Genetic dystonia-ataxia syndromes: clinical spectrum, diagnostic approach and treatment options

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ABSTRACT

Background: Dystonia and ataxia are manifestations of numerous disorders, and indeed, an ever-expanding spectrum of genes causing diseases that encompass dystonia and ataxia are discovered with the advances of genetic techniques. In recent years, a pathophysiological link between both clinical features and the role of the cerebellum in the genesis of dystonia, in some cases, has been proposed. In clinical practice, the genetic diagnosis of dystonia-ataxia syndromes is a major issue for genetic counseling, prognosis and, occasionally, specific treatment.

Methods: For this pragmatic and educational review, we conducted a comprehensive and structured literature search in Pubmed, OMIM and GeneReviews using the key words “dystonia” and “ataxia” to identify those genetic diseases that may combine dystonia with ataxia.

Results: There is a plethora of genetic diseases causing dystonia and ataxia. We propose a series of clinico-radiological algorithms to guide their differential diagnosis depending on the age of onset, additional neurological or systemic features and imaging findings. We suggest a sequential diagnostic approach to dystonia-ataxia syndromes. We briefly highlight the pathophysiological links between dystonia and ataxia and conclude with a review of specific treatment implications.

Conclusion: The clinical approach presented in this review is intended to improve diagnostic success of clinicians when facing with patients with dystonia-ataxia syndromes.

Introduction

Dystonia is characterized by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both"[1]. It can be the manifestation of a plethora of diseases, and indeed, with the advances of genetic techniques, we recognize an ever-expanding spectrum of genes causing various dystonia syndromes[2]. For clinical practice, the new classification of dystonia fosters a phenomenological approach with categorization according to recognizable common associations, which allows narrowing down the differential diagnosis[1]. Such associations are for example the combined dystonia syndromes like dystonia-myoclonus and dystonia-parkinsonism, with well-described differential diagnoses[3]. In contrast, scarce information exists about the combination of dystonia and ataxia. Interestingly, there is also pathophysiological link between both phenotypes and the role of the cerebellum in the genesis of dystonia has been the focus of research lately[4-6]. Based on a broad and exhaustive literature review we here review the spectrum of disorders that can present with dystonia and ataxia, and propose a clinico-radiological diagnostic algorithm. We examine existing evidence regarding different pathophysiological mechanisms, and discuss specific treatment implications.

Methods

We conducted a comprehensive and structured search in Pubmed, OMIM and GeneReviews using the key words "dystonia" and "ataxia" to identify those genetic diseases that may combine dystonia with ataxia. Publications written in English and Spanish and published up to December 31, 2017 were reviewed.

Diagnostic approach to genetic causes of dystonia-ataxia

There is a plethora of more than 100 genetic disorders giving rise to dystonia-ataxia syndromes. In clinical practice, when evaluating patients with dystonia-ataxia, the differential diagnosis can be largely guided by the age of onset, additional neurological or systemic features and radiological findings. Clinical diagnostic algorithms that take into account the presence or absence of additional clinical clues and relevant complementary studies are illustrated in Figure 1(infancy/childhood onset) and Figure 2 (adulthood onset). For didactic purposes, both figures include disorders that are most prevalent or relevant from a therapeutic perspective and which therefore should be suspected first, according to authors' opinion. Table 1 provides a more comprehensive list of differential diagnoses. Entities where dystonia and ataxia are prominent and frequent features are considered first, before thinking of disorders where the combination of dystonia and ataxia is found only occasionally. A comprehensive summary of all diseases in which dystonia and ataxia were reported with their respective clinical features and relevant complementary studies is presented according to mode of inheritance in Supplementary Table 1. Sometimes, there are certain clinical clues ("red flags"), which can guide the differential diagnostic considerations (Table 2) and should therefore not be missed. Similarly, imaging findings are often helpful in directing further diagnostic evaluations (Figure 3).

Dystonia and ataxia may develop during the disease course sequentially, or in rare cases, simultaneously. Interestingly, some disorders that usually present with specific features, like ataxia in ataxia-telangiectasia, can also have a very different clinical picture, with isolated or predominant dystonia without ataxia[7,8]. In line with

this, some complex phenotypic disorders may initially mimic isolated dystonia before other clinical characteristics become evident, e.g. in Wilson´s disease or in several spinocerebellar ataxias[9,10].

