CHAPTER 14

MACHADO-JOSEPH DISEASE AND OTHER RARE SPINOCEREBELLAR ATAXIAS

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Abstract: The spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterised by progressive lack of motor coordination leading to major disability. SCAs show high clinical, genetic, molecular and epidemiological variability. In the last one decade, the intensive scientific research devoted to the SCAs is resulting in clear advances and a better understanding on the genetic and nongenetic factors contributing to their pathogenesis which are facilitating the diagnosis, prognosis and development of new therapies. The scope of this chapter is to provide an updated information on Machado-Joseph disease (MJD), the most frequent SCA subtype worldwide and other rare spinocerebellar ataxias including dentatorubral-pallidoluysian atrophy (DRPLA), the X-linked fragile X tremor and ataxia syndrome (FXTAS) and the nonprogressive episodic forms of inherited ataxias (EAs). Furthermore, the different therapeutic strategies that are currently being investigated to treat the ataxia and non-ataxia symptoms in SCAs are also described.

INTRODUCTION

Ataxias are a heterogeneous group of diseases characterised by progressive lack of motor coordination due to degeneration of the cerebellum and its connections. They fall into three categories: (1) acquired ataxias with nongenetic causes (2) hereditary ataxias, comprising recessive, dominant and X-linked inherited ataxias, and (3) sporadic ataxias. They are rare disorders with a prevalence of 10-15 per 100,000 population and affect mostly young adults. Due to their progressive nature they can lead to major disability and premature death.

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The spinocerebellar ataxias (SCAs) are highly heterogeneous neurodegenerative diseases[1,2] characterised by lack of coordination of the gait and are often associated with poor coordination of hands, speech and eye movements. The term "spinocerebellar ataxias" is commonly used for those inherited ataxias presenting an autosomal dominant inheritance. SCAs are usually slowly progressive and often associated with cerebellar and brain atrophy as seen from brain imaging studies. Up to date, there are more than 35 different SCA subtypes (see Chapter 27) where the age of onset and clinical symptoms overlap in most of them and thus it is often difficult to distinguish among them based only on clinical or neuroimaging assessment. SCAs can be diagnosed via identifying the relevant genetic deficit which enables molecular diagnosis of at risk, a/presymptomatic, prenatal or pre-implantation of the different SCA subtypes and facilitates genetic counselling. The prevalence of individual SCA subtypes varies from region to region, because of the founder effects.

The scope of this chapter is to provide updated information on SCA3, also known as Machado-Joseph (MJD) disease, the most frequent SCA subtype worldwide and other rare spinocerebellar ataxias including dentatorubral-pallidoluysian atrophy (DRPLA), the X-linked fragile X tremor/ataxia syndrome (FXTAS) and the nonprogressive episodic forms of inherited ataxias (EAs). Furthermore, the therapeutic strategies that are currently being investigated to treat the ataxia and non-ataxia symptoms in SCAs are also described.

SPINOCEREBELLAR ATAXIA TYPE 3 (SCA3) [MIM #109150]

Clinical Features

SCA3, also known as Machado-Joseph disease (MJD) (from here we call it SCA3/MJD), is the most common dominantly inherited cerebellar ataxia worldwide and is characterised by cerebellar ataxia and pyramidal signs variably associated with a dystonic-rigid extrapyramidal syndrome or peripheral amyotrophy.[3-6] The age of onset of SCA3/MJD is variable, but most commonly in the second to fifth decade. In a large cohort of affected individuals from the Azores, the mean age of onset was 37 years. The variable range of symptoms at onset largely reflects differences in the length of a CAG repeat located within the *ATXN3* gene which is the molecular causative defect in SCA3/MJD. Presenting features include gait problems, speech difficulties, clumsiness and often, visual blurring and diplopia. Progressive ataxia, hyperreflexia, nystagmus and dysarthria may occur early in the disease. Upper motor neuron signs often become prominent early on. Ambulation becomes increasingly difficult, leading to the need for assistive devices (including wheelchair) ten to 15 years following onset. Saccadic eye movements become slow and ophthalmoparesis develops, resulting initially in up-gaze restriction. Disconjugate eye movements result in diplopia. Since squint angles commonly vary over the years, diplopia should not be treated by eye surgery. Most patients find substantial relief from prism glasses that compensate for the main angle of strabismus. At the same time, a number of other "brain stem" signs develop, including temporal and facial atrophy, characteristic action-induced perioral twitches, vestibular symptoms, tongue atrophy and fasciculations, dysphagia and poor ability to cough and clear secretions. Often, a staring appearance to the eyes is observed, but

