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CLINICAL SCIENCE

Retinal Nerve Fibre Layer and Macular Thinning in Spinocerebellar Ataxia and Cerebellar Multisystem Atrophy

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ABSTRACT

The spinocerebellar ataxias, like all neurodegenerative diseases, lack objective disease- and stage-specific biomarkers. Based on reports of clinically evident optic disc atrophy or retinal disease in some ataxia patients, and the discovery that pre-symptomatic retinal thinning occurs in other neurologic diseases such as multiple sclerosis, we tested the hypothesis that subclinical neuronal or axonal loss in the retina could occur in the degenerative ataxias. Spectral domain optical coherence tomography was performed on 29 ataxia patients with genetically proven spinocerebellar ataxia (SCA) 1, 2, 3, or 6, or multisystem atrophy type C (MSA-C) and 27 age-matched normal subjects. Ataxia patients were assessed using the scale for assessment and rating of ataxia. Compared with normal control subjects, retinal nerve fibre layer (RNFL) thickness was reduced for patients with SCA2 and SCA3, and thickness in the macular region was reduced for all SCAs but SCA2.

Keywords: ataxia, multisystem atrophy, neuro-ophthalmology, trinucleotide repeat diseases

INTRODUCTION

The spinocerebellar ataxias (SCAs) are a genetically diverse group of autosomal dominant neurodegenerative disorders characterised by ataxia, ocular motor abnormalities, and variable other neurological features, such as pyramidal tract, basal ganglia, or brainstem dysfunction.[1,2] The SCAs have been previously classified based on clinical or pathological criteria, but are now organized on the basis of genotype. SCA1, 2, 3, and 6, the most common forms, are caused by expansions of trinucleotide CAG repeats encoding glutamine tracts in four unrelated proteins. SCA1, 2, and 3 are characterised by cerebellar cortical degeneration and variable degrees of involvement of other central nervous system (CNS) gray matter regions in a genotype-specific fashion, whereas SCA6 is associated with nearly pure cerebellar atrophy.[1] Multisystem atrophy type C (MSA-C) is a sporadic form of progressive cerebellar ataxia that resembles the SCAs. It is frequently associated with autonomic dysfunction, and usually lacks any identified inheritance pattern or genetic abnormality. The diagnosis is based on clinical grounds according to consensus criteria.[3]

With the exception of SCA7, notable for retinal pigmentary degeneration, visual disturbances in SCAs mainly reflect problems with the efferent visual system.[4–6] Both cerebellar and brainstem pathology are responsible for the various ocular motor abnormalities of the SCAs.[1,7] Abnormal afferent visual testing and optic atrophy have been described as a feature of SCA1.[8] Visual evoked potentials, sensitive for determining subclinical involvement of the visual pathways, are abnormal in the majority of SCA1 patients.[8,9] Optic atrophy has been described in SCA2 and SCA3, and in MSA-C.[10–13] Rarely, SCA2 is also associated with retinitis pigmentosa, most notably in the infantile form with extremely expanded CAG repeats.[14,15] Pigmentary retinopathy has been reported in a patient homozygous for a pathological repeat expansion in the SCA6 gene.[16]

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Optical coherence tomography (OCT) uses the property of light interference to measure the thickness of the retinal nerve fibre layer (RNFL) or other layers of the retina, and has shown close histological correlation.[17] The use of OCT as a surrogate marker for neurologic disease stage or activity has expanded over the last decade. Research on OCT in multiple sclerosis (MS) has been particularly active, with OCT used as an endpoint outcome measurement for treatment.[18,19] Progressive disease in MS is associated with axonal loss,[20,21] which is tracked on OCT by measuring thickness of the non-myelinated axonal layer of the retina.[22] Thickness of the RNFL correlates in MS with physical disability, clinical rating scales, cognition, and magnetic resonance imaging (MRI) measurements of brain parenchymal fraction and cerebrospinal fluid (CSF) volume.[18,19] Because retinal nerve fibre layer loss can occur without clinical manifestations, OCT can track subclinical axon loss prior to clinically evident symptoms.[23]

Unlike other SCAs, patients with SCA7 exhibit a spectrum of severity of retinal disease from mild to severe dysfunction.[24,25] Early functional abnormalities occur at both photoreceptor and post-receptor levels, with equivalent dysfunction in both cones and rods, but greater centrally than peripherally.[24–26] When characterised using OCT, SCA7 patients had altered foveal lamination accompanied in the parafovea by reduced retinal thickness at an early disease stage, and at later stages foveal and perifoveal retinal thinning.[27]

