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INTRODUCTION

The wide spectrum of spinocerebellar ataxias (SCAs)

MARIO-UBALDO MANTO

FNRS-Neurologie, Hôpital Erasme-ULB, Bruxelles, Belgium

Abstract
Spinocerebellar ataxias (SCAs) are a clinically heterogeneous group of disorders. Current molecular classification corresponds to the order of gene description (SCA1–SCA 25). The prevalence of SCAs is estimated to be 1–4/100.000. Patients exhibit usually a slowly progressive cerebellar syndrome with various combinations of oculomotor disorders, dysarthria, dysmetria/kinetic tremor, and/or ataxic gait. They can present also with pigmentary retinopathy, extrapyramidal movement disorders (parkinsonism, dyskinesias, dystonia, chorea), pyramidal signs, cortical symptoms (seizures, cognitive impairment/behavioral symptoms), peripheral neuropathy. SCAs are also genetically heterogeneous and the clinical diagnosis of subtypes of SCAs is complicated by the salient overlap of the phenotypes between genetic subtypes. The following clinical features have some specific values for predicting a gene defect: slowing of saccades in SCA2, ophthalmoplegia in SCA1, SCA2 and SCA3, pigmentary retinopathy in SCA7, spasticity in SCA3, dyskinesias associated with a mutation in the fibroblast growth factor 14 (FGF14) gene, cognitive impairment/behavioral symptoms in SCA17 and DRPLA, seizures in SCA10, SCA17 and DRPLA, peripheral neuropathy in SCA1, SCA2, SCA3, SCA4, SCA8, SCA18 and SCA25. Neurophysiological findings are compatible with a dying-back axonopathy and/or a neuronopathy. Three patterns of atrophy can be identified on brain MRI: a pure cerebellar atrophy, a pattern of olivopontocerebellar atrophy, and a pattern of global brain atrophy. A remarkable observation is the presence of dentate nuclei calcifications in SCA20, resulting in a low signal on brain MRI sequences. Several identified mutations correspond to expansions of repeated trinucleotides (CAG repeats in SCA1, SCA2, SCA3, SCA6, SCA7, SCA17 and DRPLA, CTG repeats in SCA8). A pentanucleotide repeat expansion (ATTCT) is associated with SCA10. Missense mutations have also been found recently. Anticipation is a main feature of SCAs, due to instability of expanded alleles. Anticipation may be particularly prominent in SCA7. It is estimated that extensive genetic testing leads to the identification of the causative gene in about 60–75 % of cases. Our knowledge of the molecular mechanisms of SCAs is rapidly growing, and the development of relevant animal models of SCAs is bringing hope for effective therapies in human.

Key words: *Ataxia, dysarthria, nystagmus, ataxic gait, cerebellar atrophy, ADCA, polyglutamine, expansions*

Spinocerebellar ataxias (SCAs, previously named autosomal dominant cerebellar ataxias ADCAs) represent a group of disorders which is heterogeneous from the clinical and genetic point of view. SCAs were initially classified according to clinical and neuropathological descriptions. Harding suggested a classification according to the mode of inheritance and the clinical signs (ADCA I–III) (1). Current numbering corresponds to the order of gene description (SCA1–SCA8, SCA10–SCA23, SCA25, mutations in the gene encoding fibroblast growth factor 14 (FGF14), dentatorubral-pallidoluysian atrophy DRPLA). This molecular classification is the one which is currently the most accepted by the scientific community.

The prevalence of SCAs is estimated to be 1–4/100.000 (2–4), but it can be much higher in some regions because of a founder effect. This is the case for SCA2 in Cuba, SCA3 in the Azores (5,6). SCA10 has been reported in Mexico. DRPLA is predominantly observed in Japan. Frequency of genetic subtypes can show a marked variability between ethnic groups. The commonest forms are SCA1, SCA2, SCA3, SCA6 and SCA7. SCA3 could be the most prevalent SCA in the world. Average age at onset of SCAs is in the third decade, with large variations between subtypes (7). Symptoms of SCA1, SCA2, SCA3, SCA7, SCA8, SCA12, SCA13, SCA17 or SCA25 can start in the first decade, whereas ataxia can appear after 65 years in SCA6 (Figure 1). Penetrance is age-dependent, and is reduced for SCA17 (8). SCA8 shows a complex inheritance pattern with extremes of incomplete penetrance, in which often only one or two affected individuals are found in a given family (9).

