Movement Disorders
CLINICAL PRACTICE
REVIEW

Movement Disorders Associated with Hypogonadism

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ABSTRACT: A variety of movement disorders can be associated with hypogonadism. Identification of this association may aid in guiding workup and reaching an accurate diagnosis. We conducted a comprehensive and structured search to identify the most common movement disorders associated with hypogonadism. Only Case Reports and Case Series articles were included. Ataxia was the most common movement disorder associated with hypogonadism, including entities such as Gordon-Holmes syndrome, Boucher-Neuhäuser, Marinesco-Sjögren and Perrault syndrome. Tremor was also commonly described, particularly with aneuploidies such as Klinefelter syndrome and Jacob's syndrome. Other rare conditions including mitochondrial disorders and Woodhouse-Sakati syndrome are associated with dystonia and parkinsonism and either hypo or hypergonadotropic hypogonadism. We also highlight those entities where a combination of movement disorders is present. Hypogonadism may be more commonly associated with movement disorders than previously appreciated. It is important for the clinician to be aware of this association, as well as accompanying symptoms in order to reach a precise diagnosis.

Functioning at all levels of the hypothalamic–pituitary-gonadal axis is necessary for normal gonadal development and deficiencies can lead to a hypogonadal state. The causes of hypogonadism are heterogeneous and involve any level of the reproductive system,[1] with primary testicular or ovarian end-organ failure resulting in hypergonadotropic hypogonadism and hypothalamic/pituitary failure resulting in hypogonadotropic hypogonadism. In addition, gonadal steroid hormones can have permanent organizational effects on the developing brain.[2]

Although rarely highlighted, a variety of movement disorders may be associated with hypo or hypergonadotropic hypogonadism as part of their clinical picture. Identification of this and the predominant phenomenology may narrow the differential diagnosis and aid with diagnostic workup. This poses implications not only for the correct diagnosis but also may have important therapeutic consequences, namely restoring sexual function and well-being, induce and/or maintain secondary sex characteristics, restore fertility, and improve bone mineral density and muscle mass.[1] In addition, the constellation of symptoms may also aid in the elucidation of mechanisms behind distinct movement disorders. In this paper, we present a comprehensive literature review covering the spectrum of conditions that can manifest with movement disorders and hypogonadism. We have arranged the conditions according to the predominant semiology and highlight those instances where a combination of movement disorders is present (Fig. 1).

Methods

We conducted a structured search in the Medline database via PubMed using the association of the following keywords: "hypogonadism" AND "ataxia," "dystonia," "chorea," "myoclonus," "tremor," or "parkinsonism" to identify the most common movement disorders associated with hypogonadism. Only Case Reports and Case Series articles were included. Publications written in English, Spanish, Portuguese and French, published up to January 1, 2021, were reviewed. Our search presented 340 articles. After excluding duplicates, articles where the full text wasn't available and those that did not include pertinent

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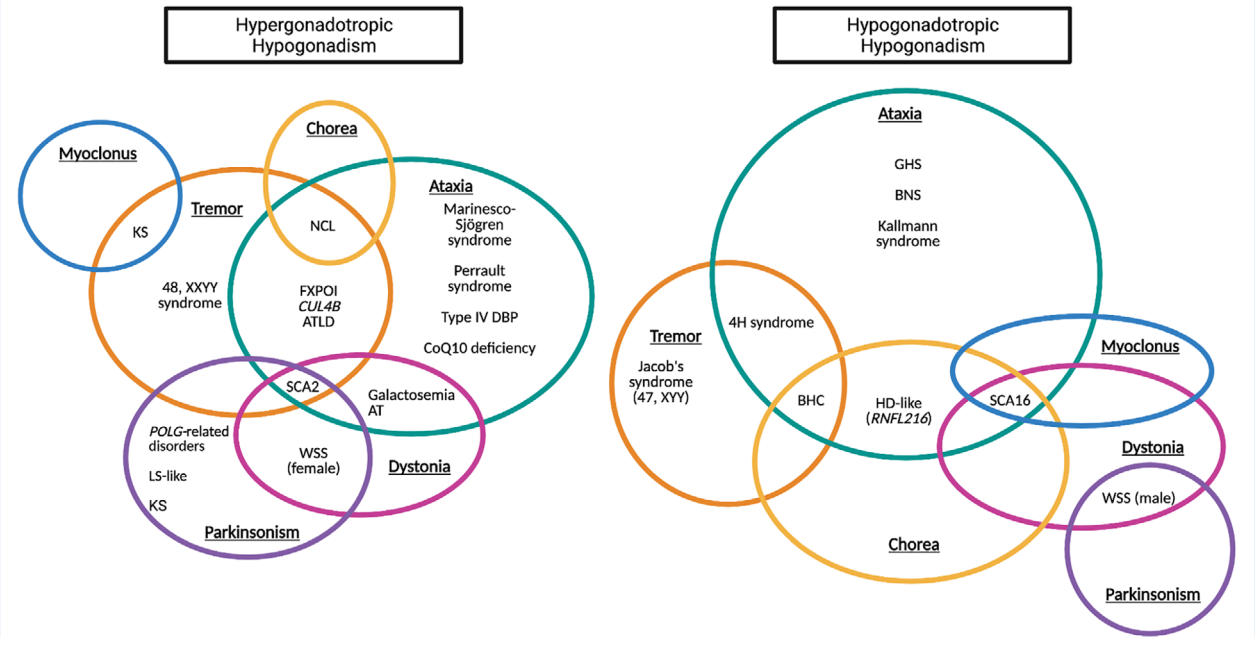

FIG. 1. Conditions presenting with specific movement disorders and hypogonadism. Conditions are classified according to type of hypogonadism (hyper or hypogonadotropic). Overlap between different "movement disorders" is represented by the intersection of the different shapes. ATLD, Ataxia-telangiectasia like disorder; AT, Ataxia-telangiectasia; BHC, Benign hereditary chorea; BNS, Bouchard-Neuhäuser syndrome; DBP, Peroxismal D-bifunctional protein; FXPOI, Fragile-X Primary ovarian insufficiency; GHS, Gordon-Holmes syndrome; HD, Huntington-disease; JS, Jacob's syndrome; KS, Klinefelter syndrome; LS, Leigh-syndrome; SCA2, Spinocerebellar ataxia type 2; SCAR16, Autosomal recessive spinocerebellar ataxia 16; WS, Woodhouse-Sakati.

clinical information, only 165 were included. Summary of the search strategy (Table S1) as well as clinical details of included cases (Table S2) can be found in the supplementary materials.

