Twenty-five years since the identification of the first SCA gene: history, clinical features and perspectives for SCA1

Vinte e cinco anos desde a identificação do primeiro gene das SCAs: história, aspectos clínicos e perspectivas para a SCA1

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ABSTRACT

Spinocerebellar ataxias (SCA) are a clinically and genetically heterogeneous group of monogenic diseases that share ataxia and autosomal dominant inheritance as the core features. An important proportion of SCAs are caused by CAG trinucleotide repeat expansions in the coding region of different genes. In addition to genetic heterogeneity, clinical features transcend motor symptoms, including cognitive, electrophysiological and imaging aspects. Despite all the progress in the past 25 years, the mechanisms that determine how neuronal death is mediated by these unstable expansions are still unclear. The aim of this article is to review, from an historical point of view, the first CAG-related ataxia to be genetically described: SCA 1.

Keywords: Spinocerebellar ataxias; ataxin 1; spinocerebellar degenerations.

RESUMO

As ataxias espinocerebelares (SCA) são um grupo clínico e geneticamente heterogêneo de doenças monogênicas que compartilham ataxia e herança autossômica dominante como características principais. Uma proporção importante de SCAs é causada por expansões de repetição de trinucleotídeos CAG na região de codificação de diferentes genes. Além da heterogeneidade genética, os aspectos clínicos transcendem os sintomas motores, incluindo aspectos cognitivos, eletrofisiológicos e de imagem. Apesar de todo o progresso feito nos últimos 25 anos, os mecanismos que determinam como se dá a morte neuronal mediada por essas expansões instáveis ainda não estão claros. O objetivo deste artigo é revisar, de um ponto de vista histórico, a primeira ataxia geneticamente relacionada com o CAG descrita: SCA 1.

Palavras-chave: ataxias espinocerebelares; ataxina 1; degenerações espinocerebelares.

EARLY STUDIES

In 1863, the German pathologist Nikolaus Friedreich described a new spinal disease, which turned out to be the first description of a hereditary ataxia[1]. The disease was characterized by cerebellar ataxia, dysarthria and deep areflexia, generally with an early age of onset and presenting an autosomal recessive pattern of inheritance[1]. Over 30 years later, Pierre Marie reported on a group of patients presenting with hereditary ataxia, but with late disease onset, mostly presenting with increased tendon reflexes and occasionally with an autosomal dominant pattern of inheritance[2]. It was later pointed out that Marie's cohort was both clinically and pathologically heterogeneous and several classifications throughout the 20th century failed to outline properly the full clinical and pathological spectrum of the autosomal dominant cerebellar ataxias (ADCA)[3,4]. The term spinocerebellar ataxia (SCA) remained from those early attempts to classify the ADCA, and nowadays they are used as synonyms. Other terms previously used to describe ADCA were Marie's Ataxia, olivopontocerebellar atrophy and cerebello-olivary atrophy[2,4,5,6,7].

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HISTORY OF SCA1 GENETICS

In the first half of the 20th century, many researchers published papers on small families segregating ADCA, raising the most diverse hypotheses on the genetic basis of the disease, usually with conflicting results[5]. Nonetheless, in the late 1940s, a North American group started following a large family of patients (n = 342) in which 45 individuals presented with the disease. At that time, the authors attempted to determine the genetic basis of the disease using linkage analyses, but they failed to uncover the responsible gene/mutation[8].

Despite the initial disappointing results, the investigators kept following these kindred. From the 1970s to the 1980s, strong evidence came out supporting that the causative gene of at least that form of ADCA was related to the HLA human complex. Further studies mapped the disease locus to the short arm of chromosome 6[9]. Finally, 100 years after Marie's original publication, in 1993, a collaborative study led by Zoghbi *et al.* was published, describing an unstable CAG trinucleotide repeat expansion at the coding region of the implicated gene as the first causative mutation of ADCA[10]. The normal SCA1 allele contained 6-38 CAG repeats interrupted by the CAT trinucleotide, in contrast with mutation carriers that had 39-44 continuous CAG repeats (Table 1). These authors also pointed out that the size of the repeat inversely correlated with the age of onset of the symptoms (anticipation phenomenon)[10,11,12].

