Title Page

Title:

Ophthalmologic features of the common spinocerebellar ataxias
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Abstract

Purpose of review: The spinocerebellar ataxias are a phenotypically and genetically diverse group of autosomal dominant disorders that cause pathological degeneration in the cerebellum, brainstem, and retina, resulting in a wide variety of ophthalmologic signs and symptoms.

Recent findings: The genetic discrimination of the spinocerebellar ataxias has advanced dramatically over the past decade. The most common genetic (mutational) mechanism for the SCAs is an abnormal expansion to a stretch of glutamine amino acid residues (polyglutamine tract) encoded by any of several SCA-causing genes. Knowledge regarding the pathophysiology of polyglutamine-expansion-induced protein dysfunction is an area of intense investigation.

Summary: The ophthalmologist may be the first to encounter a patient with spinocerebellar ataxia, and a review of the most common genetic subtypes of this disorder is helpful in diagnosis and management.

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Introduction

Ataxia is a neurologic disorder consisting of incoordination of voluntary movements associated with dysmetria and dysdiadochokinesia, in the absence of weakness. Ataxia can be either cerebellar or sensory in origin. Causes of cerebellar ataxia are extensive, and include stroke, demyelination, encephalitis, alcohol toxicity and compressive mass lesions. Progressive degenerative disorders are another cause of cerebellar ataxia, and occur sporadically or in an inherited recessive or dominant fashion.

The spinocerebellar ataxias (SCA) are a genetically diverse group of autosomal dominant disorders in which cerebellar disease can occur in isolation or concomitantly with brainstem or retinal abnormalities. Because ocular motor deficits are prominent in both cerebellar and brainstem disease, the recognition and discrimination of the SCAs is important to an ophthalmologist for proper diagnosis and evaluation.

There are 29 genetically distinct types of SCA as of July, 2010[1], but the number is sure to increase as new genotypes are found. The numbering sequence for the SCAs is up to SCA31, because SCA9 is reserved and SCA15 was found to be the same entity as SCA16. The genetic mutation of an SCA may only be found decades after its initial description.[2,3]

In this review, the most common SCAs will be described, with particular attention to their ophthalmologic features. We will focus on SCA1, SCA2, SCA3, SCA6 and SCA7, which comprise about 80% of the SCAs,[4] and are therefore the most likely to be encountered in practice. Table 1 summarizes the genetic and clinical features of the most common SCAs.

[Insert Table 1 here]

Although these disorders have differing clinical features, and different disease-causing genes, they all share a common underlying mutational mechanism: an expanded CAG repeat encoding a tract of glutamine amino acids (polyglutamine or polyQ tract). This inherited polyQ tract is increased from a normal level to a disease causing level, and passed on to approximately 50% of offspring. As with the most disorders in this category, such as Huntington's disease, age of onset varies inversely with length of repeats.

Brain imaging is helpful in all the SCAs to rule out other pathology. In cases where SCA is a diagnostic possibility, MRI abnormalities reflect clinical localization of disease. In SCA6, for example, where brainstem signs are generally absent, there is relative preservation of pontine parenchyma. SCA1, SCA2, SCA3 and SCA7 are considered olivopontocerebellar forms of SCA, and the brainstem, in addition to the cerebellum, becomes atrophic.[5] It is unclear if optic nerve atrophy is present with MRI analysis, but decreased optic nerve volume on MRI occurs in other situations where ganglion cells are lost.

Spinocerebellar Ataxia Type 1 (SCA1)

This section provides an update on the general, ophthalmologic and genetic features of SCA1.

General features of SCA1

Prior to genetic subtyping, SCA1 (together with SCA2 and SCA3) was part of the broad category called olivopontocerebellar atrophy, or autosomal dominant cerebellar atrophy (ADCA) type I (without retinal degeneration but involving extra-cerebellar structures). "Olivo-" refers to the olivary nuclei, a region of the brainstem. Figure 1 displays the representative radiological features of SCA1. Although not the most common SCA subtype, SCA1, as its name indicates, was the first autosomal dominant cerebellar ataxia for which the gene and mutational mechanism were elucidated.