Because of the widespread expression patterns of the genes responsible for SCA1, 2, 3, and 6, we reasoned that the retina may be a site of neurodegeneration in the ataxic syndromes in the absence of afferent visual symptoms.[28–30] This is supported by occasional reports of retinal or optic nerve involvement in these disorders as well as in MSA-C.[8,13,15,16] In this study we investigated the relationship of the thickness of the retinal nerve fibre layer and macula by OCT in patients with genetically confirmed SCA and MSA-C. The aim of our study was to test the hypothesis that subclinical neuronal or axonal loss in the retina may occur in the degenerative ataxias and be detected as thinning of the RNFL or macula. These findings would establish the retinal thickness as measured by OCT as a potential biomarker in the SCAs.

METHODS

Subjects

Twenty-nine ataxia patients were recruited from the Ataxia Clinic at the University of Chicago based either on the presence of an expanded CAG repeat in either allele of one of the four genes for SCA1, 2, 3, or 6, or on satisfying consensus criteria for MSA-C.[3] Patients were excluded if they had a history of ophthalmologic disease or high myopia (correction greater than −6 D). The recruitment and study protocols were established and carried out in accordance with the Institutional Review Board. All participating subjects gave informed consent.

Twenty-seven healthy normal control subjects were recruited from the community, and tested after exclusion of prior history of ophthalmologic disease other than cataract or refractive error, high myopia with a corrective sphere greater than −6 D, or if ocular pathology other than RNFL or macular thinning was found during acquisition of OCT. This protocol was used to screen out ophthalmologic conditions that could influence the RNFL or macula thickness. Because retinal thickness varies with age, controls were age matched.

Neurologic Examination and SARA Score

The Scale for the Assessment and Rating of Ataxia (SARA) was used to assess disease severity.[31] The SARA consists of eight quantitative examination features for gait, stance, sitting, speech disturbance, and limb kinetic functions and yields a composite ataxia score in the range of 0 (no ataxia) to 40 (most severe ataxia). The SARA has been found to have high inter-rater and test-retest reliability, internal consistency, to show an increase with the disease stage, and a linear relation to global assessments.[31,32] To allow uniformity in clinical comparison between all types of ataxia we also scored the cerebellar form of MSA using the SARA. Although Unified Multisystem Atrophy Scale is validated for all forms of MSA, in this context it was preferable to employ a tool that emphasized the ataxic features rather than one that incorporated multiple clinical phenotypes.

Optical Coherence Tomography

All patients and control subjects underwent spectral domain (SD)-OCT examination (Spectralis OCT, software version 5.1; Heidelberg Engineering, Vista, CA, USA) to measure RNFL and macular thickness. Scans were performed either by the physician or an optical technician trained in OCT acquisition. Throughout scanning, the patient fixated on an internal target provided by the equipment. Each subject eye underwent circle and macular protocols.

The RNFL (circle) scan protocol was captured using a preset scan protocol activated with the user interface at the acquisition screen. The active eye tracking was then engaged before centring the circle scan around the optic nerve head of the tracked fundus image. The 3.45-mm circle was scanned at high speed, equaling 768 A-scans, and 16 scans were averaged before the capture of the image. The peripapillary RNFL thickness parameters evaluated in this study were average thickness of a 360° measurement, temporal (T) (315° to 45°), temporal superior (T-S) (45° to 90°), nasal superior (N-S) (90° to

135°), nasal (N) (135° to 225°), nasal inferior (N-I) (225° to 270°), and temporal inferior (T-I) segment thickness (270° to 315°).

The macula was recorded as an overall thickness and as superior (S) (45° to 135°), inferior (I) (225° to 315°), nasal (N) (135° to 225°), and temporal (T) (315° to 45°) quadrants for both 3 mm diameter and 6 mm diameter quadrants. We define the perifoveal macula as the area within a 6 mm diameter using the foveal pit as its centre. The '6 mm diameter' quadrants only included the region extending from the 3 mm ring to the 6 mm ring of measurement. The 6 mm nasal measurement did not contain the optic nerve head but might overlap with the RNFL temporal measurement.