Different types or forms of dystonia were described in the genetic diseases listed: focal, segmental, generalized and hemidystonia (e.g. in autosomal dominant progressive external ophthalmoplegia type 1 due to POLG mutations[11] and in Coats plus syndrome[12]) as well as task-specific dystonia (e.g. in several spinocerebellar ataxias[10,13], mitochondrial disorders[14], ataxia-telangiectasia-like disorder type 1[15] and in L-2-hydroxyglutaric aciduria[16]), paroxysmal or episodic dystonia (paroxysmal kinesigenic dyskinesia due to PRRT2 mutations[17], episodic ataxia type 2[18] and biotin-thiamine-responsive basal ganglia disease due to SLC19A3 mutations[19]). The Supplementary Table 1 lists the various forms of dystonia described in genetic dystonia-ataxia syndromes. In some cases, dystonia can spontaneously attenuate over time as occurs in ataxia-oculomotor apraxia type 4[20,21], or is induced by different triggers, e.g. exercise, infections, or emotional stress (PxMD-SLC2A1 disorders[22,23], pyruvate dehydrogenase E1-alpha deficiency[24], biotin-thiamine-responsive basal ganglia disease[25]). In some unusual cases, a phenotype of dystonia can replace or overshadow ataxia during the disease course (e.g. in ataxia with vitamin E deficiency[26]) or viceversa (SCA-CACNA1A[27]). Lastly, the combination of dystonia and ataxia often correlates with disease course or severity. For example, the presence of dystonia was associated with greater severity of ataxia in the spinocerebellar ataxias SCA-ATXN1, SCA-ATXN2, and SCA-ATXN3[28]. In line with this observation, SCA-ATXN2 and SCA-ATXN3 patients with dystonia showed

greater CAG repeat expansion[28,29]. In contrast, dystonia was associated a slower progression in SCA-CACNA1A[29].

Diagnostic management.

After careful clinical examination, MR imaging is essential as the presence or absence of cerebellar atrophy and other structural abnormalities will crucially guide differential diagnostic considerations. An initial screening of certain biochemical markers would depend on age of onset and clinical suspicion, but should always include serum copper and ceruloplasmin (plus 24h urinary copper excretion depending on the level of probability). Other parameters in peripheral blood useful to screen for more common conditions with specific treatment implications include vitamin E levels (ataxia with vitamin E deficiency), glucocerebrosidase enzyme activity in leukocytes (reduced in Gaucher disease), and triol levels (elevated in Niemann-Pick disease type C). If the differential diagnosis includes ataxia teleangiectasia (AT) and its lookalikes, serum testing should include alpha-fetoprotein (elevated in AT and ataxia-oculomotor apraxia type 2), immunoglobulin levels (often reduced in AT), albumin (reduced in ataxia-oculomotor apraxia type 1), and cholesterol (increased in ataxia-oculomotor apraxia type 1). In case of suspected glucose transporter type 1 deficiency syndrome, serum and CSF should be tested for the glucose levels (CSF glucose concentration <60 mg/dL) and its ratio (<0.4). If these tests were negative, genetic testing of most frequent causes of dystonia-ataxia syndromes, like Friedreich ataxia, and several spinocerebellar ataxias (SCA-ATN1, SCA-ATXN2, SCA-ATXN3, SCA-CACNA1A, SCA-TBP and SCA-ATXN1) should be explored first (again depending on clinical features and age). These are all disorders caused by repeat expansions and are therefore not

detectable by next-sequencing genetic tests. After these common causes were ruled out, genetic testing should be continued with whole exome sequencing or comprehensive dystonia and ataxia panels that include the dystonia-ataxia syndromes here described.

The role of the cerebellar dysfunction in dystonia

Dystonia is usually associated with dysfunction of basal ganglia circuits, rather than alteration of the cerebellum[30]. Many of the genetic diseases here reviewed, encompass complex phenotypes due to neurodegeneration of multiple systems and structures, including the alteration of both basal ganglia and cerebellum, which may explain the occurrence of dystonia in the setting of ataxia and other neurological features. There is a growing evidence of an important role of the cerebellar dysfunction in dystonia[4-6,31-36]. Animal models of generalized dystonia showed abnormal cerebellar activity[37-39] and, dystonia can be independent of the basal ganglia, and can be alleviated or abolished by inactivation of the cerebellum[40-42]. Moreover, a sophisticated network approach strongly suggested that the molecular pathways of ataxia and dystonia are closely related[43]. Thus, the large numbers of disorders featuring both dystonia and ataxia is not too surprising. However, correlational studies, such as these network approaches cannot dissect cause and effect.

Treatment

Rehabilitation, physical, occupational and speech therapy are usually combined with pharmacological treatment where appropriate[44,45]. Unfortunately, there exists no medication to date that has been approved for the treatment of cerebellar ataxia or

that can prevent or slow down neurodegenerative processes that are not related to metabolic diseases, with the exception of aminopyridines and acetazolamide for episodic ataxia in episodic ataxia type 2[44]. Most drugs used to treat ataxia or other cerebellar features failed to achieve significant and sustained improvement[44,45]. For patients with Friedreich ataxia or spinocerebellar ataxia, riluzole showed modest improvement in ataxia at 12 months in a Class I study[46] (Supplementary Table 2). Careful attention should be paid to drugs that can exacerbate ataxia, such as alcohol, lithium, phenytoin and phenobarbital[47] or factors that can precipitate episodic ataxia in paroxysmal kinesigenic dyskinesia and episodic ataxia type 2, like physical or emotional stressful situations, alcohol, fatigue or exertion. Likewise, drugs that are capable of exacerbating dystonic symptoms, like neuroleptics, piperazine derivatives with calcium antagonist properties (cinnarizine, flunarizine,) or antiemetics (metoclopramide), among others, should be avoided[48].

Disorders with specific management implications.

