Original Article

Familial Restless Legs Syndrome: A Family with all Female Patients

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Abstract

Background: Restless legs syndrome (RLS) is a chronic condition characterized by odd sensations in the body, most commonly in the legs and an irresistible urge to move them. More than half of the patients with RLS have a family history. Most of the RLS cases are women and most of the families show characteristics of an autosomal dominant pedigree. Here, we shall present a family consisting only of women; to our knowledge, such a family has not been reported yet.

Methods: The family presented here met the diagnosis criteria specified by International Restless Legs Syndrome Study Group (IRLSS). Clinical characteristic are described along with demographic properties.

Results: The patients were between 12 and 59 years of age with a mean age of 35.3 ± 14.4 years. All 7 cases were women. The pedigree of the patients exhibited an autosomal dominant inheritance pattern.

Conclusions: The present family tree indicates that familial RLS can exhibit a heredity pattern which shows autosomal dominant inheritance. The present family is still under follow-up. Future research is required to support the present data.

Keywords: Autosomal dominant inheritance, familial, pedigree, restless legs syndrome

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Introduction

Restless legs syndrome (RLS) is a chronic, progressive disorder characterized by abnormal senses and it presents while at rest or due to rest with an impulse or need to move the legs.[1] Symptoms generally occur at night, in the legs and rarely in the arms; they are bilateral and symmetric, become worse with inactiveness and recover with movement. The complaints start as mild but may become severe in time. Remission is seen in 15% of patients.[2] The diagnosis is made based on history and generally over the age of 50. It is seen 1.5–2 times more in women compared to men. While the symptoms can start at any age, the age of onset is under 20 years in 38–45% of cases.[3] Iron and dopamine are factors which are blamed in the pathogenesis of RLS. Iron plays a role in pathophysiology both directly (night drops in serum levels) and indirectly (cofactor of thyrosine hyrdoxylase in dopamine synthesis).[4] Studies have shown that genetics play a role in the pathogenesis of patients with restless legs syndrome.[5] RLS presents itself in two different ways as idiopathic (familial) and sporadic. In familial RLS cases which are included in the idiopathic group, symptom onset age can be earlier (under the age of 20) and symptoms can be more severe. Various studies have reported that familial transmission rate has 60–65% autosomal dominant character.[2–4] This study presents a family with Restless Legs Syndrome who are thought to have an autosomal dominant inheritance.

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Materials and Methods

Seven individuals with similar complaints from the same family who were admitted to Ondokuz Mayıs University Faculty of Medicine Neurology Polyclinic between the August 2012 and November 2012 were assessed. The patients' RLS diagnosis was made based on the diagnostic criteria specified by the International Restless Legs Syndrome Study Group. All patients underwent neurological examination and electroneuromyography, as well as total blood, biochemical and hormonal blood tests. Restless legs syndrome grading, sleep quality index, fatigue severity scale and Beck Depression Scale tests were used to assess the patients' quality of life.

Results

The patients were between 12 and 59 years of age with a mean age of 35.3 ± 14.4 years. All 7 cases were women. Their neurological examinations were normal. Two of the cases had low serum ferritin, one had low vitamin B12, and three had laboratory findings compatible with iron deficiency anemia. Two of the cases were found to have mild RLS, four were found to have moderate RLS and one was found to have severe RLS. Four of the cases had fatigue and deterioration in sleep quality and seven cases had depression – moderate in one and mild in six. In our study, the onset age of the complaints was 20 in one of the cases and between 32 and 40 in the other six. Tables 1 and 2 show the laboratory findings, and demographic and clinical features of the patients. Figure 1 shows the abbreviated pedigree of the Turkish restless legs syndrome family, all female patients, and the index case is identified.

Table 1. Demographic and Clinical Characteristics of 7 Female Cases.

