RESEARCH ARTICLE

Restless Legs Syndrome in Friedreich Ataxia: A Polysomnographic Study

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ABSTRACT: Friedreich ataxia (FA) is the most common type of hereditary ataxia. Frataxin deficiency due to a GAA expansion in the first intron of chromosome 9 results in intramitochondrial iron accumulation. On the basis of the patients' complaints about sleep disturbance and pathophysiological considerations, we systematically assessed sleep history and polysomnography in FA. We included 16 consecutive FA patients (11 men, 5 women; mean age, 35.4 ± 11.1 years) with a mean disease duration of 16.5 ± 7.0 years. All patients underwent a standardized protocol including a detailed sleep history and polysomnographic recordings. Eight out of 16 patients were diagnosed with restless legs syndrome (RLS). In seven patients, RLS onset was after the onset of FA. Interestingly, FA patients with RLS had significantly lower serum ferritin levels than FA patients without RLS (76.3 ± 56.0 μg/L vs. 176.3 ± 100.7 μg/L; $P = 0.043$ after correction for sex and age). Moreover, periodic leg movements in wakefulness (PLMW) indices were significantly higher in FA patients with RLS than FA patients without RLS (FA with RLS, 118.1 ± 50.7; FA without RLS, 65.6 ± 44.2; $P = 0.028$). There was an inverse correlation between serum ferritin levels and PLMW indices obtained in all FA patients (rho −0.538, $P = 0.039$). RLS is common in FA. Its frequency in this primarily spinal ataxia appears consistent with the concept of dysfunctional spinal sensorimotor integration in the pathophysiology of RLS. The finding that RLS is more frequent in the context of lower serum ferritin levels in FA is interesting, but requires further investigation in larger patient samples. © 2010 *Movement* Disorder Society

Key Words: sleep disturbance; restless legs syndrome; Friedreich ataxia; ferritin; periodic leg movements; polysomnography

Friedreich ataxia (FA) is the most common autosomal recessive heredoataxia. In Indo-Europeans, it affects one in 50,000 people.[1,2] Clinically, FA is characterized by progressive spinocerebellar ataxia, peripheral neuropathy, diabetes mellitus, and hypertrophic cardiomyopathy.[3] FA is caused by a GAA-trinucleotide expansion in the first intron of the frataxin gene in most cases. This expansion results in a reduced expression of frataxin, a small mitochondrial protein.[4] Frataxin's exact physiological function is unknown, but it may be involved in mitochondrial iron homeostasis and/or assembly of iron-sulfur (FeS) proteins and heme synthesis. Intramitochondrial iron accumulation has been postulated to initiate the production of hydroxyl radicals by Fenton chemistry, leading to inactivation of FeS enzymes, lipid peroxidation, and damage to nucleic acids, proteins, and finally resulting in cell death.[5] Intramitochondrial iron accumulation is found in the heart, liver, nervous system, and spleen of FA patients. The presence of increased levels of soluble transferrin receptors, an indicator for cytosolic iron deficiency, causes controversies about intracellular iron distribution in FA.[6] Although several therapy studies are under way, there is currently no effective treatment of FA available.[7]

Additional Supporting Information may be found in the online version of this article.

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Recurrent complaints of sleep disturbance obtained in FA patients in our ataxia outpatient clinic led us to systematically assess sleep history.

To assess all possible causes of sleep disturbance in a multi-system degenerative disease which also includes cardiomyopathy, we decided to additionally perform polysomnographic recordings in our FA patients.

Patients and Methods

Patients

Consecutive consenting patients with genetically proven FA were included in this study. The study was approved by the local ethics committee of Innsbruck Medical University. Ataxia was scored using a standardized protocol including the scale for assessment and rating of ataxia (SARA)[8] and the FA rating scale (FARS).[9] The scorings were performed by the same neurologists (SH and SMB). Routine laboratory assessments included vitamin B levels, folate, and iron parameters. Blood samples were obtained at 7.00 a.m.

Sleep History

A structured sleep history was obtained in all patients. It included sleep habits and times (bedtime, subjective sleep onset latency, subjective total sleep time, nocturnal awakenings, refreshed feeling when getting up, planned daytime naps). RLS was diagnosed according to standard criteria,[10] and RLS mimics[11] were excluded by a board certified neurologist experienced in RLS (BF). RLS severity was assessed by the International RLS Study Group rating scale (IRLS).[12] Patients were asked for the onset of RLS, total RLS duration in years, the temporal relation between RLS onset and onset of FA, and the use of RLS specific medication. Patients were further asked for snoring or witnessed apneas during the night. Daytime sleepiness was assessed by history and the Epworth sleepiness scale (ESS).[13] A cut-off level of > 10 for ESS was selected a priori to differentiate between normal and pathological daytime sleepiness. In all patients, the presence of Non-REM and REM parasomnias was assessed by history.