Hypogonadism and Movement Disorders

Hypothalamic–Pituitary-Gonadal (HPG) Axis

Pulsatile secretion of gonadotrophin-releasing hormone (GnRH) by the hypothalamus regulates activity of the pituitary-gonadal reproductive axis and leads to gonadarche, which refers to the onset of gonadal sex steroid production. GnRH secretion leads to release of the pituitary gonadotropins: luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates Leydig cell hyperplasia and testosterone release in males. FSH plays a role in sperm maturation in males and production of estradiol via ovarian follicular development. Testosterone and estradiol lead to the development of secondary sexual characteristics. Deficiencies at any level of the axis can lead to a hypogonadal state. Hypogonadotropic hypogonadism occurs with abnormalities within the hypothalamus or pituitary whereas hypergonadotropic hypogonadism is characterized by primary gonadal failure.[1] It is also of importance to distinguish congenital and acquired forms of hypogonadism. Acquired forms of hypogonadism should be suspected in a child with normal growth and sexual maturation until a certain age, who demonstrates sudden halt in growth and sexual maturation. Common acquired causes include central nervous system insults such as trauma, irradiation, intracranial tumors, nutritional status (such as anorexia nervosa), chronic disease, medication use, or psychosocial.[1] In adult patients, one of the most frequent causes of acquired hypogonadotropic hypogonadism is hyperprolactinemia. This can result mainly from the use of drugs that interfere with the dopaminergic system, prolactinomas, or from any hypothalamic or pituitary stalk disorder that interrupts hypothalamic inhibition of prolactin secretion.[3]

Clinical Approach to Hypogonadism

The clinical manifestations of hypogonadism vary according to the age of onset, severity of deficiency of sexual hormones, and gender. In children, hypogonadism is usually characterized by delayed development of secondary sex characteristics with or without delayed growth. Assessment of the patient's growth pattern is critical as well as whether there have been any signs of

pubertal development that subsequently disappeared or halted. Another important clue is to inquire about olfactory function and note any malformations such as midline defects, renal agenesis, syndactyly, or dental agenesis, since these are features suggestive of Kallmann syndrome.[4] In males, common signs suggestive of fetal hypogonadism are developmental anomalies associated with the genital system (such as micropenis, cryptorchidism, ambiguous genitalia, small testes), eunuchoid stature, scant facial, axillary and pubic hair and high-pitched voice. When hypogonadism develops during prepuberty, eunuchoid height, small testes and penis, scant facial, axillary, and pubic hair, and high-pitched voice continue to be common features. After puberty, height is usually normal, testes and penile atrophy is less pronounced, facial, axillary and pubic hair are usually thinner and it is common to present a lack of male pattern of baldness. Adult men may present with decreased libido, erectile dysfunction, low energy, low mood, sleep disturbance, gynecomastia, or infertility. Of note, in hypergonadotropic hypogonadism, spermatogenesis tends to be impaired to a greater degree than Leydig cell function, at least in its early stages. In contrast, both functions are impaired to the same degree in hypogonadotropic hypogonadism. Gynecomastia is more likely to occur in hypergonadotropic hypogonadism.[5]

Females with hypogonadism usually present with primary amenorrhea, underdeveloped breasts, short stature, eunuchoidism, or infertility. Post-pubertal clinical manifestations include secondary amenorrhea, hot flashes, decreased libido, galactorrhea, or symptoms suggestive of androgen excess, such as acne or hirsutism, changes in mood and energy levels, and osteoporosis.[4] Hypergonadotropic hypogonadism is most common in women, where Turner's syndrome and idiopathic ovarian failure are common causes.[1]

The above symptoms and signs are listed only to highlight the most common features that may alert the clinician to the presence of a possible association with an hypogonadal state. If suspected and confirmed on preliminary screening (see below) it should be complemented by a full endocrinological assessment.

Diagnostic Approach to Hypogonadism in Movement Disorders

A complete and comprehensive approach to hypogonadism is outside the scope of the present review and should be conducted by the respective medical specialties. It is important to note that different ages of onset may require different approaches; the present section will focus mostly on the screening assessment of adult patients. Measuring the levels of gonadal hormones in serum, namely testosterone and estradiol as well as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) should be the first step. If low levels of gonadal hormones are observed, a second confirmatory test should be obtained.[3,6] In some men, in whom total testosterone is near the lower limit of normal, measurement of free or bioavailable testosterone levels is recommended.[3] A diagnosis of hypergonadotropic hypogonadism should be suspected if the serum testosterone or estradiol levels are low and the LH and FSH levels are elevated. If LH and FSH levels are low or inappropriately normal, hypogonadotropic hypogonadism is the suspected diagnosis. In this context, anterior pituitary function must be also investigated to rule out a more complex endocrine disorder with multiple hormone deficiencies. If a more complex endocrine disorder is suspected, thyroid stimulating hormone (TSH), free T4, insulin-like growth factor 1 (IGF-1) and growth hormone (GH) can be used to evaluate the somatotropic axis. Prolactin levels should be assessed if acquired causes of hypogonadism are suspected.[3] The practical value of measuring gonadotropin-releasing hormone (GnRH) levels has been questionable because of its low cost-effectiveness, particularly since baseline GnRH values provide no clear additional diagnostic information relative to baseline gonadotropin levels.[3] Nonetheless, stimulation of the pituitary gland with GnRH can be used if basal hormone measurements are indeterminate or if there is strong clinical evidence of a multiple pituitary hormone deficiency.[6]

In the prepubertal period, the evaluation of hypogonadotropic hypogonadism may be difficult due to physiological quiescence of the hypothalamic–pituitary-gonadal axis. Inhibin B is produced by Sertoli cells in males and serves as a marker for functioning of seminiferous tubules. Inhibin B levels are low in hypogonadotropic hypogonadism and can differentiate this entity from constitutional delay of puberty.[3]

