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Primary and secondary ataxias

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Abstract

Purpose of review—This article discusses recent advances in the understanding of clinical and genetic aspects of primary ataxias, including congenital, autosomal recessive, autosomal dominant, episodic, X-linked, and mitochondrial ataxias, as well as idiopathic degenerative and secondary ataxias.

Recent findings—Many important observations have been published in recent years in connection with primary ataxias, particularly new loci and genes. The most commonly inherited ataxias may present with typical and atypical phenotypes. In the group of idiopathic degenerative ataxias, genes have been found in patients with multiple system atrophy type C. Secondary ataxias represent an important group of sporadic, cerebellar, and afferent/sensory ataxias.

Summary—Knowledge of primary ataxias has been growing rapidly in recent years. Here we review different forms of primary ataxia, including inherited forms, which are subdivided into congenital, autosomal recessive cerebellar ataxias, autosomal dominant cerebellar ataxias, episodic ataxias, X-linked ataxias, and mitochondrial ataxias, as well as sporadic ataxias and idiopathic degenerative ataxias. Secondary or acquired ataxias are also reviewed and the most common causes are discussed.

Keywords

autosomal recessive cerebellar ataxias; congenital ataxias; secondary ataxias; spinocerebellar ataxias; sporadic ataxias

INTRODUCTION

Ataxia is a disorder of balance and coordination [1■]. The commonest forms are cerebellar ataxia, in which the cerebellum and its afferent or efferent projections are affected, and afferent/sensory ataxia, in which the proprioceptive pathways are affected [1■,2]. Cerebellar ataxia is a syndrome that includes several signs and symptoms, such as gait ataxia,

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Conflicts of interest

There are no conflicts of interest.

dysarthria, nystagmus, tremor, and cognitive dysfunction [1■,2–4]. Ataxias can be classified as primary or secondary, as well as hereditary or sporadic [1■,2–4].

PRIMARY ATAXIAS

Primary cerebellar ataxias are further subdivided into sporadic and hereditary ataxias. The latter include autosomal recessive cerebellar ataxias (ARCAs), autosomal dominant cerebellar ataxias, currently known as spinocerebellar ataxias (SCAs), episodic ataxias, X-linked cerebellar ataxias, and mitochondrial ataxias. Idiopathic degenerative cerebellar ataxias include the cerebellar form of multiple system atrophy (MSA-C) and idiopathic late-onset cerebellar ataxias [3–9].

CONGENITAL ATAXIAS

Congenital ataxias can be caused by cerebellar mal-formations or pontocerebellar hypoplasia and present with cerebellar ataxia. The most widely known form is Joubert's syndrome, a rare autosomal recessive disease characterized by a congenital hind-brain malformation, which can be identified on MRI as the 'molar tooth sign' [10,11] (Fig. 1). The clinical picture includes neonatal hypotonia, cerebellar ataxia, ocular motor apraxia, breathing dysregulation, and multiple organ involvement. To date, more than 20 causative genes have been identified, most of which encode proteins of the primary cilium, a subcellular organelle involved in crucial cellular functions. Joubert's syndrome is part of an emerging class of genetic disorders known as ciliopathies [10,11].

INHERITED ATAXIAS

Inherited cerebellar ataxias constitute an extensive group of clinically and genetically heterogeneous, complex neurodegenerative disorders caused by a large number of genetic mutations. Among the hereditary cerebellar ataxias, there are almost 40 forms of SCAs, more than 30 ARCAs, two X-linked ataxias, and several forms of mitochondrial ataxias [7-9,12,13■].

SCAs are predominantly caused by unstable repeat expansions in either coding (SCAs types 1, 2, 3, 6, 7, and 17, and dentatorubral-pallidoluysian atrophy) or noncoding (SCAs types 8,10, 12, 31, and 36) regions of the relevant genes [3,4,9,12,13■]. More rarely, they are caused by conventional mutations, such as missense mutations, insertions, and deletions (SCAs types 5, 11, 13, 14, 15, 20, 23, 27, 28, and 35). SCAs caused by unstable repeat expansions in the coding area of the relevant genes have a trinucleotide (CAG) repeat, which causes cells to produce expanded polyglutamine tracts. These diseases are known as polyglutamine disorders [9,12,13■,14]. Another group of inherited ataxias are episodic ataxias due to ion channel mutations [15]. Among the ARCAs, Friedreich's ataxia (FRDA) is associated with homozygous triplet GAA expansions in the *FXN* gene [7,8,16]. The ataxia telangiectasia gene, known as *ATM,* is located on chromosome 11q22–23 [7,8,14,17■]. Other ARCAs are associated with different, conventional mutations. Some, such as fragile X-associated tremor/ataxia syndrome (FXTAS), are X-linked, whereas others are mitochondrial ataxias [polymerase γ (POLG) ataxia] [18■,19].

AUTOSOMAL RECESSIVE CEREBELLAR ATAXIAS

ARCAs are included in the heterogeneous group of inherited ataxias. They are typically characterized by cerebellar and spinal cord degeneration and have a relatively early age of onset [3,4,7,8]. The most common forms of ARCAs that have been genetically defined are shown in Table 1. In white children, the most common form is FRDA, followed by ataxia telangiectasia [7,8,16,17■].

