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REVIEW

Myoclonus-Ataxia Syndromes: A Diagnostic Approach

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Abstract: Background: A myriad of disorders combine myoclonus and ataxia. Most causes are genetic and an increasing number of genes are being associated with myoclonus-ataxia syndromes (MAS), due to recent advances in genetic techniques. A proper etiologic diagnosis of MAS is clinically relevant, given the consequences for genetic counseling, treatment, and prognosis.
Objectives: To review the causes of MAS and to propose a diagnostic algorithm.
Methods: A comprehensive and structured literature search following PRISMA criteria was conducted to identify those disorders that may combine myoclonus with ataxia.
Results: A total of 135 causes of combined myoclonus and ataxia were identified, of which 30 were charted as the main causes of MAS. These include four acquired entities: opsoclonus-myoclonus-ataxia syndrome, celiac disease, multiple system atrophy, and sporadic prion diseases. The distinction between progressive myoclonus epilepsy and progressive myoclonus ataxia poses one of the main diagnostic dilemmas.
Conclusions: Diagnostic algorithms for pediatric and adult patients, based on clinical manifestations including epilepsy, are proposed to guide the differential diagnosis and corresponding work-up of the most important and frequent causes of MAS. A list of genes associated with MAS to guide genetic testing strategies is provided. Priority should be given to diagnose or exclude acquired or treatable disorders.

Syndromes that combine dystonia and parkinsonism, dystonia and myoclonus, and dystonia and ataxia have been extensively reviewed.[1,2] The association of myoclonus and ataxia has received less attention in the literature. The combination of myoclonus and ataxia can be the manifestation of a plethora of diseases.[3,4] In clinical practice, recognition of these entities and orchestrating the appropriate work-up are often challenging.

Within the genetically determined myoclonus syndromes, ataxia is the most common associated movement disorder and a highly frequent accompanying clinical feature, only surpassed by epilepsy and cognitive decline.[3] Traditionally, the combination of these two movement disorders is linked to the syndrome of progressive myoclonus ataxia (PMA), previously referred to as Ramsay Hunt syndrome. The PMA share overlapping clinical features with the progressive myoclonus epilepsies (PME).[5] According to the new refined definition,[5] PMA is mainly separated from PME by the considerably lower frequency of seizures, less frequent mental deterioration, and often slower progression. PMA will often be of genetic origin, but still in many cases the etiology remains unclear despite the wide use of next generation sequencing (NGS) diagnostics.

In this systematic review, we will list the disorders that may combine myoclonus and ataxia, capture the causes of progressive myoclonus ataxia (PMA) and propose diagnostic algorithms and clinical clues for the most important and frequent causes of myoclonus-ataxia syndromes (MAS). In addition, we will provide a list of genes associated with MAS for guidance in diagnostic NGS strategies.

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TABLE 1 Myoclonus-ataxia syndromes