Some of the genetic dystonia-ataxia syndromes are preventable by avoiding triggers or are treatable, either by reduction of toxic products, dietary interventions, or vitamin supplements[49]. Early diagnosis and therapy may slow or halt the clinical course, partially reverse symptoms or prevent their development altogether (Supplementary Table 2). In general, the response to treatment is more likely at early stages of the disease and in children than in adults.

Symptomatic therapy of dystonia

Treatment of dystonic features remains difficult. In very rare cases, they can resolve spontaneously and completely over time, e.g. in ataxia-oculomotor apraxia type 4

and SCA-CACNA1A[21,27]. Without counting on these exceptions, dystonic symptoms are always persistent and hardly alleviated with drugs, like levodopa, anticholinergics or botulinum toxin[13,26,50-53]. It is important to emphasize that botulinum toxin use can be dangerous in the treatment of cervical or oromandibular dystonia in patients with spinocerebellar ataxias, because dysphagia is very common in this group of neurodegenerative diseases[54]. In some of the genetic dystonia-ataxia syndromes, like SCA-ATXN2, SCA-ATXN3 and ataxia-telangiectasia, dystonic features can show a marked response to levodopa[8,55,56] and illustrate the rationale of a trial with this drug[10,11,13,57-59]. Indeed, dopamine replacement therapy was established in 16 of 140 (11%) patients with spinocerebellar ataxia, with a partial response in 75% of the cases[13]. Pharmacological treatment with trihexyphenidyl, baclofen, benzhexol, diazepam or clonazepam may also produce variable relief of dystonic postures[26,60-62]. Currently, there is lack of evidence for the efficacy of non-invasive brain stimulation techniques, like transcranial magnetic stimulation and transcranial direct/alternating current stimulation in patients with dystonia[63]. In contrast, surgical interventions for dystonia such as GPi-DBS have been found effective to some extent in patients with Wilson disease[64,65], ataxia-telangiectasia and its variant[64,66], spinocerebellar ataxias[64,67-69], episodic ataxia type 2[70], Cockayne syndrome[71,72], PLA2G6-associated neurodegeneration[73], and neurodegeneration with brain iron accumulation type 1 due to mutations in the PANK2 gene[74-77]. Responses are often transient or partial, usually in the range of 10-30% of improvement, which is far lesser as the benefit reported in patients with primary generalized dystonia[64,76], but greater improvements of approximately 70% during the first years after surgery were also found[74,75]. Patients with dystonia combined with parkinsonism showed a greater response than those with dystonia-ataxia syndromes[64]. Surgical outcome seems to

be independent from age at surgery or duration of disease or dystonic features at surgery or dystonia severity[64].

Concluding remarks

The dystonia-ataxia syndromes are a clinically and genetically heterogeneous group of disorders that hold a major diagnostic challenge for neurologists. In clinical practice, the etiological diagnosis of dystonia-ataxia syndromes is key in guiding genetic counseling, prognosis, and specific treatment in some cases[49]. Clinico-radiological algorithms serve to narrow down the differential diagnosis for genetic testing and are crucial to avoid unnecessary complementary studies in scenarios where next-generation techniques are inaccessible to physicians or unaffordable to patients[2,9,78-80]. In addition, algorithms and lists of genes associated with dystonia-ataxia syndromes may direct genetic research and are also important to assist molecular geneticists in the interpretation of whole exome or genome sequencing data to achieve high diagnostic accuracy[80]. For example, as more than 100 genes and/or genetic diseases need to be screened to diagnose dystonia-ataxia syndromes, clinico-radiological algorithms may facilitate the implementation of disease-focused gene panels or dedicated exome strategies to prioritize those genes that overlap between dystonia and ataxia[43]. Most important useful handles in guiding diagnosis with the herein proposed clinical algorithms for dystonia-ataxia syndromes include the age of disease onset, some associated clinical clues and particular imaging findings. However, major criticism to clinical algorithms arise on the clinical and genetic heterogeneity[81], e.g., many entities or combined syndromes are not distinct conditions, but may represent a continuum between different phenotypes, as is the case for ATP1A3-, or PLA2G6-related disorders[82-86]. In addition, clinical

algorithms may not fit for atypical phenotypes or be useless if they are too simplistic or rigid, as they may delay or obstruct the identification of the underlying genetic cause in a determined patient[80,81]. In our opinion, clinical algorithms should be use as tools that can orient to specific disorders and can also be useful to validate genetic findings. The modern next-sequencing genetic tests do not eradicate the need for an exhaustive clinical assessment and are not extent of limitations as the inability to detect copy number variations or repeat expansions that cause, e.g., Friedreich ataxia and several spinocerebellar ataxias[79,80].

The list of genetic diseases that display either dystonia or ataxia or both in combination as dystonia-ataxia syndromes will continue to increase with the more widespread access to next-generation sequencing techniques. Continuous updating of dystonia-ataxia syndromes will be possible with online resources, such as GeneReviews (available at https://www.ncbi.nlm.nih.gov/books/NBK1116/) and the International Parkinson and Movement Disorder Society Genetic Mutation Online Database (available at http://www.mdsgene.org/)[87].

In conclusion, the clinical approach here presented is intended to improve diagnostic success of clinicians when facing with patients with dystonia-ataxia syndromes. Future perspectives resides in research that would provide a better understanding of the role of the cerebellum in dystonia, that in turn, may result in targeted treatment approaches to help both dystonia and ataxia features.