FRIEDREICH'S ATAXIA

Since the identification of the FRDA gene and the GAA trinucleotide expansion that leads to FRDA, phenotypic variants of this ataxia have frequently been reported in individuals carrying pathogenic mutations, some of which do not fit the classic descriptions of this condition [16,20]. Atypical phenotypes include late-onset and very-late-onset ataxia, with small GAA expansions, retained reflexes, pyramidal signs, and movement disorders [21,22]. FRDA is predominantly an afferent/sensory ataxia; however, the presence of a cerebellar component was confirmed in neuropathological studies and recently in neuroimaging studies (Fig. 2) [16,20,23]. Although there is no consensus regarding treatment, antioxidants such as coenzyme Q10 and its derivatives, including idebenone, have been used. Idebenone has shown significant benefits for hypertrophic cardiomyopathy but is ineffective for neurological conditions [24,25]. More recently, new drugs have been tested, including deferiprone, as well as epigenetic therapy [26,27].

ATAXIA TELANGIECTASIA

Since the *ATM* gene was first described, over 200 potentially pathogenic mutations involving almost all coding exons of this gene have been reported [28]. In addition to the classical phenotype, with cerebellar ataxia and oculocutaneous telangiectasia (Fig. 3), many cases of ataxia telangiectasia with milder phenotypes have been described [28]. These phenotypes include later disease onset; slower progression; longer life expectancy; a predominance of movement disorders, such as dystonia, myoclonus, and chorea, instead of cerebellar ataxia; the absence of ocular telangiectasia; and lower levels of chromosomal instability and cellular radiosensitivity [17■,28]. In fact, ataxia telangiectasia represents a multisystem entity with variable neurological and systemic manifestations. ATM syndrome has been proposed as a more adequate designation for this entity (H.A.G. Teive, unpublished).

OTHER AUTOSOMAL RECESSIVE CEREBELLAR ATAXIAS

Gordon Holmes' syndrome, a peculiar form of ARCA, is characterized by hypogonadotropic hypogonadism, and different mutations have been found in patients with this form of ataxia, including *STUB1, RNF216, OTUD4,* and *PNPLA6* gene mutations [29■,30]. PNPLA6 mutations also cause Boucher-Neuhauser syndrome, a combination of ARCA and hypogonadotropic hypogonadism, which is also associated with chorioretinal dystrophy and hypersegmented neutrophils [29■,31–33]. Another form of early-onset ARCA associated with retinal dystrophy is caused by a homozygous *GRID2* deletion [34]. Mutations in the

SNX-14 gene cause a rare form of ARCA associated with sensorineural hearing loss and intellectual disability [35]. Childhood-onset progressive myoclonic ataxia (Ramsay Hunt syndrome) is associated with a novel mutation in the *GOSR2* gene [36]. Although significant progress has been made in the identification of ARCA genes, the genetic cause of disease remains undetermined in about 40–50% of ARCAs [30,37,38■,39–43]. There is no treatment for these ataxias, with the exception of ataxia due to vitamin E deficiency and a group of ataxias associated with coenzyme Q10 deficiency [3,4,37,38■].

SPINOCEREBELLAR ATAXIAS

SCAs constitute a large, complex group of heterogeneous autosomal dominant degenerative diseases characterized by progressive degeneration of the cerebellum and its afferent and efferent connections, as well as other nervous system structures [3–6,9,12,13■,44■■,45■■]. Table 2 shows the main types of SCAs currently known (from SCA type 1 to SCA type 40) and gives the genetic loci, mutations, and proteins associated with each disease. SCA type 3 is the commonest form of the disease worldwide; types 1, 2, 6, and 7 have greatly varying prevalences depending on the ethnic background of the population [3–6,9,12,13■].

SPINOCEREBELLAR ATAXIA TYPE 3 (MACHADO-JOSEPH DISEASE)

The clinical picture of SCA type 3 is pleomorphic, with cerebellar ataxia in association with pyramidal signs; peripheral amyotrophy; nystagmus, ophthalmoparesis, and bulging eyes (Fig. 4); fasciculations of the face, tongue, and, occasionally, the limbs; and dystonia and parkinsonism [3,4,12,13■,46,47]. Non-motor and extracerebellar features are common in patients with SCA type 3, particularly sleep disorders, cognitive and affective disturbances, movement disorders, psychiatric symptoms, olfactory dysfunction, peripheral neuropathy, pain, cramps, fatigue, nutritional problems, and dysautonomia [48–51].

OTHER SPINOCEREBELLAR ATAXIAS

Other SCAs encompass a broad spectrum of clinical features and include SCA type 10 (caused by an expansion of an ATTCT pentanucleotide repeat), which is the second most common SCA in Mexico and the South of Brazil (Fig. 5) [52]. In the latter, the main phenotype observed is pure cerebellar ataxia, unlike the typical phenotype, which consists of cerebellar ataxia and epilepsy [52]. More recently, several new forms of SCAs with new loci and gene mutations have been described. These include SCA types 31, 34, 35, 36, 37, 38 and 40 (Fig. 6) [53–60]. In spite of the very large number of mutations described in individuals with SCA, many patients (30–40%) remain without a genetic/molecular diagnosis [12,13■, 14].