Other researchers such as Harry T. Orr and Sandro Banfi played key roles in the description and characterization of the *ATXN1* gene[10,13]. The disease locus was named *ATXN1* and those presenting with the mutation would thereafter be definitively classified as having SCA type 1[4]. Curiously, the gene related to Friedreich's ataxia was only described three years later. Hence, SCA1 was indeed the first hereditary ataxia to have its genetic basis elucidated[3,10,13].

The *ATXN1* gene encodes a protein called ataxin 1, which has nuclear location inside neurons, but cytoplasmic location in other peripheral tissues. Mutation carriers produce an abnormal form of ataxin 1 with an excessive number of consecutive glutamine residues. Less than five years after the gene description, experimental studies with transgenic mice showed that the pathogenesis by which the mutation causes disease is a toxic gain of function[4]. Zoghbi's group then revealed the specific role of protein misfolding in the pathogenesis of SCA1, a finding that has proved relevant to

other polyglutamine disorders[14]. After this, the group started looking at potential pharmacological interventions in animal models[15].

DEMOGRAPHIC DATA AND PHENOTYPIC CHARACTERIZATION

The SCAs are rare diseases with prevalence rates ranging from 1-4 per 100,000 and SCA1 accounts for between 3% and 16% of all autosomal dominant SCAs[16]. The search for relative frequencies of SCAs in Brazilian cohorts have shown that SCA1 represents 4.2% of all SCAs; generally, it is the 4th or 5th most frequent SCA, after SCA3, SCA2 and SCA7[17,18,19,20]. The first descriptions of Brazilian patients with SCA1 are relatively recent. All patients attending our reference center in southeastern Brazil have descended from Italian immigrants[21]. The relative frequencies of SCA1 patients in different populations are shown in Table 2[22,23,24].

Clinical aspects

The up-to-date clinical description of SCA1 is a late-onset cerebellar syndrome, with ocular movement disturbances, in particular, hypermetric saccades, pyramidal or extrapyramidal signs and peripheral neuropathy[3,4]. A phenomenon of progressive worsening of the phenotype across generations has been observed previously[4]. The first symptoms often include gait disturbances, later followed by diplopia, dysarthric speech, uncoordinated handwriting and episodic vertigo. Patients may less commonly present with vocal cord abductor paralysis or psychosis[3]. The average age of onset of SCA1 is between the third and fourth decades, but there is clear variability even within families. Survival from disease onset is around 15 years, but again there is remarkable variability (range 10 to 28 years)[3,5].

In a recent series of Brazilian patients[17], the most frequent clinical findings were, in descending order: ataxia (100%), pyramidal findings (89%), dysarthria and/or dysphagia (89%), alterations in ocular movements (44%), nystagmus (33%), rigidity (33%), palpebral retraction (22%), sensory loss (11%), dystonic movements (11%), seizures (11%). Absent reflexes, amyotrophy, visual loss, tremor and cognitive decline were not found.

Disease progression has recently been assessed in a large multicentric European study[25]. Authors found that SCA1 progresses faster than other types of SCAs, with a mean annual

Table 1. *ATXN1* allele ranges.

Allele types	(CAG) repeat length	Penetrance
Normal	6–38; 39–44 CAT interrupted	None
Intermediate	44 CAT interrupted*	Partial
Expanded	39–44 CAGs uninterrupted; 45–91	Full

*A woman with 44 CAG repeats with CAT repeat interruptions had an affected father but was herself asymptomatic at age 66 years[9].

Table 2. Relative frequency of SCA1 in different populations.

Author / Year	Country	Cohort size (n)	Relative frequency
Filla *et al* 2000[22]	Italy	116 families	24%
Illarioshkin *et al* 1996[23]	Russia	15 families	33%
Krysa *et al* 2016[24]	Poland	203 families	68%
de Castilhos *et al* 2014[17]	Brazil	359 families	4.2%

progression in ataxia score of 2.11 (Scale for the Assessment and Rating of Ataxia). Within the SCA1 group, patients who had a shorter duration of follow up, older age at initial evaluation and longer CAG repeats progressed at faster rates. It remains to be investigated whether such rates of progression also take place in SCA1 patients coming from other regions. Although ataxia is the main and most disabling symptom in most patients with SCA1, many have additional non-ataxia symptoms, which have a great impact on the quality of life of these patients.