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Legends to figures

Figure 1. Clinical diagnostic algorithm for genetic dystonia-ataxia syndromes with infancy or childhood onset

GLUT1: glucose transporter type 1; BG: basal ganglia; AR: autosomal recessive; AD: autosomal dominant. “Red flags” are shown in bold and “possible symptoms” are in italic type.

Figure 2. Clinical diagnostic algorithm for genetic dystonia-ataxia syndromes with adulthood onset

SCA: spinocerebellar ataxia type; DRPLA: dentatorubral-pallidoluysian atrophy; AR: autosomal recessive; AD: autosomal dominant. “Red flags” are shown in bold and “possible symptoms” are in italic type.

Figure 3. Predominant imaging findings in genetic dystonia-ataxia syndromes

NBIA: neurodegeneration with brain iron accumulation; BG: basal ganglia. For didactic purposes we show only the predominant imaging findings of the diseases that can present with dystonia and ataxia that are most representative, either by its frequency or its ability to be treatable.

Tables

Table 1: Genetic dystonia-ataxia syndromes

Table 2. Clinical clues associated with main genetic dystonia-ataxia syndromes.

Supplementary Material

Supplementary Table 1: Genetic diseases that may combine dystonia with ataxia.

Supplementary Table 2. Specific treatment implications

Table 1: Genetic dystonia-ataxia syndromes

A) Concomitant dystonia and ataxia

Spinocerebellar ataxias: SCA-ATN1*; SCA-ATXN2*; SCA-ATXN3* and SCA-TBP*

Friedreich ataxia (FXN)*

Ataxia-telangiectasia (ATM)*

Ataxia with isolated vitamin E deficiency (TTPA)*

Niemann-Pick disease type C (NPC)*

Wilson disease (ATP7B)*

POLG-disorders (POLG)*

L-2-hydroxyglutaric aciduria (L2HGDH)*

TUBB4A-disorders (TUBB4A)*

ATP1A3-disorders (ATP1A3)*

PLA2G6-associated neurodegeneration (PLA2G6)*

Glucose transporter type 1 deficiency syndrome (SLC2A1)*

Ataxia-oculomotor apraxia type 4 (PNKP)

Autosomal recessive spastic paraplegia type 48 (KIAA0415)

Autosomal recessive spastic ataxia type 3 (MARS2)

Autosomal recessive spastic ataxia with hypomyelinating leukodystrophy (NKX6-2)

Cerebroretinal microangiopathy with calcifications and cysts or Coats plus syndrome (CTC1)

Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (SQSTM1)

Birk-Landau-Perez syndrome (SLC30A9)

Pyruvate dehydrogenase E2 deficiency (DLAT)

Recessive dystonia-ataxia syndrome due to mitochondrial complex IV deficiency (COX20)

Mitochondrial complex III deficiency, nuclear type 4 (UQCRQ)

B) Occasional dystonia-ataxia combination

Spinocerebellar ataxias: SCA-ATXN1; SCA-SPTBN2; SCA-CACNA1A; SCA-ATXN7; SCA-ATXN8OS; SCA-ATXN10; SCA-PPP2R2B; SCA-KCNC3; SCA-PRKCG; SCA-KCND3; SCA-AFG3L2; SCA-TGM6; SCA-NOP56 and SCA/HSP-VAMP1

Ataxia-oculomotor apraxia type 1 (APTX) and type 2 (SETX)

Gaucher disease, type III (GBA)

Chediak-Higashi syndrome (LYST)

Cockayne syndrome (ERCC)

Tay-Sachs disease or GM2-gangliosidosis type I (HEXA)

Biotin-thiamine-responsive basal ganglia disease (SLC19A3)

PRRT2-associated disease spectrum (PRRT2)

Myoclonic epilepsy of Unverricht and Lundborg (CSTB)

Fatty acid hydroxylase-associated neurodegeneration or autosomal recessive spastic paraplegia-35 (FA2H)

Neurodegeneration with brain iron accumulation-1 or pantothenate kinase-associated neurodegeneration (PANK2)

Mitochondrial complex I deficiency (multiple genes)

Mitochondrial complex III deficiency, nuclear type 2 (TTC19)

Mitochondrial disorder due to genomic rearrangements affecting the ATAD3 gene

Mitochondrial DNA depletion syndrome type 13 (FBXL4)

Combined oxidative phosphorylation deficiency type 29 (TXN2)

Pyruvate dehydrogenase E1-alpha deficiency (PDHA1)

Allan-Herndon-Dudley syndrome or monocarboxylate transporter type 8 deficiency (SLC16A2)

Sulfocysteinuria or sulfite oxidase deficiency (SUOX)

Primary coenzyme Q10 deficiency type 4 (ADCK3)

Autosomal recessive spinocerebellar ataxia type 5 or Galloway-Mowat syndrome (WDR73)

Autosomal recessive spastic ataxia type 5 (AFG3L2)

Brain-lung-thyroid syndrome and benign hereditary chorea (NKX2-1)

Congenital disorder of glycosylation type Ia (PMM2)

