Movement Disorders
CLINICAL PRACTICE

REVIEW

Cardiac Involvement in Movement Disorders

Malco Rossi, MD, PhD,[1,2,*] Nestor Wainsztein, MD, FCCP, FCCM, FAHA,[3] and Marcelo Merello, MD, PhD[1,2,4]

ABSTRACT: Background: Several conditions represented mainly by movement disorders are associated with cardiac disease, which can be overlooked in clinical practice in the context of a prominent primary neurological disorder.

Objectives: To review neurological conditions that combine movement disorders and primary cardiac involvement.

Methods: A comprehensive and structured literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria was conducted to identify disorders combining movement disorders and cardiac disease.

Results: Some movement disorders are commonly or prominently associated with cardiac disease. Neurological and cardiac symptoms may share underlying physiopathological mechanisms in diseases, such as Friedreich's ataxia and Wilson's disease, and in certain metabolic disorders, including Refsum disease, Gaucher disease, a congenital disorder of glycosylation, or cerebrotendinous xanthomatosis. In certain conditions, such as Sydenham's chorea or dilated cardiomyopathy with ataxia syndrome (ATX-*DNAJC19*), heart involvement can present early in the course of disease, whereas in others such as Friedreich's ataxia or Refsum disease, cardiac symptoms tend to present in later stages. In another 68 acquired or inherited conditions, cardiac involvement or movement disorders are seldom reported.

Conclusions: As cardiac disease is part of the phenotypic spectrum of several movement disorders, heart involvement should be carefully investigated and increased awareness of this association encouraged as it may represent a leading cause of morbidity and mortality.

Cardiac abnormalities may be a significant source of morbidity and premature mortality[1–4] and can occur in numerous neurological diseases, manifesting as cardiomyopathy, arrhythmias, conduction defects, structural malformations, coronary disease, valvulopathies, or cardiac autonomic dysfunction. In neurological conditions mainly manifested by movement disorders, cardiac disease can be a frequent and predominant clinical feature, or only be reported in isolated cases, and can be of early presentation, or occur only during later stages of disease.[5,6] In diseases such as Friedreich's ataxia (FRDA), where the need for heart monitoring is well established, a cross-sectional healthcare resource study revealed that recommended annual cardiac evaluations had not been conducted in up to 23% of patients with FRDA in the United States and 14% in Canada.[7] These figures may be even higher in other parts of the world.

In this educational review, we describe and list movement disorders with cardiac involvement as part of the clinical picture.

Methods

A comprehensive and structured search in PubMed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org) was conducted. Keywords included in the search were the following: movement disorders, parkinsonism,

[1]*Sección Movimientos Anormales, Departamento de Neurociencias Instituto de Investigaciones Neurológicas Raúl Carrea, Fleni, Buenos Aires, Argentina;* [2]*Argentine National Scientific and Technological Research Council, Buenos Aires, Argentina;* [3]*Departamento de Medicina Interna, Unidad de Cuidados Críticos, Fleni, Buenos Aires, Argentina;* [4]*Pontificia Universidad Católica Argentina, Buenos Aires, Argentina*

***Correspondence to:** Dr. Malco Rossi, Sección Movimientos Anormales, Departamento de Neurología, Fleni, Montañeses 2325, Ciudad Autónoma de Buenos Aires (1428), Argentina; E-mail: mrossi@fleni.org.ar
Keywords: cardiac, cardiomyopathy, cardiovascular, arrhythmia, heart.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 16 May 2020; revised 23 February 2021; accepted 2 March 2021.
Published online 7 April 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13188

Parkinson's disease, parkinsonian disorders, chorea, Huntington disease, neuroacanthocytosis, Tourette syndrome, tic disorders, myoclonus, dystonia, tremor, ataxia, spastic paraparesis, spastic paraplegia, restless legs syndrome, periodic leg movements of sleep, hypokinetic, and hyperkinetic, in combination with heart, cardiac, cardiovascular, cardiomyopathy, cardio, cardiopathy, coronary disease, arrhythmia, conduction defect, valvular, valvulopathy, mitral, aortic, autonomic dysfunction, dysautonomia, and sudden death. Publications written in English and published up to October 2020 were reviewed. Types of publications screened included case reports, case series or case-controlled studies, literature reviews, and any other type of publication that could contain clinical information on cardiac involvement in movement disorders. Full texts containing the clinical data of patients with movement disorders and comorbid heart disease were analyzed. A back search of retrieved publication reference lists was conducted to identify the gray literature. Conditions with autonomic dysfunction secondary to other cardiac causes, such as dysautonomia attributed to spinal cord impairment, or other types of peripheral or autonomic neuropathy were not included. Because of the prominent involvement of the autonomic nervous system in multiple system atrophy (MSA), only specific cardiac issues related to the condition are discussed. Similarly, cardiac autonomic dysfunction in Parkinson's disease (PD) measured by heart rate variability (HRV) or myocardial scintigraphy is not described in this review as the topic is extensively reviewed in other publications.

Results

Movement disorders with common and prominent cardiac involvement are shown in Table 1. Other acquired or inherited conditions that were either only occasionally or rarely associated with movement disorders or cardiac disease are listed in Table 2 and further described in Table S1.

Ataxia as the Predominant Movement Disorder

FRDA (or ATX-FXN)

FRDA, the most common inherited ataxia, is an autosomal recessive, multisystem disorder associated with pathologic GAA repeat expansions in the first intron of the *FXN* gene that leads to decreased expression of the encoded gene product frataxin, a ubiquitous mitochondrial protein involved in the creation of iron-sulfur clusters.[8] The onset is commonly around puberty, but in some cases it can occur later in life or during early childhood.[8] The hallmark neurological features of FRDA include progressive afferent and cerebellar ataxia, dysarthria, ocular fixation instability, deep sensory loss, lower limb areflexia, and pyramidal signs. Scoliosis, foot deformity, diabetes mellitus, and cardiomyopathy are frequent nonneurological features.[8–10] Cardiomyopathy, usually in its hypertrophic form, is a cardinal feature of FRDA and the cause of death in between 60% and 80% of patients.[8–11] The frequency of cardiomyopathy is 4% to 5% at disease onset and increases to 40% to 90% during the course of disease.[8–10,12] Cardiomyopathy is typically asymptomatic with normal or lower than normal systolic function. During later disease stages, dilated cardiomyopathy is predominant and associated with a higher risk of arrhythmia and mortality.[13–15]

The frequency and severity of cardiomyopathy was found to be related to the length of the GAA repeat expansion,[8,9,16] young age at onset of FRDA,[5] angiotensin II type 1 receptor polymorphism,[17] but not to neurological involvement or severity.[5,9,18] Patients with delayed-onset FRDA (≥25 years) do not commonly exhibit typical clinical features of cardiac disease.[10,12,19–22] Likewise, compound heterozygous patients (approximately 4% of FRDA cases) are less likely to present cardiomyopathy than homozygous GAA expansion carriers.[23]

The pathogenesis of cardiomyopathy in FRDA involves a severe reduction of cardiac frataxin levels, failure to clear iron from myocytes, ferroptosis (a recently identified pathway of regulated, iron-dependent cell death, distinct from apoptosis), lack of oxidative phosphorylation, reduced adenosine triphosphate production, chronic inflammation, and disorganization of intercalated discs (plasma membrane specializations that connect heart fibers end to end and provide mechanical cohesion and ionic coupling).[24,25] Frataxin is crucial for neuron and cardiomyocyte survival, and its deficiency has been recently linked to low levels of HAX-1, a regulator of cardiomyocyte death, which could be a potential biomarker of cardiac disease in FRDA.[26] Early clinical indicators of myocardial involvement include elevated serum cardiac troponin I levels[27] and electrocardiographic (ECG) abnormalities, which are present in as many as 93% of patients.[9,14] T-wave inversion is the most common ECG abnormality detected, followed by abnormally broad Q waves, signs of left ventricular hypertrophy, a short PR interval, and arrhythmias such as atrial fibrillation or flutter.[5,10,13,14,18] Cardiovascular dysautonomia is very rare,[28] but some patients may show tachycardia at rest and during orthostatic challenge.[29,30] Early markers of myocardial dysfunction in cases with normal left ventricular ejection fraction include reduced longitudinal myocardial strain on echocardiography[31] and signs of cardiac remodeling on cardiovascular magnetic resonance.[32,33] Patients with progressive declining left ventricular ejection fraction, usually below 55%, have worse outcome.[5,9] According to consensus clinical management guidelines for FRDA, an ECG and an echocardiogram should be performed at diagnosis and at least annually thereafter.[33] In addition, Holter and/or Loop monitor assessment should be performed in cases presenting palpitations. Management of cardiomyopathy in FRDA has been challenging as there is no specific treatment. Although some low-quality evidence for a decrease in cardiac hypertrophy with idebenone has been published, its clinical significance remains uncertain. Further trials will be needed to establish its true potential.[34–36] Table 3 summarizes the most important treatment recommendations for FRDA.

Refsum Disease (ATX-PHYH and ATX-PEX7)

This rare autosomal recessive inborn error of lipid metabolism causing accumulation of phytanic acid is classically characterized

TABLE 1 Neurological conditions mainly manifested by movement disorders with common and prominent cardiac involvement

		Cardiac Manifestations							
Entity	Movement Disorders	Hypertrophic or Dilated Cardiomyopathy	Electrocardiographic Abnormalities	Structural Heart Defects	Coronary Disease	Valvulopathy	Cardiac Autonomic Dysfunction	Amyloid Deposition	Sudden Cardiac Death
Friedreich ataxia (ATX-*ATM*; MIM #229300)	Ataxia, chorea, myoclonus, spastic ataxia, dystonia	X (hypertrophic > dilated)	X (atrial fibrillation, flutter, T-wave inversion, abnormally broad Q waves, short PR interval, other repolarization abnormalities, right QRS axis deviation)			X	X		X
Refsum disease (ATX-*PHYH*; MIM #266500 and ATX-*PEX7*; MIM #614879)	Ataxia	X (hypertrophic and dilated)	X (first-degree atrioventricular block, bundle branch block)						X
Phosphomannomutase-2 deficiency-congenital disorder of glycosylation (ATX-*PMM2*; MIM #601785)	Ataxia, dystonia	X (hypertrophic)		X					
Dilated cardiomyopathy with ataxia syndrome (ATX-*DNAJC19*; MIM #610198)	Ataxia, dystonia, tremor, and dyskinesia	X (dilated)	X (long QT syndrome or nonspecific ST/T wave changes)						X
Huntington's disease (CHOR-*HTT*; MIM #143100)	Chorea, parkinsonism, dystonia, myoclonus		X (atrial and ventricular fibrillation, decreased RR interval, prolonged QRS, QTc, intraventricular conduction delay, and right bundle branch block)		X		X		X
Sydenham's chorea	Chorea		X (prolonged PR and QTc intervals)			X (especially mitral valve)			
McLeod syndrome (CHOR-*XK*; MIM #300842)	Chorea	X (hypertrophic > dilated)	X (atrial fibrillation or flutter, slowing of atrio-ventricular conduction and repolarization alterations)		X	X			X
Chorea-acanthocytosis (CHOR-*VPS13A*; MIM #200150)	Chorea, dystonia, parkinsonism	X (hypertrophic and dilated)	X (ventricular tachycardia or sick sinus syndrome with severe bradycardia and pacemaker implantation)						