Movement Disorders with Hypogonadism

Cerebellar Ataxia and Hypogonadism

Isolated Cerebellar Ataxia and Hypogonadism

The combination of cerebellar ataxia and hypogonadism is frequently encountered in patients with autosomal-recessive cerebellar ataxias. The most common causes include Gordon Holmes syndrome (GHS) and Boucher-Neuhäuser syndrome (BNS). GHS was first described in 1907[7] and is characterized by the clinical association of ataxia, hypogonadotropic hypogonadism and progressive cognitive decline. Symptom onset is usually in the second or third decade.[8–16] Hypogonadotropic hypogonadism has been described in most cases, although some patients experience normal puberty followed by oligomenorrhea and amenorrhea in women and erectile dysfunction in men.[17] GHS is most often caused by mutations in the *RNF216* gene, which encodes an E3 ubiquitin ligase and plays a role in the ubiquitin-proteasome system; specifically, GHS-associated variants lead to a loss of ubiquitination activity.[18] Interestingly,

inactivating mutations in other ubiquitination-related genes including *STUB1*[11,19] and *OTUD4*[17] have also been associated with GHS.

Similar to Gordon Holmes syndrome, BNS presents with a combination of cerebellar ataxia and hypogonadotropic hypogonadism. Visual impairment due to chorioretinal dystrophy is a consistent feature.[20] Age of onset has ranged from age 1 to 40, with ataxia or vision loss being the most common initial symptoms. Pyramidal tract signs and peripheral neuropathy are also frequent features. Chorioretinal degeneration has been reported in all cases.[10,13,21–28] Hypersegmented neutrophils can also be found.[25,29] The most commonly associated causative gene, *PNPLA6* (patatin like phospholipase domain containing 6) is involved in neuronal differentiation and gonadotropin release from the pituitary gland, mediated through impaired vesicular transport.[13,14] Interestingly, several cases of GHS have also been associated with the *PNPLA6* gene.[9,10,22] A 5.5 Kb mitochondrial DNA (mtDNA) deletion causing respiratory chain complex I deficiency has also been associated with BNS.[30]

Marinesco-Sjögren syndrome (MSS), characterized by cerebellar ataxia, congenital cataracts and delayed psychomotor development,[31] has also been associated with hypogonadism. Most patients present before age 5, with ataxia or cataracts. Hypergonadotropic hypogonadism has been described in two-thirds of reported patients.[32] Myopathy is common and has been confirmed with EMG or muscle biopsy in almost all tested patients.[32] MSS is associated with homozygous or compound heterozygous variants in the SIL1 nucleotide exchange factor (*SIL1*) gene.[32–34] *SIL1* encodes a nucleotide exchange factor for the heat-shock protein (HSP70) and plays an important role in the degradation of misfolded proteins and response to cellular stress, suggesting that MSS is a disease of endoplasmic reticulum dysfunction.[32,33,35]

Perrault syndrome is a recessive disorder characterized by sensorineural deafness in both males and females and ovarian dysgenesis in females. Some patients also have neurological manifestations including mild developmental delay and cerebellar involvement.[36] Due to its clinical heterogeneity, Perrault syndrome can be classified into type I, which is usually static and without neurologic disease and type II with progressive neurologic disease.[36] Perrault syndrome is also genetically heterogeneous, with variants described in the *HSD17B4* gene,[36] *HARS2* gene,[37] *CLPP* gene,[38] *LARS2* gene,[39] *TWNK* gene.[40] Peroxismal D-bifunctional protein (DBP) deficiency can overlap clinically with Perrault syndrome and is also associated with variants in the *HSD17B4* gene.[41] Recently, a clinical entity termed "**type IV DBP deficiency**" was described in four patients with a juvenile-onset condition comprising cerebellar ataxia, hearing loss, peripheral neuropathy and premature ovarian failure.[36,42] Interestingly, in contrast to infantile onset DBP deficiency, phytanic acid accumulation in peripheral blood and very long-chain fatty acids are not found in juvenile-onset DBP (ie, type IV). This is important to highlight since these are routinely considered valuable screening tests for types I, II and III DBP.[43]

The presence of hypogonadotropic hypogonadism and anosmia characterize **Kallmann syndrome**.[44] Kallmann syndrome can also present with central nervous system symptoms including sensorineural deafness and synkinesia.[45] Cerebellar dysfunction with dysmetria, dysarthria and ataxic gait has also been reported[46] and foot dystonia has been described in one case.[45]

Several genes have been associated with this syndrome, including *KAL1, FGFR1, FGF8, PROKR2*, and *PROK2*; nonetheless variants in these genes account only for 30% of all cases,[47] suggesting that most cases are sporadic.

Ataxia Associated with Other Movement Disorders and Hypogonadism

Autosomal recessive spinocerebellar ataxia type 16 (SCAR16) is a progressive neurologic disorder originally characterized by truncal and limb ataxia, dysarthria, nystagmus, hyperreflexia, spasticity, cognitive impairment, and peripheral sensory neuropathy.[15] Hypogonadotropic hypogonadism has been described in some cases, although it is not an obligatory feature.[19,48,49] In described cases, mean age of symptom onset is 20.4 $\pm$ 13.9 years. Other hyperkinetic movements including chorea, athetosis, dystonia and myoclonus can accompany ataxia.[19,48] **Spinocerebellar ataxia 48** (SCA48) is characterized by gait ataxia and cognitive symptoms. Variable symptoms include parkinsonism, tremor, chorea and dystonia. Hypogonadotropic hypogonadism has been described in only one case.[50] Interestingly, apart from cerebellar atrophy, brain MRI images in a case series of SCA48 patients confirmed the common occurrence of T2-weighted signal hyperintensities in the dentate nuclei,[50] a feature also described in other disorders such as SPG7 patients, Alexander's disease, Canavan's disease, glutaric aciduria, Wilson's disease and metronidazole toxicity.[51] SCAR16 and SCA48 have been associated with variants in the STIP1 homologous and U box-containing protein 1 (*STUB1*) gene (biallelic mutations in SCAR16 and heterozygous mutations in SCA48). *STUB1* is an E3 ubiquitin ligase that participates in protein quality control, by targeting misfolded chaperone protein substrates for degradation.[52] As noted above, variants in this gene have also been associated with GHS.

