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Restless Legs Syndrome in X-linked Adrenoleukodystrophy

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Abstract

Objective/Background: X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disease that causes progressive gait and balance problems. Leg discomfort, sleep disturbances, and pain contribute to daily disability. We sought to investigate the prevalence and severity of Restless Legs Syndrome (RLS) in patients with ALD.

Patients/Methods: We administered questionnaires and conducted diagnostic telephone interviews to assess RLS severity. We retrospectively extracted data from neurological examinations, functional gait measures, and laboratory assessments.

Results and Conclusions: Thirty-two adults with ALD (21 female, 11 male) were recruited to participate. Thirteen patients (40.6%) had RLS (10/21 females and 3/11 males). The median age of RLS onset was 35 years [IQR = 22 – 54]. Patients with RLS had more signs and symptoms related to myelopathy, but not the brain demyelination seen in ALD. This pilot study suggests a high prevalence of RLS in adults with ALD, which may contribute to sleep problems and impair quality of life.

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Keywords

adrenoleukodystrophy; adrenomyeloneuropathy; RLS; myelopathy

1. INTRODUCTION

X-linked adrenoleukodystrophy (ALD) is a progressive neurodegenerative disease caused by mutations in the *ABCD1* gene, which result in dysfunctional ABCD1, a membrane protein that normally transports very long chain fatty acids (VLCFAs) into peroxisomes for degradation¹. In men, mutations in *ABCD1* lead to progressive spinal cord disease in all, primary adrenal insufficiency in 80%, and cerebral inflammatory disease in 60% across the lifespan². As ALD is an X-linked disease, women were previously considered asymptomatic carriers. It is now known that although adrenal insufficiency and cerebral disease occur in less than 1% of females, more than 80% will eventually develop progressive spinal cord disease^{3,4}.

Restless Legs Syndrome (RLS) is a sensory-motor neurological disorder characterized by an intense urge to move the legs, often with dysesthesias, which interferes with sleep and impairs quality of life⁵. It is more common in conditions with iron deficiency⁶, but has been associated with a variety of neurological disorders (Friedrich's Ataxia⁷, peripheral neuropathy⁸, multiple sclerosis⁹, and Parkinson's disease¹⁰). To our knowledge, no data has been published regarding RLS in patients with ALD. In our clinical experience, leg discomfort, sleep disturbance, and pain are prominent in both males and females with ALD and contribute to daily disability. While spasticity and neuropathy may contribute to leg discomfort, the degree of sleep disturbance at times appeared out of proportion to these symptoms alone. We therefore sought to investigate the prevalence, associations, and severity of RLS in this patient population.

2. MATERIALS AND METHODS

2.1 Design

The study was reviewed and approved by the Mass General Brigham Human Research Committee. All participants provided written informed consent prior to enrollment. Males and females over the age of 18 years with a genetically or biochemically confirmed diagnosis of ALD were recruited from the Leukodystrophy Clinic at Massachusetts General Hospital¹¹. We included participants with genetically confirmed ALD, without radiographic evidence of inflammatory disease on brain MRI. We excluded individuals with other confounding neurological deficits that could affect participation in phone interviews or gait and balance assessments.

2.2 Diagnostic Interviews

Clinical telephone interviews were conducted using the Hopkins Telephone Diagnostic Interview (HTDI), a validated structured diagnostic RLS assessment¹². Diagnostic criteria for RLS are based on a patient report of (1) urge to move the legs, usually accompanied or caused by uncomfortable leg sensations, which (2) begin or worsen during rest or inactivity

and are (3) partially or totally relieved by movement. The symptoms above are (4) worse in the evening or night than during the day. The HTDI was independently administered by a board-certified sleep professional with expertise in RLS (J.W.) and a neurologist experienced in ALD (F.E.), who were blinded to each other's assessments, and each decided whether the participant had "definite", "probable", "possible" or "not" RLS. Those with "definite" or "probable" RLS were considered RLS positive. Participants were identified as having "probable" rather than "definite" RLS if they satisfied all four characteristics of RLS but also met one of the following criteria: presence of leg discomfort with some features of neuropathy, the occurrence of symptoms only while sitting, or a morning onset from the beginning of symptom history. Differences in RLS diagnosis between the two clinicians were adjudicated in discussion and, if indicated, re-interview of the participant. An International Restless Legs Scale (IRLS) was administered to those with RLS, assessing severity of RLS symptoms in the past week¹³.