neither this nor the perioral fasciculations are specific for SCA3/MJD. Other findings may include the following: (i) vocal cord paralysis, described in three of 19 persons with SCA3/MJD;[7] (ii) vestibular dysfunction;[8] (iii) autonomic problems, including bladder and thermoregulation disturbances;[9] (iv) a disabling sleep disturbance, rapid eye movement behaviour disorder,[10,11] and restless legs syndrome.[12,13] Some SCA3/MJD individuals have impaired executive and emotional functioning that is unrelated to ataxia severity. Evidence of peripheral polyneuropathy may appear with loss of distal sensation, ankle reflexes and sometimes other reflexes as well and with some degree of muscle wasting. Severe ataxia of limbs and gait (with either hyperreflexia or areflexia) associated with muscle wasting is observed. Sitting posture is compromised, with affected individuals assuming various tilted positions. Late in the disease course, individuals are wheelchair bound and have severe dysarthria, dysphagia, facial and temporal atrophy, poor cough, often dystonic posturing and ophthalmoparesis and occasionally blepharospasm. The disease progresses relentlessly; death from pulmonary complications and cachexia occurs from six to 29 years after onset.[14]

Occasionally, family members with mutations of the same allele may exhibit other clinical features such as a dystonic-rigid syndrome, a parkinsonian syndrome, or a combined syndrome of dystonia and peripheral neuropathy. Individuals with later adult onset often have a disorder that combines ataxia, generalized areflexia and muscle wasting. Based on this phenotypic variability, SCA3/MJD has been classified into several types.[15,16] In some individuals one type can evolve into another during the course of the disease: (i) Type I disease (13% of cases) is characterised by onset at a young age and prominent spasticity, rigidity and bradykinesia, often with little ataxia; (ii) Type II disease, the most common (57%), is characterised by ataxia and upper motor neuron signs. Spastic paraplegia can be part of the phenotype; (iii) Type III disease (30%) manifests at a later age with ataxia and peripheral polyneuropathy. A fourth disease type characterised by DOPA-responsive Parkinsonism and neuropathy has also been described. Other features are not restricted to a specific subtype including ophthalmoplegia (56% of patients), double vision (79%), faciolingual fasciculation (35%), dysphagia (75%), weight loss without loss of appetite (54%), incontinence (29%) and restless legs syndrome (45%). Cognitive disturbances in SCA3 are mild and rarely develop into relevant dementia.

Brain imaging studies reveal pontocerebellar atrophy. The most commonly observed abnormality is enlargement of the fourth ventricle, moderate shrinkage of cerebellar vermis and hemispheres as well as pontine atrophy. The degree of brain atrophy detectable by MRI varies greatly, consistent with the wide clinical variability observed. Abnormal linear high intensity of the globus pallidus interna on T2 and FLAIR images has also been observed.[17] Nerve conduction velocity studies often reveal evidence for involvement of the sensory nerves as well as the motor neurons.

Neuropathology has been extensively studied in SCA3/MJD.[18-22] Neuropathologic studies typically reveal that the cerebellum typically shows atrophy, but in some individuals Purkinje cells and inferior olivary neurons are relatively spared.[14] Neuronal loss is revealed in the pons, substantia nigra, thalamus, anterior horn cells and Clarke's column in the spinal cord, vestibular nucleus, many cranial motor nuclei and other precerebellar brain stem nuclei.[19,20,23]

Genetics of SCA3/MJD

SCA3/MJD is associated with CAG repeat expansions in the *ATXN3* gene. Normal alleles contain fewer than 44 CAG repeats. Overall, 93.5% of normal alleles have fewer than 31 CAG repeats. Mutable normal alleles have yet to be convincingly associated with a phenotype, but can manifest meiotic instability resulting in a pathologic expansion in a subsequent generation. Alleles with 45 to 51 CAG repeats have reduced or incomplete penetrance and individuals with a reduced penetrance allele may or may not manifest the disorder during their lifetime. Abnormal expanded alleles with full penetrance contain 52 to 86 CAG repeats and are associated with the SCA3/MJD phenotype. The CAG repeat does not completely explain the age of onset (correlation ranging from −0,67 to −0,87) suggesting that additional genetic and nongenetic factors account for this variability. Repeats of more than 73 CAG motifs are frequently associated with a pyramidal phenotype whereas patients with less than 73 repeats more likely develop neuropathy.

DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY (DRPLA) [MIM #125370]

Clinical Features

Dentatorubral-pallidoluysian atrophy (DRPLA), also known as Naito-Oyanagi disease, consists of progressive ataxia, choreoathetosis and dementia or character changes in adults and ataxia, myoclonus, epilepsy and progressive intellectual deterioration in children.[24,25] The age of onset is from one to 62 years with a mean age of onset of 30 years. The clinical presentation varies depending on the age of onset. The cardinal features in adults are ataxia, choreoathetosis and dementia. Cardinal features in children are progressive intellectual deterioration, behavioural changes, myoclonus and epilepsy. Atrophic changes in the cerebellum and brain stem, in particular the pontine tegmentum, are the typical MRI findings of DRPLA. Quantitative analyses revealed that both the age at MRI and the size of the expanded CAG repeat correlate with the atrophic changes. Diffuse high-intensity areas deep in the white matter are often observed on T2-weighted MRI in individuals with adult-onset DRPLA of long duration.[26] The major neuropathologic changes detected are relatively simple and consist of combined degeneration of the dentatorubral and pallidoluysian systems of the central nervous system.

Genetics of DRPLA

The diagnosis of DRPLA rests on positive family history, characteristic clinical findings and the detection of an expansion of a CAG trinucleotide/polyglutamine tract in the *ATN1* (*DRPLA*) gene. Normal alleles range from 6 to 35 CAG repeats. Mutable normal alleles contain 20-35 CAG repeats and are found in Caucasian populations. They are not associated with symptoms, but are unstable and can expand on transmission resulting in occurrence of symptoms in the next generation, albeit this is a very rare event. The CAG repeat length in individuals with DRPLA ranges from 48 to 93.

FRAGILE X TREMOR AND ATAXIA SYNDROME (FXTAS) (MIM #300623)

Clinical Features

FXTAS is characterised by late-onset progressive cerebellar ataxia and intention tremor.[27,28] Other neurologic findings include short-term memory loss, executive function deficits, cognitive decline, progressive dysarthria, dementia, parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, spastic paraparesis and autonomic dysfunction. A definite diagnosis of FXTAS requires the presence of a premutation in the *FMR1* gene and white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem, the major neuroradiologic sign, with either intention tremor or gait ataxia which are the two major clinical signs. Other minor clinical criteria include parkinsonism, moderate to severe working memory deficits, or executive cognitive function deficits. Neuroradiologic signs including decreased cerebellar volume, increased ventricular volume and increased white matter hyper-density, all correlating with the premutation CGG repeat length.[29] Another study correlated the CGG repeat length with the peripheral nerve conduction velocities in motor and sensory nerves.[30] The penetrance varies and is age related, ranging from 5-10% in female carriers to 17-75% in male carriers of 50 years and over.[31] Tremor usually precedes ataxia onset. Life expectancy after onset of symptoms ranges from five to 25 years.

Genetics of FXTAS

The diagnosis relies on the detection of the CGG expansion within the *FMR1* gene ranging from 59 to approximately 200 repeats. Alleles of this size are not associated with mental retardation, but do convey increased risk for FXTAS. Women with alleles within this range are at risk of having offspring affected with fragile X syndrome. Because of the high prevalence of the *FMR1* premutation among individuals presenting late-onset ataxia (up to 3%) and the overlap with the clinical symptoms, FXTAS should be included onto any spinocerebellar ataxia genetic screening protocol. Early diagnosis of FXTAS patients benefits them and their relatives who may be thus advised for FRAXA.

EPISODIC ATAXIA TYPE 1 (EA1) (MIM #160120)

Clinical Features

The physiopathology and molecular genetics of known episodic ataxia syndromes have been reviewed elsewhere.[32,33] Episodic ataxia Type 1 (EA1) is a potassium channelopathy characterised by constant myokymia and dramatic episodes of spastic contractions of the skeletal muscles of the head, arms and legs with loss of both motor coordination and balance. During attacks some individuals may experience vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, clumsiness, stiffening of the body, dysarthric speech and difficulty in breathing. Onset is in childhood or early adolescence. Other findings include delayed motor development, cognitive disability, choreoathetosis and carpal spasm.