(Continues)

TABLE 1 *Continued*

Entity	Movement Disorders	Cardiac Manifestations							
		Hypertrophic or Dilated Cardiomyopathy	Electrocardiographic Abnormalities	Structural Heart Defects	Coronary Disease	Valvulopathy	Cardiac Autonomic Dysfunction	Amyloid Deposition	Sudden Cardiac Death
Parkinson's disease (including *SNCA*-related Parkinson's disease)	Parkinsonism, tremor, dystonia dyskinesia				X		X		X
Dementia with Lewy bodies	Parkinsonism, tremor, dystonia, dyskinesia						X		X
22q11.2 deletion syndrome-associated Parkinson's disease (MIM #192430)	Parkinsonism, tremor, myoclonus			X					X
Restless legs syndrome and periodic leg movements of sleep	RLS, PLMS		X (atrial fibrillation)		X		X		
Wilson's disease (*DYT/ATX-ATP7B*; MIM #277900)	Dystonia, parkinsonism, ataxia, chorea, myoclonus, tremor, orofacial dyskinesias	X (hypertrophic > dilated)	X (supraventricular tachycardia, extrasystolic beats, atrial and ventricular fibrillation, cardiac arrest, early repolarization, ST depression, T-wave inversion, wide QRS complex, premature atrial or ventricular contractions, sinoatrial block, Mobitz type 1 atrioventricular block)				X		X
Mitochondrial disorders: MERRF and MELAS syndromes (mt-MTTK; MIM #590060), Kearns-Sayre syndrome (MIM #530000), Leigh syndrome (MIM #256000 and MIM #220111), NARP syndrome (MIM #551500), and oxidative phosphorylation and respiratory chain disorders, Leber hereditary optic	Myoclonus, dystonia, ataxia, parkinsonism, tremor, spastic paraparesis	X (hypertrophic and dilated)	X (symptomatic bradycardia, sinus tachycardia, supraventricular tachycardia, nonsustained ventricular tachycardia, ventricular extrasystoles, bundle branch block, complete atrial-ventricular block, heart block, and Wolff–Parkinson–White syndrome)		X	X			X

(Continues)

TABLE 1 *Continued*

Entity	Movement Disorders	Cardiac Manifestations							
		Hypertrophic or Dilated Cardiomyopathy	Electrocardiographic Abnormalities	Structural Heart Defects	Coronary Disease	Valvulopathy	Cardiac Autonomic Dysfunction	Amyloid Deposition	Sudden Cardiac Death
neuropathy (MIM #535000), *POLG*-related disorders, including SANDO syndrome (MIM #607459, #258450, #203700, #613662)									
Cerebrotendinous xanthomatosis (*ATX-CYP27A1*; MIM #213700)	Ataxia, parkinsonism, dystonia, myoclonus, spastic paraplegia,	X (hypertrophic)	X (ventricular tachycardia and atrial fibrillation)		X		X		X
ATP1A3-related syndromes	Dystonia, parkinsonism, ataxia, paroxysmal movements		X						X

X indicates the presence of the corresponding heart manifestation.
MIM, Mendelian Inheritance in Man; PLMS, periodic limb movements of sleep; RLS, restless legs syndrome; MERRF, myoclonic epilepsy associated with ragged-red fibers; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; NARP, neuropathy, ataxia, and retinitis pigmentosa; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.

by ataxia, peripheral neuropathy, amyotrophy, retinopathy, ichthyosis, anosmia, deafness, and multiple epiphyseal dysplasia. It is frequently accompanied later in life by cardiac manifestations, such as arrhythmias or conduction defects (eg, first-degree atrioventricular block, bundle branch block), and hypertrophic or dilated cardiomyopathy, leading to heart failure and sudden death.[34,35] At autopsy, high phytanic acid concentrations are found in the heart.[36] Whether cardiac manifestations correlate with phytanic acid plasma levels has not been established.[37] However, appropriate treatment including a phytanic acid–restricted diet, plasmapheresis, or low-density lipoprotein LDL-apheresis does prevent and/or limit progression of several clinical manifestations of the disease.[38] Treatment of hypertension may help delay cardiomyopathy, which inevitably leads to arrhythmias. Amiodarone should not be used as an antiarrhythmic because of the risk of hyperthyroidism, which increases catabolism and phytanic acid release from tissues.[35] Cardiac transplantation can be lifesaving in severe cardiomyopathy.[35]

Phosphomannomutase-2 Deficiency-Congenital Disorder of Glycosylation (ATX-PMM2)

This autosomal recessive congenital disorder of glycosylation is divided into three subtypes: infantile multisystem, late-infantile and childhood ataxia-intellectual disability, and adult stable disability. Clinical presentation and course are highly variable. In the infantile multisystem subtype, axial hypotonia, feeding problems, impaired growth, developmental delay, hyporeflexia, esotropia, and abnormal subcutaneous fat distribution with inverted nipples are commonly observed. The late-infantile and childhood ataxia-intellectual disability subtype is characterized by hypotonia, ataxia, severe intellectual, and motor disability, often associated with stroke-like episodes, seizures, skeletal deformities, and retinopathy.

In the adult stable disability type, intellectual disability is typically stable rather than progressive, and patients usually exhibit ataxia, peripheral neuropathy, skeletal deformities, thrombotic events, hypogonadotropic hypogonadism, and other endocrine abnormalities.[39] Hypoglycosylation of glycoproteins creates abnormal neural crest cell migration, leading to conotruncal heart defects, such as common arterial trunk defect and tetralogy of Fallot.[40] In addition, hypoglycosylation of dystrophin-associated glycoproteins in the sarcolemmal plasma membrane affects signal transduction pathways and calcium homeostasis, leading to hypertrophic cardiomyopathy.[41] Cases of pericardial effusion leading to cardiac tamponade and death within the first years of life have also been reported.[41] Treatment guidelines for heart disease in this condition are lacking.

Dilated Cardiomyopathy with Ataxia Syndrome (ATX-DNAJC19)

This autosomal recessive disorder is characterized by cerebellar ataxia, developmental delay, intellectual disability, muscle weakness,

TABLE 2 Conditions that associate movement disorders with cardiac involvement but with infrequent combination of clinical manifestations of both [*] [**]

Disorders listed according to the predominant movement disorder	
Ataxia	**Dystonia**
Dandy-Walker syndrome [HD-M, heart insufficiency]	GM1-gangliosidosis, type III (*DYT/PARK-GLB1*) [CVA]
Ataxia-telangiectasia (ATX-*ATM*) [CAD, CVA, HD-M]	*ATP1A3*-related syndromes (*DYT-ATP1A3*) and CAPOS syndrome [electrocardiographic abnormalities]
Primary coenzyme Q10 deficiency (*COQ2* and *COQ4*) [HC, arrhythmias]	Primary coenzyme Q10 deficiency type 5 (*COQ9*) [HC, arrhythmias]
CANVAS (*RFC1*) [CAD]	Glutaric aciduria or acidemia, type I (*GCDH*) [HD-M, cardiomyopathy, cardiac arrest]
Autosomal recessive spinocerebellar ataxia type 8 (ATX-*SYNE1*) [HC, arrhythmias] Autosomal recessive spinocerebellar ataxia type 23 (*TDP2*) [arrhythmias]	3-methylglutaconic aciduria, type VIII (*HTRA2*) [arrhythmias]
Spinocerebellar ataxias (ATX-*ATXN1*, ATX-*ATXN2*, ATX-*ATXN3*) [CAD], (ATX-*ATXN7*), [HD-M, CHF, cardiomyopathy, pericardial effusion], (ATX-*ATXN10*) [HD-M], (ATX-*PRKCG*) [cardiomyopathy]	Early infantile epileptic encephalopathy type 75 (*PARS2*) [HC, DC]
Cockayne syndrome (*ERCC4*, *ERCC5*, *ERCC6*, *ERCC8*) [DC, arrhythmias, HD-M]	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (*SERAC1*) [HD-M, HC, arrhythmias]
Thiamine metabolism dysfunction syndrome-5 or episodic encephalopathy attributed to thiamine pyrophosphokinase deficiency (*TPK1*) [HC]	17-beta-hydroxysteroid dehydrogenase X deficiency or HSD10 mitochondrial disease (*HSD17B10*) [HC, DC, CCD]
Sandhoff disease (ATX/*HSP-HEXB*) [CVA, HC, DC]	Severe dystonia, cerebellar atrophy, and cardiomyopathy likely caused by a missense mutation in *TOR1AIP1* (*TOR1AIP1*) [DC]
Galactosialidosis (*CTSA*) [CVA]	Baraitser-Winter syndrome (*ACTB*) [HD-M]
Transthyretin-related hereditary amyloidosis (*TTR*) [cardiac amyloid deposition, CCD, HC, CAD, heart failure]	Rett syndrome (*MECP2*) [CAD, arrhythmias]
Achalasia-addisonianism-alacrimia syndrome (*AAAS*) [CAD]	**Chorea**
Congenital disorder of glycosylation, type IIf (*SLC35A1*) [aortic insufficiency]	*ADCY5*-related movement disorders (*ADCY5*) [DC, congestive heart failure]
Bardet-Biedl syndrome (*BBS1*) [HC, HD-M]	Paraneoplastic movement disorders [cardiac papillary fibroelastoma or mixoma]
Wolfram syndrome (*WFS1*) [HD-M]	Polycythaemia vera or attributed to secondary causes [CVA, HD-M]
Dihydrolipoamide dehydrogenase deficiency or Maple syrup urine disease type II (*DLD*) [HC]	Systemic Lupus erythematosus or antiphospholipid syndrome [CVA, coronary disease, cardiomyopathy]
Combined oxidative phosphorylation deficiency (*TSFM*, *AIFM1*, *MTO1*, and *MTFMT*) [HC, DC, HD-M, CCD]	**Myoclonus**
Mitochondrial DNA depletion syndrome type 13; encephalomyopathic type (*FBXL4*) [HC, arrhythmias, CCD, HD-M]	Myoclonic epilepsy of Lafora (*MYC*/ATX-*EPM2A* and *MYC*/ATX-*NHLRC1*) [CCD, heart failure, sudden death]
Thiamine-responsive megaloblastic anemia syndrome (*SLC19A2*) [HD-M, arrhythmias, HC, DC]	Action myoclonus-renal failure syndrome (*SCARB2*) [DC]
Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (*TRNT1*) [DC, heart failure]	Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements (*CACNA1B*) [arrhythmias]
Peroxisome biogenesis disorder 9B (ATX-*PEX7*) [cardiomyopathy, arrhythmias, heart failure]	TBC1D24-related disorders—DOORS syndrome—and familial infantile myoclonic epilepsy (*TBC1D24*) [arrhythmias, cardiac arrest, HD-M]
Short stature, microcephaly, and endocrine dysfunction syndrome (*XRCC4*) [DC]	*PURA*-related neurodevelopmental disorders (*PURA*) [HD-M]
Recurrent metabolic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (*TANGO2*) [HC, DC, arrhythmias]	Microcephaly-capillary malformation syndrome (*STAMBP*) [HD-M, HC]
Mental retardation and distinctive facial features with or without cardiac defects (*MED13L*) [HD-M]	Silver-Russell syndrome, chromosome 11p15.5; dystonia is also a main movement disorder in this condition [HD-M, DC, arrhythmias]
Harel-Yoon syndrome (*ATAD3A*) [HC]	Combined oxidative phosphorylation deficiency type 35 (*TRIT1*) [HD-M]
Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions (*TWNK*) [HC, CCD, arrhythmias]	**Parkinsonism**
Tics	Multiple system atrophy [CAD, sudden death]
Tourette syndrome [coronary disease, arrhythmias, CVA]	Progressive supranuclear palsy [CAD]
Tremor	Gaucher disease (*GBA*) [HD-M, CVA, HC, DC, CAD, arrhythmias, cardiac amyloidosis]
Fragile X-associated tremor/ataxia syndrome (*FXTAS*, ATX-*FMR1*) [CVA, arrhythmias]	Fabry disease (*GLA*) [HC, CCD, arrhythmias, coronary disease, CVA, sudden death]