The **4H syndrome** is characterized by hypomyelination, hypodontia and hypogonadotropic hypogonadism[53] and belongs to a group of Pol III-related leukodystrophies. Neurological manifestations include progressive ataxia and pyramidal findings.[54] Additional findings include tremor, spasticity, dysarthria and hypometric saccades.[53,55,56] Most cases have been associated with *POLR3A/3B* gene mutations. *POLR3A* encodes the largest subunit of the DNA-dependent RNA polymerase III.[57] This same phenotypical expression has been described in a young adult with clinical symptoms of the 4H syndrome due to a novel homozygous mutation in the Ring Finger Protein 216 (*RNF216*) gene expanding the list of genetic conditions associated with this clinical syndrome.[58]

Delayed puberty and early menopause due to premature ovarian failure are common among patients with **ataxia-telangiectasia (AT).**[59] AT may be associated with a variety of different movement disorders in addition to ataxia including

dystonia, parkinsonism, choreoathetosis, myoclonus and tremor.[60] AT is caused by variants in the *ATM* gene, which encodes for a phosphatidylinositol 3-kinase, which phosphorylates key substrates involved in DNA repair and cell cycle control.[60] Hypergonadotropic hypogonadism has also been described in a 14-year-old female with **ataxia-telangiectasia-like disorder (ATLD)** caused by a variant in the *MRE11A* gene. She had progressive cerebellar ataxia, bilateral intention tremor and oculomotor apraxia since age 2. At age 14 she also developed a focal limb dystonia when writing.[61] *MRE11A* also participates in telomere length maintenance and DNA double-strand break repair.[62]

Heterozygous sequestome 1 (*SQSTM1*) gene variants have been recently associated with a progressive childhood-onset neurodegenerative disorder characterized by cognitive decline, ataxia, dystonia, and gaze palsy. Hypergonadotropic hypogonadism has been described in two cases.[63,64]

Tremor and Hypogonadism

Isolated Tremor and Hypogonadism

Isolated tremor and hypogonadism occur in a number of chromosomal aneuploidy disorders, most notably **Klinefelter syndrome (KS, 47,XXY)**. KS is the classical male form of hypergonadotropic hypogonadism due to primary testicular failure and the most common chromosomal aneuploidy, with a prevalence of 0.1% to 0.2% in the general population.[65] In these patients, tremor is present predominantly in the upper limbs while holding a posture and with action, resembling an Essential Tremor-like (ET-like) phenotype. Less commonly, voice and head tremor, as well as resting tremor have been described.[66] Tremor prevalence seems to be greater compared to the general population.[67] A recent series included 44 KS patients and 95 controls with XXY genotype without other features of KS; a significantly higher number of KS patients reported experiencing an action tremor. Accelerometry and surface EMG findings were similar to those of ET.[68] Compared to ET, only a small proportion of patients had a positive family history. Although imaging is normal in most cases, there is a case report that demonstrated lesions affecting the subcortical white matter, with multiple white matter T2/Flair hyperintensities in both hemispheres, confluent in subcortical frontal areas, as well as in putamen and thalamus.[66] In regard to treatment, response to propranolol and other medications commonly used in ET remains inconclusive, although there have been cases reported with response to deep brain stimulation of the ventral intermediate nucleus of the thalamus.[69] Interestingly, there is one case report of tremor improvement after initiation of testosterone supplementation.[70] Importantly, while hypogonadism is a characteristic finding, the degree of abnormalities may differ between patients and sometimes only subtle findings suggest the diagnosis. Thus, male patients with presumed essential tremor, should also be evaluated for features consistent with KS.[65]

Another common aneuploidy is the **Jacob's syndrome (JS, 47, XYY)**, which affects 1 of every 1000 males.[71] In a cohort of 90 patients with 47, XYY karyotype, 43% had a mild resting or intention tremor. Seizures were more prevalent than in the general population. Cognition seems to be associated with timing of diagnosing and a lower IQ has been described for those diagnosed postnatally. Decreased fertility, with elevated FSH levels and low inhibin B have also been described in some patients.[72]

48, XXYY syndrome is a form of sex chromosome aneuploidy that affects between 1 in 18,000 and 1 in 40,000 males. The phenotype is similar to KS and interestingly, a prominent postural and kinetic tremor of the upper limbs is common and becomes more prevalent with age, affecting 71% of patients over age 20.[73] In a recent case report, surface EMG from wrist flexor and extensors showed segregated 5–7 Hz bursts on posture and intention.[74] No benefit has been described with medications commonly used for ET.[73]

Tremor Associated with Other Movement Disorders and Hypogonadism

Among the reports evaluated in our literature review, tremor was most commonly associated with ataxia.

Primary ovarian insufficiency (POI) is characterized by at least 4 months of unpredictable or absent menstrual periods and two serum FSH levels in the menopausal range at least 1 month apart.[75] POI has been associated with a "premutation" state in the *FMR1* gene, which is the cause of Fragile X syndrome.[76] Ovarian insufficiency occurs as early as 11 years of age, presenting with primary amenorrhea and delayed puberty and women have high rates of infertility and menopausal-type symptoms.[76] Elevated rates of neurologic findings such as tremor and ataxia have been reported in individuals carrying a premutation. A study of 110 daughters of men with the Fragile X Tremor Ataxia Syndrome (FXTAS) demonstrated an increased incidence of neurologic symptoms including tremor and "balance problems," compared to controls.[77]

Hypergonadotropic hypogonadism and POI are frequent long-term complications of classic **galactosemia**.[78] Long-term complications also include tremor, cerebellar ataxia and dystonia.[79] Galactosemia is caused by a deficiency in Galactose-1-phosphate uridylyltransferase (GALT). Interestingly, there seems to be an association between GALT enzyme activity and long-term complications. Demirbas et al (2019) reported on 160 individuals with galactosemia; among them, ataxia, dystonia, tremor and POI occurred more often in patients with 0% GALT activity. These symptoms occur despite strict adherence to a lactose-free diet.[80]