Tomography images were constructed from a series of axial reflectance profiles (A-scans) over 1.8 mm of depth in less than 1 s. Macular and RNFL thickness were calculated by processing the cross-sectional images using computer algorithms to detect boundaries by searching each A-scan for the highest rates of changes in reflectivity. Retinal thickness was determined as the distance between the first reflection at the vitreo-retinal interface and the anterior boundary of the second reflective layer, corresponding to Bruch's membrane. RNFL thickness was automatically assessed by this computer algorithm, assuming correlation with the highly reflective layer at the vitreo-retinal interface. The posterior margin of the RNFL was automatically located by starting with the identification of Bruch's membrane and then searching anteriorly in the image for the RNFL reflectance.

Mean OCT values were calculated from the values of three scans. Scans with poor image quality were defined as scans with a quality score of less than 20 dB, and poor quality scans or non-reproducible scans were not included.

Statistical Analysis

For each subject, the OCT measurements were averaged across the two eyes. There were two control and six patient cases in which measurements from one eye were invalid for technical reasons or ocular anomalies. For those cases the value for only the other eye with the valid measurement was used. Differences between the five patient groups and controls were assessed using a one-way analysis of variance (ANOVA), followed by a post hoc test for comparing individual patient and control groups. Pearson correlation was used to examine the relation between the OCT measurements and disease severity/duration (SPSS V. 16; Chicago, IL, USA).

TABLE 1 Patient and normal control demographic characteristics.

Characteristic	Patient	Control
Age at exam—mean (years)	58	56
Age at exam—median (range) (years)	60 (24–75)	61 (27–86)
Female/Male	18/11	18/9

RESULTS

Patient Demographic and Disease Characteristics

The 29 patients with genetically confirmed SCA and MSA-C included SCA1 (n = 7), SCA2 (n = 7), SCA3 (n = 5), SCA6 (n = 5), and MSA-C (n = 5). Table 1 lists the age and gender of the patients and normal control subjects. The disease duration, defined as the number of years since the first onset of gait instability, is shown in Table 2, along with the SARA score and the mean number of repeats in the pathologically expanded allele.

Retinal Nerve Fibre Layer Thickness

The overall thickness of the RNFL was significantly different among the groups ($F(5, 48) = 4.5$, $p < 0.005$). Compared with control group, post hoc tests indicated that overall thickness of RNFL measures at the optic nerve head was significantly reduced for the SCA2 and SCA3 patients only (Table 3 and Figure 1A).

Macular Thickness

We compared the retinal thickness in the macular region because this region of the retina contains more layers than does the RNFL at the optic nerve head. The overall thickness in the macular region within a 3 mm diameter from the fovea (central macula) was significantly different among the groups ($F(5, 48) = 4.5$, $p < 0.005$). Post hoc test further indicated that the overall thickness in the macular region was significantly thinner for all ataxias studied except SCA2 (Table 3, Figure 1B).

For macular thickness within a 6 mm diameter from the fovea (perimacular), the overall thickness was marginally

TABLE 2 Patient disease characteristics.

Characteristic	SCA1	SCA2	SCA3	SCA6	MSA-C
Mean number of repeats	46.8	41.2	66.8	22.0	N/A
SARA score	14.0	18.1	11.2	19.0	16.5
Duration of disease (years)	8.25	18.7	18.2	17.2	5.1
Range (years)	4–15	5–36	10–32	12–29	5–27

thinner than normal subjects for SCA6, but not SCA1, SCA2, SCA3, or MSA-C ($F(5, 48) = 2.2$, $p < 0.05$) (Table 3). Because there was a trend towards macular thinning at 6 mm diameter for other SCA types, we evaluated macular thickness within individual quadrants. In sector analysis for SCA3 patients we noted that the inferior and nasal quadrants were significantly thinned. For the MSA-C group the temporal quadrant of the perimacular region alone was significantly thinned. These changes are summarised in Table 3 and illustrated in Figure 1C.

SARA Score Correlation with RNFL Thinning

Among the disease groups that had unique genotypes, SCA2 and SCA3 were found to have evidence of retinal thinning, therefore we correlated the OCT measurements and disease severity and duration for these two subgroups. We found a significant negative correlation between disease severity (SARA score) and RNFL thickness, $r = -0.76$ for SCA2 and $r = -0.89$ for SCA3 ($p < 0.05$). Higher SARA scores, indicating increased disease severity, correlated with a greater thinning of the RNFL in these groups.