Ataxia-telangiectasia-like disorder-1 (MRE11A)

Pelizaeus-Merzbacher disease or hypomyelinating leukodystrophy type 1 (PLP1)

Progressive leukoencephalopathy with ovarian failure (AARS2)

Progressive encephalopathy with or without lipodystrophy (BSCL2)

Episodic encephalopathy due to thiamine pyrophosphokinase deficiency (TPK1)

Limb-girdle muscular dystrophy type 2S (TRAPPC11)

Juvenile amyotrophic lateral sclerosis-2 (ALS2)

X-linked spinocerebellar ataxia type 1 (ATP2B3)

X-linked syndromic mental retardation, Christianson type or Angelman-like syndrome (SLC9A6)

Kallmann syndrome (KAL1)

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*Most frequent causes of concomitant dystonia and ataxia.

Table 2: Clinical clues associated with main genetic dystonia-ataxia syndromes

Clinical features	Disease (gene name)
Developmental delay/mental retardation	Glucose transporter type 1 deficiency syndrome (SLC2A1)
	PLA2G6-associated neurodegeneration (PLA2G6)
	TUBB4A-disorders (TUBB4A)
	L-2-hydroxyglutaric aciduria or academia (L2HGDH)
	Recessive dystonia-ataxia syndrome due to mitochondrial complex IV deficiency (COX20)
	Pyruvate dehydrogenase E2 deficiency (DLAT)
Cognitive decline	Wilson disease (ATP7B)
	Niemann-Pick disease (NPC)
	PLA2G6-associated neurodegeneration (PLA2G6)
	Glucose transporter type 1 deficiency syndrome (SLC2A1)
	Autosomal recessive spastic ataxia type 3 (MARS2)
	Cerebroretinal microangiopathy with calcifications and cysts syndrome (CTC1)
	Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (SQSTM1)
	Ataxia-oculomotor apraxia type 4 (PNKP)
	Dentatorubral-pallidoluysian atrophy (ATN1)
	Spinocerebellar ataxia type 17 (TBP)
Opthalmoparesis	Spinocerebellar ataxia type 1 (ATXN1)
	Spinocerebellar ataxia type 2 (ATXN2)
	Spinocerebellar ataxia type 3 (ATXN3)
	Niemann-Pick disease (NPC)
	Gaucher disease, type III (GBA)
	POLG-disorders (POLG)
	Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (SQSTM1)
Oculomotor apraxia	Ataxia-telangiectasia (ATM)
	Ataxia-oculomotor apraxia type 1 (APTX)
	Ataxia-oculomotor apraxia type 2 (SETX)
	Ataxia-oculomotor apraxia type 4 (PNKP)
	Gaucher disease, type III (GBA)
	Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (SQSTM1)
Retinopathy	Cerebroretinal microangiopathy with calcifications and cysts (CTC1)
	Ataxia with isolated vitamin E deficiency (TTPA)
Optic atrophy	Friedreich ataxia (FXN)
	PLA2G6-associated neurodegeneration (PLA2G6)
	L-2-hydroxyglutaric aciduria or academia (L2HGDH)
	Cerebroretinal microangiopathy with calcifications and cysts (CTC1)
	ATP1A3-disorders (ATP1A3)
Abnormal eye	Spinocerebellar ataxia type 1 (ATXN1)

movement saccades	Spinocerebellar ataxia type 2 (ATXN2)
	Spinocerebellar ataxia type 3 (ATXN3)
	Spinocerebellar ataxia type 6 (CACNA1A)
	Friedreich ataxia (FXN)
	PLA2G6-associated neurodegeneration (PLA2G6)
Seizures	Niemann-Pick disease (NPC)
	PLA2G6-associated neurodegeneration (PLA2G6)
	Dentatorubral-pallidoluysian atrophy (ATN1)
	Spinocerebellar ataxia type 17 (TBP)
	TUBB4A-disorders (TUBB4A)
	Glucose transporter type 1 deficiency syndrome (SLC2A1)
	L-2-hydroxyglutaric aciduria or academia (L2HGDH)
Peripheral neuropathy	Friedreich ataxia (FXN)
	Ataxia with isolated vitamin E deficiency (TTPA)
	Ataxia-telangiectasia (ATM)
	Ataxia-oculomotor apraxia type 1 (APTX)
	Ataxia-oculomotor apraxia type 2 (SETX)
	Ataxia-oculomotor apraxia type 4 (PNKP)
	PLA2G6-associated neurodegeneration (PLA2G6)
	POLG-disorders (POLG)
	ATP1A3-disorders (ATP1A3)
Spasticity	Spinocerebellar ataxia type 2 (ATXN2)
	Spinocerebellar ataxia type 3 (ATXN3)
	TUBB4A-disorders (TUBB4A)
	Autosomal recessive spastic ataxia type 3 (MARS2)
	Autosomal recessive spastic paraplegia type 48 (KIAA0415)
	Cerebroretinal microangiopathy with calcifications and cysts (CTC1)
	PLA2G6-associated neurodegeneration (PLA2G6)
	Glucose transporter type 1 deficiency syndrome (SLC2A1)
	Niemann-Pick disease (NPC)
Myoclonus	Wilson disease (ATP7B)
	Ataxia-telangiectasia (ATM)
	Niemann-Pick disease (NPC)
	Dentatorubral-pallidoluysian atrophy (ATN1)
	Glucose transporter type 1 deficiency syndrome (SLC2A1)
Parkinsonism	Spinocerebellar ataxia type 2 (ATXN2)
	Spinocerebellar ataxia type 3 (ATXN3)
	Spinocerebellar ataxia type 17 (TBP)
	Wilson disease (ATP7B)
	ATP1A3-disorders (ATP1A3)
	PLA2G6-associated neurodegeneration (PLA2G6)
	Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (SQSTM1)

