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Sleep Disorders in Hereditary Ataxias

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Abstract

Purpose of Review In this review, we aim to describe the main sleep disorders observed in patients with different forms of hereditary ataxias and discuss the main pathophysiological mechanisms.

Recent Findings Several pathological studies have demonstrated that the degenerative process in patients with hereditary ataxias may involve not only the cerebellum, but also other areas of the nervous system, and explain noncerebellar symptoms, such as sleep disorders.

Summary Hereditary ataxias are neurodegenerative disorders with heterogeneous genetic and clinical presentation. This group of diseases usually affects other areas of the nervous system, besides the cerebellum, and noncerebellar signs and symptoms may occur, such as sleep disorders. The main sleep disorders related to hereditary ataxias include REM sleep behavior disorder, insomnia, excessive daytime sleepiness, obstructive and central sleep apnea, periodic leg movement in sleep, and restless legs syndrome.

Keywords Sleep disorders · Hereditary ataxias · Spinocerebellar ataxias

Introduction

Hereditary ataxias are neurodegenerative disorders with heterogeneous genetic and clinical presentation. This group of diseases usually affects other areas of the nervous system, besides the cerebellum, and noncerebellar signs and symptoms may occur [1•, 2••]. Several pathological studies have demonstrated that the degenerative process in patients with hereditary ataxias may involve not only the cerebellum, but also the basal ganglia, midbrain, pons, medulla oblongata, peripheral nerves, spinal cord, thalamus, and the cortex [3]. The involvement of different areas of the nervous system may explain extra cerebellar symptoms in patients with hereditary ataxias: movement disorders, pain, cramps, dysautonomia, cognitive impairment, psychiatric manifestations, olfactory deficits, fatigue, nutritional issues, and sleep disorder [4].

Although there is no specific treatment to block the disease progression in patients with hereditary ataxias, we can treat the symptoms, such as sleep disorders, in order to improve the quality of life of these patients. In this review, we aim to describe the main sleep disorders observed in patients with different forms of hereditary ataxias and discuss the main pathophysiological mechanisms [4].

Sleep Disorders in Neurogenetic and Neurodegenerative Diseases

The main sleep disorders related to neurodegenerative diseases include (rapid eye movement) REM sleep behavior disorder (RBD), insomnia, excessive daytime sleepiness (EDS), obstructive and central sleep apnea, periodic leg movement in sleep (PLMS), and restless legs syndrome (RLS) [5•]. The areas of the brain affected by the degeneration process and the related sleep disorders are variable. The brainstem circuits associated with RBD are sublaterodorsal tegmental nucleus, gigantocellular reticular nucleus, dorsal raphe nucleus, and pedunculopontine nucleus, while RLS and EDS are frequently

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related to dopaminergic dysfunction [6]. Figure 1 is a summary of the presumed anatomical structures involved in different types of sleep disorders related to neurological diseases.

The main neurodegenerative diseases with sleep disorders are synucleinopathies, tauopathies, spinocerebellar ataxias (SCAs), and amyotrophic lateral sclerosis [5•, 6]. Understanding and recognizing the sleep disorders in neurodegenerative and neurogenetic diseases may provide not only important insights into the pathophysiological mechanisms, but also have a practical issue, since sleep disorders are usually treatable [6, 7]. Sleep disorders may appear before the motor symptoms. A most typical situation is RBD in Parkinson's disease and other synucleinopathies. Indeed, these observations may provide future perspectives for possible neuroprotective therapies [5•, 6].

Although sleep disorders commonly are associated with neurodegenerative diseases, neurogenetic syndromes may also be correlated with poor sleep quality. The sleep symptoms may be directly linked to the genetic mutation or secondary to neurologic symptoms that predispose to sleep disorder. Neurogenetic syndromes most commonly related to sleep disorders are muscular dystrophies, Nieman–Pick type C, Prader–Willi, Huntington disease, and hereditary cerebellar ataxias [8].

Table 1 summarizes the main sleep disorders related to the subtype of hereditary ataxia.

Classification of the Hereditary Ataxias

Cerebellar ataxias are classified on a genetic basis in autosomal dominant, autosomal recessive, X-linked cerebellar ataxia, mitochondrial, and congenital ataxias. The two most important groups are autosomal dominant or SCAs and recessive ataxias. Currently, there is no established classification for other subtypes of ataxia because they are rare [1•].

SCAs are a heterogeneous group of disorders characterized by progressive ataxia due to degeneration of the cerebellum and its efferent and afferent pathways. There are 48 SCA subtypes described, and the most common include SCA1, SCA2, SCA3 or Machado–Joseph disease (MJD), SCA6, SCA7, and SCA10. Also, dentatorubropallidoluysian atrophy (DRPLA) and the eight forms of episodic ataxias (EA) may be included in the list of autosomal dominant hereditary ataxias. SCAs usually are caused by microsatellite repeat expansions or by point mutations [9].