[Insert figure 1 here]

Clinically, typical SCA1 presents around age 30 with symmetric, progressive ataxia and gait dysfunction due to cerebellar disease. There is however a wide range in age of onset, even within some families, ranging from 7 to 50 years, due entirely to genetic mechanisms. SCA1 is also characterized by extra-cerebellar features. The most frequent non-cerebellar signs involve the efferent visual system, discussed below, followed by corticospinal tract abnormalities such as hyperreflexia and spasticity in over 50%.[6] Many patients are wheelchair bound by 15-20 years. Pathologic findings correlate with atrophy in the Purkinje cells of the cerebellum as well as the pons and middle cerebellar peduncle.

Ophthalmologic features of SCA1

Distinguishing the different forms of SCA by examining ocular motor features is critical to obtaining an accurate diagnosis. Even with genetic testing, eye movement characteristics can be extremely valuable. For example, if the diagnosis of SCA1 is not suspected based on an ophthalmologic evaluation, but SCA6 is suspected, single gene confirmatory testing would cost much less than a broad genetic SCA panel. This being said, there are many ocular motor features of the different SCA types which overlap, and not all features may be present in some groups.

SCA1 can result in ocular motor disruptions involving cerebellar connections, such as gaze-evoked and rebound nystagmus and reduced smooth pursuit gain.[7] Pursuit gain is the ratio of eye velocity to target velocity. Saccadic dysmetria is observed to due cerebellar dysfunction. Saccade hypermetria in SCA1 was distinguished from the hypometric saccades of SCA3 in one study,[8] but this pattern was not seen in another report which found hypermetric saccades in both.[7] Because of involvement of brainstem pathways such as the parapontine reticular formation, saccades can also slow in SCA1[7], correlating in time of onset and severity to the number of abnormal repeats.[9]

Despite prior studies which suggested that the optic nerve and retina are not affected in SCA-1[10], disc atrophy has been described in SCA1[11] and visual evoked potentials, which indicate subclinical involvement of the visual pathway, are abnormal in the majority of patients.[12]

We have also observed cases of abducens palsy occurring in the setting of SCA1. Localization of these deficits to the fascicular sixth nerve is suspected.

Genetics of SCA1

The gene for SCA1 contains an expanded CAG repeat encoding a polyQ tract in a protein termed ataxin-1, and resides on chromosome 6p23.[13] The length of the repeat expansion varies between individuals, even within families, with age of onset inversely correlating to the length of the repeat expansion. The mutated ataxin-1 protein forms abnormal protein aggregations in neuronal nuclei and is thought to mediate disease through a gain of function toxicity.[14] The abnormal interaction of the misfolded ataxin-1 protein with other cellular elements within and outside of these protein aggregates results in neuronal dysfunction and degeneration, and ultimately to the phenotypic abnormalities seen in SCA1.[15] Normal SCA1 alleles have approximately 6-38 repeats. SCA1 results from pathological expansions between 39-83 repeats.

Spinocerebellar Ataxia Type 2 (SCA2)

This section provides an update on the general, ophthalmologic and genetic features of SCA2.

General features of spinocerebellar ataxia type 2 (SCA2)

SCA2 is relatively common and like SCA1, involves clinical deficits in both cerebellar and brainstem functions. Age of onset is in the mid-30s. In addition to progressive cerebellar ataxia, non-cerebellar symptoms include myoclonus and muscle fasciculations. Abnormal corticospinal tract function resulting in spasticity and Babinski reflexes is less frequently encountered compared to SCA-1.[6] SCA2 has a severe congenital onset variant associated with failure to thrive, infantile spasms, pigmentary retinopathy and infantile mortality.