Cognitive impairment

It is known that the cerebellum contributes to cognitive tasks, including executive and language functions[26]. In particular, patients with isolated acute or chronic focal cerebellar lesions show frontal-like and parietal-like symptoms; this clinical picture is referred to as the cerebellar cognitive affective syndrome[26]. The neuroanatomical basis for this syndrome is not fully clear, but at least two hypotheses have been raised: it may stem either from the interruption, as in a disconnection syndrome, or from a dysfunctional contribution of the cerebellum in the neocerebellar–neocortical reverberation network. This syndrome is characterized by impairments in executive functions (deficiency in planning, set-shifting, abstract reasoning, working memory, verbal fluency), language disorders, disturbances in spatial cognition, and personality changes[26].

Several studies have reported the neuropsychological features of patients with SCA1, and most show impaired executive function, attention, visuospatial perception, verbal fluency, immediate and delayed memory[27]. Fancellu et al. reported that patients had significant deficits compared to controls, mainly in executive functions (phonemic and semantic fluencies, attentional matrices) and the dissociation in the progression of motor disability and cognitive impairments, suggesting that motor and cognitive functions might be related to different progression rates in SCA1[28].

Ma et al. reported that SCA1 causes mild impairment in executive function, temporal orientation and logical thinking. The cognitive deficits were correlated with clinical severity of ataxia symptoms, but not age, age of onset, years of education and disease duration[29]. Klinke et al. showed that asymptomatic SCA1 carriers have normal cognitive test scores, thus suggesting that cognitive dysfunction does not seem to precede cerebellar ataxia[30]. While some phenotypic traits, such as age of onset, progression rate and disease severity are directly related to genotype (CAG expansion length), it is unclear whether the occurrence and severity of cognitive impairment also depend on it. Moriarty et al. reported impairments in executive functions, speed, attention, visual memory and theory of mind in SCA1 patients. These authors also found SCA1 patients to have the fastest cognitive decline when compared with the other SCA patients, a finding in line with the motor deterioration pattern in SCAs[30].

The pattern of alterations in executive and visuospatial functions described in SCA1[27] suggests a frontoparietal dysfunction that could be caused by an alteration in the fronto-ponto-cerebello-thalamo-cortical circuits[26]. A direct dysfunction of frontoparietal areas could be hypothesized; however, impairments in these cortical areas have not yet been proven in SCA1. In addition, the involvement of subcortical structures, such as the basal ganglia, could play a role in the development of cognitive dysfunction[31].

Depression

Patients with cerebellar degenerative diseases have greater apathy, depression, anxiety and personality changes than normal individuals, especially when the cerebellar degeneration is associated with basal ganglia involvement[26,27]. It is hypothesized that these symptoms could be caused by a dysfunction in the connections between the prefrontal cortex (dorsolateral, orbitomedial, dorsomedial) and the basal ganglia[32]. Fancellu et al. reported that SCA1 patients had significantly higher depression scores and apathy than controls[28]. Klinke et al. showed a mildly depressed mood (*Beck Depressive Inventory* score 11–18) in 50% of SCA1 patients, though no patient showed scores indicating a severely depressed mood (score ≥18)[27]. McMurtray et al. identified depressive and memory symptoms as heralding features of SCA1 in 25% and 42% of the patients, respectively[33].

Sleep disorders and fatigue

Hypersomnolence in SCA1 patients can interfere with daytime functioning and periodic limb movements can be a cause of sleep fragmentation in these patients[34]. Obstructive sleep apnea can coexist with SCA1, possibly as a manifestation of pharyngeal dilator muscle incoordination in response to impending airway collapse[34]. According to Abele et al., restless legs syndrome is significantly more frequent in patients with SCA1 than in the general population and is present in 28% of patients[35]. Fatigue is a major manifestation in SCA1 patients and related to disease duration, depression and probably disease severity[36].

