One of the rare causes of foveal hypoplasia: autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS)

Muhammet Emre Eryilmaz[1], *Serhat Sahin*[1], *Berrak Sekeryapan Gediz*[1]

ABSTRACT

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare disease that was first described in 1978. With the development of optical coherence tomography (OCT), ophthalmological findings, especially peripapillary retinal nerve fiber thickening, have been identified. In this article, we will present a patient diagnosed with ARSACS who has low vision and foveal hypoplasia, which is detected by OCT and OCT-Angiography. Based on this case, we aimed to evaluate ophthalmological findings of ARSACS disease, which is one of the rare causes of foveal hypoplasia.

Keywords: ARSACS, Autosomal recessive spastic ataxia of Charlevoix-Saguenay, Foveal hypoplasia, OCT, OCT-Angiography.

INTRODUCTION

Charlevoix-Saguenay autosomal recessive spastic ataxia (ARSACS) is a rare neurodegenerative disease characterized by slowly progressive cerebellar ataxia, spasticity, and demyelinating peripheral neuropathy due to atrophy of the upper vermis, cervical spinal cord, cerebellum, and cerebral cortex. It causes coordination disorders, dysarthria, weakness in the extremities, muscle cramps, and distal amyotrophy. Common ophthalmological findings in ARSACS include nystagmus, increased thickness of the inner retinal layers, and oculomotor neuropathies, while a limited number of cases have reported foveal hypoplasia.[1]

Although mitochondrial dysfunction is often blamed in the pathogenesis of the disease, the pathophysiology of the structural retinal anomalies observed during fundus examinations and revealed by optical coherence tomography (OCT) remains unclear.[2-4] This article discusses the ocular findings identified in a patient diagnosed with ARSACS and aims to emphasize the potential role of foveal hypoplasia in visual dysfunction in individuals with this condition.

CASE PRESENTATION

A 37-year-old male patient, followed up by the Physical Medicine and Rehabilitation clinic with a diagnosis of ARSACS, was referred to us due to complaints of reduced vision. In the ophthalmological examination, the best-corrected visual acuity was 20/40 in the right eye and 20/32 in the left eye. Intraocular pressure measurements were 13 mmHg in both eyes. The pupils were symmetric, and both direct and indirect light reflexes were positive, with no relative afferent pupillary defect noted. Eye movements were free in all directions; however, there was increased spontaneous nystagmus with fixation in the primary position and increased horizontal nystagmus in the horizontal gaze positions in both eyes. The anterior segment examination was unremarkable bilaterally. In the dilated fundus examination, notable findings included abnormal tortuosity of vascular structures, arteriovenous notching, a sclerotic appearance of the retinal arterioles, and prominent white striations in the peripapillary region of the retinal nerve fiber layer (RNFL) (Figure 1). In the systemic evaluation of the patient, no findings were identified that could explain the retinal vascular changes, such as systemic hypertension or conditions associated