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy	
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response	Electrophysiological Characteristics of Epilepsy (EEG)
1) Non-genetic or acquired						
Opsoclonus-myoclonus-ataxia syndrome[6–12]	Infancy, childhood, adulthood	Opsoclonus, behavioral changes, insomnia, neoplasms, infections	BM[a] Extremities, axial muscles; Spontaneous, action	Burst duration <100 ms; No EMG-EEG correlates	Not described	Normal
Celiac disease[13–22]	Adulthood	Peripheral neuropathy, gastrointestinal symptoms	CM[a] Multifocal; Spontaneous, action and stimulus sensitive	Cortical reflex myoclonus	Seizures; Frequency unknown	Multifocal epileptiform discharges
Multiple system atrophy[23–27]	Adulthood	Parkinsonism, autonomic dysfunction, orofacial dystonia, disproportionate antecollis, inspiratory sighs, severe dysphonia, dysarthria	CM Stimulus-sensitive, action- or posture induced myoclonus. Small-amplitude, distal areas Polyminimyoclonus	Positive JLBA, Giant SSEP	Not described	Not described
Acquired or sporadic prion diseases (iatrogenic, variant and sporadic Creutzfeldt-Jakob disease)[28–33]	Adulthood	Dementia, aphasia, behavioral disorders, parkinsonism, ophthalmoparesis	CM, SCM[a] Multifocal Both positive and negative jerks Spontaneous	Either short burst of 54.1 ± 15.8 ms or long burst of >200 ms. In most cases a positive jerk-locked back-averaging was present. Giant SSEP	Rarely occurring epileptic seizures (GTC)	Diffuse slow activity. Typical periodic sharp wave discharges and paroxysmal discharges
2) Autosomal recessive diseases						
Myoclonic epilepsy of Unverricht and Lundborg (MYC/ATX-CSTB)[34–44] #MIM 254800	Childhood, adolescence		CM Multifocal; Action and stimulus sensitive (stress, touch, PS)	Cortico-muscular coherence present	GTC, C; Infrequent 1-3/year; Responsive to therapy	Normal to slightly slow background; Brief and rare epileptiform discharges
Myoclonic epilepsy of Lafora (MYC/ATX-EPM2A[44–49] – #MIM 254780 and MYC/ATX-NHLRC1[50–53] #MIM 254780)	Childhood, adolescence	Cognitive decline, hallucinations	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, sound, touch, PS) Positive and negative jerks	Brief and small bursts; Cortico-muscular coherence present	GTC, Ab, M and V; Frequent; Intractable	Slow and poor topographic organization of background; Diffuse epileptiform discharges
North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2)[54–58] **#MIM 614018**	Infancy	Scoliosis, areflexia, pes cavus, syndactyly, dysarthria, cognitive decline (rare)	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, PS)	Burst duration <100 ms; Time-locked association between cortex and bursts; Giant SSEP	Tonic, GTC, clonic, drop attacks; Infrequent	Slow background; Generalized epileptiform discharges Photoparoxysmal responses
Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6)[59–66] #MIM 204300	Adolescence adulthood	Dystonia, bradykinesia, dementia, mental retardation, behavioral disorders	CM Multifocal; Spontaneous, action and stimulus sensitive Positive and negative jerks	Time-locked association between cortex and bursts; Giant SSEP	GTC; Rare and infrequent	Background can be preserved; Interictal epileptiform discharges; Photoparoxysmal responses
Progressive myoclonic epilepsy type 3 or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7)[67–71] #MIM 611726	Infancy	Neurologic regression following seizure onset, mental retardation, pyramidal signs, microcephaly, scoliosis	Myoclonus of unknown origin Multifocal; Spontaneous, action and stimulus sensitive (stress) Positive and negative jerks	No association with epileptic discharges on EEG and myoclonic bursts on EMG; No giant SSEP	M, GTC, Ab, A; Frequency variable Treatment responsive; Status epilepticus not uncommon	Slow background; Prominent epileptic activity; Photoparoxysmal response
Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1)[72–74] **#MIM 616187**	Infancy, childhood, adolescence	Cognitive decline	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, sound, startle, menses) Positive and negative jerks	Cortico-muscular coherence present. Giant SSEP Enhanced C reflexes	GTC; Infrequent; Responsive to therapy	Preservation of background; Generalized epileptiform discharges
Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2)[75–86] #MIM 254900	Adolescence, early adulthood	Tremor, renal failure, peripheral neuropathy	CM Multifocal; Spontaneous, action, stimulus-induced (auditory, visual, touch, stress, fever, menses) Positive and negative jerks	Burst duration <50 ms; Positive cortical spike back-averaging	GTC; Frequency variable	Slow background; Fast epileptiform discharges Photoparoxysmal response

(Continues)