Electrophysiological features

Multisystem involvement in SCA1 is common and electrophysiology is a potent tool to uncover impairment of multiple neuronal systems and even to decipher subclinical affective functions. Electrooculography reveals quantitatively abnormal eye movements, such as gaze-evoked nystagmus and slowing of saccades[37]. Visual-evoked potentials reveal decreased amplitude and/or prolonged latency of P100 wave[38]. Abnormal acoustic-evoked potential findings include loss of waves as well as increased interpeak intervals[38].

Somatosensory-evoked potentials also show impairment of central or peripheral sensory tracts in SCA1. Using somatosensory-evoked potentials, Abele et al. showed loss of P40 in 100% of patients. Motor-evoked potentials are helpful

to show subclinical affective functions of the corticospinal tracts, which is very frequent in SCA1[38]. Almost all patients presented with prolonged central motor conduction times and peripheral motor conduction times in all extremities[38,39].

Nerve conduction studies reveal mildly reduced nerve conduction velocities in sensory and motor nerves, but amplitude reduction is much more prominent in sensory nerves than motor nerves[39]. Electromyography often reveals signs of chronic denervation affecting proximal and distal muscles. The pattern may resemble a distal neuropathy in some patients, but in others, it is much like a diffuse motor neuronopathy[39]. In a recent study, Linnemann *et al*. reported on the features of peripheral neuropathy in SCA1, in which mixed neuropathy was the most frequent pattern (83%), followed by axonal (11%) and demyelinating (6%) disease[40].

Neuropathology

Spinocerebellar ataxia type 1 is characterized macroscopically by olivoponto-cerebellar atrophy[41]. On microscopy, there is dramatic loss of cerebellar Purkinje cells as well as of neurons of the dentate nuclei, basal pontine and other brainstem areas, including the red nuclei, vestibular and motor cranial nerve nuclei[41,42]. In contrast, the pars compacta of the substantia nigra, the basal ganglia, thalamus, cerebral cortex and hippocampus are usually spared[41]. Hence, SCA1 neuropathology can involve components of the cerebello-thalamocortical loop, the basal ganglia-thalamocortical loop, the visual system and the somatosensory system[43]. The impairment of the spinal cord is conspicuous. It is characterized by gross atrophy, caused by loss of anterior horn cells, fibers in the posterior columns and neurons from the Clarke's column[44].

Neuroimaging

Schulz *et al*. evaluated volumetric changes in SCA1 using voxel-based morphometry in a multicenter study with 48 patients. The authors reported gray matter volume loss in the cerebellar hemispheres, vermis, brainstem and white matter loss in the midbrain, pons, middle cerebellar peduncles, and cerebellar hemispheres. The brainstem and pons volumes correlated inversely with ataxia severity[45].

Analyses of supratentorial structures revealed gray matter volume loss in the caudate nuclei, putamina and temporal lobes, but no correlations with clinical or molecular data were found[45]. In a two-year prospective study, Reetz *et al*. evaluated 37 patients with SCA1. Cross-sectional analyses found a significant decline in gray matter volume for the whole brainstem, left anterior and posterior cerebellum and the right putamen and pallidum compared to healthy controls. The length of the expanded CAG repeat allele correlated with cerebellum and pons volume loss in these patients. Longitudinal analyses identified progressive atrophy in the brainstem, pons, putamen, left caudate and left cerebellar hemisphere after two years. The length of the expanded CAG repeat allele correlated with the rate of cerebellar volume loss. In the same

study, authors attempted to compare the rates of atrophy within different SCA subtypes. The SCA1 group indeed had an increased rate of volume loss in the whole brainstem, left cerebellar hemisphere, and putamen, when compared with the SCA3 group[46].

Other studies using voxel-based morphometry also reported volume loss in the cerebellum and brainstem involving both gray and white matter[47]. Regional damage to cerebral white matter in individuals with SCA1 has repeatedly been demonstrated by diffusion tensor imaging in several studies[48].