Chorea	Wilson disease (ATP7B)
	PLA2G6-associated neurodegeneration (PLA2G6)
	Ataxia-telangiectasia (ATM)
	Dentatorubral-pallidoluysian atrophy (ATN1)
	Spinocerebellar ataxia type 17 (TBP)
Gelastic cataplexy	Niemann-Pick disease (NPC)
Hypogonadism	Ataxia-telangiectasia (ATM)
	Congenital disorder of glycosylation type Ia (PMM2)
	Kallmann syndrome (KAL1)
Telangiectasias	Ataxia-telangiectasia (ATM)
Macrocephaly	Mitochondrial complex I deficiency (multiple genes)
Anosmia	Kallmann syndrome (KAL1)
Hepatic disease	Niemann-Pick disease (NPC)
	Wilson disease (ATP7B)
	Mitochondrial complex I deficiency (multiple genes)

Infancy/childhood onset dystonia-ataxia syndromes

Developmental delay, psychomotor regression, mental retardation and/or acute/subacute encephalopathy with seizures

No

Oculomotor abnormalities

No

Peripheral neuropathy

No

Prominent bulbar involvement

No

Other causes (see Tables 1 and 2)

Oculomotor apraxia

Ataxia telangiectasia **(AR)**
Telangiectasias and other skin problems, immunodeficiency, predisposition to neoplasia, *chorea, myoclonus, tremor, diabetes*

Ataxia-oculomotor apraxia type 1 **AR)**
Peripheral neuropathy, ophthalmoparesis, *chorea, tremor, pes cavus, scoliosis*

Ataxia-oculomotor apraxia type 2 **(AR)**
Peripheral neuropathy, *pyramidal signs, chorea, head tremor, strabismus*

Ataxia-oculomotor apraxia type 4 **(AR)**
Peripheral neuropathy, *cognitive impairment, distal muscle weakness and atrophy, chorea*

Gaucher disease, type 3 **(AR)**
Tonic-clonic or myoclonic seizures, pancytopenia, hepatosplenomegaly, bone affectation, *bulbar and pyramidal signs, cognitive decline, parkinsonism*

Horizontal supranuclear gaze palsy

Ophthalmoparesis

Vertical supranuclear gaze palsy

Niemann-Pick disease (type C) **(AR)**
Gelastic cataplexy, jaundice, hepatosplenomegaly, *behavior disorders, cognitive impairment, seizures, myoclonus, tremor, spasticity*

PLA2G6 disorders **(AR)**
Truncal hypotonia followed by spastic tetraparesis, parkinsonism, *strabismus, optic atrophy, nystagmus, tremor, peripheral neuropathy, autonomic dysfunction*

TUBB4A disorders **(AD)**
Pyramidal and bulbar signs, oculogyric crisis, *truncal hypotonia, tremor, nystagmus, microcephaly, short stature*

GLUT1 deficiency syndrome **(AD/AR)**
Paroxysmal movements (exercise-induced dystonia), acquired microcephaly, spasticity, *myoclonus, chorea, tremor*

L-2-hydroxyglutaric aciduria **(AR)**
Optic atrophy, spastic tetraparesis, intention tremor, action-induced negative myoclonus, pyramidal signs, brain tumors

