Short communication

Finding of retinal nerve fiber layer hypertrophy in ataxia of Charlevoix-Saguenay patients

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Purpose/methods: To present the neuro-ophthalmology examination in 5 spastic ataxia of Charlevoix-Saguenay (ARSACS) patients showing significant increases in retinal nerve fiber layer (RNFL) thickness.
Results/conclusions: All patients showed abnormal visual fields, normal optic discs with increased visibility of RNFL in color stereo-photographs, normal examination with Heidelberg Retina Tomography instrument, and moderate to markedly increased RNFL thickness in Cirrus Optical Coherence Tomography evaluation (average thickness: 119–220 μm). We found evidence that RNFL hypertrophy may be an alternative funduscopic finding to the hypermyelinated retinal fibers in previous reports. A revision of ARSACS diagnostic criteria, particularly with regard to retinal alterations, is necessary.

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Hallazgo de hipertrofia de la capa de fibras nerviosas de la retina en pacientes con ataxia de Charlevoix-Saguenay

Resumen

Objetivo/método: Se presenta la evaluación neurooftalmológica de cinco pacientes con ataxia espástica de Charlevoix-Saguenay (ARSACS).
Resultados/conclusiones: Los pacientes mostraron alteración en el campo visual, aumento de la visualización de la CFNR en las estereofotografías, nervio óptico de morfología normal en la evaluación con Heidelberg Retina Tomograph e incremento marcado del espesor de la CFNR en la tomografía de coherencia óptica (119–220 μm). Encontramos evidencia de que la hipertrofia de CFNR puede ser un hallazgo funduscópico alternativo a la persistencia de...
Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a neurodegenerative disease highly prevalent in the region of Québec (Canada).

Patients exhibit difficulty for motility and deambulation since an early age (12–18 months). It usually expresses with ataxia, dysarthria, spasticity in extension plantar reflexes, sensitive/motor neuropathy and horizontal nystagmus. At the mean age of 41, patients need wheelchairs but cognitive abilities are preserved and they are able to carry out daily activities.

Fig. 1 – Representation of visual field and papillary morphology of one patient by Heidelberg Retina Tomograph (HRT).
activities up to later stages of adulthood. Generally, demise takes place in the sixth decade. Neuroimaging tests such as nuclear magnetic resonance (NMR) reveal atrophy in the upper vermis, cervical spinal cord and brain cortex.

Said disease is associated to mutations in gene SACS.\textsuperscript{3,4} Even though the initial descriptions of the disease were made in the province of Québec, genetically confirmed cases have been described in France, Tunisia, Italy, Spain, Japan and Turkey. Its true incidence is unknown but is probably underdiagnosed.\textsuperscript{3}

Several authors have described persistence of myelin fibers in these patients which focally cover retinal vessels from the papilla and advance radially extending toward the peripheral retina. However, these findings are not constant in individuals with ARSACS of European or Turkish inheritance.\textsuperscript{5}

Five patients (10 eyes) exhibiting significant RNFL thickness increase without signs of myelin persistence are presented. It is believed that RNFL hypertrophia found in these patients contributes a new clinical sign useful for diagnostic which would occur in some cases as reported by other authors who observed myelin fiber persistence in ocular fundus examinations.

**Clinic cases**

Five patients with clinic, genetic and molecular diagnostic of ARSACS without familial relationships between them were assessed. All exhibited spasticity in lower limbs, ataxia and abnormal reflexes. Molecular study demonstrated mutations in gene SACS, heterozygote in 4 patients and homozygote in one.

Complete neuro-ophthalmological examination including visual equity measurement, anterior segment biomicroscopy, gonioscopy, Goldman type applanation tonometry, central corneal thickness ultrasound pachymetry (DGH 500; DGH Technology, Exton, PA, United States), posterior segment ophthalmoscopy, automated perimetry with Humphrey Field analyzer (model 750i, SITA Standard 24-2 strategy) (Carl ZeissMeditec, Dublin CA), ocular fundus photographs, optic disk topographic analysis with Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering, Heidelberg, Germany), and optic coherence tomography (OCT) with Cirrus HD OCT (Carl ZeissMeditec, Dublin, CA).