SPINOCEREBELLAR ATAXIAS – TREATMENT

To date, there is no effective treatment for SCAs [62]. Neurorehabilitation is mandatory, and different studies using motor training, including physiotherapy or whole-body controlled videogames (‘exer-games’), have shown significant benefits for patients with SCAs [63,64■]. New treatment options, including RNA interference therapy, and mesenchymal and cerebellar neural stem-cell transplantations, have been tested [65–68]. Treatment of SCA

type 3 mouse models with the Hsp90 inhibitor 17-DMAG or overexpression of beclinl (an autophagy-related protein) was shown to mitigate motor and neuropathological deficits in SCA type 3 [69,70].

HEREDITARY EPISODIC ATAXIAS

Hereditary episodic ataxias are characterized by recurrent episodes of ataxia and vertigo, as well as progressive cerebellar ataxia [15,71,72■]. To date, seven forms of episodic ataxia have been identified, the most common being types 1 and 2. Both are secondary to mutations in genes coding for ion channels and transport proteins [15,71,72■]. Recently, mutations in the *PRRT2* gene that cause autosomal dominant paroxysmal kinesigenic dyskinesia were associated to episodic ataxia [73] (Table 3). Acetazolamide, a carbonic-anhydrase inhibitor, may reduce the frequency and severity of attacks [15,71,72■].

X-LINKED ATAXIAS

X-linked SCAs are very rare forms of ataxia caused by X-linked recessive mutations [18■]. At present, the most clinically relevant and common form is FXTAS [18■]. FXTAS occurs predominantly in males over 50 years of age and is characterized by action tremor with an important kinetic component, cerebellar ataxia, cognitive dysfunction, and, occasionally, parkinsonism and autonomic dysfunction. It is caused by an intermediate CGG expansion (between 55 and 200 repeats) in the fragile X mental retardation 1 gene [18■].

MITOCHONDRIAL ATAXIAS

In mitochondrial ataxias, cerebellar and sensory ataxias are usually combined with other features and are the result of abnormalities in mitochondrial DNA [19]. These forms of ataxia include maternally inherited heredoataxias due to point mutations in genes coding for RNAs and respiratory chain subunits or deletions/duplications of the mitochondrial DNA [19,74]. Mitochondrial recessive ataxia syndrome is caused by a mutation in the mitochondrial DNA *POLG* gene [19,74]. POLG-related ataxia is a mixed ataxia (with cerebellar and afferent/sensory ataxia) and presents with a large number of nonataxia features, such as sensory neuropathy, external ophthalmoplegia, ptosis, epilepsy, and hyperkinetic movement disorders [19,74].

IDIOPATHIC DEGENERATIVE ATAXIAS

Idiopathic cerebellar degeneration includes a group of disorders of unknown cause, such as MSA-C and idiopathic late-onset cerebellar ataxia, also known as sporadic adult-onset ataxia of unknown cause (SAOA) or even idiopathic sporadic cerebellar ataxia [3–5,75■,76].

MULTIPLE SYSTEM ATROPHY

MSA is a sporadic and progressive neurodegenerative disease characterized by parkinsonism, cerebellar ataxia, and autonomic failure [75■] (Fig. 7). In most Western populations, the clinical picture is dominated by parkinsonian features (defined as MSA-P), but cerebellar ataxia represents the most important motor feature in one-third of patients

(defined as MSA-C). However, in Japan, there is a predominance of MSA-C (83.8%) [3,4,75■]. Recently, homozygous and compound heterozygous mutations in the coenzyme Q2 gene *(COQ2)* were identified in Japanese patients with familial and sporadic MSA [77]. Although the frequency of mutations in *COQ2* in a group of Chinese patients with MSA was 1.28%, [78] other studies failed to confirm the association between mutant *COQ2* and MSA [79]. MSA and amyotrophic lateral sclerosis have been associated with a hexanucleotide repeat expansion in the protein C9orf72. This mutation has very diverse clinical presentations, including amyotrophic lateral sclerosis and frontotemporal dementia [80].

SPORADIC ADULT-ONSET ATAXIA OF UNKNOWN CAUSE

SAOA is an idiopathic neurodegenerative disorder previously defined as cerebello-olivary degeneration or pure cerebello-olivary degeneration of Marie, Foix, and Alajouanine [81]. Clinically, it presents as slowly progressive cerebellar ataxia, with onset after the age of 50 years and noncerebellar signs, such as chorea, and pyramidal and sensory signs [3,4,81]. The diagnosis is one of exclusion after secondary inherited ataxias and MSA have been eliminated [3,4]. In a Brazilian case series of eight elderly patients with SAOA, mild cognitive impairment and visual loss due to macular degeneration were observed in 50% of cases in addition to slowly progressive gait ataxia and cerebellar atrophy. Chorea was found concomitantly in three patients (H.A.G. Teive, unpublished).

WHOLE-EXOME SEQUENCING IN INHERITED AND SPORADIC ATAXIAS

Investigation of inherited ataxias is a challenge for neurologists because there is great clinical and genetic heterogeneity and a genetic diagnosis can only be made in 60% of cases [82]. Many patients therefore fail to receive a genetic diagnosis, limiting genetic counseling and prenatal diagnosis [83]. A powerful new tool that can be used to investigate these patients with undiagnosed inherited and sporadic ataxias is exome sequencing. Several studies have recently been published confirming that this is a very useful technique for evaluating this group of patients with primary ataxia [83,84■].