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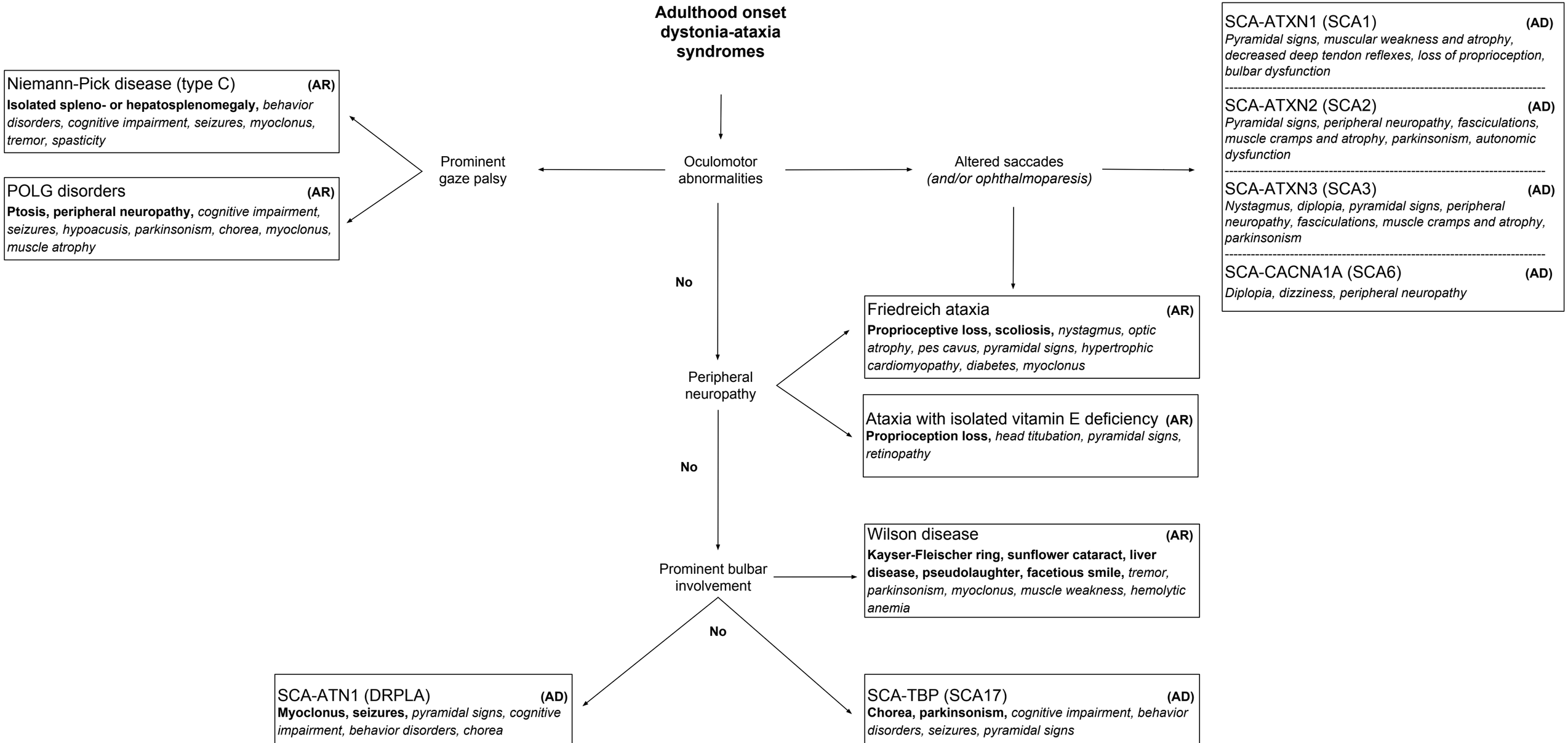
Biotin-thiamine-responsive BG disease **(AR)**
Rigidity, pyramidal signs, *supranuclear facial nerve palsy, external ophthalmoplegia, dysphagia*

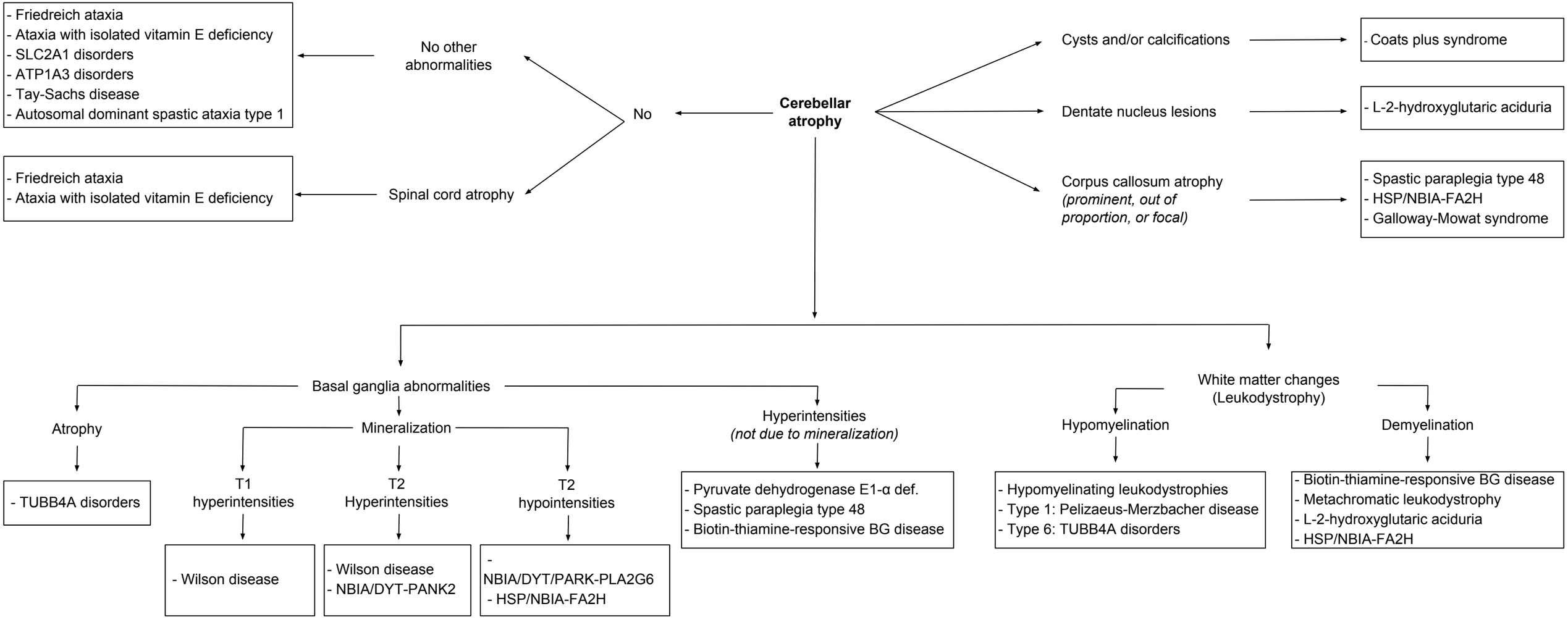
Friedreich ataxia **(AR)**
Scoliosis, *nystagmus, optic atrophy, pes cavus, pyramidal signs, hypertrophic cardiomyopathy, diabetes, myoclonus*