TABLE 1 *Continued*

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy	
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response	Electrophysiological Characteristics of Epilepsy (EEG)
Ataxia-telangiectasia, including variant ataxia-telangiectasia (ATX-ATM)[87–94] #MIM 208900	Neonatal, infancy	Telangiectasias and other skin alterations, oculomotor apraxia, dystonia, chorea, tremor, peripheral neuropathy, distal muscular atrophy, short stature, immunodeficiency, predisposition to neoplasia	SCM Multifocal; Spontaneous, action, not stimulus-sensitive	Burst duration 20-385 ms; No cortical correlation No giant SSEP	Not described	Not described.
Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1)[95–98] #MIM 615768	Variable	Nystagmus, external ophthalmoplegia, pyramidal signs, tremor, dystonia, cognitive impairment, peripheral neuropathy, hypogonadism	CM[a] Multifocal; Spontaneous, action	Not described	Not described	Not described
Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1)[99–106] #MIM 256550	Variable	Cognitive decline, cherry-red spots, dysmorphic features, hearing loss, cataracts, hepatosplenomegaly, cardiomyopathy, skeletal malformations, short stature	CM Multifocal; Spontaneous, action, stimulus sensitive (sound, touch, PS) Positive and negative jerks	Highly frequent and rhythmic bursts; Positive cortical spike back-averaging; Cortico-muscular coherence present; Giant SSEP	M, GTC; Frequent; Usually treatment-responsive	Normal EEG in majority present; In some cases epileptiform discharges
Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1)[107,108] #MIM 204500	Infancy	Developmental regression, speech and language difficulties, progressive vision loss with retinopathy, dystonia	Not described	Not described	M, GTC, Ab; Frequent; Intractable	Slow background; Focal or generalized epileptiform discharges
POLG-ataxia and allelic disorders: MIRAS, SANDO, and Alpers-Huttenlocher syndrome (POLG)[109–114] #MIM 607459, #MIM 203700, #MIM 613662	Infancy, childhood, adulthood	Cognitive decline, developmental delay, peripheral neuropathy, muscle weakness and atrophy, behavioral disorders, parkinsonism, dystonia, tremor, dysarthria, nystagmus, ophthalmoparesis, cataracts, optic atrophy, hypogonadism, stroke-like episodes, gastroparesis, cardiomyopathy, hepatic dysfunction	Myoclonus of unknown origin Multifocal; Stimulus sensitive Positive and negative jerks	Not described	M, motor, visual, G; Frequent; Refractory	Slow background; Epileptiform discharges
Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3)[115–120] #MIM 612016	Childhood, (early adulthood onset is rare)	Muscle weakness, exercise intolerance, episodes of vomiting, hypotonia, pes cavus, developmental delay, cognitive impairment, dystonia	SCM[a] Not described; Not action-induced or stimulus sensitive	Low amplitude jerks; Burst duration 80-135 ms; No cortical correlation	M, GTC; Infrequent	Normal background; Interictal epileptiform discharges
Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2)[73,121,122] #MIM 614487	Infancy or early childhood	Spastic paraparesis, oculomotor apraxia, ptosis, dystonia, distal muscle atrophy and weakness, peripheral neuropathy	Myoclonus of unknown origin Multifocal; Spontaneous, action, stimulus sensitive; Interictal myoclonus	Not described	GTC; Infrequent	Normal or epileptiform discharges on EEG
Congenital disorder of glycosylation, type Ic (ATX-ALG6)[123,124] #MIM 603147	Infancy or early childhood	Developmental delay, hypotonia, behavioral disorders, strabismus, retinopathy, cataracts, peripheral neuropathy, proximal muscle weakness	-	Not described	M or infantile spasms; Frequent; Refractory	Slowed background; Generalized epileptiform discharges
Neuronal ceroid lipofuscinosis type 7 (MFSD8)[125–128] #MIM 610951	Infancy or early childhood	Developmental regression, cognitive decline, speech impairment, optic atrophy, retinopathy	-	Not described	M, GTC; Frequent; Poorly responsive to therapy	Slow background; Focal or generalized epileptiform discharges
Progressive myoclonic epilepsy type 1B (PRICKLE1)[35,129–132] #MIM 612437	Infancy or early childhood	Developmental delay, reduced upward gaze, action tremor, pyramidal signs, peripheral neuropathy	Myoclonus of unknown origin Multifocal; Not described	Delayed cortical response during SSEP	GTC; Infrequent; Usually treatment-responsive	Generalized epileptiform discharges
3) Autosomal dominant diseases						
Dentatorubral-pallidoluysian atrophy (ATX-ATN1)[38,133–140] MIM #125370	Adulthood	Chorea, cognitive decline, behavioral disorders, pyramidal signs	Myoclonus of unknown origin Multifocal; Stimulus sensitive	No giant SSEP	GTC, M, A; Intractable	Diffuse epileptiform discharges; Photoparoxysmal response
Spinocerebellar ataxia type 2 (ATX-ATXN2)[141–152] MIM #183090	Adulthood	Altered saccadic eye movements, ophthalmoparesis, parkinsonism, behavioral disorders, muscle atrophy, autonomic dysfunction	SCM Multifocal; Spontaneous, action, stimulus-sensitive (touch)	High-amplitude bursts; Burst duration 40-60 ms	Not described	Not described
Spinocerebellar ataxia type 14 (ATX-PRKCG)[153–163] #MIM: 605361	Adulthood	Nystagmus, saccadic intrusions, cognitive decline, behavioral disorders, dystonia, pyramidal signs	SCM Multifocal; Spontaneous, action-induced	Normal SEP, no cortical correlates	Not described	Not described

(Continues)

TABLE 1 *Continued*

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy	
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response	Electrophysiological Characteristics of Epilepsy (EEG)
Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5)[164–165] MIM #162350	Adulthood	Cognitive impairment, parkinsonism, behavioral disorders, dysarthria	Myoclonus of unknown origin	Not described	M, GTC; Frequent; Intractable	Generalized epileptic discharges
Prion disease: Familial Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease and familial fatal insomnia (PRNP)[29,33,166–177] MIM #123400, MIM #137440, MIM #600072	Adulthood	Cognitive decline, behavioral disorders, parkinsonism, pyramidal signs, ophthalmoparesis, refractory insomnia, apraxia, mutism	CM[a] or SCM[a] Multifocal; Spontaneous, action and stimulus sensitive (touch) Positive and negative jerks Polymorphic presentation of myoclonic jerks (rhythmic, dystonic and periodic)	Either burst duration of 54.1 ± 15.8 ms or > 200 ms; Positive cortical spike back-averaging; Giant SSEP	GTC	Slow background; Epileptic discharges
Autosomal dominant mental retardation type 5 (SYNGAP1)[178–181] MIM #612621	Infancy	Developmental delay or regression, mental retardation, hypotonia, behavioral disorders, autism spectrum disorder, facial dysmorphism, orthopedic abnormalities, sleeping problems, microcephaly	-	Not described	M, A, Ab, GTC, febril, reflex (eating, sound, touch); Frequent	Slow background; Focal or multifocal epileptic discharges; Photoparoxysmal response
SCN1A-related disorder (SCN1A)[182–186] #MIM 607208	Infancy	Psychomotor retardation, pyramidal signs	CM Multifocal; Spontaneous, action; Interictal myoclonus	EMG bursts in beta frequency during active movements, brief ranging from 24–48 ms. Giant SEPs. Presence of cortico-muscular coherence and jerk-locked backaveraging.	M, GTC, A, Ab; Frequent; Refractory	Interictal generalized, focal, and multifocal epileptic discharges; Photoparoxysmal response is rare
SLC6A1-related disorder (SLC6A1)[187–190] #MIM 616421	Infancy	Developmental delay, mental retardation, autistic features, tremor	-	Not described	M, A, Ab; Treatment-responsive	Generalized epileptic discharges; Photoparoxysmal response
4) Mitochondrial diseases						
MERRF and MELAS syndromes (mt-MTTK)[191–198] MIM #590060	Adulthood (Infancy and childhood is rare)	Cognitive impairment or mental regression, hearing loss, muscle weakness, behavioral disorders, dysarthria, dysphagia, short stature, stroke-like episodes, cardiac abnormalities, migraine, respiratory dysfunction, gastrointestinal symptoms	CM[a] Not described; Action and stimulus sensitive	Giant SSEP	GTC	Slow background; Epileptic discharges

