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


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 inactivity 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 tyrosine hydroxylase 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.

Materials and Methods

Seven individuals with similar complaints from the same family who were admitted to Ondokuz Mayis 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 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 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.

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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. 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 PRYHWKHOHJVPDNHVLWGLI¿FXOWIRUWKHSDWLHQWWRUHVWIDOODVOHHS or go back to sleep after waking up. One study showed that 84.7% RIWKHSDWLHQWVZLWK5/6KDGGLI¿FXOW\IDOOLQJDVOHHSZKLOH falling asleep and maintaining sleep. 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 LURQGH¿FLHQF\RUDQHPLD,QFDVHVZLWK5/6ZKLFKKDGVHUXP IHUULWLQOHYHOVXQGHUȝJ/ZLWKRXWDQHPLDRUDOLURQSUHSDUDWLRQV resulted in obvious recovery in symptoms.10

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

<table>
<thead>
<tr>
<th>Age</th>
<th>DD (Year)</th>
<th>RLSS</th>
<th>EMG</th>
<th>BD</th>
<th>PSQI</th>
<th>FSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84</td>
<td>42</td>
<td>Mild</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>25</td>
<td>Intermediate</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>15</td>
<td>Mild</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>14</td>
<td>Intermediate</td>
<td>Normal</td>
<td>Intermediate</td>
<td>Bad</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>1</td>
<td>Intermediate</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>2</td>
<td>Severe</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>1</td>
<td>Intermediate</td>
<td>Normal</td>
<td>Mild</td>
<td>Good</td>
</tr>
</tbody>
</table>

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

Table 2. Laboratory Characteristics of Cases.

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

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 (0,2–4,2Qu/mL); fT3 = Free Triiodothyronine (2,0–4,4 pg/mL); fT4 = Free Thyroxine (0,9–1,7 ng/mL).

Figure 1. Abbreviated pedigree of the Turkish restless legs syndrome family who are female patients. Square = male, Circle = female.
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 anaemia and iron deficiency are more common. 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. 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%. 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. Positive family history in cases whose restless legs syndrome complaints start early is strong evidence supporting genetic transmission. In a study by Gotbou et al., autosomal dominant spontaneous transmission in RLS was shown clearly and this group was reported to be more resistant to treatment. In a study conducted on monozygotic twins, the genetic basis was found to be more obvious in patients with idiopathic RLS. In another study conducted on monozygotic and dizygotic twins, RLS symptoms were found as 61% and 45%, respectively. 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. 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)]. 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.

**Financial disclosure**

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**References**