SECONDARY ATAXIAS

Secondary or acquired ataxias include ataxias because of exogenous or endogenous nongenetic causes, including those of a toxic, paraneoplastic, immune-mediated, nutritional, and infectious nature, as well as focal injury to the cerebellum [3,4]. In this setting, neuroimaging studies are of capital importance in defining focal lesions in the cerebellum and its connections caused by, for example, neoplastic, inflammatory, demyelinating, and vascular disorders [3,4]. Ataxia can also be the result of the adverse effects of different drugs [85■]. Drug-induced cerebellar ataxia is most commonly due to antiepileptic medicines (including oxcarbazepine, lamotrigine, and phenytoin), benzodiazepines (nitrazepam and triazolam), and antineoplastic/immunosuppressive drugs (cytarabine, tacrolimus, and cyclosporine) [85■]. Chemicals such as alcohol, lithium, and toluene are also known to cause ataxia [85■,86]. Several infectious disorders, such as syphilis and Whipple’s disease, mumps, and infectious mononucleosis, can lead to cerebellitis with cerebellar ataxia [3,4]. Endocrine abnormalities, particularly hypothyroidism, may present with cerebellar ataxia.

Steroid-responsive encephalopathy associated with autoimmune thyroiditis, also known as Hashimoto's encephalopathy, is defined by the presence of cerebellar ataxia, tremor, and myoclonus, as well as cognitive disorders and high serum levels of thyroperoxidase antibodies. As its name suggests, steroid-responsive encephalopathy associated with autoimmune thyroiditis responds well to steroid treatment [3,4]. Cerebellar and afferent/sensory ataxias can occur in individuals with a deficiency of vitamins such as thiamine, tocopherol, and cobalamine [3,4]. Paraneoplastic cerebellar degeneration is an immune-mediated cerebellar disorder associated with malignancy, particularly small-cell lung, breast, and ovary carcinomas, and Hodgkin's lymphoma [87]. In paraneoplastic cerebellar degeneration, several types of autoantibodies are directed against neuronal antigens, the most common being anti-Yo, anti-Hu, and anti-Tr [3,4,87]. Cerebellar ataxia may occur in association with antibodies to glutamic acid decarboxylase (GAD), originally described in patients with stiff-person syndrome [3,4,87,88]. Anti-GAD ataxia is more common among women and can co-occur with insulin-dependent diabetes mellitus and thyroid diseases. Anti-GAD ataxia is variably responsive to intravenous immunoglobulins and steroids [3,4,87,88]. Gluten ataxia is another immune-mediated disorder caused by ingestion of gluten in patients who are genetically susceptible to this protein composite [89]. Gluten ataxia is characterized by progressive adult-onset gait ataxia with gaze-evoked nystagmus associated with signs of peripheral neuropathy. The antigliadin antibody is positive in 100% of patients. A gluten-free diet can improve gluten ataxia [89]. However, the relationship between cerebellar ataxia and antigliadin antibodies is currently very controversial, and several studies failed to confirm this association [90]. Finally, Miller Fisher syndrome, a Guillain-Barre syndrome variant, should also be considered in the differential diagnosis of cases with acute sensory ataxia [3,4].

CONCLUSION

Primary ataxias represent a very large group of neurodegenerative diseases and include sporadic and inherited forms, which are subdivided into congenital ataxias, ARCAs, SCAs, episodic ataxias, X-linked ataxias, mitochondrial ataxias, and idiopathic degenerative ataxias. Despite the increase in the number of defined genetic causes of primary ataxias, around 30–40% of patients remain without a diagnosis. Furthermore, to date, there is no cure for the majority of primary ataxias. Secondary ataxias are an important group of sporadic diseases and include immune-mediated ataxias and ataxias due to toxic agents and vitamin deficiencies among other causes.

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KEY POINTS

- ARCAs are a group of primary ataxias; more than 30 forms have been described recently.
- Autosomal dominant cerebellar ataxias or SCAs are a very large group of clinically and genetically very heterogeneous degenerative ataxias.
- Other peculiar forms of primary ataxias are episodic ataxias, X-linked ataxias, and mitochondrial ataxias.
- MSA-C and SAOA of unknown cause are idiopathic, degenerative forms of primary ataxias.
- Secondary or acquired ataxias are immune-mediated ataxias or ataxias caused by toxic agents, particularly drugs and alcohol, and vitamin deficiencies.