Recessive ataxias are a group of complex and rare hereditary degenerative diseases. The most frequent recessive

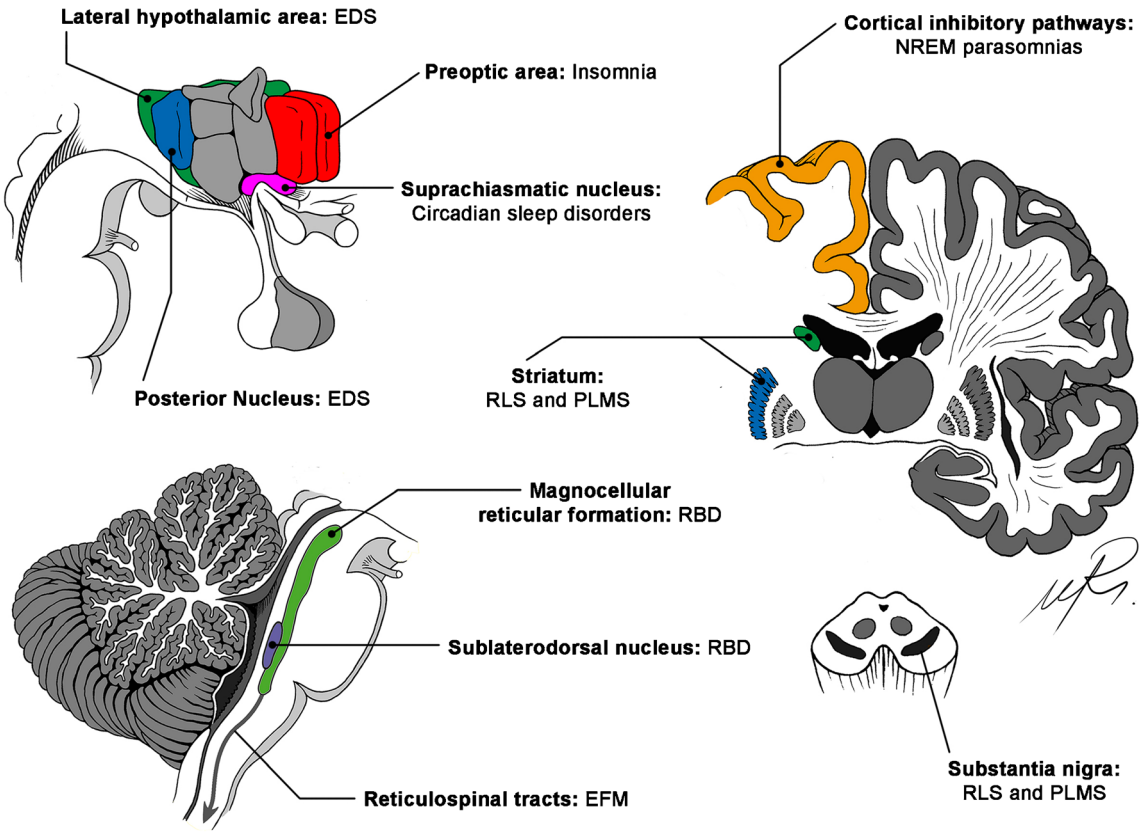

Fig. 1 Summary of the presumed anatomical structures involved in different types of sleep disorders related to neurological diseases. EDS excessive daytime sleepiness, NREM non-REM (sleep), RLS restless legs syndrome, PLMS periodic limb movements in sleep, RBD REM sleep behavioral disorder, EFM excessive fragmentary myoclonus

Table 1 Main sleep disorders related with the hereditary ataxia subtype

Subtype of hereditary ataxia	Most common related sleep disorders
SCA1	EDS, RLS, OSA
SCA2	EDS, insomnia, RBD, PLMD
SCA3	EDS, insomnia, RLS, PLMD, RBD, confusional arousal and sleep terrors, OSA
SCA6	Snoring, poor sleep efficiency
SCA10	EDS
SCA13	RLS and insomnia
SCA17	Laryngeal stridor
SCA 31	RBD
FXTAS	RLS, OSA
Friedreich ataxia	RLS, OSA, NREM parasomnia, nocturnal leg cramps
Ataxia telangiectasia	Hypoventilation during sleep
Joubert syndrome	OSA, central sleep apnea
CPEO	EDS, RLS
NARP	EDS, OSA, central sleep apnea
Keanr–Sayre syndrome	EDS
Leigh necrotizing encephalomyelopathy	EDS, OSA

SCA, spinocerebellar ataxia; *EDS*, excessive daytime sleepiness; *RLS*, restless legs syndrome; *OSA*, obstructive sleep apnea; *RBD*, REM behavior disorder; *PLMD*, periodic limbs movement disorder; *FXTAS*, Fragile X–associated tremor/ataxia syndrome; *CPEO*, chronic progressive external ophthalmoplegia; *NARP*, neurogenic muscle weakness, ataxia and retinitis pigmentosa

ataxias are Friedreich, ataxia–telangiectasia, and ataxia oculomotor apraxia (numbered from AOA1 to AOA4). In the last few years, especially after next-generation sequencing, many new genes and different phenotypes have been described. Common pathophysiological pathways for recessive ataxias include DNA repair deficiency, mitochondrial dysfunction, and abnormal protein folding and degradation [10].

