specific toxin or peripheral nerve symptoms due to the peripheral nervous system disease. In the other words, the damaged fibers cause paresthesia or diestesia.

Diabetic neuropathy, avitaminosis, coexistence of carcinoma suggest a defect of neuronal function. Symptoms of the syndrome were seen in the healing stages of alcoholic neuritis and diabetic neuropathy. Defective peripheral nerve lesion is thought to occur as a result. Spillane has reported the restless leg syndrome in 8 patients with chronic pulmonary disease (16). It has been suggested that the symptoms are not the result of metabolic consequences of respiratory failure but nervous system symptoms.

The present study suggests that the restless leg syndrome may be seen as heredofamilial or as single case. Chronic symptoms may be from mild to very severe intensity as seen in the pedigree. No reason could be offered in these patients. Sleep EEG study performed in 2 patients showed short deep sleep periods, frequent transition of the periods and a long time of awake. Motion was seen while the patient was awake and disturbed the sleep. The patient’s daughter had sleep periods close to normal at the examination of the sleep and the leg movements occurred in REM sleep. In this patient, the movements in REM sleep may be acceptable and she had no insomnia yet. It was confirmed by EEG in the parent that the syndrome was one of the reasons for insomnia.

Paresthesia was seen in all of our cases. As mentioned above, the painful forms are rare. The EMG evidence of peripheral neuropathy was not seen in the severe case of the disease.

No psychiatric disorders which required psychological testing were found. However, a patient mentioned that there was an association between the daily life stress and night symptoms.

Vasodilator therapy in patients without anemia may be administered. Priscoline (LX3 or 2x3), Hanieol (2 tablet x 3) or Carbachol (2 mg x 3) may be given. Good results were reported with Hexanicit. In some cases, response may be observed within 1 month. After a while the effect of the drug may disappear. Then it is useful to switch the drugs. 0.5-1 mg of sublingual nitroglycerin tablets are given as the symptoms resolve in a few minutes.

In iron deficiency, intravenous iron therapy is useful. In patients with iron level <60 mg/dL symptoms were improved with iron therapy. Iron and vasodilator may be used together. In angina pectoris, nitroglycerin and iron should be given together. Ask-Upmark has reported that lying on the back relieves symptoms since the symptoms are caused by the epidural venous congestion (1). This idea was supported by one of our patients (daughter). Preparations mentioned above are not effective in most of the cases. In this case, symptomatic treatment with analgesic, sedative and hypnotics may be tried. These can be effective in mild cases. Promethazine worsens the symptoms.

The patients reported that the barbiturates made walking difficult when the sleep medications were ineffective. Codein, opium and eueodal barbiturates have a better symptomatic effect. Because of the addiction potential, narcotics should not be used.

Spontaneous remission of subjective symptoms may occur. In the present study, only one was examined in terms of the treatment. No drugs had a benefit, consistently. Librium taken at night was relatively useful. Treatments mentioned above should be tried according to the severity of the patient’s symptoms.
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