A multicenter observational European study, with 26 presymtomatic carriers of SCA1 mutations reported gray matter loss in the medulla oblongata extending to the pons and to the lobule IX of the cerebellum in these individuals compared with matched healthy controls. These results indicate that anatomical damage takes place before symptom onset in SCA1[49]. Patients with SCA1 also have cervical spinal cord atrophy combined with anteroposterior flattening[50]. Interestingly, the spinal cord area correlates with ataxia severity, disease duration, and CAG expansion[50].

Regarding neurochemical alterations detected by proton magnetic resonance spectroscopy, measurements of metabolites such as N-acetylaspartate and myoinositol indicate neuronal loss in the cerebellum and pons in SCA1 patients. These parameters correlated with motor disability[51]. Figure 1 shows some aspects of imaging in SCA1.

DISEASE MECHANISMS AND FUTURE THERAPEUTIC PERSPECTIVES

Wild-type *ATXN1* includes a polyQ tract that normally contains 6-34 glutamines. A monopartite nuclear-localization signal motif near the carboxyl terminus directs the localization of the protein to the nucleus[52]. *ATXN1* containing a wild-type polyQ tract can move between the cytoplasm and nucleus inside neurons. On the other hand, *ATXN1* containing an expanded polyQ tract is transported to the nucleus but cannot be exported to the cytoplasm[53]. Such abnormal and obligatory localization inside the nucleus seems to be important for SCA1 pathogenesis, since the substitution of a single amino acid within the nuclear-localization signal prevents the expanded *ATXN1* from entering the cell nucleus and this mitigates its toxicity[54].

Wild-type and expanded *ATXN1* interact with various nuclear elements, such as RNA[53,54], several regulators of transcription, capicua (CIC)[54], and others. An important approach to understanding SCA1 pathogenesis has been to model disease features in mice. The importance of ataxin-1-CIC complexes in SCA1 pathogenesis is suggested by the observation that reducing CIC levels, either genetically or through exercise, decreases the deficit in motor performance and the premature lethality of the SCA1-like phenotypes in animal models[55].
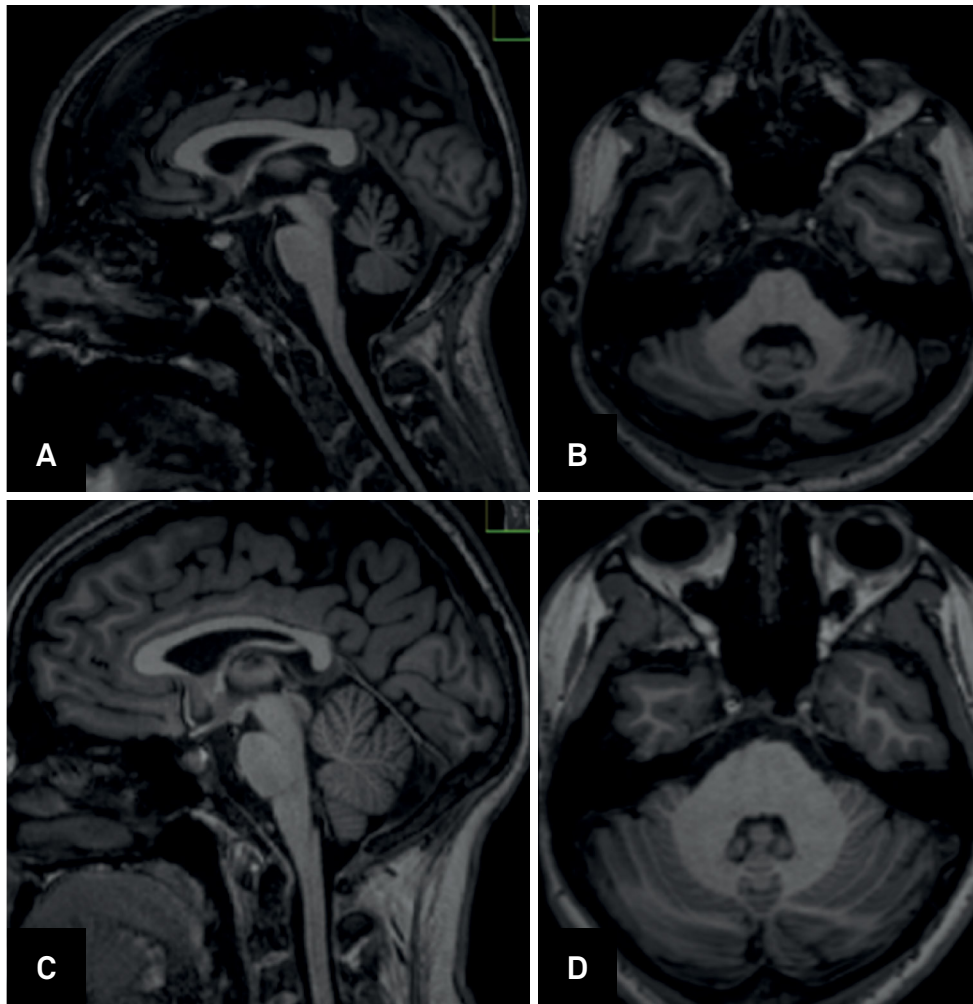
Figure 1. A. Sagittal T1-weighted brain MRI demonstrates cervical spinal cord atrophy in SCA1; B. Axial T1-weighted brain MRI shows moderate olivopontocerebellar atrophy in SCA1. C and D demonstrate spinal cord and brainstem in a healthy control.