Genetics of EA1

Diagnosis is based on clinical findings and molecular genetic testing of *KCNA1*, the only gene known to be associated with EA1. All affected individuals described so far are heterozygous for *KCNA1* mutations at amino acid residues highly conserved among the voltage-dependent K^+ channel superfamily. The mutation detection frequency using sequence analysis is approximately 90%. A novel missense mutation (F414C) has been identified in an Italian EA1 family.[34] Mutations in the *KCNA1* gene have also been identified in families with myokymia without ataxia episodes.[35]

EPISODIC ATAXIA TYPE 2 (EA2) [MIM #108500]

Clinical Features

Episodic ataxia Type 2 (EA2), the most common form of episodic ataxia, is characterised by paroxysmal attacks of ataxia, vertigo and nausea typically lasting minutes to days in duration.[36,37] Stress, exertion, caffeine and alcohol may trigger attacks that can be variably associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia and headache. In fact, EA2 is allelic with two other conditions: familial hemiplegic migraine Type 1 (FHM1) characterised by complicated migraine with hemiplegia, interictal nystagmus and progressive ataxia and spinocerebellar ataxia Type 6 (SCA6) characterised by slowly progressive ataxia of late onset, some with episodic features.[38,39] Approximately 50% of individuals with EA2 have migraine headaches. Onset is typically in childhood or early adolescence. MRI demonstrates atrophy of the cerebellar vermis. The diagnosis of EA2 is most commonly made on clinical grounds.

Genetics of EA2

EA2 is inherited as an autosomal dominant manner and more than 30 different mutations have been identified causing the disease in the *CACNA1A* gene, encoding for a P/Q type voltage-gated Ca^{2+} channel alpha subunit, abundantly expressed in the cerebellum and the neuromuscular junction.[40] The majority are nonsense mutations resulting in a truncated protein product. However, a number of nontruncating mutations, such as intronic, causing exon skipping and abnormal splicing and exonic deletions have also been reported.[41] Estimated penetrance is 80-90%.

EPISODIC ATAXIA TYPE 3 (EA3) [MIM #606554]

Clinical Features

Episodic ataxia Type 3 (EA3) was described in a large Canadian Mennonite family with episodic vertigo, tinnitus and ataxia without baseline deficits.[42] The disease manifests in early adulthood. In some individuals, slowly progressive cerebellar ataxia occurs.

Genetics of EA3

A candidate region on chromosome 1q42 has been identified.[43]

EPISODIC ATAXIA TYPE 4 (EA4) [MIM #606552]

Clinical Features

Episodic ataxia Type 4 (EA4), also known as periodic vestibulocerebellar ataxia (PATX), was described in two kindreds from North Carolina, USA, with late onset episodic vertigo and ataxia as well as interictal nystagmus not responsive to acetazolamide.[44,45] The disorder is characterised by defective smooth pursuit, gaze-evoked nystagmus, ataxia and vertigo. The age of onset ranged from the third to the sixth decade.

Genetics of EA4

Linkage analysis has ruled out the EA1 and EA2 loci, but no chromosomal locus has not yet been identified.[46]

EPISODIC ATAXIA TYPE 5 (EA5) [MIM #601949]

Clinical Features

The phenotype of Episodic ataxia Type 5 (EA5) is characterised by recurrent episodes of vertigo and ataxia that can last for several hours. Interictal examination shows spontaneous down-beat and gaze-evoked nystagmus and mild dysarthria and truncal ataxia. Acetazolamide can prevent the attacks.

Genetics of EA5

EA5 results from a mutation in the *CACNB4* gene, which encodes an auxiliary beta-4 isoform of the regulatory beta subunit of voltage-activated Ca^{2+} channels. A c.311G>T (p.Cys104Phe) mutation has been described in a French-Canadian family.[47] EA5 is allelic with juvenile myoclonic epilepsy (JME) and the semiology of seizures in EA5 is similar to JME.

EPISODIC ATAXIA TYPE 6 (EA6) [MIM #612656]

Clinical Features

Episodic Ataxia Type 6 (EA6) was initially observed in a child with episodic ataxia, attacks of hemiplegia and migraine in the setting of fever and epilepsy.[48] The disease is characterised by attacks of ataxia precipitated by fever, subclinical seizures, slurred speech followed by headache and bouts of arm jerking with concomitant confusion and

alternating hemiplegia.[49] MRI showed cerebellar atrophy and neurologic examination showed mild interictal truncal ataxia.

Genetics of EA6

EA6 results from mutations in the *SLC1A3* gene encoding the excitatory amino acid transporter 1 (EAAT1).[48,49] In cells expressing mutated proteins, glutamate uptake is reduced, suggesting that glutamate transporter dysfunction underlies the disease. The penetrance is incomplete.