Cabezas et al (2000) described a syndrome consisting of mental retardation, small testes, short stature, muscle wasting and tremor.[81] A recent case series of 250 families with **X-linked mental retardation** identified 18 patients from eight additional families. Intention tremor was present in 65% of cases, 50% had gait ataxia and 100% had mental retardation, speech delay, short stature, and macrocephaly. Pes cavus, wasted lower-leg muscles, prominent lower lip and kyphosis were also common. The type of hypogonadism was not specified but the authors reported

small testes in 67% and gynecomastia in 70% of the cases. Interestingly, known heterozygote females are essentially normal, although one case with multiple tics, attention deficit disorder and a fine tremor has been reported.[82] Missense, nonsense and splice-site variants in the *CUL4B* gene are causative.[82] *CUL4B* functions as scaffold proteins for a series of ubiquitin-protein ligase complexes. *CUL4B* is also involved in processes relating to DNA repair and cell-cycle progression, although there is no indication of cancer susceptibility in individuals with mutations in this gene.[82]

Another uncommon cause of tremor and ataxia with hypogonadism is **spinocerebellar ataxia type 2 (SCA2)**. Hypogonadism seems to have only been reported in one case, a 45-year-old man with a 37 CAG triplet expansion in the *ATXN2* gene, who manifested hypergonadotropic hypogonadism (azoospermia, micropenis and microorchidism with normal secondary sexual characteristics), unilateral hand resting tremor, impaired balance, slow saccades, upper motor neuron signs and bilateral proprioception impairment and marked atrophy of cerebellum and pons on brain imaging.[83]

A remote case report described two related patients, with cerebellar ataxia, bilateral postural and action hand tremor, head tremor, upper motor neuron signs, and sensorineural hearing loss. These patients had other male family members affected by the same problems and with a hypergonadotropic form of hypogonadism. This disease was termed **"X-linked Familial spastic paraparesis and deafness"** and no further characterization was made since no molecular diagnosis was available at that time.[84]

Myoclonus and Hypogonadism

There are few reports of hypogonadism associated with myoclonus. Myoclonus was a predominant symptom in a 27-year-old man with **Klinefelter Syndrome** who displayed continuous, irregular distal jerky movements of the hands and legs as well as proximal jerks in the trunk. EMG was consistent with myoclonus. Further work-up also showed primary hypogonadism with a testosterone level of 4.1 nmol/L (normal range:11–35 nmol/L). Interestingly, as previously reported in some patients with tremor in KS,[70] myoclonus improved once testosterone was restored to normal levels.[85] This suggests that, in male patients with unexplained tremor or myoclonus, one should screen for symptoms of KS and consider evaluating for hypogonadism with FSH, LH and testosterone, and excluding aneuploidies in appropriate cases.

In most reviewed cases, other movement disorder, such as ataxia, chorea or parkinsonism, is predominant. Some examples include SCAR16, ataxia-telangiectasia, SCA2, benign hereditary chorea and Leigh-like syndrome. These have been further described in their corresponding sections and have been highlighted in Table 1.

Dystonia/Parkinsonism and Hypogonadism

Woodhouse Sakati syndrome (WSS) is a rare autosomal recessive neuroendocrine disorder first described in 1983 in six patients from Saudi Arabia.[86] Symptoms include a distinct facial appearance with a long triangular face, prominent nasal bridge and hypertelorism, as well as alopecia, hypogonadism, diabetes mellitus, intellectual disability and sensorineural deafness.[87] Neurological manifestations are characteristically progressive, with movement disorders being a predominant symptom, including dystonia and parkinsonism.[88] Body stature is often short due to abnormal sexual hormone function.[89] Brain MRI findings are characterized by progressive fronto-parietal white matter changes, basal ganglia iron deposition and a small pituitary gland.[90] Homozygous pathogenic variants in the *DCAF17* gene have been described as the underlying cause.[91] A recent study characterized all cases of WSS at a research center in Saudi Arabia and included 38 individuals, all with the same founder *DCAF17* frameshift deletion. Dystonia was the most common neurological manifestation and focal dystonia was the most common form, with a significant percentage progressing to generalized dystonia. Rigidity, tremor, ataxia and choreoathetosis were also described in this cohort. Two distinct phenotypes were identified: Type 1 with younger onset (12.6 +/− 4.5 years) and more rapid progression, including significantly more intellectual disability, and Type 2, with later onset (18.1 +/− 4.3 years) and milder (or even absent) manifestations including non-levodopa responsive parkinsonian syndrome.[92] Hypogonadism in WSS is mixed in origin, with females presenting with hypergonadotropic hypogonadism while males tend to have characteristics of hypogonadotropic hypogonadism. Both genders share an insufficient hypothalamic–pituitary response to stimulation with GnRH.[88]

Parkinsonism and Hypogonadism

Most of the cases of parkinsonism associated with hypogonadism have been reported in the setting of **mitochondrial disorders**. Mutations in *POLG* (mitochondrial DNA polymerase γ) gene represent the most common causes of autosomal inheritance of mitochondrial disease[93] and *POLG* mutations are a common cause of **autosomal dominant progressive external ophthalmoplegia (adPEO)**. Premature menopause and progressive external ophthalmoplegia are linked to POLG *pol*-domain mutations.[94] Affected women present premature ovarian failure while testicular atrophy has been described in men.[95] These may be due to a defect in steroidogenesis, likely due to mitochondria defects. Neurologically, adPEO is further characterized by generalized myopathy, variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, and parkinsonism. In a series including seven families, symptoms usually started with hemiparkinsonism responsive to levodopa. Progressive external ophthalmoplegia developed between 10 and 54 years of age. Other common symptoms included cataracts and peripheral sensory neuropathy. Secondary amenorrhea co-segregated with progressive external ophthalmoplegia, with most women presenting a late menarche or cessation of menstruation after one pregnancy.[96]

Leigh-like syndrome refers to cases that are clinically or neuroradiologically suggestive of Leigh syndrome (LS). One case