(Continues)

TABLE 2 *Continued*

Disorders listed according to the predominant movement disorder	
Mental retardation type 34 (*NONO*) [HD-M, HC, DC]	Fahr's syndrome or idiopathic basal ganglia calcification (*SLC20A2*) [heart failure, arrhythmias, cardiomyopathy, CCD]
Multiple congenital anomalies, hypotonia, and seizures syndrome type 1 (*PIGN*) [HD-M]	
Tonne-Kalscheuer syndrome (*RLIM*) [HD-M]	
Chromosome 18q deletion syndrome [HD-M, CVA, congestive heart failure]	

*Clinical characteristics are shown in Table S1.
**Gene symbols are in parentheses.
HD-M, heart defects or malformations; CAD, cardiovascular autonomic dysfunction; CVA, cardiac valve abnormalities; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; HC, hypertrophic cardiomyopathy; DC, dilated cardiomyopathy; CHF, congestive heart failure; CCD, cardiac conduction defects.

anemia, genital anomalies in males, and 3-methylglutaconic aciduria. Other movement disorders less frequently found are dystonia, tremor, and dyskinesia. Heart involvement includes early-onset dilated cardiomyopathy (usually before the age of 3), accompanied by long QT syndrome or nonspecific ST/T wave changes on ECG in approximately one third of patients.[42–44] Mutations in the *DNAJC19* gene result in mitochondrial protein import defects that lead to mitochondrial dysfunction, impacting organs with high-energy demand, such as the heart.[42] A significant beneficial impact on both left ventricular function and structure has been reported for digoxin when added to conventional heart failure therapy.[45] Although cardiomyopathy may sometimes improve with β-blockers such as carnitine and ubiquinone,[43] it ultimately leads to progressive congestive heart failure or sudden cardiac death in the majority of patients.[42,44] Treatment guidelines for heart disease in this condition are lacking.

Cardiac involvement in other autosomal recessive ataxias or in spinocerebellar ataxias is rare and summarized in Table S1.

Chorea as the Predominant Movement Disorder

Huntington's Disease (HD or CHOR-HTT)

Cardiovascular disease leading to heart failure is a major cause of death in HD.[3,46] Premanifest mutation carriers also present higher risk of cardiovascular disease than healthy controls.[47] Cardiovascular burden in HD includes coronary heart disease, atrial and ventricular fibrillation, and sudden cardiac death.[48] Abnormal ECG variables unexplained by medications or by potentially contributing medical conditions were found in 39% of a large cohort of 590 early symptomatic (stages 1 and 2) patients with HD.[49] The most frequent ECG findings in the study were bradycardia (28.3%), prolonged QRS (4.9%) or QTc (3.7%), intraventricular conduction delay (3.4%), and right bundle branch block (1.3%), all at higher frequencies than in otherwise healthy populations.[49] Cardiac consequences of autonomic dysfunction in HD could arise from an imbalance between sympathetic (increased) and parasympathetic (decreased) activity, regulated by cortical, subcortical, brainstem or spinal structures or circuits, and assessed by HRV.[48,50–53] In particular, reduced parasympathetic HRV was associated with an increased risk of falls.[53] Parasympathetic nervous system dysfunction in HD is also evident after reaching exercise-induced exhaustion. Patients with HD may present impaired heart rate recovery, an independent predictor of mortality in healthy populations.[54] In addition, the absence of steady heart rate during low-intensity exercise requires that the exercise prescription for patients with HD be of submaximal intensity and patient recovery monitored as an indicator of intervention effectiveness.[54] Decreased vagal modulation of the heart rate, QT interval alterations, and conduction abnormalities associated with cardiac electrical remodeling may lead to cardiovascular complications such as syncope, arrhythmias, and sudden cardiac death.[48–50,55] This also has implications for prescription of QT-prolonging medications, including certain neuroleptics, amitriptyline, serotonin-uptake inhibitors, tetrabenazine, or domperidone, all of which should be used with caution in patients with HD because of the risk of torsades de pointes and potentially fatal arrhythmias or sudden death.[48] Despite an autonomic imbalance in favor of sympathetic activity, 6% of patients with early symptomatic HD may exhibit marked bradycardia (heart rate <50 bpm).[49] From a clinical perspective, cardiac function evaluation with conventional ECG is recommended in patients with HD.[48]

Sydenham's Chorea

Acute rheumatic fever is a poststreptococcal inflammatory collagen tissue disease affecting the joints, heart, skin, and nervous system. In patients presenting chorea as a manifestation of acute rheumatic fever after a streptococcal infection, the rates of cardiac involvement, mainly pericarditis, vary between 30% to 75% and commonly occur during early stages of the disease.[56–61] Valvular dysfunction, especially of the mitral valve, is commonly silent and only detectable on echocardiography when asymptomatic.[59,60,62] In almost 23% of patients, ECG findings, such as prolonged QTc and PR intervals, are present.[60,62] The duration of chorea in patients with carditis does not appear to differ from that of patients without cardiac disease,[59] but can be longer in

TABLE 3 Cardiac monitoring and treatment recommendations for disordersthat commonly combine movement disorders and heart disease*

Entity	Monitoring or Screening Recommendations	Treatment Recommendations
FRDA (ATX-*ATM*; MIM #229300)	ECG and ECHO, should be performed at diagnosis and then at least annually; a Holter and/or Loop monitor assessment should be performed in case of palpitations	*For slowing or prevention of deterioration of left ventricular contraction in asymptomatic individuals with reduced ejection fraction*: an angiotensin-converting enzyme inhibitor (Enalapril, Ramipril, Lisinopril, or Trandolapril) is first-line therapy, but if the angiotensin-converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker (Candesartan, Valsartan) should be commenced instead (second-line therapy). β-Blockers (Carvedilol, Bisoprolol, or long-acting Metoprolol) should be considered as an addition to an angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker, particularly if the heart rate is >75/min *For treatment of symptomatic heart failure with reduced LVEF*: a diuretic should be prescribed for fluid overload. An angiotensin-converting enzyme inhibitor is first-line therapy, but if the angiotensin-converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker should be commenced instead (second-line therapy). β-Blockers (Carvedilol, Bisoprolol, or long-acting Metoprolol) should be added (first-line therapy) to the angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker; however, the role of β-blockers in children is less clear. Calcium channel blockers with negative inotropic effects (Verapamil and Diltiazem) should be avoided. Digoxin should be considered for control of ventricular response if atrial fibrillation is present *For prevention of recurrence of atrial arrhythmias*: β-blockers (Metoprolol, Bisoprolol, or Carvedilol), Sotalol, Dofetilide, or Amiodarone. Agents that should be avoided include Quinidine, Flecainide, Propafenone, and Disopyramide because of their negatively inotropic and/or proarrhythmic effects. Anticoagulation should not be commenced if the LVEF is normal and there are no other risk factors for thromboembolism. Anticoagulation with Warfarin or 1 of the novel anticoagulants (Dabigatran, Rivaroxaban, or Apixaban) should be considered in paroxysmal or permanent atrial fibrillation if 1 CHADS2 risk factor is present and will be generally indicated if more than 1 CHADS2 risk factor is present *For prevention of recurrence of ventricular arrhythmias*: a β-blocker (Metoprolol, Bisoprolol, or Carvedilol) should be used, but Sotalol and Amiodarone are second-line options if there is arrhythmia recurrence despite β-blocker use *Device therapy for patients with symptomatic heart failure and reduced ejection fraction*: implantation of an automatic internal cardioverter defibrillator should be considered if LVEF is ≤35%, the individual has NYHA functional class 2 or 3 symptoms despite receiving optimal medical therapy, and the individual has a reasonable expectation of survival with good functional status for more than 1 yr. Cardiac resynchronization therapy should be considered in individuals with LVEF of ≤35%, sinus rhythm, a QRS duration ≥0.12 s, and NYHA functional class 3 or 4 symptoms despite receiving optimal medical therapy Idebenone for hypertrophic cardiomyopathy is controversial and of low-quality evidence Septal myectomy for severe hypertrophic obstructive cardiomyopathy Cardiac transplantation for heart failure secondary to dilated cardiomyopathy (case-by-case basis with specific ethical considerations)
Refsum disease (ATX-*PHYH*; MIM #266500 and ATX-*PEX7*; MIM #614879)	ECG, ECHO	Phytanic acid restriction diet, plasmapheresis, or LDL-apheresis Antihypertensive drugs to delay cardiomyopathy Antiarrhythmic drugs (amiodarone should not be used as an antiarrhythmic drug because of the risk of hyperthyroidism,

(Continues)

TABLE 3 *Continued*

Entity	Monitoring or Screening Recommendations	Treatment Recommendations
		which results in catabolism and increased phytanic acid release from tissues) Cardiac transplantation in severe cardiomyopathy
ATX-*PMM2* (MIM #601785)	ECHO	Corrective heart surgery for congenital heart defects.
ATX-*DNAJC19* (MIM #610198)	ECG, ECHO	β-blockers, digoxin, carnitine, and ubiquinone for cardiomyopathy.
Huntington's disease (CHOR-*HTT*; MIM #143100)	Baseline ECG monitoring while initiating tetrabenazine or other QT-prolonging medications	No specific recommendations
Sydenham's chorea	ECG, ECHO	Secondary prophylaxis with Penicillin G (1.2 million units by intramuscular injection every 21 days). In children younger than 6 yr of age, the dosage of penicillin G is 0.6 million units intramuscularly every 21 days. Allergic patients can be given oral sulfa drugs, such as sulfadiazine, 500 mg every 6 hr. The duration of treatment is dependent on the severity of cardiac involvement. Patients with no carditis may stop prophylaxis after 5 yr or age 18 (whichever is longer), those with mild carditis should continue for 10 yr or age 21, and those with moderate to severe carditis should receive lifelong prophylaxis. For endemic areas, it is recommended to maintain secondary prophylaxis up to age 21 yr Heart valve surgery in severe mitral or aortic valve disease
McLeod syndrome (CHOR-*XK*; MIM #300842)	ECG, ECHO	No specific recommendations
Chorea-acanthocytosis (CHOR-*VPS13A*; MIM #200150)	ECG, ECHO	Pacemaker implantation for severe arrhythmias (isolated cases)
Parkinson's disease (including *SNCA*-related PD) and Dementia with Lewy bodies	Baseline ECG monitoring while initiating domperidone, donepezil or other QT-prolonging medications	No specific recommendations
22q11.2 deletion syndrome-associated Parkinson's disease	ECHO	Corrective heart surgery for congenital heart defects
Restless legs syndrome and periodic leg movements of sleep	A recommendation for prevention of cardiovascular disease should be considered on an individual basis	No specific recommendations besides management of possible comorbidities, such as hypertension, renal failure, diabetes mellitus, iron deficiency, and insomnia or sleep fragmentation
Wilson's disease (*DYT*/ATX-*ATP7B*; MIM #277900)	ECG, ECHO	No specific recommendations other than traditional management of cardiomyopathy and arrhythmias
Mitochondrial disorders: MERRF and MELAS syndromes, Kearns-Sayre syndrome, Leigh syndrome, Leber hereditary optic neuropathy, NARP syndrome, *POLG*-related disorders, and some oxidative phosphorylation and respiratory chain disorders	ECG, ECHO	No specific recommendations other than traditional management of cardiomyopathy and arrhythmias; cardioverter-defibrillator implantation is sometimes required for cardiac conduction defects
Cerebrotendinous xanthomatosis (ATX-*CYP27A1*; MIM #213700)	ECG, ECHO	Reduced-fat diet followed by pharmacological treatment with statins and/or LDL apheresis and chenodeoxycholic acid; caution has been suggested with statins as they may induce muscle damage and rhabdomyolysis
ATP1A3-related syndromes	Baseline ECG; cardiac ultrasound, and Holter ECG; annual 12-lead ECG screening with Holter monitoring; implantation of a cardiac loop recorder in patients with abnormal ECG and cardiac symptoms	Placement of a pacemaker or implantable cardioverter-defibrillator for asymptomatic or symptomatic asystole or ventricular arrhythmias