Polysomnography and Sleep Scoring

Eight hour polysomnography was performed during two consecutive nights. The first night was used as adaptation night, the second night was used for analysis in 14 patients. Two patients refused a second polysomnographic recording. In these patients, the first study night was evaluated. Polysomnography was performed with a digital Schwarzer polygraph (Brainlab 4.0, Schwarzer, Munich, Germany). EEG included F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1, vertical and horizontal electrooculography and electromyography of mental, submental, bilateral flexor digitorum superficialis, and bilateral tibialis anterior muscles. Sleep stages were scored according to Rechtschaffen and Kales[14] with the allowance to score REM sleep despite persistence of tonic or phasic EMG activity.[15] Phasic and tonic EMG activity was scored from the mental and submental EMG recordings according to published criteria.[16] REM sleep without atonia was defined as phasic EMG activity $> 20\%$ of all individual 3 second mini-epochs.[17] Periodic leg movements (PLM) in wakefulness and sleep (PLMW, PLMS) were recorded and scored according to WASM criteria.[18] A PLM index above 15 per hour was defined as pathological.[19] The diagnosis of excessive fragmentary myoclonus was based on the AASM Manual for the Scoring of Sleep and Associated Events.[20]

Statistical Analysis

All statistical analyses were performed using the SPSS statistical analysis program (SPSS 15.0, Chicago, IL, USA). Data are reported as means $\pm$ standard deviations or frequencies (percentages), as applicable. To compare frequencies, the Fisher's exact test was used. To compare numeric variables, Mann-Whitney-U test was applied. Since ferritin values showed a skewed distribution, ferritin values were ln-transformed before applying a two-way ANOVA for correction of sex and age. The correlation between ferritin levels and PLMW indices was calculated with the Spearman correlation test. A P-value < 0.05 was considered significant.

Results

Patients

Sixteen consecutive FA patients with a mean disease duration of 16.5 ± 7.0 years were investigated between March and December 2007. All patients were homozygous for repeat GAA expansions on chromosome 9. They were 11 men and five women. The mean age at time of investigation was 35.4 ± 11.1 years. Seven patients were wheelchair-bound, three patients needed gait assistance, and six patients were able to walk unassisted. Mean SARA score was 27.8 ± 10.5, mean FARS score was 67.0 ± 23.4. All patients had electrophysiologically proven mild to moderate sensory polyneuropathy. No patient had spasticity. Hypertrophic cardiomyopathy was present in three patients. Diabetes was absent in all patients. Serum ferritin levels were obtained in all but one patient at time of polysomnography. Mean serum ferritin levels were 122.9 ± 92.7 μg/L (men, 166.1 ± 83.0 μg/L; women, 36.6 ± 24.1 μg/L). Hemoglobin levels, CRP values, vitamin B12, and folate were within normal limits. For individual data refer Table 1.

Sleep History

Eight of 16 patients had RLS according to standard criteria[10] and after exclusion of RLS mimics.[11] In

TABLE 1. Demographic, clinical, and genetic variables in FA patients

	Demographics		FA features							Results on RLS/PLM			
ID	Sex	Age	FA onset	GAA repeats	CMP	PNP	Mobility	SARA	FARS	IRLS	PLMW	PLMS	AD use
RLS +													
2	m	47	25	520/650	−	+	2	25.5	82	24	62.6	5.7	−
3	w	30	16	600	+	+	2	29	77.5	0	96.4	5.8	+
6	w	47	28	240	−	+	1	20	61.5	0	209.5	22.7	+
8	m	29	19	650	−	+	0	11.5	45	20	137.8	42.5	−
9	m	28	14	NA[a]	−	+	2	24	84.5	9	125.4	21.6	−
12	w	23	13	500/600	−	+	0	13	50.5	13	116.7	9.3	−
13	m	43	26	350	−	+	1	29	87	11	49.0	1.5	−
16	w	38	6	900/900	−	+	2	98	30	23	147.0	11.0	+
RLS −													
1	m	13	10	850	−	+	0	13	44		158.9	30.4	−
4	m	31	14	850	+	+	2	32	89		27.5	19.7	+
5	m	48	32	350	−	+	0	28.5	55.5		47.7	3.0	−
7	m	42	20	420	−	+	0	16.5	48.0		44.4	2.2	−
10	m	23	12	NA[a]	+	+	2	33.5	103		93.8	34.9	−
11	w	53	36	150/190	−	+	0	10	35.5		47.2	4.8	−
14	m	40	12	1300	−	+	2	37	100.5		27.5	9.6	−
15	m	31	18	520/850	−	+	1	25	78		78.0	18.3	−

fsMobility was rated as follows: 0 = patients who need no assistance, 1 = patients who need assistance, 2 = wheelchair-bound patients.
AD, antidepressant; PNP, polyneuropathy; SARA, scale for assessment and rating of ataxia; FARS, Friedreich ataxia rating scale; Hb, hemoglobin; m, man; w, woman.
[a]GAA repeat length was not available in these patients.