EPISODIC ATAXIA TYPE 7 (EA7) [MIM# 611907]

Clinical Features

Episodic ataxia Type 7 (EA7) has been described in a four-generation family whose affected individuals showed episodic ataxia before age 20 years.[50] The disease is characterised by attacks associated with weakness, vertigo and dysarthria lasting hours to days. Attacks may also be brought about by exercise and/or excitement.

Genetics of EA7

A candidate region on chromosome 19q13, termed the EA7 locus, has been identified.[50]

AUTOSOMAL DOMINANT SPASTIC ATAXIA (ADSA) [MIM #108600]

Clinical Features

Affected individuals with autosomal dominant spastic ataxia (ADSA) initially show progressive leg spasticity of variable degree followed by ataxia in the form of involuntary head jerk, dysarthria, dysphagia and ocular movement abnormalities consisting of slow saccades, impaired vertical gaze and in some cases lid retraction.[51] The severity of the phenotype varies greatly and the age at onset appears from early childhood to early twenties, although most presented with onset of symptoms at age 10 to 20 years. Neuropathologic findings include degeneration of the corticospinal tracts and posterior columns. The life span and cognition of patients are not affected.

Genetics of ADSA

Linkage studies identified a locus on 12p13, termed SAX1.[51]

OTHER AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIAS

Cerebellar ataxia with deafness, narcolepsy and optic atrophy was described in a Swedish family.[52] CT and MRI studies revealed supratentorial atrophy, more pronounced

than infratentorial atrophy, pronounced dilatation of the third ventricle, low T2 signal intensity in the basal ganglia, loss of cerebral cortex-white matter differentiation and periventricular high-signal rims.[53] The gene has been linked to 6p21-p23.[52]

In four individuals in one family presenting ataxia, cerebellar atrophy, mental retardation and possible attention deficit/hyperactivity disorder (ADHD) described; associated the disease with a heterozygous 2-bp deletion mutation in exon 4 in *SCAN8A*, a gene encoding a sodium channel on 12q13 (MIM #600702).[54]

Genis et al[55] described a Spanish family with individuals presenting a late-onset cerebellar ataxia with thermoanalgesia and deep sensory loss. Unlike in SCA4, reflexes were preserved. MRI revealed cerebellar, medullar and spinal cord atrophy. Neurophysiological studies showed absence or marked reduction of the sensory nerve action potentials and somatosensory evoked potentials in lower and upper limbs but preservation of the soleus H reflex. The neuropathological study revealed severe loss of Purkinje cells and dentate neurons, extensive cell loss in the inferior olive and lower cranial nerve nuclei and demyelination of the posterior columns and spinocerebellar tracts. The genetic studies ruled out linkage of the disease in this SCA subtype to the SCA4 locus on chromosome 16 and the remaining previously identified SCA loci, therefore evidencing a new genetic identity for this ataxia subtype associated with thermoanalgesia as well as deep sensory loss with retained reflexes.

THERAPEUTIC STRATEGIES IN THE SPINOCEREBELLAR ATAXIAS

There are currently no known effective pharmacologic treatments to reverse or even substantially reduce motor disability caused by cerebellar degeneration in most of the SCAs or related cerebellar disorders, although some benefits on ataxic and non-ataxic symptoms have been reported in a few therapeutic clinical trials.[1,56-58] Some benefits regarding ataxic symptoms have been reported with acetazolamide and gabapentin in SCA6,[59] 5-hydroxytryptophan, clonazepam, buspirone or tansodpirone, sulfamethoxazole/trimethoprim or lamotrigine in SCA3, NMDA modulators or antagonists and deep brain stimulation in SCA2 with tremor. Amantadine, dopaminergic and anticholinergics drugs have been used to alleviate tremor, bradykinesia, or dystonia in SCA2 and SCA3.[60-62] Varenicline is currently being tested in SCA3 and FXTAS. Restless legs and periodic leg movements in sleep usually respond to dopaminergic treatment or tilidine.[12] Spasticity in SCAs are effectively treated with baclofen, tizanadine, or mimentine when combined with dopaminergic treatment. In selected cases where other treatments have failed, botulinum toxin has been successfully used to treat dystonia and spasticity in SCA3, although caution and small dosage is recommended since unusually severe and long lasting muscular atrophy occurs in some SCA3 patients with this treatment due to subclinical involvement of motor neurons in the anterior horn in the degenerative process. Intention tremor has been ameliorated with benzodiazepines, β-blockers, or chronic thalamic stimulation. Muscle cramps, which are often present at the onset of the condition in SCAs 2, 3, 7 and DRPLA, are alleviated with magnesium, chinine, or mexiletine.[63]