(Continues)

TABLE 3 *Continued*

Entity	Monitoring or Screening Recommendations	Treatment Recommendations
Autoimmune movement disorders: IgLON5-antibody-linked tauopathy, PERM, autoimmune DPPX potassium channel antibody autoimmune disorder, and autoimmune anti-LGI1 limbic encephalitis	ECG	No specific recommendations other than traditional management of cardiomyopathy and arrhythmias; placement of a pacemaker for symptomatic bradycardia (in IgLON5-antibody-linked tauopathy and autoimmune anti-LGI1 limbic encephalitis)

*These recommendations are based on the consensus clinical management guidelines for FRDA (Corben et al.) and were here applied according to the author's consideration to other disorders that commonly combine movement disorders and heart disease. These recommendations may also apply for some other conditions that infrequently associate movement disorders with cardiac involvement (see Table S1).
DPPX, Dipeptidyl-peptidase-like protein-6; FRDA, Friedreich's ataxia; IgLON5, immunoglobulin-like cell adhesion molecule 5; ECG, electrocardiogram; ECHO, echocardiogram; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LGI1, Leucine Rich Glioma Inactivated 1; NARP, neuropathy, ataxia, and retinitis pigmentosa; NYHA, New York Heart Association; PERM, autoimmune glycine-receptor antibody-related progressive encephalomyelitis.

female patients.[63] Secondary prophylaxis with penicillin G is recommended by the World Health Organization to reduce the likelihood of progression to established rheumatic heart disease, including cardiac failure and severe valvular insufficiency in patients with isolated chorea.[64]

McLeod Syndrome (CHOR-XK)

This X-linked multisystem disorder includes progressive chorea, cognitive impairment, and psychiatric symptoms. Additional features, such as seizures, sensorimotor axonopathy, muscle weakness and atrophy, cardiac alterations, and compensated hemolysis have been described as well as abnormal laboratory findings, such as acanthocytosis, elevated serum creatine kinase levels, absence of Kx erythrocyte antigen expression, and weakened expression of Kell blood group antigens. The multisystemic phenotype is the result of allelic variants or deletions involving the *XK* gene, which plays a key role in organogenesis, cellular structure, and subcellular electrolyte and nutrient exchange.[65] Cardiomyopathy is found in 65% of individuals and precipitates congestive heart failure and death in around 40% to 45% of cases.[66–68] Cardiac disease usually appears from the fifth decade onward and is characterized by concentric ventricular remodeling or ventricular hypertrophy, followed by dilated cardiomyopathy.[66,69–71] Atrial fibrillation or flutter or conduction defects such as atrioventricular conduction slowing and repolarization alterations are frequently reported.[66,67,70,71] Aortic and mitral valve dysfunction have also been reported in selected cases[69,70] as well as myocardial infarction and sudden cardiac death.[69,71]

Chorea-Acanthocytosis (CHOR-VPS13A)

This rare disorder is characterized by progressive chorea, cognitive and behavioral changes, seizures, myopathy, and red cell acanthocytosis, with onset in the third to fifth decade of life. Cardiac disease, in the form of dilated or hypertrophic nonobstructive cardiomyopathy, although found less frequently than in McLeod syndrome, may lead to decreased ejection fraction[72–74] and is the cause of death in 16% of cases.[68] Arrhythmias, such as ventricular tachycardia or sick sinus syndrome with severe bradycardia requiring pacemaker implantation, have also been reported in some cases.[72,74] Information on which to base treatment decisions for heart disease in this condition is scarce.

Parkinsonism as the Predominant Movement Disorder

PD and Dementia with Lewy Bodies (DLB)

Synucleinopathy pathology has been found in peripheral postganglionic sympathetic neurons and in the myocardium, epicardium, and perivascular nerve fibers in postmortem histopathology tissues from patients with PD.[75] Similarities between cardiovascular disease and PD with respect to biological alterations in lipid metabolism, as well as presence of oxidative stress, insulin resistance, or increased inflammation, in combination with concordant and discordant risk factors and comorbidities, have been extensively described.[6] Studies on ischemic heart disease–related mortality in patients with PD have generated conflicting results.[76–78] In those who are prescribed drugs with potential adverse effects on cardiac conduction, or drugs that increase the risk of sudden cardiac arrest, such as domperidone, donepezil, citalopram, or escitalopram, baseline ECG monitoring is advised, especially for those presenting concomitant heart disease or who are polymedicated.[79] Sudden unexpected death in PD, defined as an unexpected death of a patient with PD without evident cause on autopsy[80,81] may, on occasion, be secondary to cardiovascular events, cardiac dysautonomia, sleep apnea (which increases risk of myocardial infarction), or polypharmacy.[82–84] Sudden death has also been reported in some cases of DLB.[85]

22q11.2 Deletion Syndrome-Associated PD

This multisystem condition is characterized by a plethora of clinical manifestations, such as endocrinological disorders (ie,

hypoparathyroidism, hypocalcemia), velopharyngeal dysfunction, recurrent infection, obesity, epilepsy, myoclonus, psychiatric disorders (ie, anxiety and psychosis), and cognitive impairment.[86] Patients have an increased risk of early-onset PD as well as of parkinsonism not meeting the criteria for PD.[86] Congenital heart defects, such as tetralogy of Fallot, ventricular or atrial septal defects, truncus arteriosus, patent ductus arteriosus, dilated aortic root, or interrupted aortic arch are present in 50% to 75% of patients, and 30% to 40% may require corrective heart surgery.[86,87] Heart disease in this condition may be underestimated given that many patients also present cardiovascular risk factors, such as psychiatric disorders and related comorbidities, including smoking, obesity, and use of antipsychotics.

Restless Legs Syndrome and Periodic Leg Movements of Sleep (RLS-PLMS)

Large cross-sectional observational studies have found that both restless legs syndrome RLS and/or periodic leg movements of sleep (PLMS) are associated with an approximately 2-fold increase in the risk of coronary artery disease as well as of other types of cardiovascular disease, including heart failure, myocardial infarction, and hypertension, even after excluding for confounding cardiovascular risk factors, particularly in patients with more severe or frequent RLS symptoms.[4,88–91] In a large cohort of more than 3 million US veterans, incident RLS was associated with an almost 4 times higher risk of coronary heart disease (hazard ratio [HR], 3.97; 95% confidence interval [CI], 3.26–4.84).[92] When RLS symptom duration was analyzed in a prospective study of 70,977 women free from coronary heart disease at baseline and followed for 6 years, patients with symptoms lasting for at least 3 years showed an increased risk of coronary heart disease (multivariable-adjusted HR,1.80; 95% CI, 1.07–3.01).[93] Lastly, a systematic review and meta-analysis including cross-sectional and prospective studies on PLMS found a significantly elevated prevalence of coronary artery disease (odds ratio, 1.56; 95% CI, 1.2–2.1) and cardiovascular disease in the study population (odds ratio, 1.27; 95% CI, 1.1–1.5).[94]

RLS may favor cardiovascular disease through autonomic changes, modifying cardiovagal control, specific to arterial baroreflex, leading to greater peripheral vascular resistance and sympathetic overactivity[95–97] and ultimately increasing cardiovascular disease prevalence.[95] A recent cross-sectional study of a large population-based cohort of health outcomes in the Canadian general population aged 45 to 85 years found that the mean carotid intima-media thickness, an objective measure of atherosclerosis, was higher in the group of patients with probable RLS (0.755 ± 0.17; n = 2047) in comparison with a control group (0.736 ± 0.17; n = 24257) with an adjusted mean difference of 0.016 (95% CI, 0.008–0.024). Abnormal carotid intima-media thickness (>1 mm) was observed 33% more often in patients with RLS compared with controls (adjusted odds ratio, 1.33; 95% CI, 1.09–1.61). These findings persisted even after excluding those individuals with prior histories of any atherosclerotic conditions or diabetes mellitus.[98] The mechanisms for the connection between RLS and atherosclerosis is unclear: in some of them, such as microcirculation impairment in the legs and/or global hypoxia, atherosclerosis could cause RLS, and in others, such as sympathetic hyperactivity, autonomic fluctuations, and hypertension that occur with PLMS, RLS could accelerate atherosclerosis.[98]

In addition, as PLMS is present in more than 80% of patients with RLS, a high frequency of leg movements (usually hundreds per night) can cause repetitive sympathetic activation, increasing HRV, resulting in hypertension and left ventricular hypertrophy.[88,97,99–102] Lastly, comorbidities associated with RLS/PLMS, such as renal failure, diabetes mellitus, iron deficiency, and insomnia or sleep fragmentation may predispose patients to heart disease.[96,103] Randomized interventional studies specifically targeting treatment of PLMS and evaluating the effect on cardiovascular disease morbidity and mortality are required. Meanwhile, recommendations for the prevention of cardiovascular disease should be considered on an individual basis.[104]

Neurological Conditions That Can Present with Varying Types of Movement Disorders

Wilson's Disease

Wilson's disease (WD) is a rare autosomal recessive inherited multisystemic disorder of chronic copper toxicity primarily affecting the liver and the brain. The disease usually manifests in children and young adults with liver failure and/or with movement disorders, such as parkinsonism, dystonia, tremor, or chorea as well as with cognitive or behavioral problems.[105] The characteristic Kayser-Fleischer rings are frequently present and result from copper deposition in Descemet's membrane of the cornea.[105] Cardiac abnormalities in WD have been widely reported, are mostly asymptomatic or mild without systolic or diastolic dysfunction, and may be present already during childhood (eg, subclinical diastolic dysfunction).[106,107] Cardiac disease in WD encompasses hypertrophic cardiomyopathy, ECG abnormalities (early repolarization, ST depression, T-wave inversion, wide QRS complex, premature atrial or ventricular contractions, sinoatrial block, Mobitz type 1 atrioventricular block), and arrhythmias (supraventricular tachycardia, extrasystolic beats, atrial and ventricular fibrillation) or conduction defects that can cause heart failure and/or sudden cardiac death.[107–109] In a large longitudinal cohort study of 463 patients with WD, a 29% higher risk of atrial fibrillation (HR, 1.29; 95% CI, 1.15–1.45; $P < 0.0001$) and a 55% higher risk of heart failure (HR, 1.55; 95% CI, 1.41–1.71; $P < 0.0001$) were found, both before and after adjusting for potential confounders and mediators.[110] Hypertrophic cardiomyopathy commonly starts early as concentric ventricular remodeling and progresses with thickening of the interventricular septum and the posterior ventricular wall.[107] Less frequently, dilated cardiomyopathy is also observed in patients with severe heart disease.[108] Left ventricle hypertrophy, prolonged QT, and

QTc intervals or cardiac autonomic dysfunction have been reported more commonly in patients with neurologic involvement rather than predominantly hepatic compromise.[111–113] Mortality attributed to cardiac complications is less frequent than from liver failure, esophageal hemorrhage, or infections in patients with advanced disease who are bedridden.[114–116] Cardiac evaluation of patients with WD should be part of the routine clinical examination as the presence of cardiac arrhythmia and cardiomyopathy may have therapeutic and prognostic implications.