TABLE 1 Movement disorders presenting with hypogonadism

Syndrome	Genes	Associated movement disorder	Associated clinical findings	Hypogonadism	Imaging
Ataxia					
Marinesco-Sjögren syndrome	*SIL1*	Ataxia	Cataracts; developmental delay; myopathy; skeletal abnormalities	Hypergonadotropic	Cerebellar atrophy
Gordon-Holmes syndrome	*RNF216* *STUB1* *OTUD4* *PNPLA6*	Ataxia	Progressive cognitive decline	Hypogonadotropic	Diffuse supratentorial white matter hyperintensities Cerebellar and cortical atrophy
Boucher-Neuhäuser syndrome	*PNPLA6* 5.5 Kb mitochondrial DNA deletion	Ataxia	Chorioretinal dystrophy; oculomotor abnormalities; horizontal gaze-evoked nystagmus	Hypogonadotropic	Cerebellar atrophy Brainstem atrophy Subcortical T2-white matter hyperintensities. Small pituitary
Perrault syndrome	*HSD17B4* *HARS2* *CLPP* *LARS2* *TWNK*	Ataxia	Sensorineural deafness	Hypergonadotropic	Cerebellar atrophy
Type IV DBP deficiency	*HSD17B4*	Ataxia	Hearing loss; peripheral neuropathy	Hypergonadotropic	Cerebellar atrophy
Kallmann syndrome	*ANOS1* *KAL1* *FGFR1* *FGF8* *PROKR2 PROK2*	Ataxia	Sensorineural deafness; anosmia; synkinesia; congenital paresis of cranial nerves VII, III; unilateral renal agenesis; brachydactyly of fourth metacarpal	Hypogonadotropic	Abnormal or absent olfactory bulbs Agenesis of corpus callosum Dandy-Walker malformation
SCAR16	*STUB1* (biallelic mutations)	Ataxia; chorea; dystonia; myoclonus	Cognitive impairment; nystagmus; hyperreflexia; peripheral sensory neuropathy	Hypogonadotropic	Cerebellar atrophy
SCA48	*STUB1* (heterozygous mutations)	Ataxia; parkinsonism; tremor; chorea; dystonia	Cognitive impairment	Hypogonadotropic	Atrophy of cerebellar vermis Bilateral T2-weighted hyperintensities of dentate nuclei ("crab sign")

(Continues)

TABLE 1 *Continued*

Syndrome	Genes	Associated movement disorder	Associated clinical findings	Hypogonadism	Imaging
4H Syndrome (hypomyelination, hypodontia and hypogonadotropic hypogonadism)	*POLR3A/3B RNF216*	Ataxia; tremor	Hypodontia; dysarthria; hypometric saccades	Hypogonadotropic	Hypomyelination of the supratentorial white matter Thin corpus callosum Prominent cerebellar atrophy Extensive T2-weighted white matter hyperintensities[a]
Ataxia-telangiectasia	*ATM*	Ataxia; dystonia; parkinsonism; chorea; myoclonus; tremor	Sinopulmonary infection; malignancy; conjunctival telangiectasias; oculomotor apraxia	Hypergonadotropic	Cerebellar atrophy
Ataxia-telangiectasia-like disorder	*MRE11A*	Ataxia; tremor; dystonia	Oculomotor apraxia	Hypergonadotropic	Cerebellar atrophy
Sequestome 1 associated neurodegenerative disorder	*SQSTM1*	Ataxia; dystonia; chorea	Ophthalmoparesis; cognitive impairment	Hypergonadotropic	Cerebellar atrophy; iron accumulation in basal ganglia
Tremor					
Klinefelter syndrome (47, XXY)		Postural and action tremor of upper extremities; ataxia; myoclonus; parkinsonism	Gynecomastia; cognitive and behavioral abnormalities; tall stature	Hypergonadotropic	Normal in most cases
Jacob's syndrome (47, XYY)		Resting or action tremor	Tall stature; macrocephaly; macroorchidism; hypotonia	Hypogonadotropic	Normal in most cases
48 XXYY syndrome		Postural and kinetic tremor of upper extremities	Tall stature; learning or behavioral disorders; dental problems; ADHD; asthma	Hypergonadotropic	Normal in most cases
Fragile X Primary Ovarian insufficiency syndrome	*FMR1*[b]	Tremor; ataxia	Primary ovarian insufficiency	Hypergonadotropic	Normal in most cases
Galactosemia (Long-term complications)	*GALT*	Tremor; ataxia; dystonia	Developmental and language delay; dysarthria	Hypergonadotropic	Cerebellar atrophy Frontoparietal white matter abnormalities

(Continues)

TABLE 1 *Continued*

Syndrome	Genes	Associated movement disorder	Associated clinical findings	Hypogonadism	Imaging
Mental retardation, X-linked, syndromic 15	*CUL4B*	Tremor; ataxia	Mental retardation; speech delay; short stature; macrocephaly; microorchidism; gynecomastia	Unspecified	Ventriculomegaly Simplified gyral pattern Cortical dysplasia Thin corpus callosum Cerebellar vermis atrophy
SCA 2	*ATXN2*	Tremor; ataxia; parkinsonism; dystonia; myoclonus; chorea.	Upper motor neuron signs; slow horizontal saccades; reduced vestibulo-ocular reflex; ophthalmoplegia; peripheral neuropathy; dysautonomia; dleep disorders (RLS, PLMS, RBD)	Hypergonadotropic[c]	Pontine and cerebellar atrophy
Parkinsonism and dystonia					
Woodhouse Sakati syndrome	*DCAF17*	Dystonia-parkinsonism	Long triangular face; prominent nasal bridge; hypertelorism; alopecia; short stature; diabetes mellitus; intellectual disability; sensorineural deafness	Females: Hypergonadotropic Males: Hypogonadotropic	Progressive fronto-parietal white matter changes Basal ganglia iron deposition (variable) Small pituitary gland
POLG-related disorders	*POLG*	Parkinsonism	Progressive external ophthalmoplegia; generalized myopathy; sensorineural hearing loss; cataracts; sensory axonal neuropathy; ataxia; depression; diabetes mellitus	Hypergonadotropic	Stroke-like lesions T2-hyperintense thalamic, basal ganglia and cerebellar lesions Generalized brain atrophy Enhancement of bilateral cranial nerves (III, V, to X) and cervical nerve roots T2-hyperintensity in inferior colliculus
Leigh-like syndrome	*>75 genes*	Dystonia; ataxia; chorea; ballism; athetosis; myoclonus; parkinsonism	Relapsing encephalopathy; developmental delay or psychomotor regression; external ophthalmoplegia; seizures; lactic acidosis; myopathy; peripheral neuropathy; diabetes mellitus; short stature; hypertrichosis; cardiomyopathy; renal failure; vomiting or diarrhea	Variable	Necrotic lesions with spongy changes and microcysts in basal ganglia (putamina and caudate nuclei), thalamus, substantia nigra, brainstem, and spinal cord