Ophthalmologic features of SCA2

The most consistently abnormal ocular motor feature in SCA2 is substantial slowing of saccadic velocities.[16] In fact, even pre-symptomatic carriers of the ataxin-2 mutation have a decreased maximum saccadic velocity versus patients without the mutation. Larger expansions of the CAG repeat region are associated with a greater velocity reduction in these pre-symptomatic patients.[17] This characteristic decrease in saccadic velocity has also been described by Baloh's group, who note that the typical gaze-evoked nystagmus of cerebellar disease can be absent in SCA2 due to impaired ability to produce

saccadic corrective phases.[7] A pathological evaluation of the brain of a patient with SCA2 revealed that there was cell loss specifically in the excitatory burst neurons of the brainstem saccade generators, correlating to the decreased saccade velocity.[18]

Although ocular motor abnormalities are most prominent, optic atrophy has also been noted in early descriptions of SCA-2.[19]. As noted, the rare congenital variant of SCA2 is associated with pigmentary retinal degeneration.

Genetics of SCA2
The gene for SCA2 resides at the genetic locus 12q24 and encodes a protein termed ataxin-2. The ataxin-2 gene contains a polyQ tract that is pathologically expanded in SCA2. Like SCA1, age of onset varies inversely with repeat length. The abnormal ataxin-2 produces a cytosolic protein that results in aberrant interactions with cytosolic constituents, instability of calcium signaling pathways, disrupted calcium regulation, and cellular toxicity.[20] Normal SCA2 alleles have approximately 32 repeats. Typical SCA2 results from pathological expansions of 32-100 repeats, and the infantile form results from expansions of 100-500 repeats.

Spinocerebellar Ataxia Type 3 (SCA3)
This section provides an update on the general, ophthalmologic and genetic features of SCA3.

General features of spinocerebellar ataxia type 3 (SCA3)
Despite abandonment of most other historical nomenclature associated with the dominantly inherited ataxias, SCA3 continues to be known by its eponym, Machado-Joseph disease (MJD). SCA3/MJD is one of the most prevalent dominantly inherited cerebellar ataxias in the world, and the most common in the US, at ~20%.

SCA3/MJD has a variable clinical presentation, due to genetic mechanisms. The most common form of disease presents in the fourth decade with prominent cerebellar signs. There is a mild form associated with peripheral neuropathy and sleep disturbances, and a severe form associated with dystonia and rigidity.

Ophthalmologic features of SCA3
The neuro-ophthalmologic manifestations of SCA3/MJD are variable. Cerebellar dysfunction in SCA3/MJD results in saccadic pursuits as well as gaze evoked and rebound nystagmus (Figures 2 and 3). Unlike SCA1 or SCA2, patients with SCA3/MJD also show impaired vestibulo-ocular reflex (VOR) gain.[7] VOR gain reflects integrity of connections between the vestibular system and the extra-ocular muscles. VOR gain can be estimated by the head impulse test (head thrust maneuver), in which saccades back to target are noted upon rapid passive turn of the head. Decreased VOR gain reflects

pathologic involvement of the vestibular nuclei in the lateral brainstem apart from the cerebellum.[21]

[Insert Figures 2 and 3 here]

Jardim et al described clinical findings in 62 consecutive patients with SCA3/MCD and found nystagmus in 92%, internuclear ophthalmolplegia, or upgaze/convergence paresis in 52.5%, eyelid retraction in 27.4%, optic atrophy in 22.8%, and "nuclear ophthalmoplegia" in 10%. Ophthalmoplegia, but not the other signs, was correlated with disease duration. Nuclear ophthalmoplegia in particular was associated with a more severe disease course. Repeat length did not correlate with nystagmus, lid retraction or optic atrophy.[22]

The finding of optic atrophy in SCA3/MJD has been described previously, but is less well recognized than the ocular motor features.[23]

Genetics of SCA3
Like SCA1 and SCA2, SCA3/MJD is caused by a pathologically expanded polyQ-encoding CAG repeat within the ataxin-3 gene, located on chromosome 14q24.3-q31. Age of onset, severity and clinical features are worse with longer repeats. A high number of repeats are associated with early onset of disease and extensive dystonia and rigidity. The ataxin-3 protein is normally involved in the ubiquitin protein degradation pathway,[24] and pathogenesis of SCA3/MJD may be related to a toxic gain in function or altered ubiquitin function in the polyQ-expanded ataxin-3 protein.

Spinocerebellar Ataxia Type 6 (SCA6)
This section provides an update on the general, ophthalmologic and genetic features of SCA6.