	Age	DD (Year)	RLSS	EMG	BD	PSQİ	FSS
1	84	42	Mild	Normal	Mild	Good	Present
2	57	25	İntermediate	Normal	Mild	Bad	Present
3	55	15	Mild	Normal	Mild	Good	Absent
4	47	14	İntermediate	Normal	İntermediate	Bad	Present
5	36	1	İntermediate	Normal	Mild	Bad	Present
6	22	2	Severe	Normal	Mild	Bad	Absent
7	18	1	İntermediate	Normal	Mild	Good	Absent

DD = Disease duration; RLSS = Restless Leg Syndrome Scala; EMG = Electromyography; BD = Beck depression; PSQİ = Pittsburgh Sleep Quality İndex; FSS = Fatigue Serious scale; Ferritin (Normal: 4,6–204 ng/mL)

Table 2. Laboratory Characteristics of Cases.

	Gluc.	Hb	MCV	Ferr.	B12	Fol. As.	TSH	fT3	fT4
1	108	12,2	88,1	22	245	6,7	2,2	2,9	1,1
2	109	12,1	94,3	29	286	8,3	2,5	2,6	0,9
3	106	14,2	85,2	54	401	8,4	1,4	3,5	1,3
4	85	5,9↓	71↓	2,2↓	527	5	2,1	2,4	0,9
5	88	12,7	87,4	15	150↓	6,8	1,5	3,0	1,2
6	98	10,1↓	71,2↓	3↓	250	7,2	0,9	3,1	1,1
7	79	11,↓	77↓	5	276	6,9	1,9	2,8	1,0

Gluc = Glucose (70–110 mg/dL); Hb = Hemoglobin (12,0–15,0 g/dL); MCV = Mean Corpuscular Volume (78,5–96,4 fL); Ferr = Ferritin (4,6–204 ng/mL); B12 = Cyanocobalamine (197–886 pg/mL); Fol. As. = Folic Acid (4,6–18,7 ng/mL); TSH = Thyroid stimulating Hormone (0,2–4,2Qıu/mL); fT3 = Free Triiodothyronine (2,0–4,4 pg/mL), fT4 = Free Thyroxine (0,9–1,7 ng/dL).

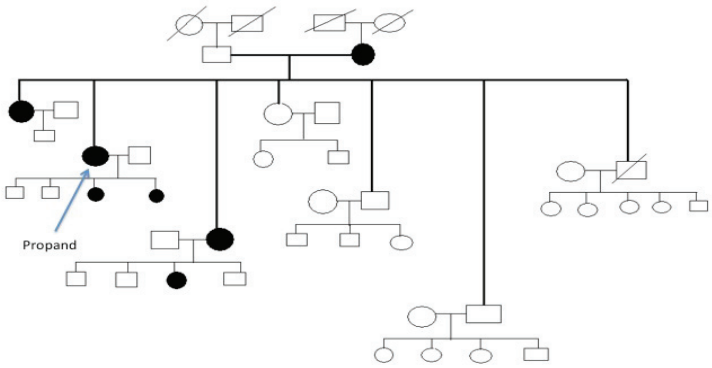

Figure 1. Abbreviated pedigree of the Turkish restless legs syndrome family who are female patients. Square = male, Circle = female.