In spite of the lack of effectiveness in the treatment of ataxia symptoms in most SCAs, treatment in some spinocerebellar ataxias has proven successful. Coenzyme Q10 administration was shown to be effective in treating ataxia symptoms in patients with CoQ10 deficiency.[64] Furthermore, most autoimmune cerebellar ataxias, such as anti-glutamic acid decarboxylase (GAD)-antibody-positive cerebellar ataxia and gluten ataxia, have

proven to be treatable.[65,66] In the remaining ataxias, physiotherapy is currently being used as an alternative effective treatment. Ataxia improves with daily autonomous training of gait and stance in combination with physiotherapy. Other neurological symptoms such as dysarthria and dysphagia warrant logopedic treatment to maintain the ability to communicate and to prevent pneumonia from aspiration. Valproate and piracetam have been used to treat myoclonus and/or dementia/cognitive decline.

A clinical trial with the aim of assessing the safety, tolerability and the effects of lithium in SCA1 has recently been completed and patients are being recruited to assess lithium carbonate therapy in SCA2 and SCA3. Albeit there are clinical benefits of lithium treatment; common side effects include muscle tremors, twitching, ataxia and hypothyroidism. Long term use of lithium has been linked to hyperparathyroidism http://en.wikipedia.org/wiki/Lithium—cite_note-49, hypercalcaemia (bone loss), hypertension, kidney damage, nephrogenic diabetes insipidus (polyuria and polydipsia), seizures and weight gain. Although lithium or a bioactive analogue may be a promising drug that can potentially benefit ataxia patients, clinical and biological responses to a range of doses throughout an extended time period need to be carefully evaluated and monitored in any forthcoming clinical trial. Other ongoing clinical trials in SCAs include memantine in fragile X tremor and ataxia syndrome (FXTAS).

A few innovative approaches at the preclinical and in some cases at the clinical level include the use of RNA interference (RNAi) aiming to inhibit the expression of mutated polyglutamine-proteins in those SCAs, caused by expanded polyglutamine mutations. Prevention of protein misfolding and aggregation by over-expression of chaperones by pharmacological treatments and the regulation of gene expression by application of histone deacetylase inhibitors are giving promising results in preclinical trials and are currently being tested in some ataxia patients. In SCA1, intracerebellar injection of vectors, expressing short hairpin RNAs, profoundly improves motor coordination, restores cerebellar morphology and prevent the characteristic ataxin-1 inclusions in Purkinje cells in transgenic mice.[67] While these results show that RNAi therapy improves cellular and behavioural characteristics in preclinical trials, its application in patients to protect or even reverse disease phenotypes shall be delayed until proper toxicity tests are assessed.

Pointing to a different target, molecular chaperones provide a first line of defence against misfolded, aggregation-prone proteins. Many studies have analysed the effects of chaperone over-expression on inclusion body formation and toxicity of pathogenic polyQ fragments in cell culture and it is clear that over-expression of molecular chaperones might prove beneficial for the treatment of neurodegenerative diseases.[68] They prevent inappropriate interactions within and between nonnative polypeptides, enhance the efficiency of de novo protein folding and promote the refolding of proteins that have become misfolded as a result of the mutations and cellular stress.[69] Chemical and molecular chaperones might also prevent toxicity by blocking inappropriate protein interactions, by facilitating disease protein degradation or sequestration, or by blocking downstream signalling events leading to neuronal dysfunction and apoptosis. Congo Red, thioflavine S, chrysamine G and Direct Fast have proven effective in suppressing aggregation in vitro and in vivo,[70,71] albeit their specific efficacy in vivo is limited by their variable abilities to cross the blood-brain barrier and proper pharmacologic analogues may need to be developed for further clinical considerations.