2.3 Retrospective Chart Review

To assess the extent of myelopathy-associated signs and symptoms, we retrospectively reviewed medical charts of patients who participated in the HTDI phone interviews. We extracted data on 12 major neurological signs and symptoms including the presence of muscle weakness, spasticity, impaired coordination, hyperreflexia, lower extremity sensory loss, positive Romberg test, gait/balance difficulty, paresthesia, neuropathic pain, bladder dysfunction, bowel dysfunction, and erectile dysfunction (in male patients). Neurological examinations were conducted by two neurologists with expertise in neuromuscular disorders (F.E. and R.S.). We also collected data from laboratory testing for ferritin levels. Neither limb actigraphy or polysomnography, either home or in-laboratory, was performed. Therefore, objective data on sleep or periodic limb movements in sleep was not available.

2.4 Functional Gait Assessment

Participants performed functional gait assessments including the 25-Foot Walk test (25-FW), the Timed Up and Go test (TUG), and Six Minute Walk test (6MW). The average of two trials was recorded for both the 25FW and TUG.

2.5 Statistical Analysis

Contingency tables were created and Fisher's exact test statistics were used to assess the relationship between RLS and presence of neurological signs and symptoms.

2.6 Data Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. RESULTS

We evaluated 32 patients (21 female, 11 male) with ALD (Table 1). The median age of our cohort was 45.9 years [IQR=36.4–57.5] (females, 49.5 [IQR=43.7–58.6]; males, 36.0 [IQR=21.7–40.0]). Of the 27 patients with symptoms of myelopathy, the median age of onset was 34 years [IQR=30–38]. Eleven patients used walking aid for ambulation. Median

scores for EDSS, 6MW, TUG, and 25-FW were 2.5 [IQR=1.5–3.5], 460 meters [IQR=359–549], 8.1 seconds [IQR=7.0–9.1], and 5.6 seconds [IQR=5.0–6.5], respectively. Patients with RLS had more neurological signs and symptoms, many related to their myelopathy (Figure 1). These myelopathy symptoms encompassed not only motor and sensory symptoms, but also bladder and bowel dysfunction as well as erectile dysfunction. Presence of RLS was significantly associated with patient reports of gait/balance difficulty ($p=0.024$) as well as pain ($p=0.024$). Seven patients had non-inflammatory brain lesions affecting the white matter. Nine patients (all male) had adrenal insufficiency.

Thirteen patients (40.6%) were diagnosed with RLS by the HDTI interviews (10/21 [47.6%] females; 3/11 [27.3%] males) (Table 1). The median age of RLS onset was 35 years [IQR=22–54] (females, 44 [IQR=24–56]; males, 30 [IQR=26–33]). In the 7 patients with brain lesions, only two had a diagnosis of RLS; interestingly, these patients displayed very mild RLS (Table 1). Of note, none of the females in our study developed brain disease. Of the 13 patients with RLS, 6 (46.2%) had tried a medication to relieve their symptoms. Nine patients (8 with RLS, 1 without RLS) had a history of antidepressant use.

Six patients (5 females, 1 male) with RLS reported a history of anemia or iron deficiency. Ferritin levels were available for 14 patients (8 females with RLS, mean ferritin level of 74.0 ± 71.6 ug/L; 4 females and 2 males without RLS, mean ferritin level of 99.5 ± 79.2 ug/L).

4. DISCUSSION

In this pilot study, we found RLS in 40% of adults with ALD, with females more commonly affected than males. This is substantially higher than that in the general adult population, in which the prevalence is 5–10%¹⁴. Those with RLS also had more signs and symptoms of myelopathy, suggesting that ALD's pathologic effect on spinal pathways could contribute to RLS.

The myelopathy of ALD is associated with neuronal loss and shrinkage in the dorsal root ganglia and the Clarke column of the spinal cord¹⁵. Such spinal sensory dysregulation may also be implicated in the genesis of RLS (see reviews¹⁶). In multiple sclerosis, in which roughly 25% of patients have RLS, spinal pathology is thought to play a role in RLS pathophysiology¹⁷. Further, transcutaneous spinal cord direct stimulation has shown promise as a treatment for RLS¹⁸.

Consistent with patterns observed in the general population⁵, risk factors for RLS in this cohort of adults with ALD included female gender, increased age, lower iron indices, and use of serotonergic antidepressants. Presence of myelopathy signs/symptoms was more frequent in those with RLS than in those without RLS. By contrast, brain disease associated with ALD did not predispose to RLS, as even the 2 patients with cerebral disease diagnosed with RLS had the mildest severity seen (IRLS=0). Therefore, it may be that ALD patients affected by the phenotype of adrenomyeloneuropathy are more predisposed to RLS symptoms.

Both idiopathic and secondary RLS are independently associated with substantial long-term detrimental effects on health, cognition, quality of life, psychiatric morbidity, and

all-cause mortality¹⁹. For instance, in multiple sclerosis, RLS is associated with reductions in functional capacity as well as physical and psychological health-related quality of life, sleep quality, fatigue, depression, and anxiety^{20,21}. Thus, sleep disturbance associated with RLS may, in our cohort, also have functional consequences and worsen the manifestations of myelopathy in ALD.