On entering the nuclei of Purkinje cells, ataxin-1 binds to CIC. Although ataxin-1 alone does not bind to DNA[54,55], the ataxin-1-CIC complex is targeted to chromatin and transcription sites, binding DNA. Noticeably, as transcription proceeds, ataxin-1 is hypothesized to shuttle between complexes with CIC and the splicing factor RNA-binding motif protein (RBM)17. Ataxin-1 can be found in two high-molecular-weight soluble complexes: one that includes CIC and another that includes RBM17[55]. These two ataxin-1 complexes could be in a dynamic equilibrium and the dynamics of the complexes affect gene expression. An altered balance in the interaction of expanded ataxin-1 with CIC and RBM17 could drive pathogenesis in SCA1. In this way, expansion of the polyQ tract in ataxin-1 favors ataxin-1-RBM17 complex formation[56], implicating this complex in SCA1 pathogenesis (Figure 2).

Like other neurodegenerative disorders, such as Huntington disease[57], mechanistic target of rapamycin (mTOR) signaling is altered in SCA1. In the cerebellar proteomes of transgenic mice with ataxin-1[82Q]-expressing Purkinje cells, mTOR levels were decreased before the onset of symptoms[58]. The DNA-damage and DNA-repair pathways have also been implicated in the pathogenesis of SCA1[59]. In *Sca1154Q/2Q* mice, enhanced expression of proteins that function in several DNA-repair pathways and restoration of mitochondrial DNA repair by expressing the DNA-repair protein[60], could improve motor performance, Purkinje cell morphology, molecular functions and attenuate SCA1-like phenotypes.

Furthermore, early changes in the expression of specific receptors and ion channels that are important for regulating membrane excitability, such as the dysregulation of calcium-activated potassium channel physiology, contribute not only to motor dysfunction but also to structural changes in neurons that consistently precede cell death, changing the intrinsic excitability of Purkinje neurons[61].