(Continues)

TABLE 1 *Continued*

Syndrome	Genes	Associated movement disorder	Associated clinical findings	Hypogonadism	Imaging
Chorea					
Huntington-disease-like	*RNF216*	Chorea; ataxia	Cognitive decline; behavioral abnormalities; personality changes	Hypogonadotropic	Cortical and cerebellar atrophy Diffuse white matter lesions in the cerebellum Atrophy of the putamen
Benign hereditary chorea	*NKX2-1*	Chorea; ataxia; dystonia; myoclonus	Motor developmental delay; microcephaly; hypotonia; short stature; pyramidal signs; congenital/compensated hypothyroidism; neonatal respiratory distress; interstitial lung disease; pulmonary fibrosis	Hypogonadotropic	Normal in most cases
Neuronal Ceroid Lipofuscinosis	*CLN6* *CTSF* *PPT1* *CLN5* *CTSD* *GRN* *CLN3* *MFSD8* *DNAJC5*	Chorea; tremor; tics; stereotypies; parkinsonism	Epilepsy; cognitive decline; behavioral changes; visual loss; cardiac disease	Hypergonadotropic	Diffuse cerebral/cerebellar atrophy Non-specific white matter changes Thalamic T2-hypointensities

[a]This was described exclusively in the case associated with *RNF216* gene (see text for details).
[b]Premutation state (55–199 expanded CGG repeats in the untranslated 5′ region).
[c]Only one case described with hypogonadism.
Abbreviations: ADHD, Attention-deficit hyperactivity disorder; DBP, Peroxismal D-bifunctional protein; PLMS, Periodic limb movement of sleep; RBD, Rapid-eye-movement sleep behavior disorder; RLS, Restless legs syndrome; SCA2, Spinocerebellar ataxia 2; SCA16, spinocerebellar ataxia 16; SCA48, spinocerebellar ataxia 48.

of LS-like syndrome due to a heteroplasmic m.4296G>A mutation in the *MT-TI* gene. At 9 years of age, he presented with suspected hypogonadism and obesity. By age 16 he developed behavioral and cognitive changes; on exam, genitals were prepubertal and there was parkinsonism (responsive to levodopa but limited to 100 mg daily due to restlessness and aggressive behavior). Brain MRI showed bilateral necrotic changes in putamina and caudate nuclei and laboratory findings showed low testosterone, FSH and LH and elevated prolactin.[97]

Klinefelter syndrome and parkinsonism was first reported in one case of a 27-year-old male who developed unilateral tremor and bradykinesia. Testosterone levels were in a low range (3.67 μg/L, range 2.41–8.30) with increased LH concentrations (16.82 mIU/mL, range 1.5–9.3). Interestingly, he had several family members diagnosed with Parkinson's disease (PD).[98] Two other cases of KS and parkinsonism have since been described. A 37-year-old male with a history of action and postural tremor since childhood, who developed bilateral bradykinesia, rigidity and asymmetric rest tremor.[99] ^{18}F-fluorodopa positron emission tomography showed an asymmetric decrease of uptake in the putamen which correlated with symptom severity. Treatment with levodopa/carbidopa and pramipexole had good effect on bradykinesia but only a partial benefit on tremor.[99] More recently, a 60-year-old with KS presented with a one-year history of bradykinesia and shuffling gait. No tremor was evident on exam. Symptoms were significantly improved with pramipexole and rasagiline.[100] It has been proposed that altered melatonin levels in KS may interfere with dopamine release and may contribute to the development of parkinsonism in these patients.[98,100]

Chorea and Hypogonadism

Hypogonadism has been rarely described associated with chorea and in the majority of the cases reviewed, chorea was associated with other movement disorders.

A **Huntington-disease-like (HDL)** disorder has been described in four patients from two unrelated Belgian families. One patient had isolated facial, axial and appendicular chorea[101] while the other three displayed ataxia as well as chorea involving limbs and face.[101,102] All had personality changes, inappropriate behavior, and progressive cognitive changes. Brain imagining showed cortical atrophy, cerebellar degeneration, diffuse white matter lesions in the cerebellum and atrophy of the putamen. Additionally, while hypogonadism had not been suspected clinically, three of the four subjects had laboratory evidence of hypogonadotropic hypogonadism. Symptomatic treatment with typical and atypical antipsychotic medications including risperidone, tiapride, olanzapine and haloperidol, as well as other medications such as trihexyphenidyl and levodopa were tried, with variable benefit on motor symptoms.[101,102] Interestingly, all patients had pathological variants in the *RNF216* gene, which has classically been associated with GHS.[18]

Variants in the *NKX2-1* gene, a common cause of **benign hereditary chorea**, have also been associated with chorea and hypogonadism. A 46-year-old man presented with a pathogenic variant in *NKX2-1* gene. Initial symptoms included ataxic gait and perioral dyskinetic movements, as well as cervical dystonia. Myoclonic movements affected predominantly the abdominal musculature. At age 45 he was found to have low testosterone and LH levels in the background of erectile dysfunction. Interestingly, his daughter shared the same variant and also presented with gait ataxia, chorea and myoclonus. Although no hypogonadism was evident on exam or laboratory testing, she required growth hormone supplementation due to short stature. Both had an empty sella on brain MRI. Both received tetrabenazine for the treatment of chorea and the daughter was also started on levetiracetam for treatment of myoclonus.[103]

Finally, generalized chorea, as well as tremor and ataxia associated with hypergonadotropic hypogonadism was described in a 14-year-old female with a diagnosis of "**neuronal ceroid lipofuscinosis**."[104]