Cerebrotendinous Xanthomatosis (*ATX*-CYP27A1)

This autosomal recessive neurometabolic disorder is characterized by infantile or early childhood onset of chronic diarrhea, tendon xanthomas, cataracts, and neurological manifestations, such as cognitive impairment, behavioral disorders, peripheral neuropathy, epilepsy, dystonia, parkinsonism, palatal tremor, myoclonus, and cerebellar ataxia. Frequency of cardiovascular disease ranges between 10% and 20%.[117,118] Patients may present severe premature coronary heart disease that can cause angina pectoris, myocardial infarction, and sudden death.[117,119,120] Interestingly, dyslipidemia and other atherogenic risk factors are usually not associated.[121] This discrepancy suggests that atherosclerosis is likely to be induced by a single mechanism of disturbed lipoprotein metabolism responsible for cholestanol deposition in subendothelial vessel layers.[122–124] In addition, other pathophysiological causes of atherosclerosis may be present, including a lack of sterol 27-hydroxylase activity in cellular constituents of the atheroma and altered reverse cholesterol transport, which are pathways whereby cholesterol is removed from peripheral tissues and delivered to the liver to be excreted in bile or degraded into bile acids before elimination from the body.[122–124] Lipomatous hypertrophy of the atrial septum, atherosclerotic aneurysms in coronary arteries, cardiac autonomic dysfunction, and arrhythmias such as ventricular tachycardia and atrial fibrillation have also been reported.[125–128] The presence of cardiovascular disease should be investigated even in asymptomatic patients, and prevention and treatment prescribed when necessary, including a reduced-fat diet followed by pharmacological treatment with statins or even LDL apheresis and chenodeoxycholic acid.

Mitochondrial Disorders

Patients with mitochondrial alterations often present with movement disorders.[129] Because cardiac metabolic demand is high, and mitochondrial function a key determinant of myocardial performance, cardiac involvement is common in patients with mitochondrial disorders (up to 40% of cases).[130,131] Hypertrophic and/or dilated cardiomyopathy is frequently observed.[2,131,132] Arrhythmias (eg, sinus tachycardia, supraventricular tachycardia, nonsustained ventricular tachycardia, ventricular extrasystoles) and conduction defects (eg, bundle branch block, ventricular premature beats, and Wolff–Parkinson–White syndrome) occur in a significant proportion of patients leading to premature death.[132,133] Conduction defects are particularly characteristic of Kearns-Sayre syndrome, a disorder caused by single or multiple large mitochondrial DNA deletions, commonly associated with ataxia.[2,134] Myoclonic epilepsy associated with ragged-red fibers (MERRF) and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes are disorders commonly associated with myoclonus and ataxia. The m.8344A>G pathogenic variant in *MT-TK* in MERRF in particular has been linked to cardiac abnormalities (30% to 50% of patients).[132,133] *POLG*-related disorders can manifest with movement disorders, such as ataxia, parkinsonism, and dystonia as well as cardiac disease, including cardiomyopathy (generally dilated), mitral valve prolapse and insufficiency, and cardiac conduction defects.[135–138] Other mitochondrial disorders that frequently combine cardiac disease and movement disorders, such as ataxia, dystonia, tremor, or spastic paraparesis include Leigh syndrome, Leber hereditary optic neuropathy, neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome as well as certain oxidative phosphorylation and respiratory chain disorders, such as coenzyme Q10 deficiency. These are frequently overlapping syndromes caused by alterations in both nuclear and mitochondrial genes involved in energy metabolism, frequently presenting hypertrophic or dilated cardiomyopathy, arrhythmias, and cardiac conduction defects.[2,139–143] Detailed cardiac manifestations of these disorders can be found in Tables 1 and 2 and Table S1.

ATP1A3-Related Syndromes

The *ATP1A3*-related disorders include 3 different heterogeneous and overlapping phenotypes: rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS).[144] ECG abnormalities were found in up to 60% of the patients with AHC, a disorder characterized by early-onset, recurrent, often alternating, and hemiplegic episodes and is also associated with seizures and nonparoxysmal neurological features.[144,145]

In RDP, which is characterized by an abrupt onset and rapidly progressive asymmetric dystonia and parkinsonism in adolescence or young adulthood, associated with predominant bulbar symptoms and gait instability occurring commonly with a rostrocaudal gradient patter of neurologic deterioration, and in CAPOS syndrome, ECG abnormalities were found in 67% of patients (6 of 9 patients with RDP and 2 of 3 patients with CAPOS syndrome).[144] ECG abnormalities included dynamic alterations of the repolarization phase, with or without intraventricular conduction delay, or incomplete right bundle branch block and J-wave or J-point changes (but no Brugada syndrome pattern).[144,145] Rarely, asystole has been reported.[144,146] These ECG changes occurred independently of structural abnormalities detectable on echocardiography and were unrelated to seizures or plegic episodes. However, they may account for some of the unexplained premature mortality.[144,145] Syncope, which can be present in up to 3% of patients with AHC, is often associated with atrioventricular block, ventricular ectopy or asystole,

requiring the implantation of a cardiac loop recorder to identify patients potentially at higher risk of sudden cardiac death who may benefit from the insertion of a pacemaker or implantable cardioverter-defibrillator.[144] Patients with *ATP1A3*-related syndromes, especially those with AHC, should have longitudinal and systematic cardiac assessments by cardiologists with expertise in inherited cardiac disease.[144]

Autoimmune Movement Disorders

Movement disorders are a prominent and common feature in several autoantibody-mediated neurological diseases.[147] Immunoglobulin-like cell adhesion molecule 5 IgLON5-antibody-linked tauopathy is characterized by prominent sleep behavior disorder, including periodic limb movements and breathing difficulties, and is often associated with bulbar symptoms, ataxia, oculmotor disturbance, cognitive decline, and central hypoventilation. In this condition, cardiac dysautonomia has been reported, including ventricular tachycardia and symptomatic bradycardia requiring pacemaker implantation[147,148] as well as isolated Takotsubo cardiomyopathy.[148,149] In Anti–*N*-methyl-D-aspartate receptor encephalitis, a condition characterized by neuropsychiatric disturbance, cognitive impairment, seizures, reduced consciousness, central hypoventilation, and movement disorders, such as orofacial and limb dyskinesia, chorea, dystonia, ataxia, myoclonus, parkinsonism, and paroxysmal dyskinesias, cardiac dysautonomia or dysrhythmias, including tachycardia or bradycardia, with prolonged pauses and even ictal asystole and torsades de pointes leading to cardiac arrest have been reported.[150–153] In a large cohort of 100 patients, cardiac dysrhythmias occurred in 37% of patients.[150] In glycine-receptor antibody-related progressive encephalomyelitis (PERM) mainly characterized by a stiff-person syndrome, myoclonus, ataxia, and acquired hyperekplexia and in Dipeptidyl-peptidase-like protein-6 DPPX potassium channel antibody autoimmune disorder (PERM-like phenotype with gastrointestinal hyper- or hypomobility and marked weight loss) ventricular tachycardia and cardiac arrest have been reported but are rare.[147,154] Finally, episodic bradycardia (usually prodromal), sinus arrest, and other arrhythmias requiring a pacemaker have been reported in autoimmune Leucine-rich glioma-inactivated 1 anti-LGI1 limbic encephalitis, a condition characterized by faciobrachial dystonic seizures, sleep behavior disorders and/or chorea, myoclonus, parkinsonism, tremor, or paroxysmal dyskinesias preceding or combined with cognitive impairment and/or hyponatremia.[155] No specific management recommendations have been published.

Movement Disorders as Neurologic Complications of Major Cardiac Surgery

Postoperative encephalopathy with choreoathetosis and post-pump progressive supranuclear palsy–like syndrome are neurologic complications of major cardiac surgeries that should not be underrecognized. Post-pump chorea has been classically recognized in 1% to 18% of children as a complication of cardiac surgery that undergoes cardiopulmonary bypass and deep hypothermia circulatory arrest, such as congenital heart defect corrective surgery, aortic surgery, or pulmonary endarterectomy, but can also occur in adults.[156–160] It consists of generalized chorea, choreodystonia including orolingual and facial musculatures or choreoballism that usually develops after a latent period of normal motor function of few hours or days postoperative with a peak of severity at 2 weeks and subsequent amelioration of choreic movements that can self-limit of even persist for several months or permanently.[156,158] The exact etiology and pathophysiology of this complication is unknown, but probably centers around several factors that may lead to partial basal ganglia ischemia.[161] Bilateral putaminal hypometabolism in [^{18}F] fluorodeoxyglucose-positron emission tomography and transient bilateral hyperintensities of globus pallidus on diffusion-weighted magnetic resonance imaging (MRI) were found.[158,160,162] Several factors may contribute with both the development and the severity of post-pump chorea, which include prolonged time on pump, duration of circulatory arrest time, lower temperature of deep hypothermia, quicker postsurgical rewarm, variability in blood pH and $PaCO_2$ resulting in fluctuations in cerebral blood flow, and age beyond early infancy.[157,159] Treatment with tetrabenazine, haloperidol, carbamazepine, pimozide, and sodium valproate were of very limited benefit in providing symptomatic relief and of no benefit in modifying evolution of the disease process or long-term outcomes.[156,158,160,162]

Post-pump progressive supranuclear palsy–like syndrome has been reported less frequently than post-pump chorea and has been described exclusively in adults after aortic surgery.[158,163–166] Symptom onset occurs usually during the first postoperative month.[158,163,164] Clinical manifestations usually include a predominant axial parkinsonism, vertical and/or horizontal gaze palsy, dysarthria, dysphagia, and postural instability, and in some cases seizures or blepharospasm were observed.[158,164,165] Clinical progression is usually rapid within a few weeks and then stabilizes without further progression and permanent disability.[158,164] The mechanism of injury remains unclear. Although brainstem lesions are usually absent on MRI imaging,[164] damage of midbrain structures were found, possibly attributed to perioperative ischemic stroke.[158,164,166] Treatment with levodopa or amantadine has been shown to be ineffective.[158,164,166]

Conclusions

The coexistence of cardiac disease and movement disorders has received little attention, especially among neurologists, who commonly leave out cardiac assessment in patients with movement disorders. This educational review has focused on movement disorders with common and prominent cardiac involvement in an attempt to heighten awareness on the need for routine cardiac assessments as well as to recommend caution

in prescribing QT-prolonging medications in this patient population.