Sleep Disorders in SCAs

As aforementioned, the most common SCAs are SCA1, SCA2, SCA3, and SCA6 [11, 12]. The degeneration involves predominantly the cerebellum and its connections, followed by brainstem and basal ganglia. The cardinal symptom is progressive cerebellar ataxia but other motor symptoms such as eye movement abnormalities, pyramidal, and extrapyramidal signs are also seen. Cognitive, psychiatry, dysautonomia, and other non-motor symptoms are nowadays well recognized, and sleep problems frequently may be a cause of impairment of quality of life in these patients [11, 12].

A large cross-section study with 123 patients with the most common SCAs (1, 2, 3, and 6) has demonstrated a high prevalence of 69% of the patients with severe fatigue. There was no significant relation between gender, age, disease duration, or SCA subtype [13]. Physical function and depression were the strongest predictive factors for the presence of severe fatigue. They also found a correlation of fatigue with sleep disturbances, characterized by 47% of poor sleep scored in the Pittsburgh Sleep Quality Index [14]. Patients related fatigue as mental slowness, especially in multitasking, so cerebellum, whose motor functions are related to executive control, attention, memory, and learning, may play a role in central fatigue model [13].

There are several evidences of each of the most common SCAs subtypes and specific sleep disturbances that we specify in the next topics and some case reports of the uncommon forms.

Sleep Disorders in SCA1

SCA1 is autosomal dominant ataxia caused by a CAG repeat expansion in the coding region of the ATXN1 gene at 6p22-p23. It is characterized by progressive cerebellar ataxia, dysarthria, and dysphagia [15]. There is little systematic evaluation of non-motor symptoms, but in a study of 12 Brazilian patients, all of them met criteria for clinically relevant fatigue in Modified Fatigue Impact Scale [16, 17]. There was a correlation between fatigue and disease duration, depression, and probably disease severity [16].

A series of two SCA1 cases have illustrated how hypersomnolence can impact the quality of life in these patients [18]. Excessive daytime sleepiness may be related with periodic limb movements and the consequent sleep fragmentation sleep onset difficulty in the context of RLS or comorbid obstructive sleep apnea as a manifestation of pharyngeal dilator muscle incoordination.

Sleep Disorders in SCA2

SCA2 is autosomal dominant ataxia caused by the expansion of the trinucleotide CAG repeats in the *ATXN2* gene. The disease is characterized by progressive cerebellar ataxia with saccade slowing, peripheral neuropathy and non-motor symptoms as cognitive dysfunctions and sleep disorders [19].

In an observational clinical and neurophysiology study of 32 Cuban SCA2 patients and controls, 21.8% complained of insomnia. Clinical event characteristics of REM sleep behavior disorder were reported by a bed partner of 2 patients. Evidence of snoring was found in 34.36% of the patients. Dream recall was sparse in more than half of the patients (56.25%), and restless legs syndrome was diagnosed in a quarter of the patients. PLM index was higher in these patients (37.5%) and had a significant association with disease duration and severity score. Regarding video-polysomnographic measures, total sleep time and sleep efficiency were

significantly decreased in SCA2 patients. Arousal index was increased in patients compared with controls. The analysis of sleep macro-architecture revealed an increase in sleep stage N1 and a reduction of sleep stage N2 and REM. Micro-architecture was also altered with reduction of REM density and augmented phasic EMG activity during REM with a higher percentage of REM sleep without atonia (RWA). RWA was substantially present in 31.3% of SCA2 patients. Analyses disclosed a significant association between the severity of motor symptoms and REM sleep percentage and REM density. The number of CAG repetition length had a significant correlation with the RWA percentage [20]. RBD has a high prevalence in SCA 2 patients, varying from 6.2 to 80% of patients according to different studies [21].

A definition of deterioration stages of REM sleep has been proposed in SCA2: a prodromal stage (I) when there is only a nonspecific disturbance with sleep fragmentation and possibly an inconspicuous reduction in REM sleep amount; a second stage (II) with REM density reduction, RWA, increased wakefulness, and sparse dream recall; a third stage (III) with more prominent REM density reduction, RWA, lack of dream recall, and increased REM latency; and a stage (IV) with REM loss, lack of dream recall, and increased slow wave sleep. These clinical stages are in resonance with the progressive anatomic degeneration, initially with loss of pontine REM-on neurons and later with degeneration of the subcoeruleus region and then thalamus. Thalamic degeneration in the later course of SCA2 is probably related to the advancement of REM sleep pathology because REM sleep is correlated with increased metabolic activities in the pons and thalamus [22].