DISCUSSION

To our knowledge, this is the first study comparing retinal thickness in distinct forms of ataxic syndromes using optical coherence tomography. Employing spectral-domain OCT, we found that SCA2 and SCA3 had thinning at the peripapillary RNFL, and SCA1, SCA3, SCA6, and MSA-C had thinning of the perifoveal macula. Segmenting of the different macular layers was not performed. RNFL and macular thicknesses, except for three patients, remained within the range of normal. This reflects that thinning, if present, is usually subclinical and subtle. Clinical utility of this finding would therefore be most relevant for group analysis rather than for individuals.

The ataxia syndromes usually have defects in ocular motility that dominate the clinical picture, and afferent visual abnormalities may go under-recognized. In a recent co-morbidity analysis using Medicare patient medical history data in the form of ICD-9 codes from 13 million patients, macular degeneration (ICD-9 362.50) was 2.7 times more likely to be diagnosed in degenerative cerebellar ataxia patients (ICD-9 23, 334.0, 334.2, 334.4, 334.8, 334.9) than controls.[33]

Our results suggest involvement of a population of cells in the eye not previously known to be affected in the SCAs,[1] although the structural basis is not known. The four SCAs in this study are caused by deleterious effects of a mutant ataxin protein containing an expanded polyglutamine tract, while the pathogenesis of MSA-C is less well understood. If the nature of the retinal neuronal involvement can be clarified through further study, it may add insights to the molecular and cellular pathogenesis of our findings. For example, in the case of retinal degeneration in SCA7, a pathologic examination of the retina showed severely degenerated photoreceptors with displacement of melanin pigment into the retina.[27] A cross-sectional study using OCT suggested that changes in SCA7 progress from altered foveal lamination to frank foveal and parafoveal retinal thinning.[27] Spectral-domain OCT analysis of individual layers of the retina in neurodegenerative diseases such as SCA and MSA-C may provide clues to the site of initial damage in the retina, and whether the photoreceptor layer might also be involved.[34]

OCT has become an important investigative tool in the documentation and study of neurologic disease. The greatest volume of data on the use of OCT for neurologic disease has been with multiple sclerosis.[20,35] Some conclusions arising from multiple sclerosis data likely pertain to SCA and MSA-C, such as that RNFL and macular thinning occur concomitant with disease progression, and that functional severity indices correlate with OCT thinning.[19] However, specific characteristics of multiple sclerosis–related OCT changes may not pertain to the ataxias, such as the correlation with brain parenchymal volume or rate of atrophy. Thinning of the RNFL has also been found in migraine,[36] Alzheimer's disease,[37] and Parkinson's disease.[38,39]

TABLE 3 Regional retinal thickness in ataxia subtypes and controls at retinal nerve fibre layer (RNFL) and macular regions.

Retinal region measured (μm)	Normal controls	SCA1 p-value	SCA2 p-value	SCA3 p-value	SCA6 p-value	MSA-C p-value
RNFL	98 (9)	93 (8) ns	84 (12) p <.001	85 (9) p < 0.01	95 (5) ns	100 (11) ns
Macula, 3 mm diameter	339 (17)	318 (28) p < 0.01	333 (18) ns	321 (7) p < 0.05	310 (5) p < 0.005	314 (12) p < 0.05
Macula, 6 mm diameter						
Global average	295 (17)	288 (18) ns	287 (10) ns	281 (3) ns	273 (5) p < 0.005	285 (15) ns
Temporal	281 (15)	274 (22) ns	279 (9) ns	264 (11) ns	260 (10) p < 0.005	265 (12) p < 0.05
Superior	296 (19)	287 (18) ns	291 (11) ns	288 (6) ns	278 (10) p < 0.05	289 (12) ns
Inferior	288 (16)	274 (18) ns	278 (12) ns	267 (11) p < 0.05	266 (9) p < 0.005	282 (20) ns
Nasal	312 (19)	309 (22) ns	301 (12) ns	288 (14) p < 0.05	286 (6) p < 0.01	299 (20) ns

SD-OCT thickness measurements (μm) of RNFL, macula at <3 mm and <6 mm diameters in SCA1, SCA2, SCA3, SCA6, and MSA-C and normal control subjects (s.d.), with p-value.