In RLS, CNS iron deficiency has consistently been identified, using CSF, transcranial Doppler, MRI and pathological investigations²². Low serum ferritin is inversely correlated with RLS severity. Oral and IV iron treatment both improve symptoms in patients with RLS, the former in those with serum ferritin levels below 75 ug/L⁶. Little is known about iron metabolism in X-ALD, although mitochondrial dysfunction, oxidative stress, and bioenergetic failure play major roles in the pathogenesis²³.

Our data supports a high prevalence of RLS in patients with ALD. Although the high rate of RLS in our patients could be an artifact of their serotonergic antidepressant use, it may be just as likely that RLS predated their mood disturbance, as depression is known to have a bidirectional relationship to RLS, potentially related to sleep disturbance or to the chronic discomfort²⁴. Awareness of RLS in patients with ALD would allow for its effective treatment²⁵ which may improve the functional impairments as well as quality of life, mood, and anxiety issues in those with ALD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALD	adrenoleukodystrophy
HTDI	Hopkins Telephone Diagnostic Interview
IRLS	International Restless Legs Scale
RLS	restless legs syndrome
TUG	Timed Up and Go test
VLCFAs	very long chain fatty acids
25-FW	25-Foot Walk test

6MW

6-Minute Walk test

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Highlights:

- Restless Legs Syndrome (RLS) is prevalent in adults with adrenoleukodystrophy (ALD)
- ALD patients with RLS have more neurological signs and symptoms
- RLS is more common in females with ALD than in males
- Awareness of RLS in patients with ALD would allow for its effective treatment

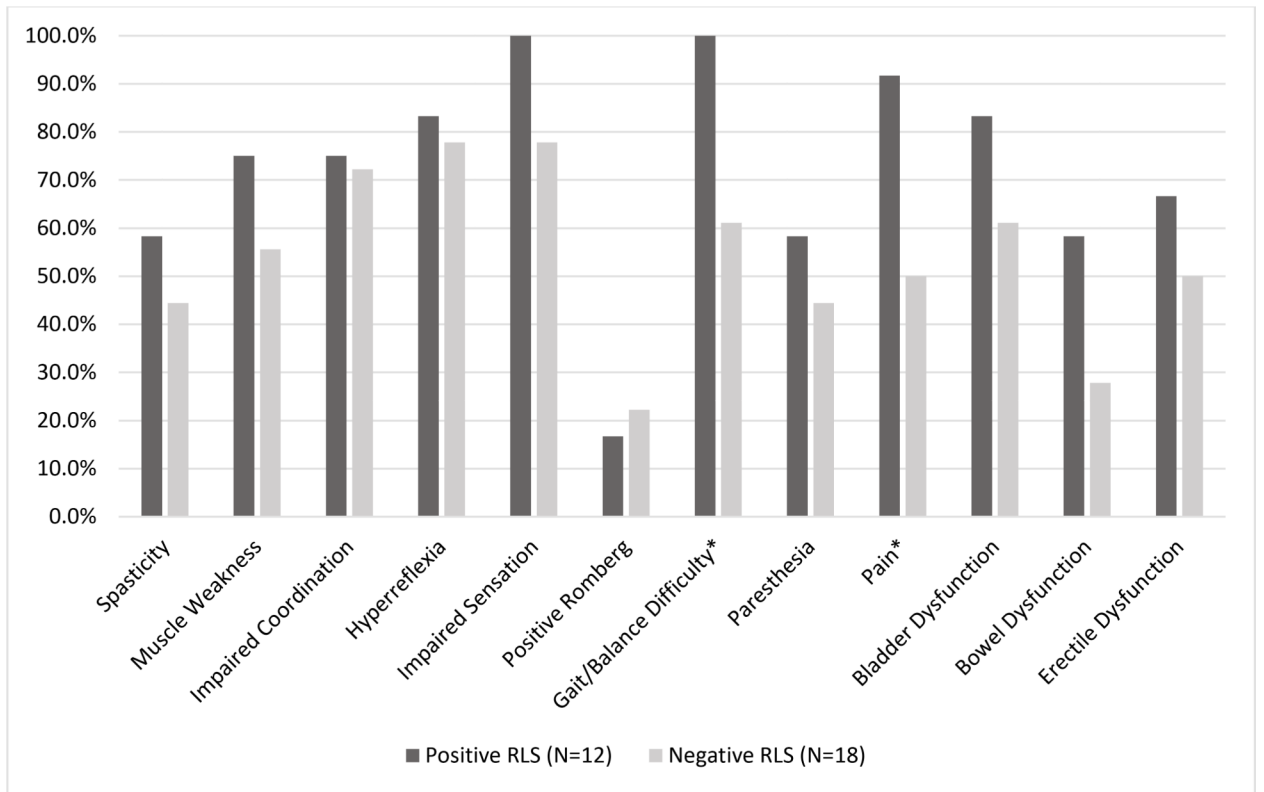


Figure 1. Percentage of patients in our cohort presenting with each neurological sign and symptom
*p<0.05

Table 1.