Discussion

Restless Legs Syndrome can start at any age, including childhood; the severity of symptoms may increase with age and some cases may be symptomatic only in advanced age.[6] In the family of our study, the onset age of complaints was 20 in one of the cases while the onset age was between 32 and 40 in the other six. The urge to move the legs makes it difficult for the patient to rest, fall asleep or go back to sleep after waking up. One study showed that 84.7% of the patients with RLS had difficulty falling asleep, while 86% had difficulty only maintaining sleep and 94% had difficulty both falling asleep and maintaining sleep.[7] With the tests we conducted on our patients (fatigue severity scale, sleep quality index), we demonstrated that quality of life could be affected, leading to depression. The course of RLS may entail remissions that last for weeks or months and relapses in which symptoms appear.[2] Ohayan *et al.* reported the prevalence of RLS as 29% in patients older than 55 and 44% in patients older than 65 years.[8] Studies have shown that 6–15% of the population have RLS.[1,3] A study in our country found that the prevalence of RLS was 3.9% in Turkey, which is lower than the rates found in America and Europe.[9] The most important factors in pathophysiology include low serum iron and dopaminergic system disorder. This is because iron is the cofactor of thyrosine hyrdoxylase which is a rate-limiting enzyme in dopamine synthesis and the iron serum level drops at night, following a circadian rhythm.[2] RLS prevalence increases with iron deficiency or anemia. In cases with RLS which had serum ferritin levels under 50 µg/L without anemia, oral iron preparations resulted in obvious recovery in symptoms.[10] The iron deficiency anemia found in three of our patients showed obvious clinical recovery with oral iron treatment. Familial (idiopathic) RLS was first defined in 1945 and this hypothesis was supported by studies conducted; however, the underlying mechanism has not been fully clarified.[11] Familial RLS can be grouped in two subgroups. In the sporadic group, only one person in the family is affected, while in the familial (idiopathic) group, more than one person in the family is affected. Its clinical features do not differ between groups.[7] In 40–60% of cases with idiopathic RLS, family history is positive. Family history increases RLS prevalence by 3–6 times compared with the normal population.[7] In familial RLS, it has been reported

that the prevalence is higher in women, the average period of illness is 24 years, the average age for onset of symptoms is 24 years of age and anemia and iron deficiency are more common.[7] In one study, out of 367 cases with RLS, 12% were found to have very severe RLS, while 34% were found to have severe RLS, 43% were found to have moderate RLS and 11% were found to have mild RLS.[6] Two of our cases were found to have mild RLS, while four of our cases were found to have moderate RLS and one of our cases was found to have severe RLS. Another study showed that following treatment, symptoms recovered in 8% of the cases with RLS, while they decreased in 15%, were stable in 41% and were progressive in 36%.[7] Young *et al.* stated that family history was 40% in cases whose RLS symptoms started before the age of 35 and 25% in cases whose RLS symptoms started after the age of 50.[12] Positive family history in cases whose restless legs syndrome complaints start early is strong evidence supporting genetic transmission. In a study by Gotbout *et al*., autosomal dominant transmission in RLS was shown clearly and this group was reported to be more resistant to treatment.[13] In a study conducted on monozygotic twins, the genetic basis was found to be more obvious in patients with idiopathic RLS.[5] In another study conducted on monozygotic and dizygotic twins, RLS symptoms were found as 61% and 45%, respectively.[14] In more than 90% of the family trees, vertical transmission compatible with dominant inheritance was shown, while transmission was recessive in some families and 2.8% of cases were found to have bilinear inheritance.[11,15] In genetic studies conducted on families with RLS (Canada, America, Italy, Germany), 9 loci were found to be related to the disease. Mutations were found in 12q (autosomal recessive), 14q (autosomal dominant), 9p (autosomal dominant), 2q, 20p, 16p, 4q, 17p, and 19p chromosome genomic areas. In genome association studies, variants with different RLS risks were found which were in 4 chromosome areas and contained 5 genes [MEIS1 (2p), BTBD9 (6p-autosomal dominant), MAP2K5/SKOR1 (15q), LBXCOR1, PTPRD (9p)].[16–23] In the family we presented, RLS affected only women in the family and since this situation has not been previously reported in the literature, we considered an autosomal dominant transmission. The limitation of our study is the absence of a genetic examination. In future studies, it will be probably possible to show more different chromosomal and genetic transmissions.

Although studies have shown autosomal dominant transmission, it can be said that there is a heterogeneous transmission in RLS genetics and no definite chromosome or locus is found.

The major limitation of our study is the lack of genetic screening.

Conflict of interest

No conflict of interest was declared by the authors.

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