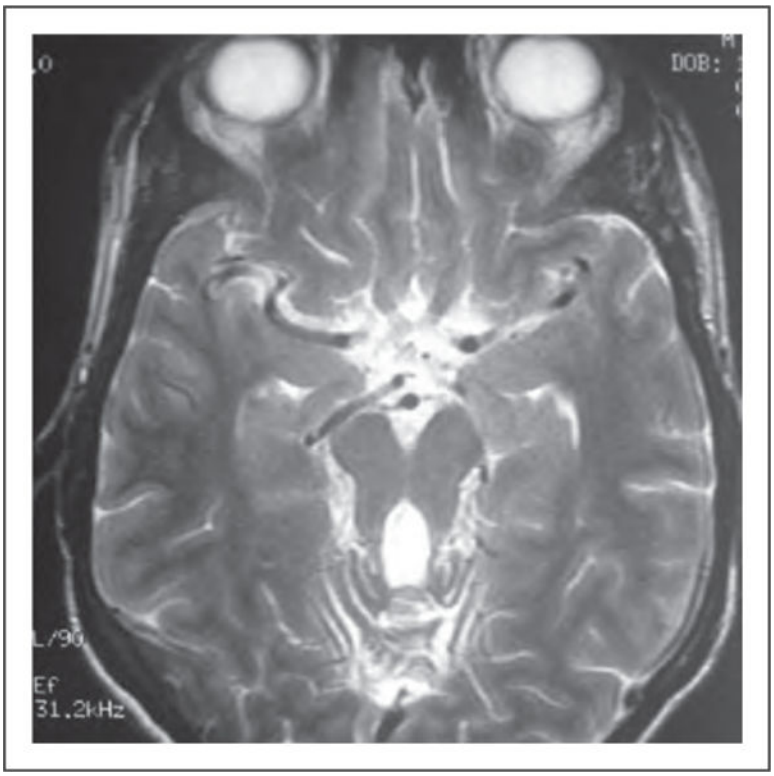

FIGURE 1.
Brain MRI, T2-weighted, axial view. Molar tooth sign, Joubert's syndrome. Adapted with permission.

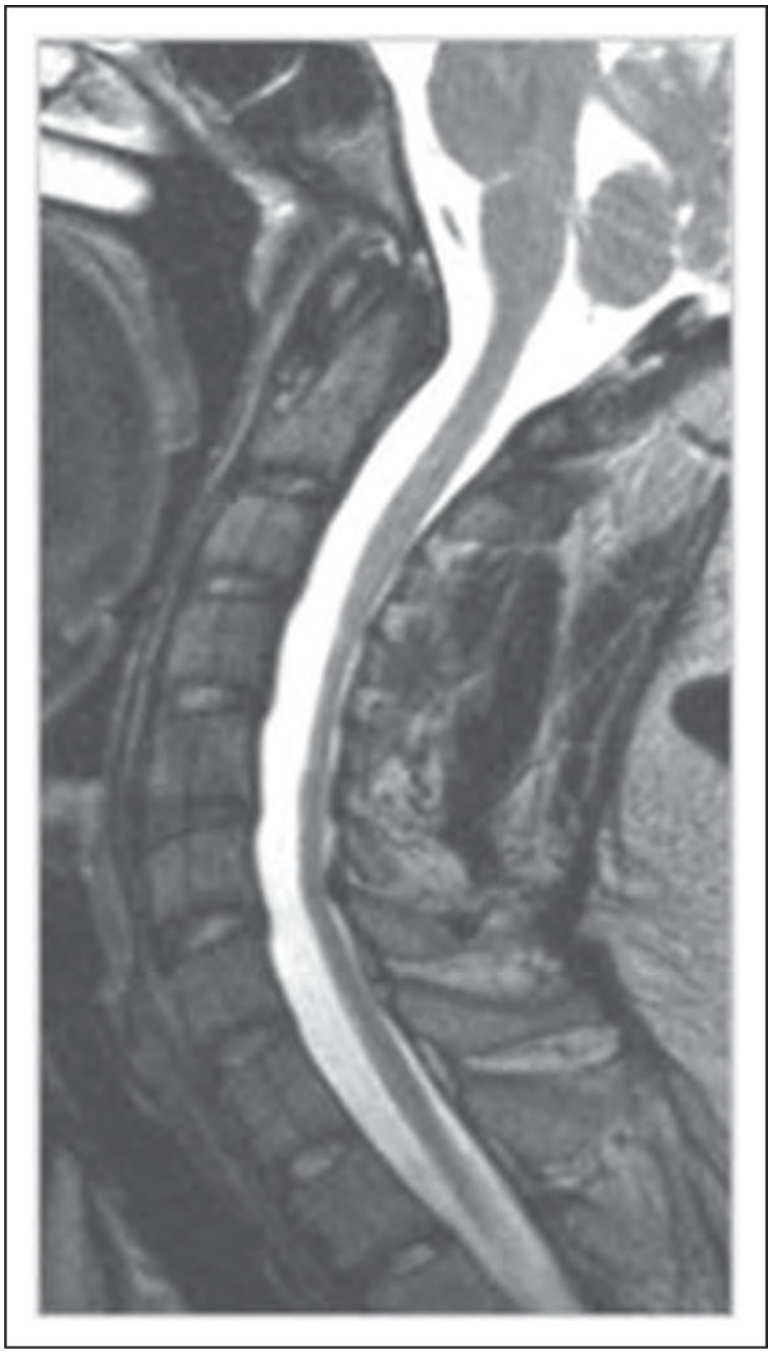

FIGURE 2.

Spinal cord MRI, T2-weighted, sagittal view.Cervical spinal cord atrophy in a patient with Friedreich's ataxia. Adapted with permission.

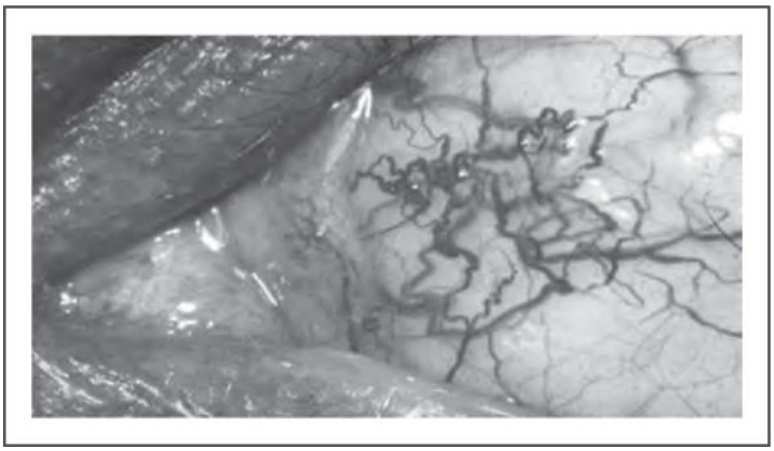

FIGURE 3.
Conjunctival telangiectasia in a patient with ataxia telangiectasia. Adapted with permission.