Another factor involving REM sleep deterioration was recently described. REM sleep is most affected in so far as the disease progresses and disability increases with impairment of oculomotor movements. The slowness of saccades in the early stages of disease affecting the rapid eye movement during REM sleep has a strong negative correlation between the daytime oculomotor dysfunctions and nocturnal oculomotor activity (REM density) [23].

Even though some authors have reported excessive daytime sleepiness was not different from controls, it appears to be most prevalent in SCA2 patients [20]. In a Brazilian study, it was found that 42% had subjective somnolence on the Epworth Sleepiness Scale. The pathophysiological mechanisms involved are unclear but they are probably related to neurodegeneration of brainstem areas and other sleep disturbances [21].

Neuropsychiatry symptoms can surge as cause, consequence, or comorbidity such as sleep disorders. The European integrated project on SCA (EUROSCA) natural history study found that degenerative cerebellar diseases tend to be associated with depressive symptoms and the estimated prevalence of depression was 17.1% according to the Patient Health Questionnaire algorithm and 15.4% following clinical approach. A series of three cases of SCA2 from the same family showed strong interrelationships between insomnia, EDS, and depression. In these cases, symptoms of insomnia and EDS had improved after pharmacological treatment of depression. It is important to highlight that depression and sleep symptoms should be treated in parallel with better results [24].

Sleep Disorders in SCA3

Spinocerebellar ataxia type 3 (SCA3) or Machado–Joseph disease is the most common autosomal dominant subtype of ataxia worldwide. It is caused by the expansion of CAG trinucleotide repeats in the ATXN3 gene. It has a variable clinical spectrum characterized by progressive ataxia, ophthalmoplegia, nystagmus, extrapyramidal features, and non-motor symptoms including cognitive and psychiatry disturbances, olfactory dysfunction, and sleep disorders. The degenerative process in SCA3 involves not only the cerebellum, but also the pons, basal ganglia, midbrain, medulla, cranial nerves, peripheral nerves, spinal cord, thalamus, and frontal, parietal, temporal, occipital, and limbic lobes [25].

A high prevalence of sleep-related complaints in patients with SCA3 was found in a Brazilian population, while insomnia was the most frequently reported sleep disorder. Symptoms of insomnia were present in 37.7% and symptoms of sleep breathing disorders in 22.6% and clinical criteria of RLS in 20.7%. Insomnia was more frequent in older, male patients with more severe disease impairment [26]. The pathophysiological mechanisms of insomnia are not clear. Insomnia may be secondary to other symptoms that disrupt sleep quality, such as nocturnal pain and muscle cramps or as a consequence of intrinsic neurodegeneration of sleep-wake cycle structures such as hypothalamus and brainstem [27]. Almost 50% of individuals with insomnia also have psychiatric comorbidity [26].

Among all subtypes of SCAs, SCA3 has the highest prevalence of RLS reaching up to 55% of patients [28]. The pathogenic mechanism remains elusive and several studies tried to correlate with basal ganglia dysfunction, neuropathy, iron metabolism, and dopaminergic function. In view of the "dopaminergic hypothesis," one study failed to find a correlation between RLS and parkinsonian symptoms, although there are clinical, imaging, and anatomopathological evidence of basal ganglia and substantia nigra degeneration in SCA3 [28–31]. A correlation between RLS frequency and ataxia severity was described [32].

Similar to RLS, RBD is a common finding in SCA3 patients (Fig. 2). It may be present in up to 50% of patients, and its pathophysiology is also still poorly understood [27]. Anatomic involvements of the striatal dopaminergic system and brainstem circuits may participate, but this correlation between striatal dopamine transporter densities imaging and