seven patients, RLS onset was several years after the onset of FA. Mean RLS duration was 8.4 ± 9.1 years. RLS symptoms were severe in two, moderate in three, and mild in one patient. Two patients had intermittent RLS with no symptoms during the last week. Mean IRLS was 12.5 ± 9.5. Two of the eight patients suffered from almost daily RLS symptoms. There was no difference in RLS severity between men and women ($P = 0.486$). No patient was on RLS specific medication at time of investigation. Three patients were on antidepressants, but they reported no temporal association between the start of the antidepressant medication and the onset of RLS (refer Table 1). Further common sleep complaints were occasional snoring or witnessed apneas (seven out of 16 patients; one had severe snoring and witnessed apneas, six had occasional snoring), non-restaurative sleep (seven out of 16), and difficulties in initiating or maintaining sleep (six out of 16 patients). Three patients complained about nocturnal leg cramps. Confusional arousals and sleep walking were present in two patients. No patient had a history of REM sleep behavior disorder and no patient had pathological increased daytime sleepiness defined as an ESS score > 10. For individual data refer Table 2.

Polysomnographic Findings

General sleep parameters are supplied as Supporting Information. All patients had a PLMW index > 15/hr (mean, 91.9 ± 53.3/hr), seven patients (43.8%) had a PLMS index > 15/hr. At visual inspection, the intermovement interval of PLMW varied over a wide range within the accepted limits of PLM between 5 and 90 seconds.[18] Four patients had excessive fragmentary myoclonus. REM sleep without atonia was present in two patients and was considered secondary to antidepressant medication (one patient was on trazodone 100 mg, one patient on fluoxetine 20 mg). Individual results are given as Supporting Information.

Associations Between RLS, PLM, and Iron Metabolism

FA patients with RLS had significantly higher PLMW indices than FA patients without RLS (FA with RLS, 118.1 ± 50.7; FA without RLS, 65.6 ± 44.2; $P = 0.028$). Moreover, FA patients with RLS had significantly lower serum ferritin levels than FA patients without RLS after correction for sex and age (male FA patients with RLS, 124.8 ± 28.3 μg/L; male FA patients without RLS, 193.7 ± 98.2 μg/L; female FA patients with RLS, 27.8 ± 15.8 μg/L; female FA patient without RLS, 72.0 μg/L; $P = 0.043$; P uncorrected = 0.049; $P = 0.09$ after correction for sex alone). This finding is illustrated in Figure 1. There was no significant association between the presence of RLS and PLMS indices > 15/hr (FA with RLS, 15.3 ± 12.6; FA without RLS, 15.0 ± 13.4; $P = 0.959$). The correlation between ferritin levels and PLMW indices obtained in all 16 FA patients was inverse (rho −0.538, $P = 0.039$). There was no association between RLS and age at time of investigation, sex, use of antidepressants, age at onset of FA, or FA severity measured by SARA or FARS ($P > 0.05$).

Discussion

To the best of our knowledge, this is the first study that systematically examined sleep history in FA patients. Additionally, polysomnographic recordings

TABLE 2. Sleep complaints in FA patients

Sleep complaints	Frequency total n/16	Individual patients															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Restless legs syndrome	8	−	+	+	−	−	+	−	+	+	−	−	+	+	−	−	+
Occasional snoring or witnessed apneas	7	−	+	−	+	+	+	−	+	−	+	−	−	−	+	−	−
Non-restaurative sleep or prolonged sleep time	7	−	−	+	+	+	−	−	−	+	−	−	+	−	−	+	+
Difficulties in initiating and maintaining sleep	6	+	−	+	−	−	−	−	+	−	−	+	+	+	−	−	−
Nocturnal leg cramps	3	+	−	−	−	−	−	+	−	−	−	−	−	−	+	−	−
Non-REM parasomnia	2	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−

were performed to detect potential sleep apnea due to concomitant cardiomyopathy in this multi-system degenerative disease.