Genes or conditions fulfilling criteria for progressive myoclonus ataxia (PMA) are shown in bold.

Abbreviations: CM, cortical myoclonus; SCM, subcortical myoclonus; BM, brainstem myoclonus; EEG, electroencephalogram; EMG, electromyography, M, myoclonic seizures, GTC, generalized tonic–clonic seizures; A, atonic seizures, Ab, absence seizures, V, visual seizures; ms, milliseconds, SEPs, somatosensory evoked potentials, MIRAS, Mitochondrial recessive ataxia syndrome; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; MERRF, Myoclonic epilepsy associated with ragged-red fibers; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; PS, photosensitive.

[a]Official myoclonus subtype is unknown.

TABLE 2 Clinical clues associated with main myoclonus-ataxia syndromes

Clinical Features	Disease (Gene Name)
Developmental delay or regression	Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) SCN1A-related disorder (SCN1A) SLC6A1-related disorder (SLC6A1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Cognitive decline or mental retardation (usually mild and/or infrequent)	Myoclonic epilepsy of Unverricht and Lundborg (MYC/ATX-CSTB) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1) Progressive myoclonic epilepsy type 1B (PRICKLE1) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1)
Cognitive impairment or mental retardation (usually moderate or severe)	Myoclonic epilepsy of Lafora (MYC/ATX-EPM2A) Myoclonic epilepsy of Lafora (MYC/ATX-NHLRC1) Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8) Autosomal dominant mental retardation type 5 (SYNGAP1) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) SLC6A1-related disorder (SLC6A1) SCN1A-related disorder (SCN1A) Spinocerebellar ataxia type 2 (ATX-ATXN2) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Prion diseases (PRNP) MERRF and MELAS syndrome (mt-MTTK)
Behavioral disorders	Opsoclonus-myoclonus-ataxia syndrome Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Prion diseases (PRNP) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) Autosomal dominant mental retardation type 5 (SYNGAP1) MERRF and MELAS syndrome (mt-MTTK)
Autistic features	SLC6A1-related disorder (SLC6A1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Insomnia	Opsoclonus-myoclonus-ataxia syndrome Prion diseases: familial fatal insomnia (PRNP) Autosomal dominant mental retardation type 5 (SYNGAP1)
Hallucinations	Myoclonic epilepsy of Lafora (MYC/ATX-EPM2A) Myoclonic epilepsy of Lafora (MYC/ATX-NHLRC1)
Opsoclonus	Opsoclonus-myoclonus-ataxia syndrome
Oculomotor apraxia	Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2)
Ophthalmoparesis	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-related ataxias (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis - SANDO) Progressive myoclonic epilepsy type 1B (PRICKLE1) Prion diseases (PRNP)
Nystagmus	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG)
Retinopathy (cherry-red spots)	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1)

(Continues)

TABLE 2 *Continued*

Clinical Features	Disease (Gene Name)
Retinopathy	Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8)
Optic atrophy	Neuronal ceroid lipofuscinosis type 7 (MFSD8) POLG-ataxia and allelic disorders (POLG)
Cataracts	POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1)
Hearing loss	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) MERRF and MELAS syndrome (mt-MTTK)
Peripheral neuropathy	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Progressive myoclonic epilepsy type 1B (PRICKLE1) Celiac disease
Muscle atrophy and weakness	MERRF and MELAS syndrome (mt-MTTK) POLG-ataxia and allelic disorders (POLG) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Spinocerebellar ataxia type 2 (ATX-ATXN2) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3)
Parkinsonism	Spinocerebellar ataxia type 2 (ATX-ATXN2) POLG-ataxia and allelic disorders (POLG) Prion diseases (PRNP) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6)
Tremor	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Progressive myoclonic epilepsy type 1B (PRICKLE1) SLC6A1-related disorder (SLC6A1) Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1) POLG-ataxia and allelic disorders (POLG)
Dystonia	Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2)
Chorea	Ataxia-telangiectasia (ATX-ATM) Dentatorubral-pallidoluysian atrophy (ATX-ATN1)
Pyramidal signs	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Progressive myoclonic epilepsy type 1B (PRICKLE1) SCN1A-related disorder (SCN1A) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Prion diseases (PRNP)
Hypogonadism	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG)
Telangiectasias	Ataxia-telangiectasia (ATX-ATM)
Pes cavus	North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3)

(Continues)