The automated perimetry was carried out adding the appropriate refraction for near vision. All patients exhibited abnormal visual fields with slight to severe nonspecific defects and a mean deviation (MD) between $-3.24$ and $-21.99$ (Fig. 1).

Simultaneous optic disc stereophotographs were taken with a Canon CF-60UV camera (Canon S.A., Tokyo, Japan) under midriasis (utilizing 0.5% tropicamide eye drops, Laboratorios Alcon S.A., Barcelona, Spain) showing normal papillae with increased RNFL visualization in all patients (Fig. 2).

A series of 5 red-free digital photographs of each eye were taken with a Canon CF-60UV camera and a filter with a maximum transmission of 490 nm for assessing RNFL. Each monochromatic photograph was centered on the optic disc. Two additional images were taken, centering the image in each arced area. The monochromatic photographs showed marked increase of RNFL visibility in all patients (Fig. 3).

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**Fig. 2** – Color and monochromatic stereophotographs of the optic disk and retina nervous fiber layer of 2 patients with ARSACS. The assessed patients exhibited marked increase of retina nervous fiber layer (RNFL) thickness and increased RNFL visibility in the ocular fundus stereo photographs.
Fig. 3 – Retina nervous fiber layer evaluation of a patient with ARSACS by means of optic coherence tomography, showing marked increase of the central thickness and in quadrants and sectors (in white). The histological sections do not show the characteristic hyper-reflective strips with screen effect typical of myelin fiber persistence.

Topographic analysis with HRT 3 (Heidelberg Engineering, Heidelberg, Germany) provided topographic measures of the optic nerve head with 16–64 optic sections at a depth of 4 mm. Optic disc margin was marked by the ophthalmologist, a neuro-ophthalmology specialist, and the overall morphometric parameters were obtained. Sector examination was within normal limits in all cases (Fig. 1).

RNFL peripapillary thickness was measured by means of Zeiss OCT Cirrus (software version: 4.0.1.3; Carl ZeissMeditec, Dublin, CA) with the optic disk protocol which generates 200 × 200 images and analyzes a 6 mm diameter cube around the optic nerve. The mean thicknesses of RNFL, the 4 quadrants (superior, inferior, temporal and nasal) and of the 12 hourly sectors were obtained, and subsequently analyzed and
compared with the standard database of this instrument. A significantly increased thickness was observed (mean thickness of 119–220 µm) vis-à-vis normal values (96.0 ± 7.7 µm)\(^5\) (Fig. 3).

**Discussion**

Previous authors have considered the presence of myelin fiber persistence at the peripapillary level a minor criterion for the clinic diagnostic of ARSACS. In all the patients reported herein the authors have observed RNFL hypertrophy which could be an alternative clinical finding to the persistence of myelin fibers. For this reason, it is suggested that it would be necessary to review the diagnostic criteria for ARSACS, particularly with regard to the retinal alterations described to date.

The authors hypothesize that the funduscopic appearance of these patients could be compatible with RNFL hypertrophy in addition to the classic myelin fiber persistence criterion described in previous reports. Said hypothesis is supported by the fact that ultrasound tests in said patients have not confirmed the presence of myelin fiber persistence around retina ganglion fibers and that the neuroimaging tests suggest that the nerve fiber hypertrophy constitutes the etiopathogenic cause of ARSACS in these patients. In addition, nerve biopsies performed in patients to date have only revealed fiber hypertrophy but not an excess of surrounding myelin.\(^5\) The results of this study suggest that the yellowish spots observed in the ocular fundus of these patients could be caused by increased retina nerve fiber density in some cases although the anatomic pathological analysis of the retina of patients who died due to ARSACS is required to confirm said hypothesis.

**Conflict of interests**

No conflict of interests has been declared by the authors.

**References**