A complete cardiac function evaluation is recommended in patients with movement disorders who present abnormalities on initial screening or conditions frequently associated with heart disease as appropriate treatment may reduce morbidity and mortality.[13,14,115,130] Management of functional or structural heart abnormalities should follow universal cardiovascular disease treatment guidelines. Monitoring and treatment recommendations for movement disorders associated with heart disease are described in Table 3.

In other conditions, association only occurs in isolated cases, probably as a result of underestimation, particularly of minor asymptomatic cardiac abnormalities, as not all patients undergo routine cardiovascular evaluation.

Heart involvement can present early, and even precede neurological manifestations, or it may only occur during later stages of disease. The question remains as to whether the same pathophysiological processes are responsible for both movement disorders and cardiac disease, as is the case in FRDA, WD, or other metabolic disorders, including Refsum disease, Gaucher disease, congenital disorder of glycosylation, or cerebrotendinous xanthomatosis or whether 1 may be the cause and the other the consequence. The hypothesis suggesting that progressive noradrenergic denervation in patients with α-synucleinopathies such as PD is the underlying cause of orthostatic hypotension, cognitive impairment, and falls and that recurrent cerebral hypoperfusion results in cognitive decline in PD remains unproven.[167–169] Nevertheless, the occurrence of movement disorders with highly prevalent cardiac diseases should always be suspected.

Increasing neurologist awareness of movement disorders associated with cardiovascular disease should be encouraged to diagnose heart involvement early and prompt appropriate management, reducing the associated patient morbidity and mortality.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

M.R.: 1A, 1B, 1C, 2A
N.W.: 1A, 1B, 1C, 2B
M.M.: 1A, 1B, 1C, 2B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. The authors confirm that patient consent was not required for this work.

Funding Sources and Conflicts of Interest: The authors declare that there are no funding sources or conflicts of interest relevant to this work.

Financial Disclosures for Previous 12 Months: Malco Rossi and Néstor Wainsztein have no disclosures to report. Marcelo Merello declares the following disclosures: consultancies with St Jude Medical (Abbott); honoraria from Glaxo, Allergan, and TEVA; royalties from Springer, Random House, Cambridge University Press, and Humana Press; and grants from Glaxo, Allergan, TEVA, and Consejo Nacional de Investigaciones Científicas y Técnicas de Argentina (CONICET). ■

References

1. Moore S, Raman SV. Cardiac involvement in hereditary ataxias. *J Child Neurol* 2012;27:1174–1178.
2. Marin-Garcia J, Goldenthal MJ, Filiano JJ. Cardiomyopathy associated with neurologic disorders and mitochondrial phenotype. *J Child Neurol* 2002;17:759–765.
3. Lanska DJ, Lavine L, Lanska MJ, Schoenberg BS. Huntington's disease mortality in the United States. *Neurology* 1988;38:769–772.
4. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* 2008;70:35–42.
5. Weidemann F, Rummey C, Bijnens B, et al. The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. *Circulation* 2012;125:1626–1634.
6. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. *Mov Disord* 2020;35:55–74.
7. Polek B, Roach MJ, Andrews WT, Ehling M, Salek S. Burden of Friedreich's ataxia to the patients and healthcare systems in the United States and Canada. *Front Pharmacol* 2013;4:66.
8. Durr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996;335:1169–1175.
9. Pousset F, Legrand L, Monin ML, et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol* 2015;72:1334–1341.
10. Reetz K, Dogan I, Hohenfeld C, et al. Nonataxia symptoms in Friedreich Ataxia: report from the registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS). *Neurology* 2018;91:e917–e930.
11. Tsou AY, Paulsen EK, Lagedrost SJ, et al. Mortality in Friedreich ataxia. *J Neurol Sci* 2011;307:46–49.
12. Reetz K, Dogan I, Costa AS, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol* 2015;14:174–182.
13. Alboliras ET, Shub C, Gomez MR, et al. Spectrum of cardiac involvement in Friedreich's ataxia: clinical, electrocardiographic and echocardiographic observations. *Am J Cardiol* 1986;58:518–524.
14. Child JS, Perloff JK, Bach PM, Wolfe AD, Perlman S, Kark RA. Cardiac involvement in Friedreich's ataxia: a clinical study of 75 patients. *J Am Coll Cardiol* 1986;7:1370–1378.
15. Pasternac A, Krol R, Petitclerc R, Harvey C, Andermann E, Barbeau A. Hypertrophic cardiomyopathy in Friedreich's ataxia: symmetric or asymmetric? *Can J Neurol Sci* 1980;7:379–382.
16. Bit-Avragim N, Perrot A, Schols L, et al. The GAA repeat expansion in intron 1 of the frataxin gene is related to the severity of cardiac manifestation in patients with Friedreich's ataxia. *J Mol Med (Berl)* 2001;78:626–632.
17. Kelly M, Bagnall RD, Peverill RE, et al. A polymorphic miR-155 binding site in AGTR1 is associated with cardiac hypertrophy in Friedreich ataxia. *J Mol Cell Cardiol* 2011;51:848–854.

18. Schadt KA, Friedman LS, Regner SR, Mark GE, Lynch DR, Lin KY. Cross-sectional analysis of electrocardiograms in a large heterogeneous cohort of Friedreich ataxia subjects. *J Child Neurol* 2012;27:1187–1192.
19. Bhidayasiri R, Perlman SL, Pulst SM, Geschwind DH. Late-onset Friedreich ataxia: phenotypic analysis, magnetic resonance imaging findings, and review of the literature. *Arch Neurol* 2005;62:1865–1869.
20. Lecocq C, Charles P, Azulay JP, et al. Delayed-onset Friedreich's ataxia revisited. *Mov Disord* 2016;31:62–69.
21. Fearon C, Lonergan R, Ferguson D, et al. Very-late-onset Friedreich's ataxia: diagnosis in a kindred with late-onset cerebellar ataxia. *Pract Neurol* 2020;20:55–58.
22. Martinez AR, Moro A, Abrahao A, et al. Nonneurological Involvement in late-onset Friedreich ataxia (LOFA): exploring the phenotypes. *Cerebellum* 2017;16:253–256.
23. Galea CA, Huq A, Lockhart PJ, et al. Compound heterozygous FXN mutations and clinical outcome in friedreich ataxia. *Ann Neurol* 2016; 79:485–495.
24. Koeppen AH, Ramirez RL, Becker AB, et al. The pathogenesis of cardiomyopathy in Friedreich ataxia. *PLoS One* 2015;10:e0116396.
25. Cotticelli MG, Xia S, Lin D, et al. Ferroptosis as a novel therapeutic target for Friedreich's ataxia. *J Pharmacol Exp Ther* 2019;369:47–54.
26. Tiano F, Amati F, Cherubini F, et al. Frataxin deficiency in Friedreich's ataxia is associated with reduced levels of HAX-1, a regulator of cardiomyocyte death and survival. *Hum Mol Genet* 2020;29:471–482.
27. Friedman LS, Schadt KA, Regner SR, et al. Elevation of serum cardiac troponin I in a cross-sectional cohort of asymptomatic subjects with Friedreich ataxia. *Int J Cardiol* 2013;167:1622–1624.
28. Takazaki KAG, Rezende TJR, Martinez ARM, et al. Sudomotor dysfunction is frequent and correlates with disability in Friedreich ataxia. *Clin Neurophysiol* 2018;129:2290–2295.
29. Pousset F, Kalotka H, Durr A, et al. Parasympathetic activity in Friedrich's ataxia. *Am J Cardiol* 1996;78:847–850.
30. Indelicato E, Fanciulli A, Ndayisaba JP, et al. Autonomic function testing in Friedreich's ataxia. *J Neurol* 2018;265:2015–2022.
31. St John Sutton M, Ky B, Regner SR, et al. Longitudinal strain in Friedreich ataxia: a potential marker for early left ventricular dysfunction. *Echocardiography* 2014;31:50–57.
32. Mavrogeni S, Giannakopoulou A, Katsalouli M, et al. Friedreich's ataxia: case series and the additive value of cardiovascular magnetic resonance. *J Neuromuscul Dis* 2020;7:61–67.
33. Milano EG, Harries IB, Bucciarelli-Ducci C. Young adult with Friedreich ataxia. *Heart* 2019;105:797–806.
34. Leys D, Petit H, Bonte-Adnet C, et al. Refsum's disease revealed by cardiac disorders. *Lancet* 1989;1:621.
35. Wanders RJA, Waterham HR, Leroy BP. Refsum disease. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews(R)*. Seattle, WA: University of Washington, Seattle; 1993.
36. Hansen RP. 3,7,11,15-tetramethylhexadecanoic acid: its occurrence in the tissues of humans afflicted with Refsum's syndrome. *Biochim Biophys Acta* 1965;106:304–310.
37. Skjeldal OH, Stokke O, Refsum S, Norseth J, Petit H. Clinical and biochemical heterogeneity in conditions with phytanic acid accumulation. *J Neurol Sci* 1987;77:87–96.
38. Ruether K, Baldwin E, Casteels M, et al. Adult Refsum disease: a form of tapetoretinal dystrophy accessible to therapy. *Surv Ophthalmol* 2010; 55:531–538.
39. Sparks SE, Krasnewich DM. PMM2-CDG (CDG-Ia). In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews(R)*. Seattle, WA: University of Washington, Seattle; 1993.
40. Romano S, Bajolle F, Valayannopoulos V, et al. Conotruncal heart defects in three patients with congenital disorder of glycosylation type Ia (CDG Ia). *J Med Genet* 2009;46:287–288.
41. Gehrmann J, Sohlbach K, Linnebank M, et al. Cardiomyopathy in congenital disorders of glycosylation. *Cardiol Young* 2003;13:345–351.
42. Davey KM, Parboosingh JS, McLeod DR, et al. Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. *J Med Genet* 2006;43:385–393.
43. Ojala T, Polinati P, Manninen T, et al. New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr Res* 2012;72:432–437.
44. Al Teneiji A, Siriwardena K, George K, Mital S, Mercimek-Mahmutoglu S. Progressive cerebellar atrophy and a novel homozygous pathogenic DNAJC19 variant as a cause of dilated cardiomyopathy ataxia syndrome. *Pediatr Neurol* 2016;62:58–61.
45. Greenway SC, Dallaire F, Hazari H, Patel D, Khan A. Addition of digoxin improves cardiac function in children with the dilated cardiomyopathy with ataxia syndrome: a mitochondrial cardiomyopathy. *Can J Cardiol* 2018;34:972–977.
46. Sorensen SA, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. *J Med Genet* 1992;29: 911–914.
47. Bellosta Diago E, Perez-Perez J, Santos Lasaosa S, et al. Neurocardiovascular pathology in pre-manifest and early-stage Huntington's disease. *Eur J Neurol* 2018;25:956–962.
48. Abildtrup M, Shattock M. Cardiac dysautonomia in Huntington's disease. *J Huntingtons Dis* 2013;2:251–261.
49. Stephen CD, Hung J, Schifitto G, Hersch SM, Rosas HD. Electrocardiogram abnormalities suggest aberrant cardiac conduction in Huntington's disease. *Mov Disord Clin Pract* 2018;5:306–311.
50. Bar KJ, Boettger MK, Andrich J, et al. Cardiovagal modulation upon postural change is altered in Huntington's disease. *Eur J Neurol* 2008;15: 869–871.
51. Sharma KR, Romano JG, Ayyar DR, Rotta FT, Facca A, Sanchez-Ramos J. Sympathetic skin response and heart rate variability in patients with Huntington disease. *Arch Neurol* 1999;56:1248–1252.
52. Andrich J, Schmitz T, Saft C, et al. Autonomic nervous system function in Huntington's disease. *J Neurol Neurosurg Psychiatry* 2002;72: 726–731.
53. Terroba-Chambi C, Bruno V, Vigo DE, Merello M. Heart rate variability and falls in Huntington's disease. *Clin Auton Res* 2020. http://dx.doi.org/10.1007/s10286-020-00669-2
54. Steventon JJ, Collett J, Furby H, et al. Alterations in the metabolic and cardiorespiratory response to exercise in Huntington's disease. *Parkinsonism Relat Disord* 2018;54:56–61.
55. Cankar K, Melik Z, Kobal J, Starc V. Evidence of cardiac electrical remodeling in patients with Huntington disease. *Brain Behav* 2018;8:e01077.
56. Strong GFA. study of one hundred cases of chorea with particular references to the cardiac complications. *Can Med Assoc J* 1923;13:92–97.
57. Dean SL, Singer HS. Treatment of Sydenham's chorea: a review of the current evidence. *Tremor Other Hyperkinet Mov (N Y)* 2017;7:456.
58. Demiroren K, Yavuz H, Cam L, Oran B, Karaaslan S, Demiroren S. Sydenham's chorea: a clinical follow-up of 65 patients. *J Child Neurol* 2007;22:550–554.
59. Kilic A, Unuvar E, Tatli B, et al. Neurologic and cardiac findings in children with Sydenham chorea. *Pediatr Neurol* 2007;36:159–164.
60. Panamonta M, Chaikitpinyo A, Auvichayapat N, Weraarchakul W, Panamonta O, Pantongwiriyakul A. Evolution of valve damage in Sydenham's chorea during recurrence of rheumatic fever. *Int J Cardiol* 2007;119:73–79.
61. Panamonta M, Chaikitpinyo A, Kaplan EL, Pantongwiriyakul A, Tassniyom S, Sutra S. The relationship of carditis to the initial attack of Sydenham's chorea. *Int J Cardiol* 2004;94:241–248.
62. Basturk A, Oztarhan K, Kavuncuoglu S, Polat C. Significance of silent carditis and investigation of follow-up signs in acute rheumatic fever. *Future Cardiol* 2016;12:281–287.
63. Cardoso F, Vargas AP, Oliveira LD, Guerra AA, Amaral SV. Persistent Sydenham's chorea. *Mov Disord* 1999;14:805–807.
64. World Health Organization. Rheumatic fever and rheumatic heart disease. *WHO Tech Rep Ser* 2004;923:1–122.
65. Roulis E, Hyland C, Flower R, Gassner C, Jung HH, Frey BM. Molecular basis and clinical overview of McLeod syndrome compared with other neuroacanthocytosis syndromes: a review. *JAMA Neurol* 2018;75:1554–1562.
66. Danek A, Rubio JP, Rampoldi L, et al. McLeod neuroacanthocytosis: genotype and phenotype. *Ann Neurol* 2001;50:755–764.
67. Witt TN, Danek A, Reiter M, Heim MU, Dirschinger J, Olsen EG. McLeod syndrome: a distinct form of neuroacanthocytosis. Report of two cases and literature review with emphasis on neuromuscular manifestations. *J Neurol* 1992;239:302–306.
68. Walker RH, Miranda M, Jung HH, Danek A. Life expectancy and mortality in chorea-acanthocytosis and McLeod syndrome. *Parkinsonism Relat Disord* 2019;60:158–161.