FIGURE 4.
'Bulging eyes' in a patient with spinocerebellar ataxia type 3. Adapted with permission.

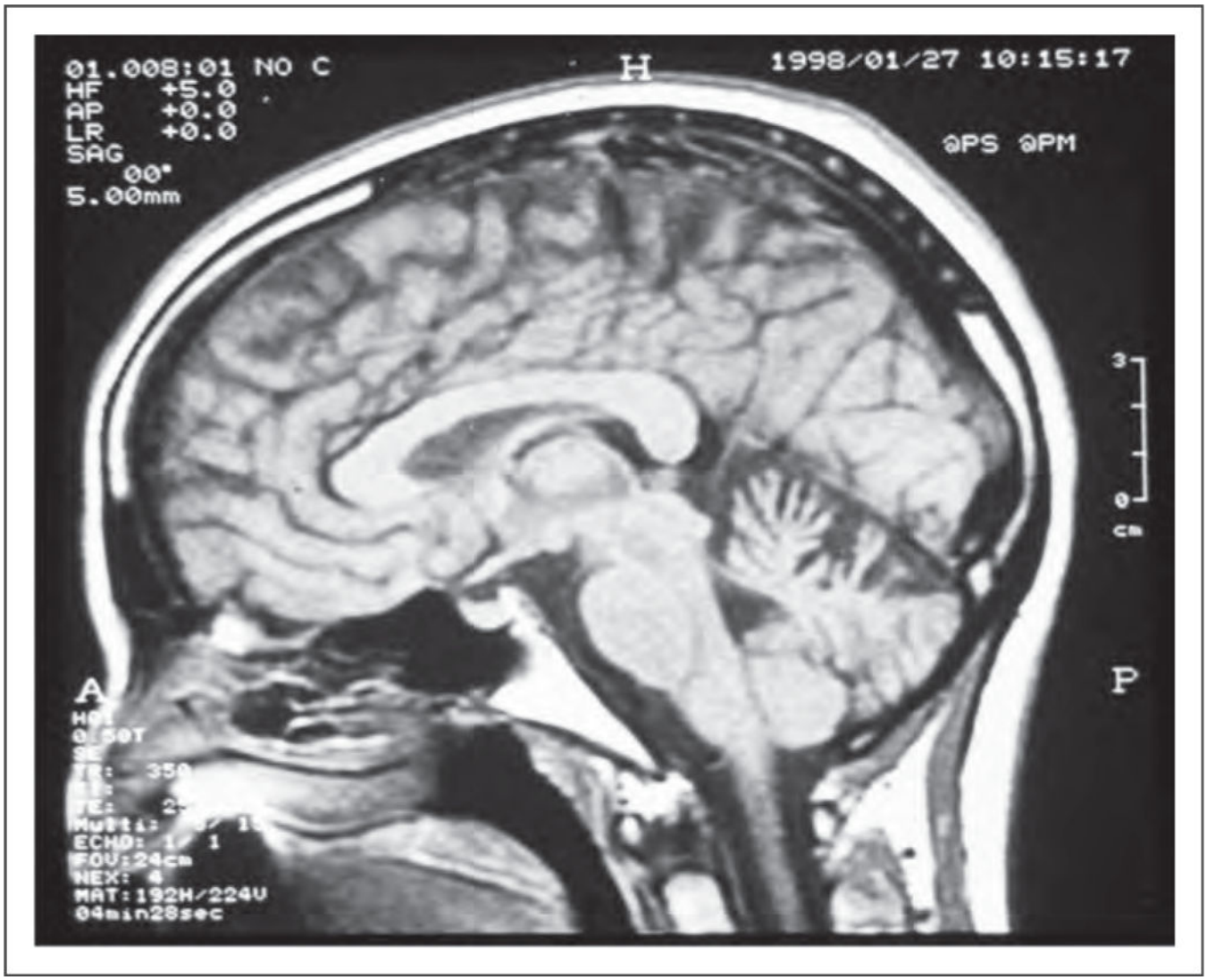

FIGURE 5.

Brain MRI, T1-weighted, sagittal view. Cerebellar atrophy in a patient with spinocerebellar ataxia type 10. Adapted with permission.