TABLE 2 *Continued*

Clinical Features	Disease (Gene Name)
Scoliosis or other skeletal deformations	Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Dysmorphic features	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Autosomal dominant mental retardation type 5 (SYNGAP1)
Microcephaly	Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Autosomal dominant mental retardation type 5 (SYNGAP1)
Stroke-like episodes	MERRF and MELAS syndrome (mt-MTTK) POLG-ataxia and allelic disorders (POLG)
Short stature	MERRF and MELAS syndrome (mt-MTTK) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Ataxia-telangiectasia (ATX-ATM)
Neoplasia	Ataxia-telangiectasia (ATX-ATM) Opsoclonus-myoclonus-ataxia syndrome
Immunodeficiency	Ataxia-telangiectasia (ATX-ATM)
Renal failure	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2)
Cardiac abnormalities	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) POLG-ataxia and allelic disorders (POLG) MERRF and MELAS syndrome (mt-MTTK)

Methods

A comprehensive and structured search in PubMed following PRISMA was performed by two independent reviewers (MR, SV) to identify those diseases that may combine myoclonus with ataxia. Disorders that presented with either myoclonus or myoclonic seizures were included, for it is historically unclear whether, despite a clear clinical difference, a neurobiological distinction exists between cortical myoclonus and myoclonic epilepsy with both cortically driven jerks. The following search strategy was conducted: ("myoclonus"[tiab] OR "myoclonus"[Mesh] OR myoclonic disorder*[tiab]) AND ("ataxia"[tiab] OR "ataxia"[Mesh] OR ataxic disorder*[tiab]) AND (gene*[tiab] OR acquired cause*[tiab] OR metabolic disease*[tiab] OR "inborn errors of metabolism"[tiab] OR etiolog*[tiab] OR "causality"[tiab] OR "drug-induced"[tiab] OR "toxin"[tiab] OR autoimmune*[tiab] OR paraneoplastic*[tiab]) AND English[LA]. Publications written in English and published up to December 31, 2018 (without a start date as limitation) were reviewed. To ensure that no genetic diseases would be missed, the key words "myoclonus" and "ataxia" were also applied in OMIM and GeneReviews.

Results

A total of 30 disorders shown in Table 1 were identified as the main MAS because of the high frequency of combined myoclonus and ataxia, of which four were acquired and 26 genetic. Hundred-and-five other disorders were either only occasionally associated with a combined myoclonus and ataxia presentation, or had an unconfirmed genetic cause; these are listed in Table S1.

An extensive review of series and cases confirmed that most MAS present as PMA or PME.[3] In general, PMA are conditions presenting first with ataxia, with the subsequent development of myoclonus, and eventually drug-responsive epilepsy with infrequent seizures. In contrast, PME disorders were characterized by frequent and refractory epilepsy with severe cognitive decline.[5] Applying the new refined definition of PMA,[5] a total of 12 entities could be classified as such (shown in bold in Table 1), of which celiac disease, prion diseases, North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2), sialidosis type I (MYC/ATX-NEU1), and spinocerebellar ataxias types 2 (ATX-ATXN2) and 14 (ATX-PRKCG) were the most relevant. One should keep in mind that these genetic disorders show variability in the clinical presentation; severe and frequent seizures can be present in some patients, in whom the clinical syndrome would be classified as PME. However, in the aforementioned 12 entities, this is true in the minority of cases. In addition, conditions like myoclonic epilepsy of Unverricht-Lundborg (MYC/ATX-CSTB)[199] and Kufs disease (MYC-CLN6)[200] are considered as PME; however, they can sometimes present as PMA.

Some PMA disorders showed ataxia as the predominant clinical sign, as was the case of ataxia-telangiectasia (ATX-ATM),[201] the spinocerebellar ataxias type 2 (ATX-ATXN2),[202,203] type 3 (ATX-ATXN3),[203] type 14 (ATX-PRKCG),[204,205] the dentatorubral-pallidoluysian atrophy (ATX-ATN1)[206] or ATX-STUB1,[207] whereas in other conditions, such as, North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2),[208] and