69. Oechslin E, Kaup D, Jenni R, Jung HH. Cardiac abnormalities in McLeod syndrome. *Int J Cardiol* 2009;132:130–132.

70. Walker RH, Jung HH, Tison F, Lee S, Danek A. Phenotypic variation among brothers with the McLeod neuroacanthocytosis syndrome. *Mov Disord* 2007;22:244–248.

71. Malandrini A, Fabrizi GM, Truschi F, et al. Atypical McLeod syndrome manifested as X-linked chorea-acanthocytosis, neuromyopathy and dilated cardiomyopathy: report of a family. *J Neurol Sci* 1994;124:89–94.

72. Kageyama Y, Matsumoto K, Ichikawa K, et al. A new phenotype of chorea-acanthocytosis with dilated cardiomyopathy and myopathy. *Mov Disord* 2007;22:1669–1670.

73. Lossos A, Dobson-Stone C, Monaco AP, et al. Early clinical heterogeneity in choreoacanthocytosis. *Arch Neurol* 2005;62:611–614.

74. Mente K, Kim SA, Grunseich C, et al. Hippocampal sclerosis and mesial temporal lobe epilepsy in chorea-acanthocytosis: a case with clinical, pathologic and genetic evaluation. *Neuropathol Appl Neurobiol* 2017; 43:542–546.

75. Gelpi E, Navarro-Otano J, Tolosa E, et al. Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. *Mov Disord* 2014; 29:1010–1018.

76. Becker C, Jick SS, Meier CR. Risk of stroke in patients with idiopathic Parkinson disease. *Parkinsonism Relat Disord* 2010;16:31–35.

77. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? *J Neurol Neurosurg Psychiatry* 1995;58:293–299.

78. Liang HW, Huang YP, Pan SL. Parkinson disease and risk of acute myocardial infarction: a population-based, propensity score-matched, longitudinal follow-up study. *Am Heart J* 2015;169:508–514.

79. Malek NM, Grosset KA, Stewart D, Macphee GJ, Grosset DG. Prescription of drugs with potential adverse effects on cardiac conduction in Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:586–589.

80. Rodrigues LD, Oliveira LF, Scorza CA, et al. We never speak about sudden unexpected death in Parkinson's disease. *Eur J Neurol* 2020;27: e30. http://dx.doi.org/10.1111/ene.14217

81. Scorza FA, Fiorini AC, Scorza CA, Finsterer J. Cardiac abnormalities in Parkinson's disease and Parkinsonism. *J Clin Neurosci* 2018;53:1–5.

82. Matsumoto H, Sengoku R, Saito Y, Kakuta Y, Murayama S, Imafuku I. Sudden death in Parkinson's disease: a retrospective autopsy study. *J Neurol Sci* 2014;343:149–152.

83. Nishida N, Yoshida K, Hata Y. Sudden unexpected death in early Parkinson's disease: neurogenic or cardiac death? *Cardiovasc Pathol* 2017; 30:19–22.

84. Scorza FA, Tufik S, Scorza CA, Andersen ML, Cavalheiro EA. Sudden unexpected death in Parkinson's disease (SUDPAR): sleep apnea increases risk of heart attack. *Sleep Breath* 2017;21:965–966.

85. Molenaar JP, Wilbers J, Aerts MB, et al. Sudden death: an uncommon occurrence in dementia with Lewy bodies. *J Parkinsons Dis* 2016;6:53–55.

86. Boot E, Bassett AS, Marras C. 22q11.2 deletion syndrome-associated Parkinson's disease. *Mov Disord Clin Pract* 2019;6:11–16.

87. Carotti A, Digilio MC, Piacentini G, Saffirio C, Di Donato RM, Marino B. Cardiac defects and results of cardiac surgery in 22q11.2 deletion syndrome. *Dev Disabil Res Rev* 2008;14:35–42.

88. Koo BB, Blackwell T, Ancoli-Israel S, et al. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of sleep disorders in older men (MrOS) study. *Circulation* 2011;124:1223–1231.

89. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res* 2002;53:547–554.

90. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord* 2001;16:1159–1163.

91. Li Y, Li Y, Winkelman JW, et al. Prospective study of restless legs syndrome and total and cardiovascular mortality among women. *Neurology* 2018;90:e135–e141.

92. Molnar MZ, Lu JL, Kalantar-Zadeh K, Kovesdy CP. Association of incident restless legs syndrome with outcomes in a large cohort of US veterans. *J Sleep Res* 2016;25:47–56.

93. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation* 2012;126:1689–1694.

94. Huang TC, Tseng PT, Wu MN, et al. Periodic limb movements during sleep are associated with cardiovascular diseases: a systematic review and meta-analysis. *J Sleep Res* 2019;28:e12720.

95. Bertisch SM, Muresan C, Schoerning L, Winkelman JW, Taylor JA. Impact of restless legs syndrome on cardiovascular autonomic control. *Sleep* 2016;39:565–571.

96. Walters AS, Rye DB. Evidence continues to mount on the relationship of restless legs syndrome/ periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. *Sleep* 2010;33:287.

97. Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. *Sleep* 1999;22:575–580.

98. Zolfaghari S, Dasgupta K, Postuma RB. Restless leg syndrome and objectively-measured atherosclerosis in the Canadian Longitudinal Study on Aging. *Mov Disord* 2020;35:2314–2318.

99. Cassel W, Kesper K, Bauer A, et al. Significant association between systolic and diastolic blood pressure elevations and periodic limb movements in patients with idiopathic restless legs syndrome. *Sleep Med* 2016; 17:109–120.

100. May AM, Blackwell T, Stone KL, et al. Longitudinal relationships of periodic limb movements during sleep and incident atrial fibrillation. *Sleep Med* 2016;25:78–86.

101. Mirza M, Shen WK, Sofi A, et al. Frequent periodic leg movement during sleep is associated with left ventricular hypertrophy and adverse cardiovascular outcomes. *J Am Soc Echocardiogr* 2013;26:783–790.

102. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. *Clin Neurophysiol* 2007;118:1923–1930.

103. Lindner A, Fornadi K, Lazar AS, et al. Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure. *J Sleep Res* 2012;21:297–307.

104. Nannapaneni S, Ramar K. Periodic limb movements during sleep and their effect on the cardiovascular system: is there a final answer? *Sleep Med* 2014;15:379–384.

105. Aggarwal A, Bhatt M. The pragmatic treatment of Wilson's disease. *Mov Disord Clin Pract* 2014;1:14–23.

106. Elkiran O, Karakurt C, Selimoglu A, et al. Subclinical diastolic dysfunction in children with Wilson's disease assessed by tissue Doppler echocardiography: a possible early predictor of cardiac involvement. *Acta Cardiol* 2013;68:181–187.

107. Hlubocka Z, Marecek Z, Linhart A, et al. Cardiac involvement in Wilson disease. *J Inherit Metab Dis* 2002;25:269–277.

108. Kuan P. Cardiac Wilson's disease. *Chest* 1987;91:579–583.

109. Quick S, Weidauer M, Heidrich FM, et al. Cardiac manifestation of Wilson's disease. *J Am Coll Cardiol* 2018;72:2808–2809.

110. Grandis DJ, Nah G, Whitman IR, et al. Wilson's disease and cardiac myopathy. *Am J Cardiol* 2017;120:2056–2060.

111. Buksinska-Lisik M, Litwin T, Pasierski T, Czlonkowska A. Cardiac assessment in Wilson's disease patients based on electrocardiography and echocardiography examination. *Arch Med Sci* 2019;15:857–864.