Ataxia with isolated vitamin E deficiency **(AR)**
Proprioception loss, *head titubation, pyramidal signs, retinopathy*

ATP1A3 disorders **(AD)**
Recurrent episodes of hemiparesis, parkinsonism, *behavior disorders, optic atrophy, hypoacusia, seizures*

Wilson disease **(AR)**
Kayser-Fleischer ring, sunflower cataract, pseudolaughter, facetious smile, liver disease, *tremor, parkinsonism, myoclonus, chorea, behavior disorders, cognitive decline, muscle weakness, hemolytic anemia*


Adulthood onset dystonia-ataxia syndromes
Oculomotor abnormalities
Prominent gaze palsy
Niemann-Pick disease (type C) (AR)
Isolated spleno- or hepatosplenomegaly, behavior disorders, cognitive impairment, seizures, myoclonus, tremor, spasticity
POLG disorders (AR)
Ptosis, peripheral neuropathy, cognitive impairment, seizures, hypoacusis, parkinsonism, chorea, myoclonus, muscle atrophy
Altered saccades (and/or ophthalmoparesis)
SCA-ATXN1 (SCA1) (AD)
Pyramidal signs, muscular weakness and atrophy, decreased deep tendon reflexes, loss of proprioception, bulbar dysfunction
SCA-ATXN2 (SCA2) (AD)
Pyramidal signs, peripheral neuropathy, fasciculations, muscle cramps and atrophy, parkinsonism, autonomic dysfunction
SCA-ATXN3 (SCA3) (AD)
Nystagmus, diplopia, pyramidal signs, peripheral neuropathy, fasciculations, muscle cramps and atrophy, parkinsonism
SCA-CACNA1A (SCA6) (AD)
Diplopia, dizziness, peripheral neuropathy
No
Peripheral neuropathy
Friedreich ataxia (AR)
Proprioceptive loss, scoliosis, nystagmus, optic atrophy, pes cavus, pyramidal signs, hypertrophic cardiomyopathy, diabetes, myoclonus
Ataxia with isolated vitamin E deficiency (AR)
Proprioception loss, head titubation, pyramidal signs, retinopathy
No
Prominent bulbar involvement
Wilson disease (AR)
Kayser-Fleischer ring, sunflower cataract, liver disease, pseudolaughter, facetious smile, tremor, parkinsonism, myoclonus, muscle weakness, hemolytic anemia
No
SCA-ATN1 (DRPLA) (AD)
Myoclonus, seizures, pyramidal signs, cognitive impairment, behavior disorders, chorea
SCA-TBP (SCA17) (AD)
Chorea, parkinsonism, cognitive impairment, behavior disorders, seizures, pyramidal signs


- Friedreich ataxia
- Ataxia with isolated vitamin E deficiency
- SLC2A1 disorders
- ATP1A3 disorders
- Tay-Sachs disease
- Autosomal dominant spastic ataxia type 1
No other abnormalities
- Friedreich ataxia
- Ataxia with isolated vitamin E deficiency
Spinal cord atrophy
No
Cerebellar atrophy
Cysts and/or calcifications
- Coats plus syndrome
Dentate nucleus lesions
- L-2-hydroxyglutaric aciduria
Corpus callosum atrophy
(prominent, out of proportion, or focal)
- Spastic paraplegia type 48
- HSP/NBIA-FA2H
- Galloway-Mowat syndrome
Basal ganglia abnormalities
Atrophy
- TUBB4A disorders
Mineralization
T1 hyperintensities
- Wilson disease
T2 Hyperintensities
- Wilson disease
- NBIA/DYT-PANK2
T2 hypointensities
- NBIA/DYT/PARK-PLA2G6
- HSP/NBIA-FA2H
Hyperintensities
(not due to mineralization)
- Pyruvate dehydrogenase E1-α def.
- Spastic paraplegia type 48
- Biotin-thiamine-responsive BG disease
White matter changes
(Leukodystrophy)
Hypomyelination
- Hypomyelinating leukodystrophies
- Type 1: Pelizaeus-Merzbacher disease
- Type 6: TUBB4A disorders
Demyelination
- Biotin-thiamine-responsive BG disease
- Metachromatic leukodystrophy
- L-2-hydroxyglutaric aciduria
- HSP/NBIA-FA2H