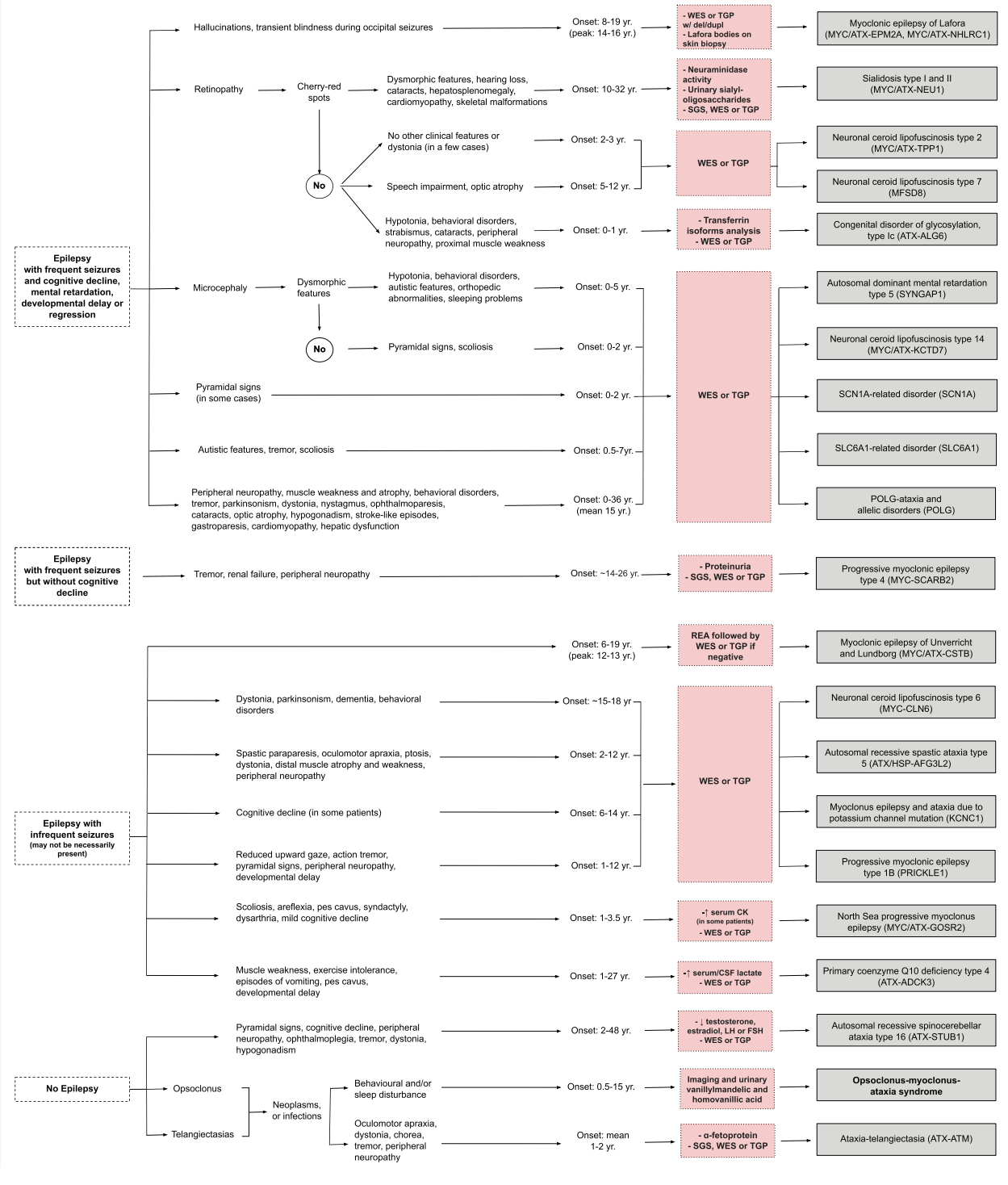

FIG 1. Clinical diagnostic algorithm for myoclonus-ataxia syndromes with onset in infancy or childhood. For didactic purposes, this figure includes the main myoclonus-ataxia syndromes (entities where myoclonus and ataxia are prominent and frequent features) and which therefore should be suspected first, before considering disorders where the combination of myoclonus and ataxia is found only occasionally. In addition, next-generation sequencing techniques can be the first step in the diagnostic process in many cases and the genetic finding can be matched or validated with the clinical features displayed in both figures. Conditions with (possible) faster disease progression are shown in bold. CMA: chromosomal microarray analysis; Del/dupl: deletions and duplications; REA: repeat expansion analysis; SGS: single gene sequencing; TGP: targeted gene panels; WES: whole exome sequencing; LH: luteinizing hormone; FSH: follicle stimulating hormone; CK: creatine kinase. Conditions with (possible) faster disease progression are shown in bold.