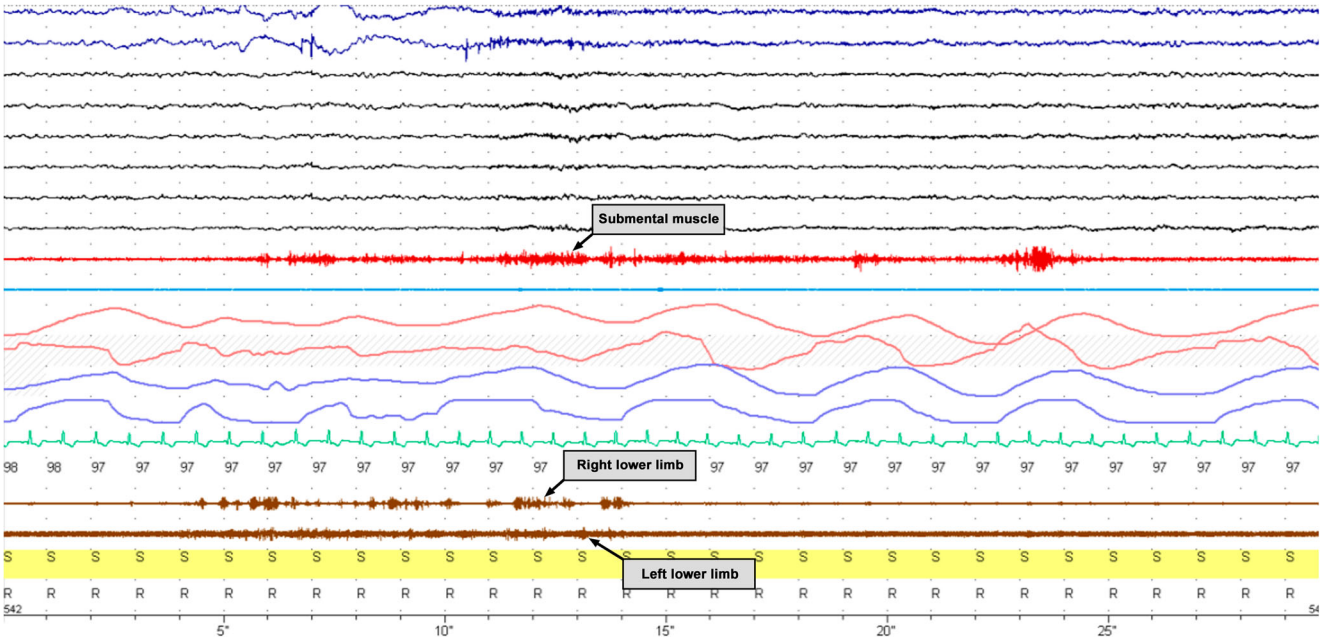

Fig. 2 Polysomnography of a patient with SCA3. There is a high amplitude of the submental muscle and lower limbs muscles characterizing the phenomenon REM without atonia for this interval (arrows). This patient had REM sleep behavior disorder

RBD was not found in one study [33]. A correlation was not found between the frequency of RBD and severity of ataxia [28]. It may be explained by the reduction of REM sleep percentage with the progression of ataxia symptoms [32]. Anxiety and depression were significantly correlated with the frequency of RDB, so in these patients non-motor psychiatric manifestations may have a stronger influence than ataxia-related motor features [28]. The treatment is important to reduce the risk of nighttime injuries, and it was described that SCA3 patients RBD symptoms responded to low doses of clonazepam [34].

Data about EDS are controversial. Although some studies have not found significant differences between patients and controls, other studies found a high frequency with prevalence rates ranging from 37.5 to 60% [27, 32, 35]. EDS is not correlated with ataxia severity, disease duration, or the expanded length of trinucleotide repeat [32].

In contrast to RBD, there are few studies describing NREM-related parasomnias in SCA3. Silva et al. demonstrated that 72% had arousals from slow wave sleep and higher complaints of arousal disorders and 40% of the patients had confusional arousals and sleep terrors. The pathophysiology of NREM-related parasomnia seen in SCA3 is unknown. Degeneration of midbrain cholinergic pathways related to higher rates of RBD may also play a role in triggering NREM-related parasomnia and a more diffuse structural damage in the central nervous system, affecting sleep-wake generating cells and their networking [36].

Although PLMS and excessive fragmentary myoclonus (EFM) are commonly observed in the general population, it is more common in neurodegenerative disease, especially in SCA3 patients. Dos Santos et al. [37] reported that half of the SCA3 patients had EFM during polysomnography (PSG) and it was more frequent in older participants. EFM is characterized by arrhythmic, asymmetric, and asynchronous jerks usually in the face, hands, or feet. Generally, the symptoms are not disabling and it is more common without clinical significant [27].

There are a small number of studies about sleep-related breathing disorders in SCA3; however, D'Abreu et al. noticed that patients have higher obstructive sleep apnea (OSA) according to standardized questionnaires than healthy controls. These patients with related snoring and possible OSA were older and with longer disease duration [26]. In China, a polysomnographic study showed that one-third of the patients had respiratory disturbance during sleep, but neither the average respiratory disturbance index nor the prevalence of respiratory disturbance was different between patients and controls [32]. Santos et al. found a similar prevalence in 34% of patients with apnea–hypopnea index (AHI) greater than 5 per hour. There were no correlations between AHI and ESS, severity ataxia scales, duration of symptoms, age at onset of symptoms, age, or body mass index. The pathophysiology involved in OSA is always complex, and it is influenced by anatomical, mechanical, functional, and neuromuscular mechanisms. Since vocal cord paralysis and dysphonia and laryngeals symptoms are frequent in SCA3, another specific mechanism in these patients is speculatively related to dystonia of the laryngeal and pharyngeal muscles or denervation of the laryngeal muscles as it is seen in multiple system atrophy [27, 34].