Individual characteristics of patients in our cohort

Pt	Sex	Age (yrs)	IRLS	RLS / meds ¹	AD meds ²	EDSS	Walking aid	Brain Lesion ³	AI	ID	AMN	AMN onset (yrs)	RLS onset (yrs)	6MW (m)	TUG (s)	25-FW (s)
RLS +																
3	F	41.6	26 (6 w/ med)	+	+	2	+	-	-	-	+	30	35	333.8	9.3	7.6
4	F	58.7	11	+	-	3.5	+	-	-	-	+	32	56	395.3	8.7	6.3
5	F	57.6	25 (20 w/ med)	+	+	2	-	-	-	+	+	37	43	534.3	6.6	5.6
17	F	57.7	13	-	+	1	-	-	-	-	+	NR	57	603.5	6.8	4.8
10	M	26.0	0	-	-	2	+	+	+	-	+	23	22	452.0	7.4	5.6
22	F	39.7	13	-	+	1.5	-	-	-	-	+	31	20	NR	NR	NR
24	M	37.6	23	-	-	3.5	+	-	-	+	+	25	30	368.8	13.7	8.6
25	M	39.1	0	-	+	3	+	+	+	-	+	30	35	358.7	8.8	7.2
26	F	73.3	26	+	+	4	+	-	-	-	+	68	68	568.1	7.0	5.0
27	F	46.3	10	-	-	1.5	-	-	-	-	+	38	45	NR	NR	NR
28	F	58.5	0	-	+	3	-	-	-	-	+	50	54	NR	NR	NR
30	F	35.4	21	-	-	1.5	-	-	-	+	+	21	20	NR	NR	NR
32	F	45.9	34 (19 w/ med)	+	+	2.5	-	-	-	-	+	38	17	NR	NR	NR
RLS -																
1	F	79.2	-	-	-	4	+	-	-	-	+	58	-	345.9	9.5	6.5
2	F	45.8	-	-	-	0	-	-	-	+	-	n/a	-	502.6	8.1	5.6
6	F	34.1	-	+	-	3	-	-	-	-	+	26	-	272.5	13.3	8.2
7	M	26.2	-	-	-	0	-	-	-	-	-	n/a	-	269.7	7.5	4.8
8	M	36.0	-	+	-	3.5	+	+	+	-	+	31	-	440.1	9.0	5.7
9	F	60.9	-	-	-	1.5	-	-	-	+	+	NR	-	487.7	6.8	5.2
11	M	20.7	-	-	-	1	-	-	+	-	-	n/a	-	518.2	5.0	4.4
12	F	49.4	-	+	-	1.5	-	-	-	-	+	NR	-	548.6	5.6	4.4
13	M	43.7	-	-	-	2.5	-	+	+	-	+	37	-	548.6	7.6	6.3

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Pt	Sex	Age (yrs)	IRLS	RLS meds ¹	AD meds ²	EDSS	Walking aid	Brain Lesion ³	AI	ID	AMN	AMN onset (yrs)	RLS onset (yrs)	6MW (m)	TUG (s)	25-FW (s)
14	M	50.8	-	-	-	3.5	-	+	+	-	+	39	-	548.6	8.2	5.5
15	F	49.8	-	+	-	3	-	-	-	+	+	37	-	377.6	8.3	6.5
16	M	21.7	-	-	+	1.5	-	-	+	-	-	n/a	-	479.1	7.8	5.2
18	M	21.6	-	-	-	4	-	+	+	-	+	21	-	576.1	7.6	4.7
19	F	40.9	-	-	-	0	-	-	-	-	-	n/a	-	NR	NR	NR
20	F	49.5	-	+	-	3	+	-	-	-	+	30	-	330.4	14.9	10.5
21	M	40.0	-	-	-	3.5	-	+	+	-	+	31	-	460.6	9.1	5.6
23	F	64.8	-	+	-	6.5	+	-	-	-	+	35	-	NR	NR	NR
29	F	47.9	-	+	-	2	-	-	-	-	+	35	-	NR	NR	NR
31	F	57.4	-	+	-	6	+	-	-	-	+	42	-	NR	NR	NR

¹ includes baclofen, gabapentin, and pramipexole

² includes venlafaxine, escitalopram oxalate, bupropion, trazodone, citalopram, desvenlafaxine succinate

³ includes self-halted and stable brain lesions

AD = anti-depressant; AI = adrenal insufficiency, AMN = adrenomyeloneuropathy; ID = iron deficiency or anemia; NR = not recorded; TUG = timed up and go test; 25-FW = 25-foot walk test; 6MW = 6-minute walk test