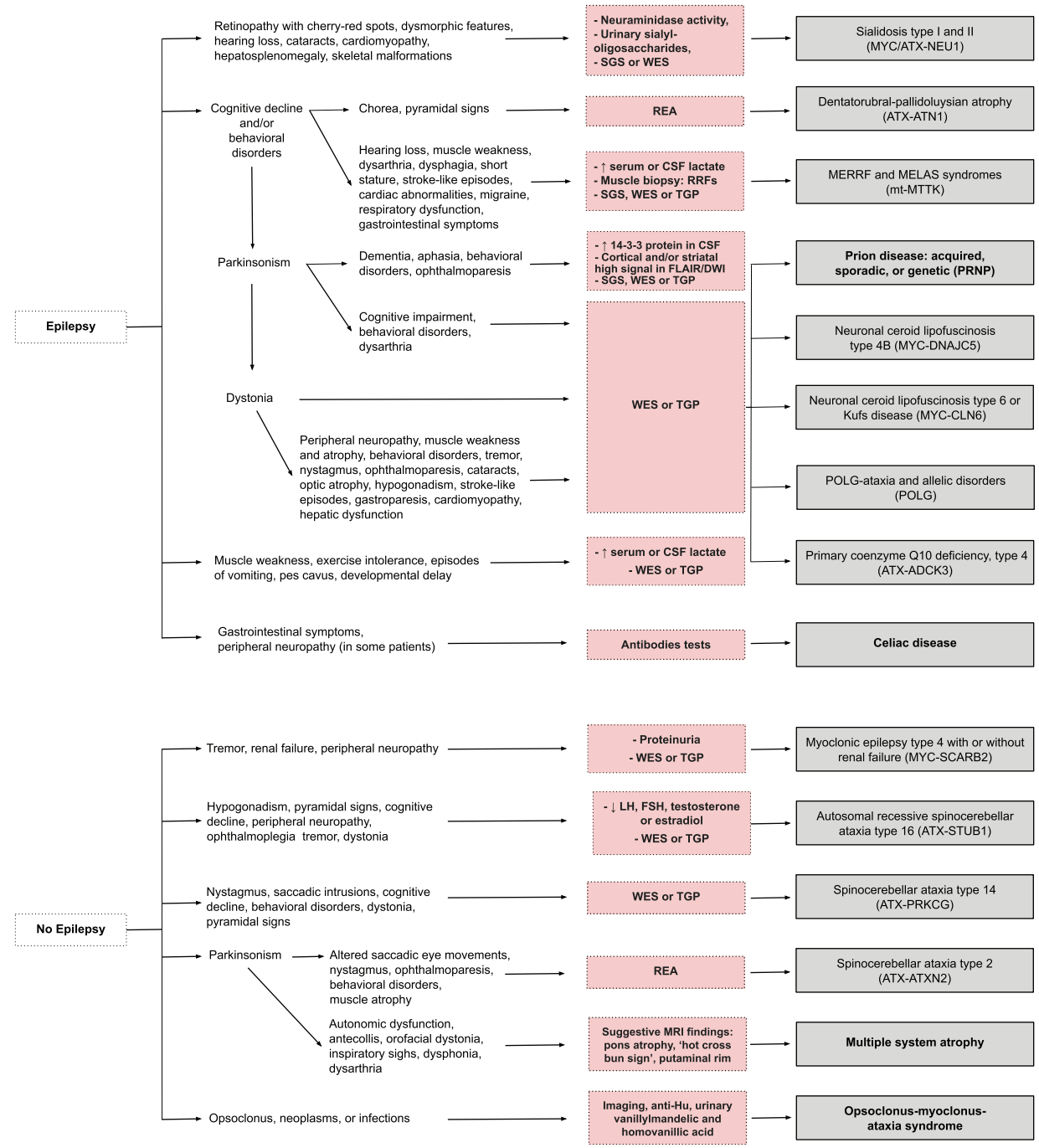

FIG 2. Clinical diagnostic algorithm for myoclonus-ataxia syndromes with onset in adulthood. For didactic purposes, this figure includes the main myoclonus-ataxia syndromes (entities where myoclonus and ataxia are prominent and frequent features) and which therefore should be suspected first, before considering disorders where the combination of myoclonus and ataxia is found only occasionally. In addition, next-generation sequencing techniques can be the first step in the diagnostic process in many cases and the genetic finding can be matched or validated with the clinical features displayed in both figures. Conditions with (possible) faster disease progression are shown in bold. CMA: chromosomal microarray analysis; Del/dupl: deletions and duplications; REA: repeat expansion analysis; RRFs: ragged red fibers; SGS: single gene sequencing; TGP: targeted gene panels; WES: whole exome sequencing; FLAIR: fluid attenuated inversion recovery; DWI: diffusion-weight imaging; LH: luteinizing hormone; FSH: follicle stimulating hormone. Conditions with (possible) faster disease progression are shown in bold.

myoclonus epilepsy and ataxia due to KCNC1 gene mutations,[209] myoclonus was often the main clinical feature.

In some cases, it is difficult to separate the effects of action myoclonus from ataxia on motor examination.[210] In children with PME, negative myoclonic jerks causing a loss of isotonic muscle activity and atonic seizures can interrupt smooth movement, affect balance and produce "pseudoataxia".[211] These presumed ataxic features may improve or cease when myoclonus is controlled by appropriate treatment.[212,213] The use of electrophysiological techniques, especially a combined electroencephalography and polymyography, can be of additional value in identifying myoclonic jerks and determine the origin of these jerks.[214]

Different types of myoclonus were described in the MAS (Table 1). In relation to the anatomical origin of myoclonus, cortical myoclonus was the most frequent type of myoclonus and presented typically as action-induced and stimulus-sensitive myoclonus, predominantly in distal limbs and face.[215,216] Cortical myoclonus was present in several conditions, such as myoclonic epilepsy of Unverricht-Lundborg, myoclonic epilepsy of Lafora or North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2). Subcortical myoclonus was present in ataxia-telangiectasia (ATX-ATM),[201] the spinocerebellar ataxias types 2 (ATX-ATXN2) and 14 (ATX-PRKCG)[204,217] and in primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3).[218] A brainstem origin of subcortical myoclonic jerks was presumed in prion diseases (although a cortical component or origin could not be completely excluded)[219] and in opsoclonus-myoclonus-ataxia syndrome.[220] Of importance, the electrophysiological interpretation of jerky movements was sometimes problematic because the myoclonic discharges were superimposed in body parts also affected by dystonia, tremor or chorea.[11,24,201,204,217]