1- Ankara Etlik City Hospital, Ophthalmology Department, Ankara, Türkiye

Received: 14.03.2024
Accepted: 29.08.2024

J Ret-Vit 2024; 33: 283-286

DOI:10.37845/ret.vit.2024.33.46

Correspondence author:
Muhammet Emre Eryilmaz
Email: emre9788@outlook.com

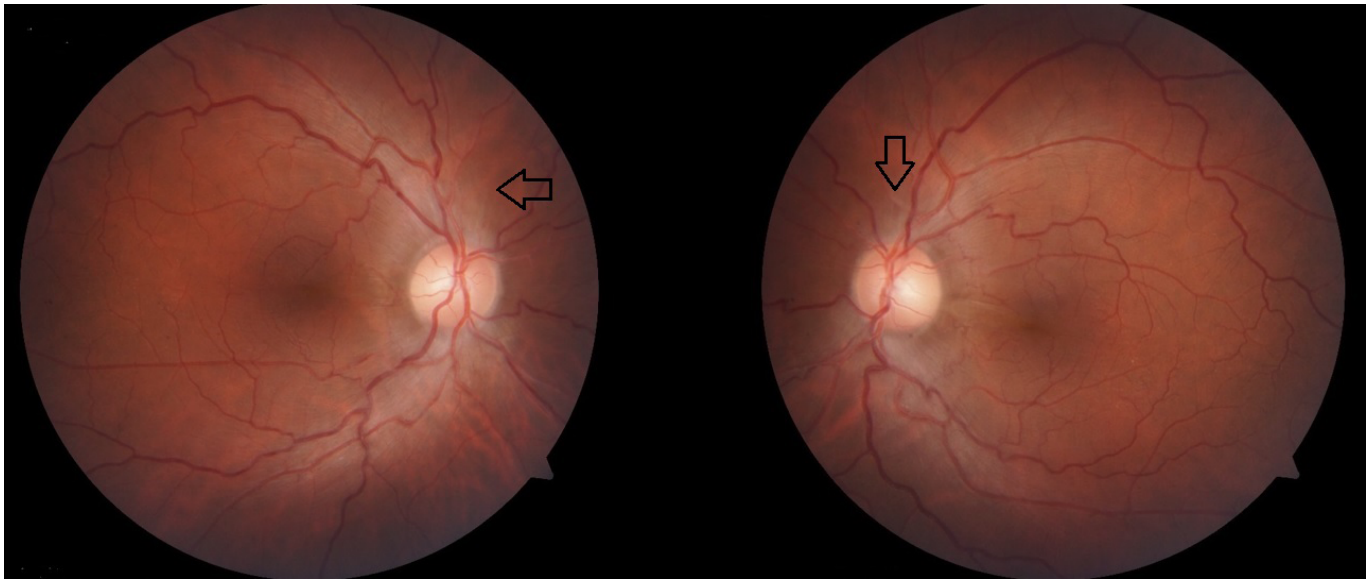

Figure 1: *In the color fundus photographs, increased tortuosity of the vascular structures and prominent white striations in the peripapillary region of the retinal nerve fiber layer (RNFL) are observed (black arrows).*

with hyperviscosity syndrome (e.g., coagulation disorders, polycythemia, sickle cell anemia, etc.). Optical coherence tomography (OCT) imaging showed increased thickness in the peripapillary retinal nerve fiber layer (RNFL) in all quadrants of both eyes, except for the nasal quadrant (Figure 2). In the OCT imaging, thickening of all inner retinal layers was observed in the peripapillary regions of both eyes, along with microcysts in the inner nuclear layer and ganglion cell layer. Additionally, prominent retinal folds resembling a "sawtooth" pattern were seen, involving the inner nuclear, outer plexiform, and outer nuclear layers. Bilateral absence of foveal pit was noted, with continuity of the inner retinal layers across the fovea (Figure 3). In the OCT angiography, the foveal avascular zone was not observed (Figure 4).

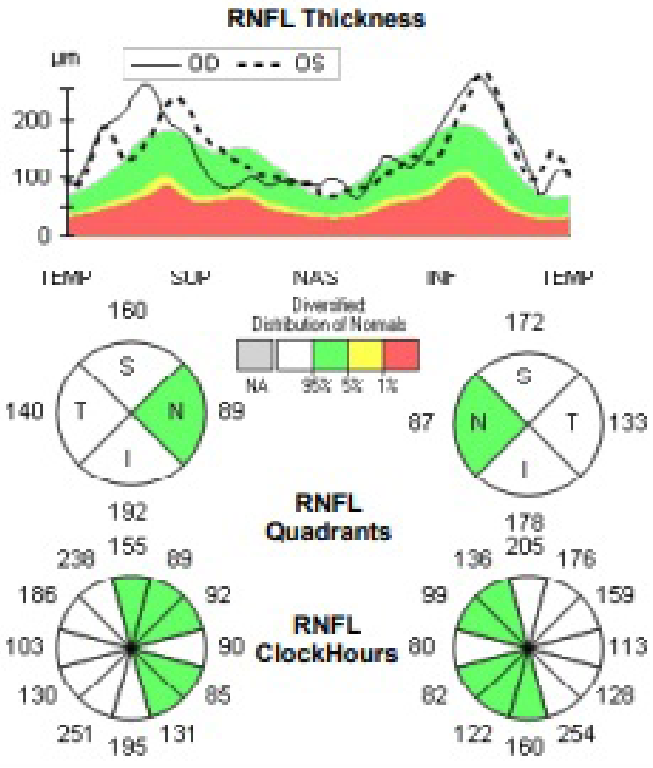

Figure 2: *The OCT RNFL thickness analysis shows an increase in thickness in all quadrants of both eyes, except for the nasal quadrant.*

DISCUSSION

ARSACS was first described in 1978 among patients in Québec, Canada. Subsequently, genetically confirmed cases have been reported from France, Spain, Japan, and Turkey. In 2000, mutations in the SACS gene localized on chromosome 13q12.12 were identified, establishing that this gene is responsible for ARSACS.[1,5] ARSACS arises from mutations in the SACS gene, which encodes the protein sacsin. The dysfunction of sacsin, a protein that shows mitochondrial localization and is especially abundant in cerebellar Purkinje cells, leads to impaired mitochondrial flow, resulting in a slowdown and edema in axoplasmic flow. This is noted to be the cause of thickening in ganglion cells and the RSLT. Thickening of the RSLT has became specific for ARSACS, especially since it is not observed in other neurological diseases that present with ataxia, and has become one of the criteria used in the diagnosis of the disease over time.[3,6] However, it has been noted that RSLT thickening occurs less frequently in patients outside of Québec, where the disease was first described. Reports from Turkey support this finding, as RSLT