Using accepted clinical criteria[10] and based on the assessment through an experienced examiner, RLS was found in 50% of FA patients. Since the prevalence of RLS in the general population of the same region is estimated to be about 10%,[21] RLS in FA patients appears to be far more common. The pathophysiological background of RLS is complex and not fully understood. Still, the observed frequency of RLS in FA together with a neuronal loss and shrinkage in the dorsal root ganglia and in the Clarke column of the spinal cord, the neuropathological hallmarks in FA,[22] may strengthen current hypothesis of spinal sensory dysregulation in the genesis of RLS.[23,24] This is underlined by the finding that the LBX-1 gene which plays a critical role in the development of sensory pathways in the spinal cord appears to be a genetic risk factor for RLS.[25] Another explanation for the increased prevalence of RLS in FA might derive from a disturbed intracellular iron metabolism. In FA, serum ferritin levels are generally normal as found in our FA patient group.[26] Still, differentiated for sex, we found an amazingly low mean serum ferritin value below 50 μg/L in female FA patients. Moreover, the presence of increased levels of soluble transferrin receptors, an indicator for cytosolic iron deficiency may point to a disrupted intracellular iron distribution in FA.[6] The precise role of the mitochondrial protein frataxin, that is decreased in FA,[27] is not entirely clear. However, frataxin is structurally reminiscent of ferritin and similarities to the mode of action of ferritin are attributed to its probable functions.[28] Mitochondrial iron exchange into the cytosol as well as intramitochondrial iron utilization in FA appears to be disrupted due to frataxin deficiency. Finally, mitochondrial iron overload results in cell death.[29]

Brain iron metabolism has been increasingly recognized to play an important role in the genesis of RLS.[30] Dysfunctional cellular iron stores in RLS are reflected by reduced H-ferritin levels, a reduced transferrin receptor density despite iron deficiency as well as a reduced IMP-1 expression in neuromelanin cells of the substantia nigra[31,32] and decreased ferritin in the cerebrospinal fluid.[33] Low serum ferritin is inversely correlated with RLS severity.[34] Iron substitution may improve RLS symptoms in patients with serum ferritin levels below 50 μg/L.[35] Interestingly, comparing FA patients with and without RLS we found significantly lower serum ferritin levels in FA patients with RLS.

Periodic leg movements (PLM) during wakefulness (PLMW) are frequent in childhood and adolescence, whereas PLM in sleep (PLMS) markedly increase after the age of 40 years.[36] PLMW indices > 15/hr were present in all, and PLMS indices > 15/hr were seen in 43.8% of FA patients. However, the relevance of this finding is unclear and has to be determined in larger series of age-matched FA patients and control subjects. FA patients with RLS had higher PLMW indices than FA patients without RLS. This is in line with current literature in RLS suggesting PLMW to be more specific for RLS than PLMS.[37,38]

In conclusion, we show RLS to be a common finding in FA. This finding may merge into current hypothesis on

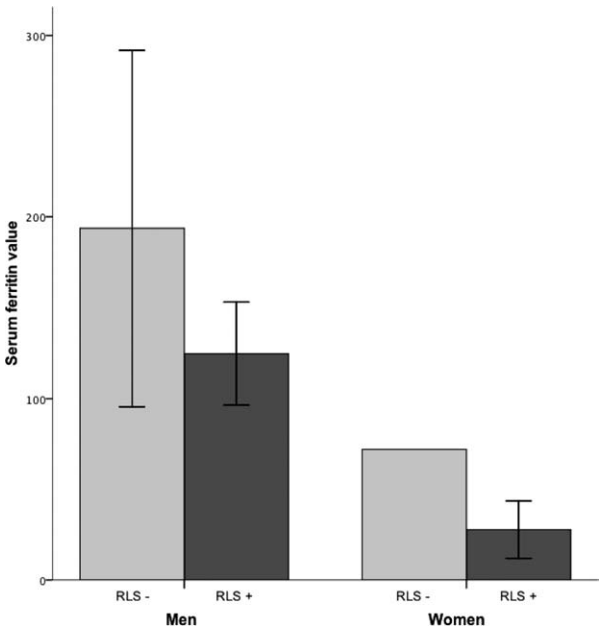

FIG. 1. Ferritin values in FA patients with and without RLS. Serum ferritin values are given as mean ± standard deviation. Light gray bars represent FA patients without RLS, dark gray bars represent FA patients with RLS.

RLS since FA is predominantly a spinal ataxia. The concept that RLS is more frequent in the context of lower serum ferritin levels in FA is interesting, but requires further investigation in larger patient samples.

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