General features of spinocerebellar ataxia type 6 (SCA6)
SCA6 is distinct from the other common SCAs in that it represents a pure cerebellar cortical syndrome with rare extra-cerebellar clinical features. Figure 4 shows the characteristic cerebellar atrophy with brainstem preservation. SCA6 typically has a mean age of onset in the 50s, and a relatively normal life span, although there is some variation in age of onset due to genetic mechanisms. It represents approximately 15% of SCA cases in the US.

[Insert Figure 4 here]

Ophthalmologic features of SCA6
There is a characteristic pattern of ocular motor and vestibular abnormalities in SCA6, consisting of horizontal and vertical nystagmus and an abnormal vestibulo-ocular reflex

(VOR).[25] An increased incidence of spontaneous downbeat nystagmus occurs in SCA6 in addition to other types of nystagmus when compared to the other SCAs.[7,26] The isolated cerebellar pathology results in severely impaired smooth pursuit gain with preserved saccadic velocity and VOR gain function.[7]

Pre-symptomatic features of SCA6 may include an increased frequency of square wave jerks.[27] Van Stavern et al described a patient with SCA6 who had the combination of periodic alternating nystagmus with periodic alternating skew deviation.[28] This unusual constellation of clinical findings suggests that the cerebellum plays an important role in concomitant regulation of VOR gain and stability of vertical vergence.

Genetics of SCA6.
Similar to SCA1, SCA2 and SCA3/MCD, SCA6 is caused by an expansion of small polyQ-encoding CAG repeat tract within the CACNA1A gene on chromosome 19p13. The repeat and expansions are smaller and more stable than those in SCA1,2, and 3, leading to less intergenerational differences in age of onset and severity. Interestingly, this gene encodes a neuronal calcium channel that and is also the target of distinct mutations that are responsible for the syndromes of familial hemiplegic migraine and episodic ataxia type 2 (EA2) in different families. When the SCA6 CAG expansion length in one allele is short, the clinical phenotype observed mimics EA2 initially, with episodic ataxia and slow progression to a fixed cerebellar dysfunction syndrome.

Spinocerebellar Ataxia Type 7 (SCA7)
This section provides an update on the general, ophthalmologic and genetic features of SCA7.

General features of spinocerebellar ataxia type 7 (SCA7)
SCA7 has long been distinguished from other SCAs because of its associated visual loss. In the early characterization of ADCA into three broad subtypes, this degenerative cerebellar ataxia in association with retinal degeneration was given its own category: ADCA2. The discovery of the genetic basis led to the distinction of ADCA2 as SCA7. Worldwide, SCA7 is one of the rarer forms of SCA (1-11%), but ranges in different populations. [29] It is rare in Japan[30] but relatively common in South African blacks and Scandinavians.[31]

A truncal/gait ataxia is one of the first features of disease, which progresses to a limb ataxia and dysarthria. The relationship of onset of visual symptoms to ataxia is variable. Visual symptoms may precede ataxia, ataxia may occur prior to visual problems, or they may occur concomitantly.[32]

Ophthalmologic features of SCA7

Of all the SCAs, the role of the ophthalmologist in diagnosis and management is most important in SCA7. As mentioned above, visual disturbances may precede other symptoms in SCA7, so a high index of suspicion is needed. A positive family history of retinal degeneration, visual loss with ataxia, or other neurologic disease should increase the possibility of SCA7. This being said, what are the symptoms and signs which are likely to occur?

It should be first noted that both afferent retinal or macular disease as well as efferent ocular motor abnormalities occur in SCA7. Presenting visual symptoms may include photophobia, dyschromatopsia, blurry vision and hemeralopia.[32] Hemeralopia is 'day blindness,' or improved vision in dim light versus bright light. This symptom is present in cone dystrophies, and SCA7 begins with preferential loss of cones prior to the global involvement of all photoreceptors.[29]

Visual acuity is affected severely, and onset of visual loss may occur in childhood. Color vision is likewise impaired. Pupillary light reactions may slow due to loss of retinal ganglion cells.