Several aspects of SCA1 pathogenesis still remain unclear 25 years after the gene/mutation description. Moreover, the studies have shown that long polyglutamine tracts expressed by the mutated gene have an increased tendency to aggregate, creating nuclear inclusion bodies in affected neurons that are ubiquitinated[3,4]. Screening is in progress to find polyQ
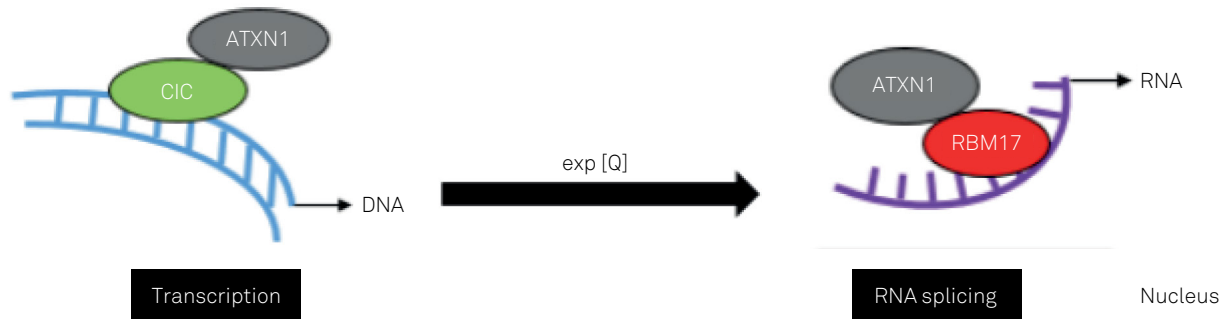
Figure 2. Illustration of a model of SCA1 pathogenesis that incorporates the crucial nuclear interactions and functions of ATXN1. On entering the nuclei of Purkinje cells, ATXN1 readily binds to CIC (transcriptional regulator capicua). Although ATXN1 alone does not bind to DNA, CIC can bind DNA. ATXN1 can be found in two high-molecular-weight soluble complexes: one that includes CIC and another, distinct complex that includes RBM17 (RNA splicing factor). Importantly, expansion of the polyQ tract in ATXN1 favors ATXN1–RBM17 complex formation, implicating this complex in SCA1 pathogenesis. PolyQ expansion is depicted by 'exp[Q]'.

aggregate inhibitors and also to check whether silencing gene expression can be an interesting therapeutic option[3,4]. However, as described above, several cellular pathways are implicated in SCA1 pathogenesis and this multipathway picture makes the development of new therapies difficult. To date, there is no curative treatment for SCA1. Nevertheless, symptomatic therapy may ameliorate symptoms, especially the nonmotor aspects, like depression and sleep disorders.

There are several lines of research on therapeutic agents for SCA1, usually based on animal and cell-based models. Given that mutant polyQ disease proteins can disturb gene expression, RNA homeostasis and protein homeostasis through diverse pathways with largely downstream consequences, acting proximally in the disease cascade to lower the levels of the toxic protein can be a useful strategy towards developing a disease-modifying therapy. In this sense, endeavors to target the expression of polyQ SCA proteins have used antisense oligonucleotides or virus-mediated delivery of short hairpin RNAs or artificial miRNAs to interfere with translation. Preclinical tests of antisense oligonucleotides or miRNA-based drugs for SCA1[56] show considerable promise, making clinical trials increasingly likely.

Experimental data suggested that lithium treatment improves motor coordination and multiple behavioral measures, and might lead to neuroprotective properties in the cerebellum of SCA1 mouse models[63]. Based on this, lithium could be a potential treatment for human SCA1. A Phase I trial of oral lithium has been completed as an intramural National Institutes of Health study, but results have not yet been published (NCT00683943). Riluzole has been shown to provide some symptomatic relief of ataxia in a mixed group of individuals including people with SCA1[64]; however, further investigation is needed, particularly long-term disease-specific trials. A double-blind randomized placebo controlled trial of a riluzole prodrug BHV4157 is ongoing (NCT02960893).

In line with other therapies, Matsuura *et al.* reported that intrathecal injection of mesenchymal stem cells into the meningeal covering of the cerebellum improved Purkinje cell organization, reduced cerebellar dendrite atrophy and normalized behavior and motor deficits in B05 mice injected at five weeks of age[65]. Thus, further investigation is needed to confirm the therapeutic potential of stem cells in SCA1. Gene therapy is based on reducing expression of the mutant *ATXN1* through gene silencing or overexpressing a paralog of *ATXN1*, ataxin-1-like (*ATXN1L*), to competitively inhibit the formation of toxic complexes by polyQ-ataxin-1[66]. This approach appears to be promising, but further clinical studies are still needed.

In conclusion, in over 100 years of research, there is still a long way to fully understanding and treating patients diagnosed with SCA1. Nevertheless, recent progress and the genetic outbreaks of the 1990s have given neurologists and neuroscientists valuable hints on where to search for answers.

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