112. Li K, Lindauer C, Haase R, et al. Autonomic dysfunction in wilson's disease: a comprehensive evaluation during a 3-year follow up. *Front Physiol* 2017;8:778.

113. Ozturk S, Gurbuz A, Efe S, Iliaz R, Banzragch M, Demir K. QTc interval is prolonged in wilson's disease with neurologic involvement. *Acta Clin Belg* 2018;73:328–332.

114. Kuan P. Fatal cardiac complications of Wilson's disease. *Am Heart J* 1982;104:314–316.

115. Czlonkowska A, Tarnacka B, Litwin T, Gajda J, Rodo M. Wilson's disease-cause of mortality in 164 patients during 1992-2003 observation period. *J Neurol* 2005;252:698–703.

116. Walshe JM. Cause of death in Wilson disease. *Mov Disord* 2007;22: 2216–2220.

117. Kuriyama M, Fujiyama J, Yoshidome H, et al. Cerebrotendinous xanthomatosis: clinical and biochemical evaluation of eight patients and review of the literature. *J Neurol Sci* 1991;102:225–232.

118. Sekijima Y, Koyama S, Yoshinaga T, Koinuma M, Inaba Y. Nationwide survey on cerebrotendinous xanthomatosis in Japan. *J Hum Genet* 2018;63:271–280.

119. Duell PB, Salen G, Eichler FS, et al. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. *J Clin Lipidol* 2018;12:1169–1178.

120. Valdivielso P, Calandra S, Duran JC, Garuti R, Herrera E, Gonzalez P. Coronary heart disease in a patient with cerebrotendinous xanthomatosis. *J Intern Med* 2004;255:680–683.

121. Burnett JR, Moses EA, Croft KD, et al. Clinical and biochemical features, molecular diagnosis and long-term management of a case of cerebrotendinous xanthomatosis. *Clin Chim Acta* 2001;306: 63–69.

122. Bjorkhem I, Andersson O, Diczfalusy U, et al. Atherosclerosis and sterol 27-hydroxylase: evidence for a role of this enzyme in elimination of cholesterol from human macrophages. *Proc Natl Acad Sci U S A* 1994;91: 8592–8596.

123. Fujiyama J, Kuriyama M, Arima S, et al. Atherogenic risk factors in cerebrotendinous xanthomatosis. *Clin Chim Acta* 1991; 200:1–11.

124. Inanloorahatloo K, Zand Parsa AF, Huse K, et al. Mutation in CYP27A1 identified in family with coronary artery disease. *Eur J Med Genet* 2013;56:655–660.

125. Dotti MT, Mondillo S, Plewnia K, Agricola E, Federico A. Cerebrotendinous xanthomatosis: evidence of lipomatous hypertrophy of the atrial septum. *J Neurol* 1998;245:723–726.

126. Potkin BN, Hoeg JM, Connor WE, et al. Aneurysmal coronary artery disease in cerebrotendinous xanthomatosis. *Am J Cardiol* 1988;61: 1150–1152.

127. Chen PS, Fleck RP, Calisi CM, Kozina JA, Feld GK. Macroreentrant ventricular tachycardia and coronary artery disease in cerebrotendinous xanthomatosis. *Am J Cardiol* 1989;64:680–682.

128. Chen SF, Tsai NW, Chang CC, et al. Neuromuscular abnormality and autonomic dysfunction in patients with cerebrotendinous xanthomatosis. *BMC Neurol* 2011;11:63.

129. Tranchant C, Anheim M. Movement disorders in mitochondrial diseases. *Rev Neurol (Paris)* 2016;172:524–529.

130. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics* 2004;114:925–931.

131. Anan R, Nakagawa M, Miyata M, et al. Cardiac involvement in mitochondrial diseases. A study on 17 patients with documented mitochondrial DNA defects. *Circulation* 1995;91:955–961.

132. Mancuso M, Orsucci D, Angelini C, et al. Phenotypic heterogeneity of the 8344A>G mtDNA "MERRF" mutation. *Neurology* 2013;80: 2049–2054.

133. Catteruccia M, Sauchelli D, Della Marca G, et al. "Myo-cardiomyopathy" is commonly associated with the A8344G "MERRF" mutation. *J Neurol* 2015;262:701–710.

134. Charles R, Holt S, Kay JM, Epstein EJ, Rees JR. Myocardial ultrastructure and the development of atrioventricular block in Kearns-Sayre syndrome. *Circulation* 1981;63:214–219.

135. Bohlega S, Tanji K, Santorelli FM, Hirano M, al-Jishi A, DiMauro S. Multiple mitochondrial DNA deletions associated with autosomal recessive ophthalmoplegia and severe cardiomyopathy. *Neurology* 1996;46: 1329–1334.

136. Horvath R, Hudson G, Ferrari G, et al. Phenotypic spectrum associated with mutations of the mitochondrial polymerase gamma gene. *Brain* 2006;129:1674–1684.

137. Rossi M, Medina Escobar A, Radrizzani M, Tenembaum S, Perandones C, Merello M. Dystonia in a patient with autosomal-dominant progressive external ophtalmoplegia type 1 caused by mutation in the POLG gene. *Mov Disord Clin Pract* 2015;4:266–269.

138. Verhoeven WM, Egger JI, Kremer BP, de Pont BJ, Marcelis CL. Recurrent major depression, ataxia, and cardiomyopathy: association with a novel POLG mutation? *Neuropsychiatr Dis Treat* 2011;7:293–296.

139. Wang SB, Weng WC, Lee NC, Hwu WL, Fan PC, Lee WT. Mutation of mitochondrial DNA G13513A presenting with Leigh syndrome, Wolff-Parkinson-White syndrome and cardiomyopathy. *Pediatr Neonatol* 2008;49:145–149.

140. Yaplito-Lee J, Weintraub R, Jamsen K, Chow CW, Thorburn DR, Boneh A. Cardiac manifestations in oxidative phosphorylation disorders of childhood. *J Pediatr* 2007;150:407–411.

141. Finsterer J, Stollberger C, Gatterer E. Wolff-Parkinson-White syndrome and noncompaction in Leber's hereditary optic neuropathy due to the variant m.3460G>A. *J Int Med Res* 2018;46:2054–2060.

142. Bower SP, Hawley I, Mackey DA. Cardiac arrhythmia and Leber's hereditary optic neuropathy. *Lancet* 1992;339:1427–1428.

143. Rotig A, Appelkvist EL, Geromel V, et al. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet* 2000;356:391–395.

144. Balestrini S, Mikati MA, Alvarez-Garcia-Roves R, et al. Cardiac phenotype in ATP1A3-related syndromes: a multicenter cohort study. *Neurology* 2020;95:e2866–e2879.

145. Jaffer F, Avbersek A, Vavassori R, et al. Faulty cardiac repolarization reserve in alternating hemiplegia of childhood broadens the phenotype. *Brain* 2015;138:2859–2874.

146. Novy J, McWilliams E, Sisodiya SM. Asystole in alternating hemiplegia with de novo ATP1A3 mutation. *Eur J Med Genet* 2014;57:37–39.

147. Balint B, Vincent A, Meinck HM, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. *Brain* 2018;141:13–36.

148. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology* 2017;88:1736–1743.

149. Montojo T, Piren V, Benkhadra F, Codreanu A, Diederich NJ. Gaze palsy, sleep and gait disorder, as well as tako-tsubo syndrome in a patient with IgLON5 antibodies. *Mov Disord Clin Pract* 2017;4: 441–443.

150. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–1098.

151. Lee M, Lawn N, Prentice D, Chan J. Anti-NMDA receptor encephalitis associated with ictal asystole. *J Clin Neurosci* 2011;18:1716–1718.

152. Inayat F, Hung Pinto WA, Ahmad S, Hussain A, Ullah W. Anti-N-methyl-D-aspartate receptor encephalitis associated with ictal torsades de pointes and cardiac arrest. *Cureus* 2019;11:e4837.

153. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;133:1655–1667.

154. Bourke D, Roxburgh R, Vincent A, et al. Hypoventilation in glycine-receptor antibody related progressive encephalomyelitis, rigidity and myoclonus. *J Clin Neurosci* 2014;21:876–878.

155. Naasan G, Irani SR, Bettcher BM, Geschwind MD, elfand JM. Episodic bradycardia as neurocardiac prodrome to voltage-gated potassium channel complex/leucine-rich, glioma inactivated 1 antibody encephalitis. *JAMA Neurol* 2014;71:1300–1304.

156. Przekop A, McClure C, Ashwal S. Postoperative encephalopathy with choreoathetosis. *Handb Clin Neurol* 2011;100:295–305.

157. Wong PC, Barlow CF, Hickey PR, et al. Factors associated with choreoathetosis after cardiopulmonary bypass in children with congenital heart disease. *Circulation* 1992;86:II118–II126.

158. Park KW, Choi N, Ryu HS, Kim HJ, Lee CS, Chung SJ. Post-pump chorea and progressive supranuclear palsy-like syndrome following major cardiac surgery. *Mov Disord Clin Pract* 2020;7:78–82.

159. Surie S, Tijssen MA, Biervliet JD, et al. Chorea in adults following pulmonary endarterectomy. *Mov Disord* 2010;25:1101–1104.

160. Medlock MD, Cruse RS, Winek SJ, et al. A 10-year experience with postpump chorea. *Ann Neurol* 1993;34:820–826.

161. Kupsky WJ, Drozd MA, Barlow CF. Selective injury of the globus pallidus in children with post-cardiac surgery choreic syndrome. *Dev Med Child Neurol* 1995;37:135–144.

162. Passarin MG, Romito S, Avesani M, et al. Late-onset choreoathetotic syndrome following heart surgery. *Neurol Sci* 2010;31:95–97.

163. Tomsak RL, Volpe BT, Stahl JS, Leigh RJ. Saccadic palsy after cardiac surgery: visual disability and rehabilitation. *Ann N Y Acad Sci* 2002;956: 430–433.

164. Nandipati S, Rucker JC, Frucht SJ. Progressive supranuclear palsy-like syndrome after aortic aneurysm repair: a case series. *Tremor Other Hyperkinet Mov (N Y)* 2013;3. http://dx.doi.org/10.7916/D8N29VNW

165. Mokri B, Ahlskog JE, Fulgham JR, Matsumoto JY. Syndrome resembling PSP after surgical repair of ascending aorta dissection or aneurysm. *Neurology* 2004;62:971–973.

166. Kim HT, Shields S, Bhatia KP, Quinn N. Progressive supranuclear palsy-like phenotype associated with bilateral hypoxic-ischemic striopallidal lesions. *Mov Disord* 2005;20:755–757.

167. McDonald C, Newton JL, Burn DJ. Orthostatic hypotension and cognitive impairment in Parkinson's disease: causation or association? *Mov Disord* 2016;31:937–946.

168. Robertson AD, Udow SJ, Espay AJ, et al. Orthostatic hypotension and dementia incidence: links and implications. *Neuropsychiatr Dis Treat* 2019;15:2181–2194.

169. Romagnolo A, Zibetti M, Merola A, et al. Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study. *J Neurol* 2019;266:85–91.

170. Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB. Consensus clinical management guidelines for Friedreich ataxia. *Orphanet J Rare Dis* 2014;9:184.

Supporting Information

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

Table S1. Conditions occasionally or rarely associated with movement disorders and cardiac involvement.