Several low molecular mass chemical chaperones, such as the organic solvent dimethylsulfoxide (DMSO) and the cellular osmolytes glycerol, trimethylamine n-oxide and trehalose, appear effective in preventing cell death triggered by mutant ataxin 3 by

increasing its stability in their native conformation.[72] Trehalose was identified in an in vitro screen for inhibitors of polyQ aggregation and its administration reduces brain atrophy, improves motor dysfunction and extends the lifespan of mice, mimicking the polyglutamine disorder Huntington's disease.[73] In vitro experiments suggest that the beneficial effects of trehalose result from its ability to bind and stabilize polyglutamine-containing proteins. More recently, a new generation of small chemical compounds, that directly target polyQ aggregation without significant cytotoxicity, have been identified in high-throughput screens using cell-free assays or by targeting cellular pathways.[74,75] These compounds inhibit polyQ aggregation in cultured cells and intact neurons and can rescue polyQ-mediated neurodegeneration in vivo.

By a different mechanism, a small molecule that acts as a co-inducer of the heat shock response by prolonging the activity of heat-shock transcription factor HSF1, arimoclomol, significantly improves behavioural phenotypes, prevents neuronal loss, extends survival rates and delays disease progression in a mouse model of neurodegeneration.[76] Similarly, activation of heat-shock responses with geldanamycin inhibits aggregation and prevents cell death.[77] This suggests that pharmacological activation of the heat shock response may be an effective therapeutic approach to treat neurodegenerative diseases. However, excessive up-regulation of chaperones might lead to undesirable side effects, such as alterations in cell cycle regulation and cancer.[78] Therefore, a delicate balance of chaperones will likely be required for a beneficial neuroprotective effect. For instance, chemical or molecular chaperones, used in combination with a pharmacological agent that up-regulates the synthesis of molecular chaperones, might be a valid therapeutic approach for treating spinocerebellar ataxias caused by polyglutamine expansions. Aggregate formation has also been successfully targeted with inhibitors of transglutaminase, such as cystamine, which reduces apoptotic cell death and alleviates disease symptoms by the expanded polyglutamine.[79,80]

Compounds targeting mitochondrial function such as coenzyme Q10,[81] creatine[82] and taurousodeoxycholic acid (TUDCA);[83] or autophagy, such as the mTor inhibitor, rapamycin and various analogous,[84] have proven effective at reducing cellular toxicity in animal models and are currently being tested in clinical trials in a few ataxia subtypes.[85] Caspase activation, which usually precedes neuronal cell death, have been targeted by inhibiting their expression, recruitment and consequent activation onto "apoptosome-like structures" or by enzymatic inhibitors all of which include minocycline, cystamine, CrmA, FADD DN and zVAD-fmk, respectively.[86] In general, the inhibitors of the different caspases have been shown to decrease microglia activation, prevent disease progression, delay onset of symptoms, enhance inclusion clearance and extend survival rates in several mouse and cell models of neurodegeneration.[87-89]

Other agents which promote the clearance of mutant proteins in the CNS or which are Ca^{2+} signalling blockers and stabilizers, such as specific inhibitors of the NR2B-subunit of N-methyl-D-aspartate glutamate receptors, blockers/antagonists of metabotropic glutamate receptor mGluR5 and inositol 1,4,5-trisphosphate receptor InsP3R1 such as remacemide; intracellular Ca^{2+} stabilizers such as dantrolene; dopamine stabilizers such as mermaid-ACR-16; dopamine depleters and agents inducing anti-excitotoxic effects such as riluzole; or agents which alleviate cognitive components such as horizon-dimebon; they all appear to be at least partially beneficial for the treatment of some neurological symptoms in spinocerebellar ataxias.[90-92] A recent clinical trial with riluzole showed a reduction of the ICARS score in patients with a wide range of cerebellar disorders.[93] Neuroprotective drugs like olesoxime have proven to increase microtubule dynamics,

re-establish neuritic outgrowth, improve myelination and prevent apoptotic factor release and oxidative stress.[94] Inhibition of potassium channels with 3,4-diaminopyridine has proven efficient in normalising motor behaviours in young SCA1 mice and in restoring normal purkinje cell volume and dendrite spine density and the molecular layer thickness in older SCA1 mice. Aminopyridines, such as fampridine and diaminopyridine, increase PC excitability and are also efficient for treating down-beat nystagmus.[95-97]