TABLE 2 Drugs described with potential to cause hypogonadism

Gonadal steroids
Glucocorticoid treatment
GnRH analogs
Dopamine receptor blocking agents:
Antipsychotics (eg, risperidone, haloperidol, fluphenazine)
Antiemetics (eg, metoclopramide, domperidone, prochlorperazine)
Dopamine depleting agents (eg, reserpine, tetrabenazine)
Tricyclic antidepressants/selective serotonin receptor inhibitors (eg, amitriptyline, clomipramine, fluoxetine)
Antiepileptics (eg, phenytoin)
Antihypertensive medications (eg, verapamil, methyldopa, labetalol)
Antihistaminergic medications (H2 receptors) (eg, cimetidine, ranitidine)
Opioids (eg, methadone, morphine, heroin)
Stimulators of serotoninergic pathway (eg, amphetamines)
Cholinergic agents (eg, physostigmine)

Abbreviation: GnRH, Gonadotropin releasing hormone.

Treatment Approach to Hypogonadism in Movement Disorders

The goal of treatment is generally to correct any reversible hormonal pathology and restore fertility.[105] This usually starts with replacement of gonadal hormones, although more complex management might be indicated. A detailed approach to the treatment of hypogonadism is beyond the scope of this review and readers are referred to McGriff et al[106] and Seppa et al[105] for a comprehensive approach.

One important consideration are acquired causes of hypogonadism, which include drug-induced hypogonadism. In

Table 2 we have listed the most common medications that can cause hypogonadism, many of which are commonly used in movement disorders patients. Most drugs have this effect by inducing hyperprolactinemia or through direct inhibition of gonadotropins. In the movement disorders field, these medications include those used for the treatment of hyperkinetic disorders (dopamine receptor blockers or dopamine depleting agents), manage mood/anxiety symptoms (tricyclic antidepressants or selective serotonin receptor inhibitors), control psychotic symptoms (dopamine receptor blockers), treat nausea (metoclopramide, domperidone, prochlorperazine) or control seizures (phenytoin). In addition, careful evaluation of dietary and nutritional supplement usage is critical, as their ingredients are not regulated by the agencies like the Food and Drug Administration (FDA).

Of note, some of the drugs used to treat hypogonadism might also have a positive impact in the control of some movement disorders. For example, there are two patients reported with KS in which the tremor in one and myoclonus in the other significantly improved after starting testosterone treatment.[70,85] However, other case reports have not described this effect.

Discussion

Co-occurrence of movement disorders and hypogonadism has historically been considered a rare association, mostly related to old syndromic descriptions. However, in this review of the literature we were able to find a wide spectrum of movement disorders that can co-occur with hypogonadism and for which the hypogonadism can be a very important clue to the diagnosis. The association between cerebellar ataxia and hypogonadism was first described in 1907 by Gordon Holmes and has been the most consistent association of hypogonadism with movement disorders. Since then, several different disorders have been described, many of them with a molecular diagnosis possible through genetic testing. Remarkably, selected spinocerebellar ataxia patients also may demonstrate hypogonadism features as shown in this review. Despite this consistent association, the mechanism by which gonadal and gonadotropic hormones influence cerebellar pathways, and vice-versa, is not understood.

Even more, as we highlight in this review, systemic and neurological features, such as cognitive impairment, cataracts, hearing loss, short or tall stature, hypodontia, white matter lesions among others may constitute precious clues for an accurate and timely diagnosis (Table 1). Nonetheless, in some cases these accompanying symptoms may be absent and the clinician requires a high level of suspicion to make the diagnosis. A good example of this is the presence of subtle features of hypergonadotropic hypogonadism in tremor patients with an ET-like phenotype occurring in KS or Jacob's syndrome, which are not uncommon in the general population. FXTAS is another good example, where features suggestive of ovarian insufficiency in women, can be easily missed due to its adult onset. Epidemiological studies suggest that the prevalence of the FMR1 premutation is 1 in 150–300 females, and 1 in 400–850 males.[107] Despite this, most cases reported in the literature describe tremor in males, which could be due to the underlying X-linked inheritance, although reporting bias may play a role, since this may be a diagnosis that is not often considered in female patients. These examples emphasize that in all patients presenting with tremor, it is important to inquire about possible features of hypogonadism.

One should also be aware that the presence of hypogonadism may only be evident on biochemical assessment of gonadal hormones. This was the case in both of the patients described here with chorea due to a novel variant in *RNF216* gene. This may constitute an important clue in HDL cases, since none of the other HDL genes have been associated with hypogonadism. In addition, systemic features such as pulmonary or thyroid disease may point to the correct diagnosis.

Not surprisingly, common causes of the association of hypogonadism with dystonia and parkinsonism are mitochondrial disorders such as Leigh-like syndrome, Woodhouse Sakati syndrome and, metabolic disorders like galactosemia.

The present review is not without some limitations. This was not a systematic review so there is the possibility that some cases were missed. One other main limitation relates to reporting bias. Many cases provided accurate endocrinology data but less detailed neurological information, or vice-versa. In many reports there was a significant amount of missing information, which precludes drawing more solid conclusions. A clear example is that of FXTAS in which no cases with tremor and hypogonadism have been described to date. There may also be a diagnostic bias related to the specialties where patients are first evaluated. For instance, in those occasions where hypogonadism is the predominant symptom, patients are likely to be evaluated by an endocrinologist, and the movement disorder component may not be as well recognized or described. Similarly, for patients evaluated by a neurologist, the specific hormonal abnormalities may not be the focus of the report. This may also explain the limited number of cases that were identified in our literature search. We hope this review will contribute to a more systematic approach and increased awareness of these issues.

In conclusion, hypogonadism may be more commonly associated with movement disorders than previously appreciated. It is important for the clinician to be aware of this association, as well as accompanying symptoms to reach a precise diagnosis.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

P.G.L.: 1B, 1C, 3A
M.S.: 1B, 1C, 3A
A.E.L.: 1A, 3B

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Supporting Information

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

Table S1. Summary of the search strategy.

Table S2. Literature review of movement disorders associated with hypogonadism.