Sleep micro-architecture and other polysomnographic parameters are also disrupted in SCA3 patients. In contrast with healthy controls, they have decreased sleep efficiency, elevated arousal index, and more fragmented sleep (more sleep stage shifts, longer wake time after sleep onset, more percentage of stage 1 sleep). REM sleep abnormalities are common such as longer REM sleep latencies and less REM sleep quantity and density, as well as more REM sleep without atonia and REM with phasic chin tonus densities [32, 34]. Sleep spindles are reduced in SCA2 and SCA3 patients compared with healthy controls, and it has a decreasing trend in SCA1. The reduction in sleep spindle density can be related to thalamic degeneration and GABAergic dysfunction [38]. There is a correlation inversely proportional between sleep efficiency and REM sleep percentage with the severity of ataxia symptoms in SCA3 [32].

Sleep Disorders in SCA6

Spinocerebellar ataxia type 6 (SCA6) is another dominant ataxia, commonly characterized by pure late-onset cerebellar ataxia, associated with nystagmus and speech impairment. Extracerebellar symptoms and signs are classically described as rare. It is the most common SCA subtype in Japan, Germany, and Australia. The causative mutation is an abnormal expansion of CAG trinucleotide expansion in the CACNA1A gene, which encodes the alpha1A subunit of the P/Q-type voltage-gated calcium channel [39].

The major findings in studies of SCA6 and sleep disorders are a reduction in slow wave sleep, higher frequency of snoring, and awakenings related to respiratory effort in a Brazilian study of 12 patients and elevated PLMS with a fragmentary myoclonus index in a pilot study with 5 patients [40, 41]. Sleep disorders classically related to other types of SCA such as RBD, RLS, insomnia, and EDS were not seen in these studies. The reason that sleep disorders are less common in SCA6 may be due to the fact that SCA6 patients, in comparison with SCA1, 2, and 3, have less widespread involvement of the nervous system and sleep-wake related structures [40]. RLS may be more common in these other types of SCA because they suffer additional peripheral neuropathy which can be a trigger for RLS [41].

Sleep Disorders in SCA10

Spinocerebellar ataxia type 10 (SCA10) is a rare disorder, found predominantly in regions of Latin America, particularly Brazil and Mexico. The underlying defect is a pentanucleotide (ATTCT) repeat expansion in the ATXN10 gene. Clinically, the patients may present with cerebellar ataxia, dysarthria, abnormal eye movements, and seizures. The phenotype with pure ataxia is also commonly observed [42].

London et al. found frequent sleep REM changes in SCA10 than those in controls. The patients have longer REM sleep onset latencies and more REM arousals. Although 3 of 23 patients had a history of clinical RBD, no evidence of this disturb was found during full-night PSG. Forty-seven percent of SCA10 patients exhibited respiratory disturbances during sleep (RDI > 5), and there was no correlation between BDI and RDI. It was not observed in any patient with RLS or PLMS [43]. In complement with that, Moro et al. found that 32% of SCA10 patients presented significant fatigue. The specific physiopathology of fatigue remains elusive but is probably multifactorial. EDS was also more frequent in healthy control group similar to those with SCA3, affecting 35% of SCA10 patients [44].

Sleep Disorders in SCA13

Spinocerebellar ataxia type 13 (SCA13) is a rare subtype of autosomal dominant ataxia. It is characterized by dysarthria, nystagmus, and cerebellar ataxia. Clinical presentation is variable ranging from slowly progressing childhood-onset ataxia along with mild intellectual disability to adult-onset progressive ataxia. Patients with SCA13 have also a tendency to have epilepsy. It is caused by mutations in KCNC3, a gene encoding a voltage-gated potassium channel [45].

There are not enough studies to define the relationship between SCA13 and sleep disorders. Although Kapoor et al. has described a female patient with mild OSA, RLS, and psychophysiological insomnia, her RLS symptoms and insomnia responded well to the prescription of dopamine agonist [46].

Sleep Disorders in SCA17

Spinocerebellar ataxia type 17 (SCA17) is characterized by ataxia, dementia, and involuntary movements, including chorea and dystonia. Other common symptoms are psychiatric disturbs, pyramidal signs, and rigidity. The mutation is an abnormal polyglutamine CAG/CAA repeat expansion in the TBP gene [47].

Kim et al. described the occurrence of stridor during sleep in a patient with SCA17. The occurrence of stridor during sleep, as in multiple system atrophy is associated with an increased risk of sudden death [48].

Sleep Disorders in SCA31

Spinocerebellar ataxia type 31 (SCA 31) is a relatively common autosomal ataxia in Japanese population but uncommon in East Asian countries, and even more rare among Caucasian populations. It is characterized by slowly progressing pure cerebellar ataxia with or without nystagmus and hearing impairment [49]. Shindo et al. reported the case of a 67-year-old Japanese woman with SCA31 that evolved after 6 years of

ataxia onset with recurrent episodes of talking and calling out loudly with confirmed REM sleep without atonia in PSG. The reason why RBD occurred is not known, but there is a possible association with alpha-synucleinopathy, since MBIG uptake was reduced on cardiac scintigraphy [50].