Specific clinical forms of myoclonus can be present. First, polyminimyoclonus, characterized by small amplitude, jerky abnormal movements in the hands and fingers, which is suggestive of multiple system atrophy[216] or opsoclonus-myoclonus-ataxia syndrome.[221] Second, excessive fragmentary myoclonus, a sleep disorder characterized by subtle and fine movements at the fingertips, feet, or lips that persist throughout all stages of sleep, which can be particularly frequent in spinocerebellar ataxia type 3 (ATX-ATXN3).[222]

Diagnostic Approach

The large number of causes of MAS as well as the phenotypic overlap of these disorders obviously poses a challenge in clinical practice to establish a proper (genetic) diagnosis. Still, certain clinical manifestations are highly suggestive of specific diseases, such as the presence of hallucinations in myoclonic epilepsy of Lafora, opsoclonus in opsoclonus-myoclonus-ataxia syndrome, oculomotor apraxia or telangiectasias in ataxia-telangiectasia, cherry-red spots in the retina in sialidosis type 1, hypogonadotropic hypogonadism in ATX-STUB1 or hypergonadotropic hypogonadism in POLG-ataxia and dysmorphic features in sialidosis type 2. These and other clinical clues than can help reducing the number of entities to consider when facing a patient with a MAS are listed in Table 2.

Diagnostic algorithms for childhood- and adult-onset MAS are illustrated in Figures 1 and 2, respectively. Acquired disorders should be initially ruled out both in adults and children as these are more common than the genetically determined MAS. These include celiac disease, multiple system atrophy type C and prion diseases in adulthood (Table 1), and the clinical syndrome of opsoclonus-myoclonus-ataxia, often associated with a neoplasm or autoimmune disease in children, and which can also be seen in adults.

Biochemical markers could be screened before genetic testing when there is a high clinical suspicion of specific disorders, such as celiac disease antibodies, alpha-fetoprotein for ataxia-telangiectasia, and neuraminidase activity or urinary sialyl-oligosaccharides for sialidosis type I. Conversely, these could be used as confirmatory markers in case genetic testing was done first.

As many of the MAS are of genetic origin, NGS techniques, i.e. targeted gene panels (TGP) or whole exome sequencing (WES), will often be needed to establish a diagnosis given the genetic heterogeneity and clinical overlap. In children with MAS, WES or TGP (preferentially including copy number variation analysis, to avoid missing some cases of myoclonic epilepsy of Lafora) could be considered first-tier genetic tests. If negative, this could be followed by repeat expansions analysis (REA) to detect myoclonic epilepsy of Unverricht-Lundborg (Fig. 1). In the pediatric population, the diagnostic and clinical utility of WES has been shown to be greater than CMA.[223] In adults with MAS, REA could be considered first-tier genetic tests if a spinocerebellar ataxia, such as ATX-ATXN2 or ATX-ATN1 is suspected. If mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome and/or myoclonic epilepsy associated with ragged-red fibers (MERRF) syndrome or the MERRF/MELAS overlap syndrome is suspected, TGP or WES of blood leukocyte DNA is suggested, taking into account the occurrence of heteroplasmy in mitochondrial disorders, which may require testing DNA isolated from other tissues, such as skeletal muscle, buccal mucosa, or cultured skin fibroblasts.

In Table S2, a total of 123 genes involved in disorders that combine myoclonus and ataxia are listed, which could be used for the development of specific TGP or for dedicated exome strategies that prioritize those genes that are associated with overlap phenotypes of myoclonus and ataxia.

The fact that numerous disorders present with the combination of myoclonus and ataxia, points to the possible pathophysiological link between the origin of myoclonus and cerebellar alterations, such as disruption of the cerebello-thalamico-cortical pathway due to loss of Purkinje cells or dentate nuclei neurons, as well as a reduction in the concentration of γ-aminobutyric acid (GABA)-ergic synapses in the sensori-motor cortex leading to cortical disinhibition.[224] In addition, most MAS have impaired posttranslational modification of proteins to which certain neuronal groups might be particularly vulnerable compared with others.[224]

It is important to early recognize the treatable acquired or metabolic disorders, such as opsoclonus-myoclonus-ataxia syndrome, celiac disease, and primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3). Patients will obviously benefit from an early diagnosis and timely treatment.

Conclusions

The MAS are a clinically and etiologically heterogeneous group of disorders. We have provided diagnostic algorithms for children and adults based on clinical manifestations that will guide diagnostic procedures. However, NGS techniques can be the first diagnostic step in many cases and the genetic finding can be matched or validated with the clinical features displayed in the diagnostic algorithms. Targeted gene panels or exome filters to genetically characterize MAS could be developed based on the list of genes associated with MAS that is provided.

Author Roles

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

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Supporting Information

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

Table S1. Diseases with only occasional combined myoclonus and ataxia presentation, or for which the presence of myoclonus or ataxia or the genetic finding itself are unconfirmed.

Table S2. The 123 genes involved in conditions that combine myoclonus and ataxia.