The appearance of the fundus in SCA7 is variable. Indeed, on initial inspection especially early in the disease course, it may appear normal. Close evaluation may reveal subtle changes such as loss of the foveal reflex or retinal arterial attenuation as the only sign of pathology.[33] When visible retinal changes are present, pigmentary changes in the macula or peripheral retina are the classic feature, but abnormalities can vary from atrophy of the macula and choroid, or minimal granular retinal pigment epithelial changes, to a bull's-eye macula. [29,32,33,34] Retinal degeneration may occur in the absence of pigmentary changes as well.[30]

Macular and retinal dysfunction may be diagnosed prior to the appearance of funduscopic abnormalities via electroretinogram (ERG)[35] or ocular coherence tomography (OCT).[36] OCT shows thinning of the macula and retinal nerve fiber layer (RNFL). This RNFL thinning may spare the temporal quadrant, which is distinct from disc atrophy due to optic neuropathy, which causes predominantly temporal thinning.

The pathophysiology of the retinal degeneration in SCA7 is becoming better understood. A pathologic examination of the retina in SCA7 showed severely degenerated photoreceptors with displacement of melanin pigment into the retina.[34]

Ocular motor abnormalities may include slowed saccades, saccadic pursuits, saccadic dysmetria and gaze-evoked nystagmus.[32] These are relatively nonspecific for the olivopontocerebellar atrophies, although when paired with the retinal abnormalities, produces a very specific diagnosis.

Genetics of SCA7
Like the other SCAs in this review, SCA7 is caused by a polyQ-encoding CAG trinucleotide repeat expansion in a novel gene. The size of the repeat expansion is rather

unstable between generations and varies inversely with age of onset. Thus, anticipation, the phenomenon of earlier phenotypic expression through the generations, appears to be especially pronounced in SCA7. The expanded polyQ tract in SCA7 leads to a toxic gain function that disturbs neuronal viability. The cause of the retinal and neuronal dysfunction and how it is related to the polyglutamine repeat is not fully understood. One possibility is a toxic effect causing down-regulation of genes involved in photo-transduction and development and differentiation of photoreceptors. [37]

Conclusion

The genetics of the spinocerebellar ataxias has advanced greatly in the past decade. Polyglutamine mutations are prevalent in the most common forms of SCAs, and genetic testing is now available. Many features of the SCAs involve the visual system, and in some it may be the presenting sign. The ophthalmologist who is aware of the differences and similarities among the SCAs can provide a significant contribution in the care of these patients.

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Figure Titles and Captions

Figure 1.

Title: Mid-sagittal T1 weighted MRI of a patient with SCA1

Caption: Typical radiographic features of SCA1 include atrophy of the cerebellum (arrow), brainstem (arrowhead) and spinal cord (open arrow).

Figure 2.

Title: Eye movement tracing showing saccadic pursuits in a patient with SCA3.

Caption: In this tracing, the blue line represents the moving target. The red/green tracing shows the patient's eye movements as saccadic and broken, not smooth and steady. Saccadic pursuits (arrows) occur with breakdown of cerebellar connections to smooth pursuit. A superimposed nystagmus is also present (arrowhead). (Tracing courtesy of Jill Aitken, MA CCC-A, Illinois Neurologic Institute, Peoria, IL)

Figure 3.

Title: Eye movement tracing showing saccadic hypermetria and gaze-evoked nystagmus in a patient with SCA3.

Caption: In this tracing, the blue line represents the target, which is static, but intermittently changes position. The red/green tracing shows the patient's eye movements. The arrow points to overshoot of the target (dysmetria), a classic finding in cerebellar disease. The arrowhead shows gaze evoked nystagmus, a byproduct of faulty gaze-holding mechanisms. (Tracing courtesy of Jill Aitken, MA CCC-A, Illinois Neurologic Institute, Peoria, IL)

Figure 4.

Title: Mid-sagittal T1 weighted MRI of a patient with SCA6

Caption: SCA6 will cause atrophy to the cerebellum (arrow), with relative preservation of the brainstem (arrowhead). This 'pure cerebellar atrophy' is in contrast to other SCAs which cause both cerebellar and brainstem atrophy.