The role that some ataxin proteins play in transcription and, more importantly, the effects mediated by some of their cotranscriptional regulators in the suppression of cytotoxicity are being used as targets to modulate the pathological effects of mutant ataxins, opening the path for new therapeutic strategies for treating some of the SCAs. Recent progress in histone deacetylase (HDAC) research has made possible the development of inhibitors of specific HDAC family proteins and these compounds could prove effective candidates for the treatment of spinocerebellar ataxias.[98,99] Neuroprotective and neurorestoration strategies, addressing specific bioenergetic defects, might hold particular promise in the treatment of spinocerebellar conditions. Drugs, such as rasagiline, have been shown efficient in protecting neuronal cells against apoptosis through induction of the pro-survival Bcl-2 protein and neurotrophic factors.[100] Recent alterations of the insulin growth factor (IGF-1) pathway have been reported to be implicated in both SCA1 and SCA7,[101] suggesting that in vivo neuroprotection exerted by IGF-1 through the PP2-regulated PI3K/Akt signalling pathway, could potentially be used to halt cerebellar neurodegeneration.[102,103]

Gene therapy and stem cell and grafting approaches are being considered for treating spinocerebellar neurodegenerations.[104] Delivery of proteins or compounds by viral vectors represents one such gene therapeutic approach. Neural cell replacement therapies are based on the idea that neurological function lost during neurodegeneration could be improved by introducing new cells that can form appropriate connections and replace the function of lost neurons. This strategy, although potentially effective, is still in early experimental stages. Since neurogenesis does occur in the adult nervous system, another approach is based on the stimulation of endogenous stem cells in the brain or spinal cord to generate new neurons. Studies to understand the molecular determinants and cues to stimulate endogenous stem cells are underway.[105] Although promising, we are only starting to learn the potential and challenges of these emerging therapies, especially their efficacy in treating human neurodegeneration.

Treatments for Episodic Ataxias

Several different drugs are reported to improve symptoms in EA1 and EA2, but so far there have been no controlled studies documenting or comparing efficacy of these different drugs. Carbamazepine, valproic acid and acetazolamide have been effective for EA1[35,106] and acetazolamide (ACTZ),[107] flunarizine,[108] 4-aminopyridine[95,109] and chlorzoxazone (CHZ)[110] have been effective in EA2 cases. The response to acetazolamide is often dramatic in EA2.[36,107] Acetazolamide, a carbonic-anhydrase (CA) inhibitor, may reduce the frequency and severity of the attacks in some but not all affected individuals with episodic ataxias. ACTZ should not be prescribed to individuals with liver, renal, or adrenal insufficiency. Chronic treatment with ACTZ may result in side effects including paresthesias, rash and formation of renal calculi.

Antiepileptic drugs (AEDs) such as carbamazepine may significantly reduce the frequency of the attacks in responsive individuals; however, the response is heterogeneous

as some individuals are particularly resistant to drugs.[35] Antiepileptic treatment with diphenylhydantoin results in reasonable control of seizures in some individuals. In particular, phenytoin treatment may improve muscle stiffness and motor performance.[111] Nevertheless, phenytoin should be used with caution in young individuals, as it may cause permanent cerebellar dysfunction and atrophy.[112] Anticonvulsant drugs such as sulthiame may reduce the attack rates. During this treatment, abortive attacks were still noticed lasting a few seconds and troublesome side effects were paresthesias and intermittent carpal spasm.

The potassium channel blocker 4-aminopyridine was found to be effective in stopping EA2 attacks in patients.[96,109] Furthermore, 3,4-diaminopyridine was demonstrated in a placebo-controlled study to improve down-beat nystagmus, which is often observed in patients with EA2.[113]

CONCLUSION

The spinocerebellar ataxias are devastating neurological diseases for which, currently, there are no effective and selective pharmacological treatments available that reverse or even substantially reduce motor disability caused by the cerebellar neurodegeneration. Thus, physical therapy is currently the sole form of intervention that can improve walking ataxia in affected individuals. Indeed, a recent study where patients with variable forms of cerebellar degenerative disease were subjected to "intensive coordinative training" showed improvement in the ataxia and balance clinical scales, indicating that rehabilitation may be of real benefit to ataxic individuals.[114] Similarly, in a specific rehabilitation program including foot sensory stimulation and balance and gait training, 24 ataxic patients, with clinically defined sensory ataxia, improved their balance with better results in dynamic conditions.[115] These studies are of particular interest because they showed how individuals with cerebellar damage can learn to improve their movements, recover the control of their balance and proprioceptive contributions enabling them to achieve personally meaningful goals in everyday life after proper training. Until effective and selective pharmacological treatment is available for ataxia patients, which should be forthcoming in the near future, physical and sensory rehabilitation are meanwhile revealing effective approaches for improving the patient's quality of life. Taken together, all the data up-to date highlights that treatment for ataxia patients is no longer an utopia, but it is possible in a foreseeable future.

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