Patients exhibit a cerebellar syndrome which includes ataxia of gait (usually the main ataxic sign), ataxia of stance, dysmetria and/or kinetic tremor in 4 limbs, as well as oculomotor deficits (nystagmus,

Correspondence: Mario-Ubaldo Manto, Neurologie – FNRS, Hôpital Erasme – ULB, 808 Route de Lennik, 1070 Bruxelles, Belgium. Tel: +32 2 555 39 92. Fax: +32 2 555 39 42. E-mail: mmanto@ulb.ac.be

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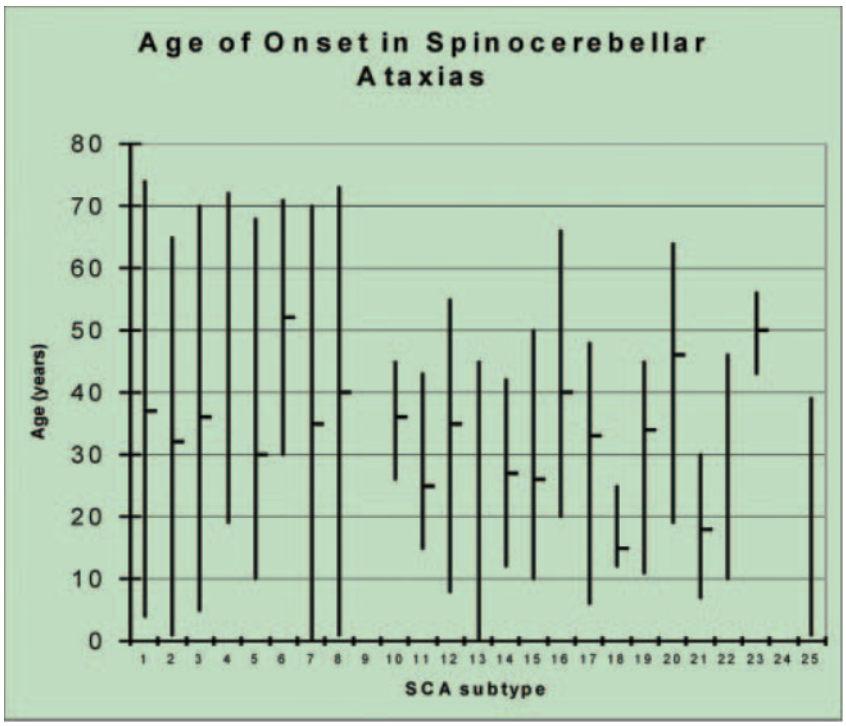

Figure 1. Mean age of onset in spinocerebellar ataxias (SCAs). The horizontal bars correspond to the mean age at onset. Not shown: DRPLA: range of 0–62 years (mean: 30); FGF14: range of 27–40 years (mean: 34).

hypermetria/hypometria of saccades). As a result of a degenerative process which is often not limited to the cerebellum, but is extended to the retina, the optic nerve, the brainstem, basal ganglia, cerebral cortex, spinal cord and peripheral nervous system, extra-cerebellar signs are often associated. Table I indicates these clinical signs. Two factors make the clinical diagnosis difficult: (1) within a genetic subtype, the clinical signs are highly variable, (2) there is a striking phenotypic overlap between SCAs. From the radiological point of view, 3 patterns of atrophy can be observed: a pure cerebellar atrophy (in SCA4, SCA5, SCA6, SCA8, SCA9, SCA10, SCA11, SCA14, SCA15, SCA16, SCA18, SCA21, SCA22), a pattern of olivopontocerebellar atrophy (SCA1, SCA2, SCA3, SCA7, SCA13), or a pattern of global cerebral atrophy (SCA12, SCA17, SCA19, DRPLA). A remarkable finding is the presence of calcifications in cerebellar nuclei in SCA20 (10). Most of the SCAs start by a cerebellar atrophy which can progress subsequently to extra-cerebellar structures.