Sleep Disorders in X-Linked Cerebellar Ataxia

X-linked cerebellar ataxias are a heterogeneous group of hereditary ataxias with polymorphic clinical conditions with cerebellar dysgenesis caused by gene mutations on the X chromosome. In childhood forms, the main symptoms are hypotonia, ataxia, other cerebellar signs, developmental delay, and intellectual disability, but other features may be present if there are other brain malformations and extraneurological involvement. It is described more than 20 genes in X chromosome whose mutation is related to ataxia and several families with X-linked inheritance ataxias. Few data are available about sleep in X-linked cerebellar ataxias [51, 52].

Sleep Disorders in Fragile X–Associated Tremor and Ataxia Syndrome

The FMR1 premutation is a common genetic condition found in 1 of 200 women and 1 of 400 men. By definition, it is characterized by an expansion of 55 to 200 CGG repeats in the FMR1 gene. When the expansion is over 200 CGG repeats, it silences completely the FMR1 and is related to fragile X syndrome. The premutation phenotype is variable and one possibility is the emergence of fragile X–associated tremor and ataxia syndrome (FXTAS). FXTAS clinically presents as late-onset intention tremor and/or gait ataxia and usually neuropathy and autonomic dysfunction [53].

Summers et al. found a significant relationship between the fragile X premutation and RLS with a prevalence of 33.1% and a relative risk of 1.86 in comparison with those healthy controls. Dopamine dysfunction is hypothesized and may play a role in the pathophysiology in these patients. Individuals with premutation have more severe insomnia, lower quality of sleep, and a trend to higher sleepiness level [54].

The relationship between sleep apnea and fragile X premutation was established by Hamlin et al. The prevalence of sleep apnea observed in patients with FXTAS was 31.4%, higher than that observed in premutation carriers without FXTAS and controls. There was a correlation between the severity stage of the disease with sleep apnea but not with the CGG expansion size and mRNA expression level of the premutation [55].

The rates of RLS and sleep apnea in FXTAS are similar to other neurodegenerative diseases. Sleep disorders can exacerbate psychiatric symptoms in these patients, and it may accelerate neuronal damage and loss and probably the progression of the disease. In conclusion, it is important to investigate sleep disorders in FXTAS because it may impact the quality of life, symptoms control, and severity of the disease [55].

Sleep Disorders in Recessive Ataxias

Friedreich Ataxia (FA)

Friedreich ataxia (FA) is the most common hereditary ataxia in the world. It is an autosomal recessive, multisystem disorder characterized by progressive cerebellar ataxia, peripheral neuropathy, scoliosis, diabetes, and hypertrophic cardiomyopathy. FA is caused by the expansion of GAA-trinucleotide in the first intron of the frataxin gene, resulting in a reduction of frataxin, a mitochondrial membrane protein related to iron homeostasis. Patients with FA have intramitochondrial iron accumulation in the heart, liver, nervous system, and spleen [56].

Fatigue is a frequent symptom reported by FA patients with impairment in quality of life. Corben et al. describe the relation between OSA and FA as one of the mechanisms of fatigue in these patients. The mean total respiratory disturb index was 18.66/h ± 18.2/h and OSA was present in, at least, 21% of the patients studied and only 2.4% with central sleep apnea, also associated with severe OSA. The risk of having OSA was 5.1 times higher compared with the general population prevalence. Different from the general population, in FA, BMI and sex had no correlation with OSA, indicating that other physiopathology and risk factors besides obesity and male gender may be involved which is usually the case with other OSA patients. OSA in degenerative ataxias may be related to vocal cord abduction palsy, as seen in spinocerebellar ataxias. Patients with longer and more severe disease had more frequent and severe OSA, which may corroborate the hypothesis that structural and functional defects in respiratory tract common in more affected patients, such as vocal cord palsy, reduced respiratory muscle strength, and kyphoscoliosis, are important factors to OSA pathogenesis [57].

Diagnosing and properly treating OSA are important in FA because it may ameliorate dysfunctional symptoms as EDS, and consequently the quality of life. In addition, OSA treatment may reduce oxidative stress and exacerbation of neurodegeneration, minimize cognitive impairment, alleviate cardiac stress in patients who are already at risk of hypertrophic cardiomyopathy, and reduce morbidity and mortality.

Another sleep disorder described in FA patients is RLS. Frauscher et al. [58] detected that 50% of patients had clinical criteria for RLS. The pathophysiological is complex and not completely elusive. It may be related to peripheral neuropathy and spinal sensory dysregulation, furthermore disturbed intracellular iron metabolism. Brain iron metabolism has been increasingly recognized to play an important role in RLS

pathogenesis [59]. Other less common sleep disturbances seen were confusional arousals, sleepwalking, and nocturnal leg cramps. REM sleep behavior disorder was not described [58].