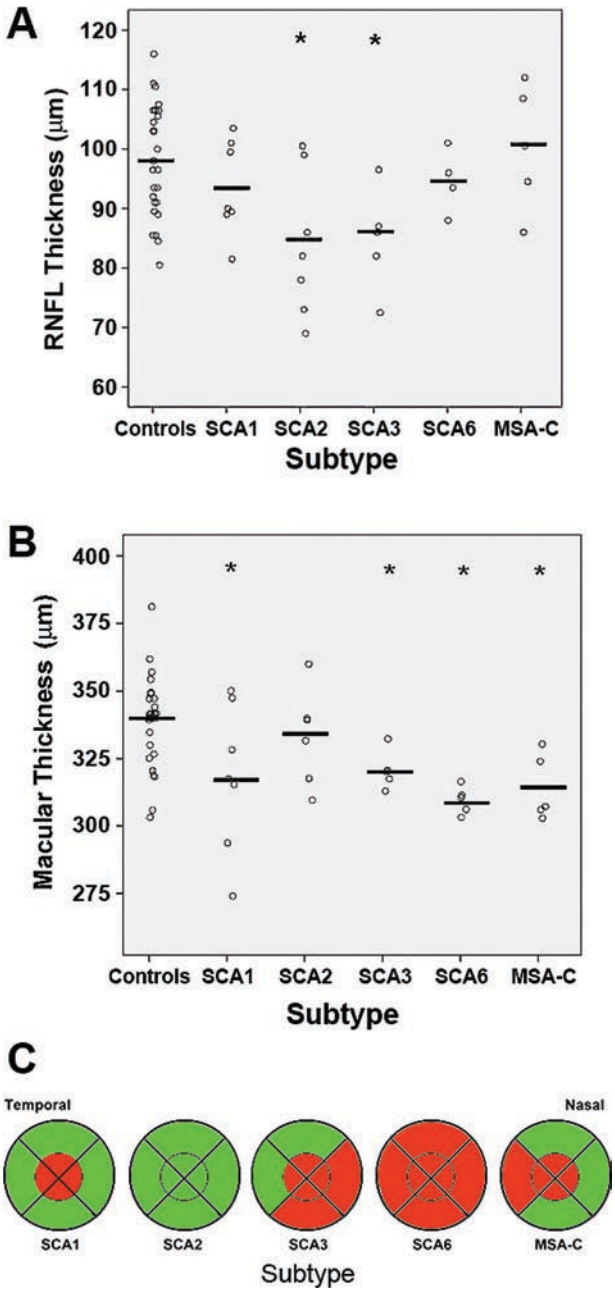

FIGURE 1 Retinal thinning in spinocerebellar ataxia. (A) Scatter plot of retinal nerve fibre layer thickness (microns) in controls and affected patients. (*significant difference from controls, $p < 0.01$). (B) Scatter plot of macular thickness (μm) at 3 mm diameter in controls and affected patients. (*significantly different from controls, $p < 0.05$). (C) Graphic summary of macular thinning at 3 mm and 6 mm diameters in each quadrant by genotype. Circles represent macula at 3 and 6 mm diameters, divided into superior, inferior, nasal, and temporal quadrants for each ataxia subtype as indicated. Dark shading indicates areas of significant thinning.

It is important to address the validity of these results with respect to age and age-related thinning of the RNFL. Although thickness maps are normalized for age during individual scan analysis, comparisons across groups require age matching, since RNFL thickness decreases with age by 0.17% annually after the age of 50.[40] In our study, the mean and median ages of our entire study population were similar to controls, but we did not control each ataxia subtype for age.

There are several other aspects of our study that require comment. First, the sample size for each ataxia subgroup was too small to make broad conclusions. However, our data provide preliminary evidence to warrant a larger study. Second, the purpose of this study was to provide correlation between an anatomic marker (RNFL/macula) and a disease state (ataxia). We did not test afferent visual function as part of this analysis. However, we acknowledge that, despite the potential confounding influence of ocular dysmotility, this would be of interest in a more extensive, separate study. Screening occurred for ocular diseases such as glaucoma or high myopia as exclusion criteria; however, a dilated ophthalmologic examination was not performed prior to OCT. Because spectral domain OCT has relatively high resolution, we would potentially have noted unexpected pathology during testing. Finally, although this was an unmasked study, since scan acquisition and analysis were not subjective, we felt that bias was minimised.

In summary, we demonstrate that retinal thinning may occur in the ataxia syndromes to a degree measurable on OCT. It is possible that patients with different subtypes of spinocerebellar ataxia exhibit distinct patterns of retinal thinning, and in some cases, disease severity may also correlate. If these results are reproduced with a larger sized cohort, posterior segment OCT would have potential to become a tool to establish surrogate biomarkers for the ataxia syndromes.

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***Note*:** Figure 1 of this article is available in colour online at www.informahealthcare.com/oph

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