As a result of the marked phenotypic variability of SCAs even within single families, the diagnosis cannot rely on the sole clinical evaluation and a detailed genetic search may be required. Currently, the majority of the SCAs are caused by an expansion of repeated trinucleotides (Figure 2; Table II). In SCAs due to a CAG expansion encoding a polyglutamine repeat (SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, DRPLA; the CAG repeat expansion in SCA12 does not encode a polyglutamine tract and an untranslated CTG repeat being found in SCA8), there is an inverse correlation between the length of the repeat and the age of onset. A main feature of SCA is anticipation, which is explained in CAG expansions by an instability of repeats, resulting in elongated polyglutamine tracts. Some correlations between CAG repeat length and phenotypic presentation has been reported (11). For instance, SCA3 patients may exhibit a syndrome of ataxia plus peripheral neuropathy or a combination of ataxia plus spasticity when the repeats are less than 73 CAG or more than 73 CAG repeats, respectively. SCAs can be due to a channelopathy (SCA6) or may be associated with impaired gene/protein expression such as SCA8, SCA10 (ATTCT repeat), SCA12, SCA17 (CAG or CAA repeat expansion in the transcription factor TBP). The number of identified inherited neurological disorders that are due to expansions which are transcribed into RNA but not translated into protein is growing (9).

There are several genetic diseases which can overlap with SCAs from the phenotype point of view. The following disorders need to be considered in the differential diagnosis of dominantly inherited diseases: episodic ataxias (EA 1–5), hereditary spastic paraplegias (HSP), Huntington disease, essential tremor, hereditary sensory-motor neuropathies (HSMN) (7). Autosomal recessive disorders, mitochondrial diseases, X-linked diseases, or even sporadic diseases can also mimic the phenotype of SCAs. In particular, leukodystrophies, mitochondrial cytopathies (Kearns-Sayre syndrome, MERRF, MELAS, NARP, Leigh syndrome), Friedreich ataxia, fragile-X syndrome, progressive myoclonic

Table I. Clinical presentation of spinocerebellar ataxias (SCAs).

A. Pure Cerebellar syndrome[1]

Pure Ataxia
SCA5*, SCA6*

B. Cerebellar Ataxia Plus

Eyes/oculomotor control	Movement disorders	Pyramidal signs	Cortical signs		Peripheral nervous system (sensory or sensorimotor axonal neuropathy)[3]
			Cognitive impairment/ behavioral symptoms	Seizures	
Slow saccades:[2] SCA1, SCA2**, SCA3, SCA7* Downbeat nystagmus: SCA6* Ophthalmoplegia: SCA1 , SCA2, SCA3 Pigmentary retinopathy: SCA7**	Parkinsonism: SCA1, SCA2, SCA3, SCA12, SCA17, SCA21 Dystonia: SCA3, SCA17 Tremor: SCA8, SCA12, SCA16 (head + hand), SCA19, SCA20 (palatal) Dyskinesias: FGF14* Myoclonus: SCA2, SCA14, SCA19, DRPLA Chorea: SCA1, SCA17, DRPLA	SCA1, SCA2, SCA3* (spasticity), SCA4, SCA7, SCA8, SCA11, SCA12, SCA13, SCA15	SCA1, SCA2, SCA3, SCA13, SCA17*, SCA19, SCA21, SCA-FGF14, DRPLA*	SCA10*, SCA17, DRPLA*	SCA1, SCA2, SCA3, SCA4*, SCA6, SCA8, SCA-FGF14, SCA12, SCA18*, SCA22, SCA25*

[1]The following SCAs may evolve from a pure cerebellar syndrome to a cerebellar ataxia plus syndrome: SCA8, SCA11, SCA14, SCA15, SCA16, SCA22. [2]Maximal saccade velocity influenced by polyglutamine size (ref. 18). [3]Dying-back axonopathy and/or neuronopathy (ref. 19). *Clinical signs which are suggestive, **Highly suggestive and with some specificity in the context of an autosomal dominant progressive cerebellar syndrome.