Ataxia–Telangiectasia

Ataxia–telangiectasia (A-T) is a rare autosomal recessive ataxia characterized by cerebellar ataxia, cutaneous telangiectasias, immunodeficiency, recurrent pulmonary infections, and lymphoreticular malignancies [60]. Progressive bulbar muscle weakness is common, and life expectancy is approximately 25 years of age. Even though with respiratory complications, McGrath-Morrow et al. did not find frequent sleep-related obstructive respiratory events or nighttime hypoxemia in adolescents with A-T. Mild hypercapnia has been observed, and it may suggest incipient hypoventilation [61].

Sleep Disorders in Congenital Ataxias

Joubert syndrome (JS) is a rare autosomal recessive neurologic disorder affecting approximately 1:100,000 children and young adults. This disorder is characterized by anatomic malformations such as hypoplasia of the cerebellar vermis, thickening of the superior cerebellar peduncle, and deepening of the interpeduncular fossa, configuring the pathognomonic radiology aspect of "molar tooth sign" in cranial magnetic resonance imaging. The consequences of these deformities are hypotonia, developmental delay, ataxia, oculomotor apraxia, dysarthria, retinitis pigmentosa, and mental retardation [62]. Patients have frequent respiratory abnormalities due to the structural defects of the brainstem, specifically pontine and medullary central respiratory centers. Although respiratory symptoms during wakefulness are described since neonates with tachypnea and apnea, similar irregularities were seen during sleep [63]. The prevalence of OSA syndrome has been estimated by Kamdar et al. with a self-reported questionnaire. Thirty-three patients scored suggesting sleep-related breathing disorder, but 100% of the patients had at least one symptom related to sleep disorders [64].

Rana et al. reported two siblings with JS and sleep-related breathing disorders. A 10-year-old male with severe OSA and severe central sleep apnea and an 8-year-old female with mild OSA. The pattern of central respiratory events was intercalated by periods of tachypnea, characteristic of periodic breathing [65].

Sleep Disorders in Mitochondrial Ataxias

Mitochondrial diseases are generally multi-organ disorders, and patients are likely to be prone to sleep disturbances. Sleep disturbances are important to recognize, because they can have a profound negative effect on the quality of life and theoretically may impair mitochondrial function and aggravate mitochondrial diseases [66].

Chronic progressive external ophthalmoplegia (CPEO) is a relatively common mitochondrial disorder. Various organs are typically affected, such as extraocular muscle, laryngeal and limb muscles, cerebrum, cerebellum, and peripheral nerves. In a group of 20 CPEO, a 75% prevalence of subjective nocturnal dysfunction was found, 35% of patients with RLS and 30% with EDS [67].

Sembrano et al. reported the case of a 23-year-old woman with mitochondrial encephalomyopathy (NARP—neurogenic muscle weakness, ataxia, and retinitis pigmentosa) who developed severe OSA associated with central apnea in a context of neuromuscular weakness, obesity, tonsillar hypertrophy, and mild retrognathia. Because the patient refused positive airway pressure during sleep treatment, a tracheostomy was performed with polysomnographic improvement of AHI index and clinical benefit of excessive daytime sleepiness and mood disorder [68].

Kearns–Sayre syndrome (KSS) is a mitochondrial disease characterized by early onset of a symptomatic triad of ophthalmoplegia and atypical retinitis pigmentosa associated with heart block, cerebellar syndrome, or elevation of cerebrospinal fluid protein over 100 mg/dl. Kotagal et al. [69] described the case of an 11-year-old child with KSS who manifested persistent hypersomnia associated with sleep microarchitecture disruption with no sleep spindle activity due to symmetric thalamic lesions.

Leigh necrotizing encephalomyelopathy is another mitochondrial disease related to cerebellar ataxia. The symptoms usually begin in infancy or early childhood and are generally psychomotor regression, dysphagia, peripheral neuropathy, progressive muscle weakness, ataxia, and respiratory failure. The disease may involve adults with adult-onset ataxia, brainstem dysfunction, and polyneuropathy [70]. Charalampos et al. reported a 24-year-old student case of rapidly worsening severe dysarthria, ataxia, daytime sleepiness, fatigue, and poor sleep quality. She underwent PSG, and the diagnosis of severe OSA was concomitant with Leigh disease. Treatment with thiamine, coenzyme Q, L-carnitine, and vitamins C and E combined with nocturnal CPAP was initiated, and after 1 year clinical and radiological improvements of the disease were observed [71].

Conclusions

Hereditary ataxias are a group of diseases that usually affects other areas of the nervous system, besides the cerebellum. Noncerebellar signs and symptoms, such as sleep disorders, are frequent and sometimes unrecognized. The main sleep disorders related to hereditary ataxias include REM sleep behavior disorder (RBD), insomnia, excessive daytime sleepiness (EDS), obstructive and central sleep apnea, periodic leg movement in sleep

(PLMS), and restless legs syndrome (RLS). Recognition of sleep disorders in hereditary ataxias is mandatory, since these symptoms may be treatable. Moreover, the acknowledgement about the pathophysiological mechanisms related to sleep disorders in hereditary ataxias is crucial to better understand the natural history and neurodegenerative process in this group of diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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