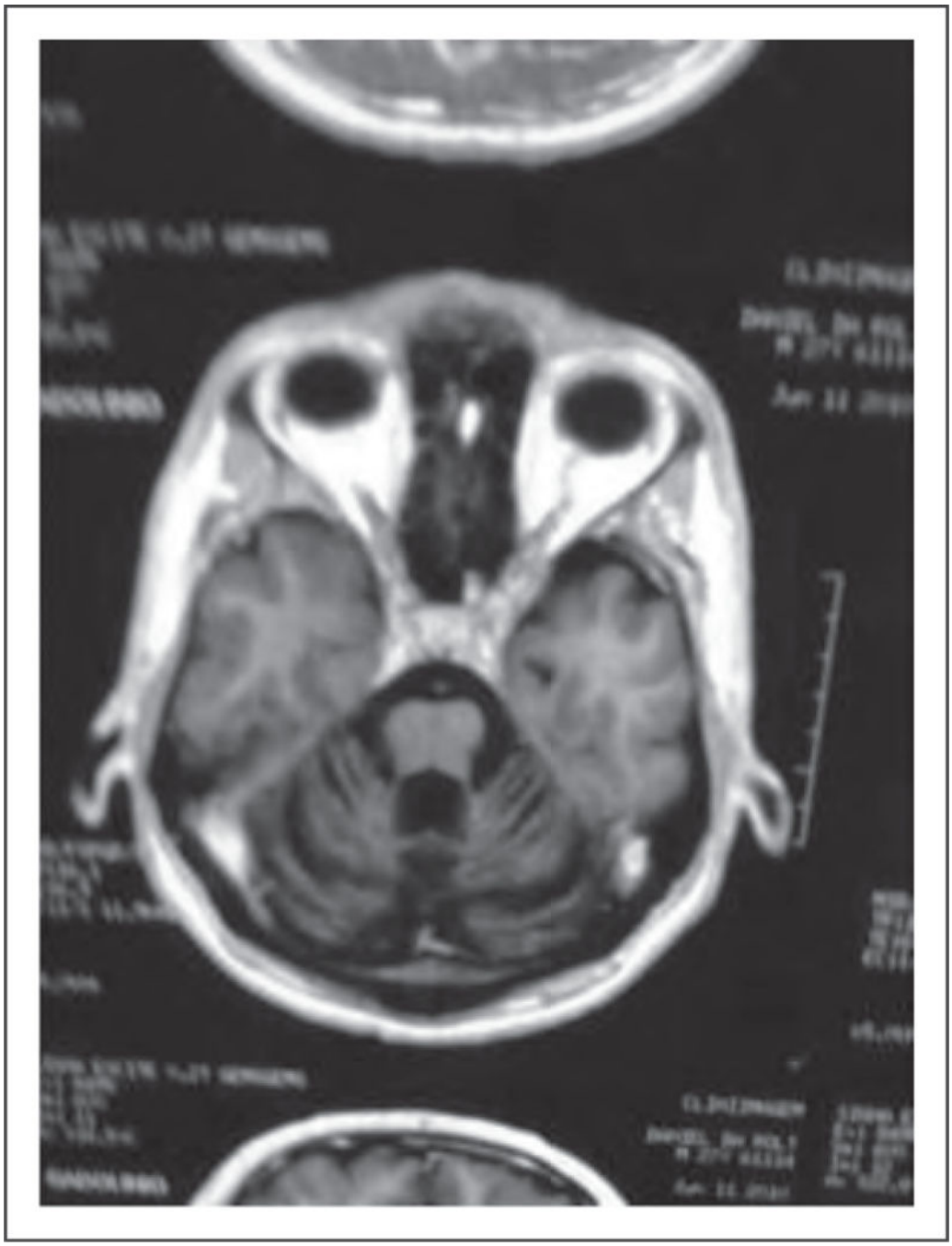

FIGURE 6.
Spinocerebellar ataxia type 34. Brain MRI, axial view, T1-weighted, showing cerebellar atrophy. Adapted with permission.

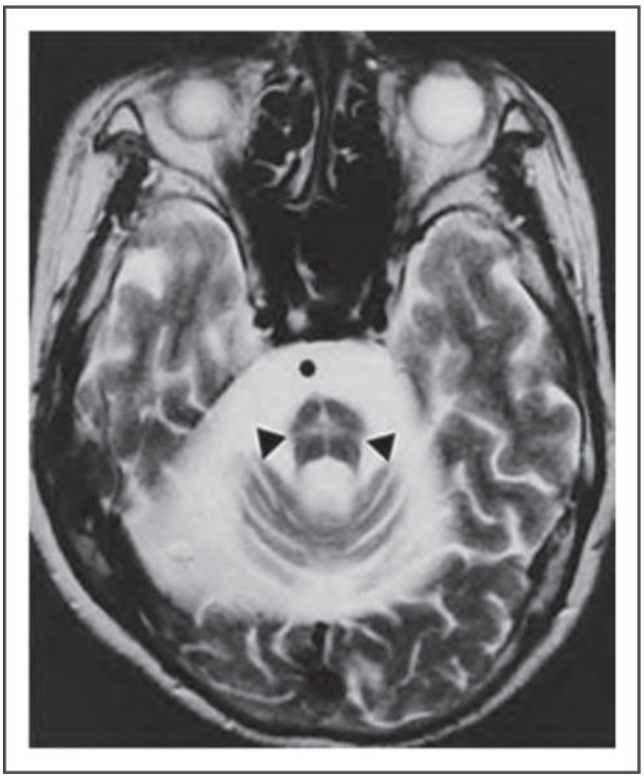

FIGURE 7.
Hot cross bun sign of cerebellar form of multiple system atrophy. Adapted with permission from [61].

Table 1.