	5'-UTR	ORF	Intron	ORF	3'-UTR
CAG repeat expansions from the ORF		SCA1 SCA2 SCA3 SCA6 SCA7 SCA17 DRPLA			
Non coding repeat expansions	SCA12 (CAG repeats)		SCA10 (ATTCT repeats)		SCA8 (CTG repeats)
Missense mutations				SCA14 (PKC gamma) FGF14	

Figure 2. Repeat expansions and missense mutations in SCAs. Adapted from Schols et al. 2004 [7]. ORF: open reading frame.

epilepsies or multiple system atrophy (MSA) should be considered (7). It should be pointed out again that family history can remain 'negative' in SCAs with late onset of symptoms (such as SCA6 (12)), in case of severe anticipation as observed in SCA7, reduced penetrance (SCA17), marked phenotypic variation (for instance marked pyramidal or extra-pyramidal signs can mask ataxia in some members of the affected family) or in case of false paternity.

Therapy of SCAs remains an open issue. Although some benefits have been reported on ataxic symptoms with 5-hydroxytryptophan or buspirone, acetazolamide in SCA6 (13), deep brain stimulation in patients presenting tremor in SCA2 (14), or on extra-cerebellar symptoms such as amantadine/levodopa/dopamine agonists in SCA2 and SCA3, or with baclofen/tizanidine facing spasticity, benefits of pharmacological treatments remain very limited. Logopedic rehabilitation and regular physiotherapy are recommended. Most patients will have some improvements with the use of orthesis, stricks or strollers. Unfortunately, the majority will become wheelchair-bound during the course of their illness. Increasing insights of molecular and pathophysiological mechanisms of SCAs are leading to new therapies. Several new strategies are currently tested in animal models of SCAs, mainly

Table II. Loci of SCAs.

SCA subtype (gene product)	Locus	Selected reference
SCA1 (ataxin 1)	6p23	Orr et al. 1993 [20]
SCA2 (ataxin 2)	12q24.1	Pulst et al. 1996 [21]
SCA3 (ataxin 3)[a]	14q24.3–q31	Kawaguchi et al. 1994 [22]
SCA4	16q22.1	Flanigan et al. 1996 [23]
SCA5	11p12	Ranum et al. 1994 [24]
SCA6 (CACNA1A)	19p13	Zhuchenko et al. 1997 [25]
SCA7 (ataxin 7)	3p12–13	David et al. 1997 [26]
SCA8	13q21	Koob et al. 1999 [27]
SCA9		
SCA10 (ataxin 10)	22q13	Matsuura et al. 2000 [28]
SCA11	15q14–21.3	Worth et al. 1999 [29]
SCA12	5q31–33	Holmes et al. 1999 [30]
SCA13	19q13.3–q13.4	Herman-Bert et al. 2000 [31]
SCA14 (PKCgamma)	19q13.4–qter	Yamashita et al. 2000 [32]
SCA15	3p24.2–pter	Knight et al. 2003 [33]
SCA16	8q22.1–q24.1	Miyoshi et al. 2001 [34]
SCA17 (TATA-box binding protein)	6q27	Koide et al. 1999 [35]
SCA18	7q22–q32	Brkanac et al. 2002 [36]
SCA19 [b]	1p21–q21	Verbeek et al. 2002 [37]
SCA20	11 ?	Knight et al. 2004 [10]
SCA21	7p21.3–p15.1	Vuillaume et al. 2002 [38]
SCA22[b]	1p21–q23	Chung et al. 2003 [39]
SCA23	20p13–12.3	Verbeek et al. 2004 [40]
FGF14	13q34	Van Swieten et al. 2003 [41]
SCA25	2p15–p21	Stevanin et al. 2004 [42]
DRPLA (atrophin 1)	12p13.31	Koide et al. 1994 [43]

[a]Allelic to Machado-Joseph Disease (MJD); [b]CA19 might be allelic with SCA22.

transgenic models (*C. elegans*, drosophila, mice), either with new drugs, with RNAi (RNA interference with the aim of inhibiting polyglutamine-induced neurodegeneration), or using transplantation of stem cells (15). Prevention of protein misfolding and aggregation by overexpressing chaperones and application of histone deacetylase inhibitors are being tested (16,17). Results of these pre-clinical trials should be available within 3 years.

In this issue, we have gathered several important contributions which highlight the large spectrum of SCAs from the clinical, radiological, genetical, pathological and pathophysiological points of view. New mechanisms and recent discoveries are pointed out. We thank all the contributors for their outstanding and timely work.

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