Autosomal recessive cerebellar ataxias – most common forms with genetic definition

ARCAs	Locus	Gene	Protein
FRDA	9q13	*FXN*	Frataxin
AVED	8q12.3	*TTPA*	α-Tocopherol transfer protein
ARSACS	13q12	*SACS*	Sacsin
AT	11q22.3	*ATM*	Serine protein kinase
ATLD	11q21	*MRE11*	Meiotic recombination 11
AOA1	9p13	*APTX*	Aprataxin
AOA2	9q34	*SETX*	Senataxin
MIRAS/SANDO	15q25	*POLG1*	DNA polymerase subunit g-1
MSS	5q31	*SIL1*	Nucleotide exchange factor SIL1
ARCA1	6q25	*SYNE1*	Nesprin-1
ARCA2	1q42.2	*CABC1*	Chaperone activity of bc1 complex like
ARCA3	3p22.1	*ANO10*	Anoctamin-10

AOA1, ataxia with oculomotor apraxia type 1; AOA2, ataxia with oculomotor apraxia type 2; ARCA1, autosomal recessive cerebellar ataxia type 1; ARCA2, autosomal recessive cerebellar ataxia type 2, with coenzyme Q10 deficiency; ARCA3, autosomal recessive cerebellar ataxia type 3 caused by mutations in *ANO10;* ARSACS, autosomal recessive spastic cerebellar ataxia of Charlevoix-Saguenay; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; FRDA, Friedreich's ataxia; MIRAS, mitochondrial recessive ataxia syndrome; MSS, Marinesco-Sjogren syndrome; SANDO, sensory ataxic neuropathy, dysarthria, and ophathalmoparesis

Table 2.

Spinocerebellar ataxias – summary of genetic characteristics

SCA	Locus	Gene	Mutation	Potentially distinguishable clinical features
SCA1	6p22–23	*ATXN1*	CAG	
SCA2	12q23–24.1	*ATXN2*	CAG	Slow saccades, areflexia
SCA3	14q32.1	*ATXN3/DMJ*	CAG	Bulging eyes, fasciculations
SCA4	16q22.1	*SCA4*	–	
SCA5	11q13.2	*SPTBN2*	–	Down-beat nystagmus
SCA6	19p13	*CACNA1A*	CAG	Coarse nystagmus and saccadic intrusion
SCA7	3p21.1-p12	*ATXN7*	CAG	Visual loss
SCA8	13q21	*ATXN8OS*	CAG/CTG	Reduced penetrance
SCA10	22q13.31	*ATXN10*	ATTCT	Epilepsy
SCA11	15q15.2	*TTBK2*	–	
SCA12	5q32	*PPP2R2B*	CAG	Arm tremor
SCA13	19q13.33	*KCNC3*	–	Absent eye findings
SCA14	19q13.4	*PRKCG*	–	Tremor, myoclonus, facial myokymia
SCA15	3p26.1	*ITPR1*	Allelic to SCA16, 29	
SCA16	3p26.1	*ITPR1*	Allelic to SCA15, 29	
SCA17	6q27	*TBP*	CAG	Huntington disease like
SCA18	7q22-q32	*IFRD1*	–	
SCA19	1p13.2	*KCND3*	Allelic to SCA22	
SCA20	11p11.2-q13.3	*SCA20*	Multiple gene duplication	Spasmodic dysphonia
SCA21	7p21.3-p15.1	*SCA21*	–	
SCA22	1p13.2	*KCND3*	Allelic to SCA19	
SCA23	20p13	*PDYN*	–	
SCA25	2p21-p15	*SCA25*	–	
SCA26	19p13.3	*EEEF2*		
SCA27	13q34	*FGF14*	–	Mental retardation, tremor
SCA28	18p11	*AFG3L2*	–	
SCA29	3p26.1	*ITPR1*	Allelic to SCA15, 16	Congenital nonprogressive ataxia
SCA30	4q34.3-q35.1	*SCA30*	–	

SCA	Locus	Gene	Mutation	Potentially distinguishable clinical features
SCA31	16q22	*SCA31*	TGGAA	
SCA32	7q32-q33	*SCA32*	–	
SCA34	6q12.3-q16.1	*ELOVL4*	–	Erythrokeratodermia
SCA35	20p13	*TGM6*	–	
SCA36	20p13	*NOP56*	GGCCTG	ALS/FTD like
SCA37	1p32	*SCA37*		
SCA38	6p12.1	*ELOVLE5*		
SCA40	14q32	*CCDC88C*		
DRPLA	12p13.31	*ATN1*	CAG	Huntington's disease like

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; SCA, spinocerebellar ataxia.

Table 3.

Episodic ataxias

EA	Chromosome	Gene	Additional clinical features	Duration of ataxia attacks
EA-1	12p13	*KCNA1*	Facial myokimia/neuromyotonia	Seconds/up to 2 min
EA-2	19p13.2	*CAGNAIA*	Nystagmus	Hours/days
EA-3	1q42	–	Tinnitus/headache	–
EA-4	–	–	Diplopia	Minutes/hours
EA-5	2q22–23	*CACNB4*	Epilepsy, vertigo	–
EA-6	5p13	*SLCA3*	Headache/hemiplegia	2–3 h
EA-7	19q13	–	Weakness	–
EA-Other	–	*UBR4*	Weakness	–
EA-Other	–	*PPRT2*	Paroxysmal dyskinesias	–

EA, episodic ataxia; EA-Other, new loci of episodic ataxia, identified but still not confirmed.

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