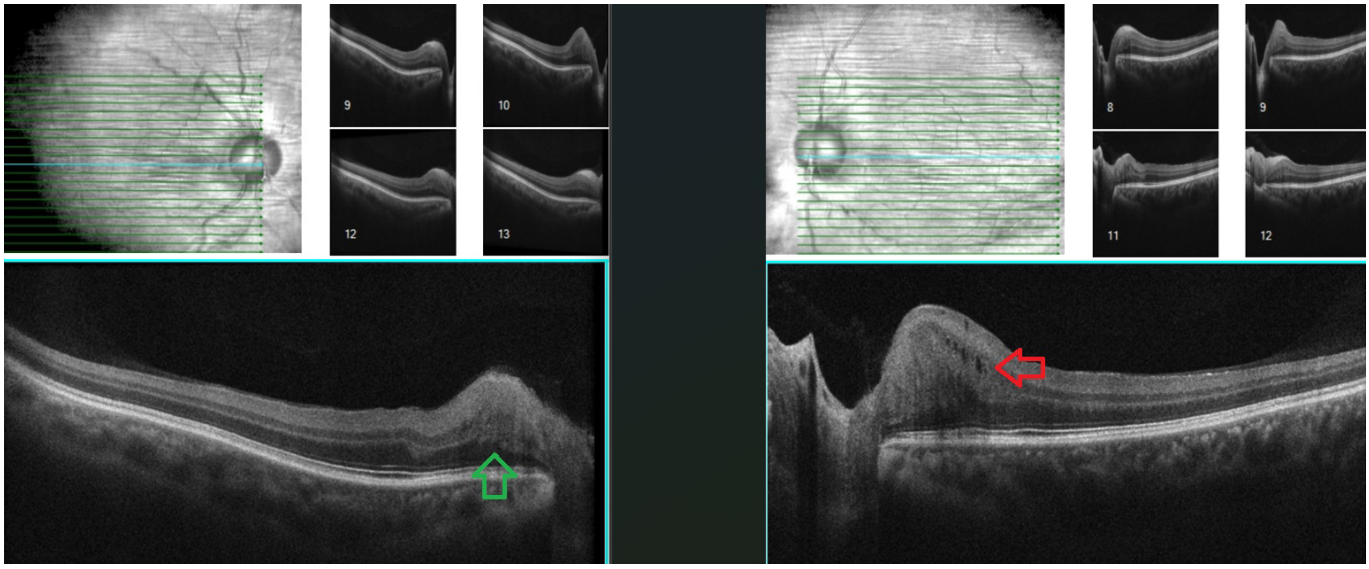

Figure 3: *In the OCT imaging, thickening of all inner retinal layers is observed in the peripapillary regions of both eyes, along with microcysts in the ganglion cell layer and inner nuclear layer (red arrow). Prominent retinal folds resembling a "sawtooth" pattern, involving the inner nuclear, outer plexiform, and outer nuclear layers (green arrow), indicate the absence of the foveal pit, consistent with foveal hypoplasia in cross-sections through the fovea and perifoveal region.*

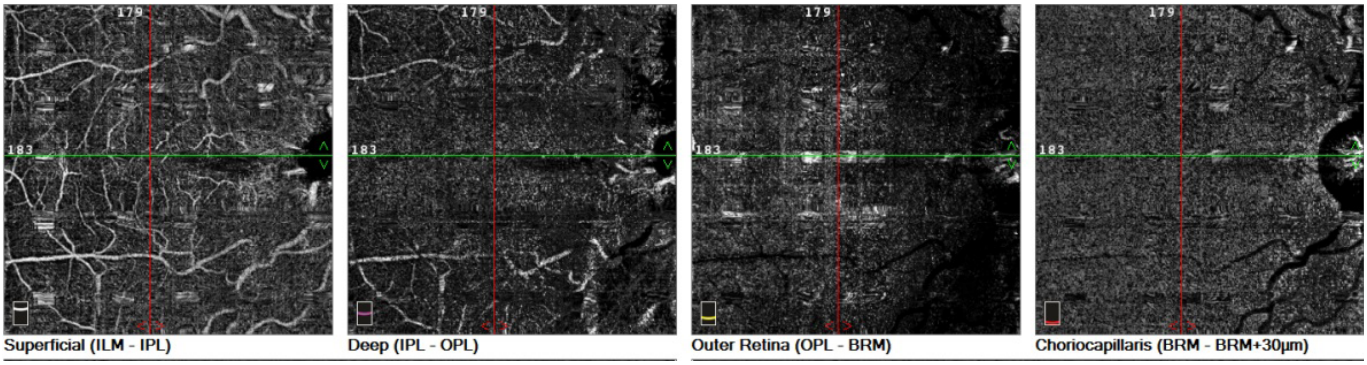

Figure 4: *The OCT angiography image shows the absence of the foveal avascular zone in the right eye. (Due to increased horizontal nystagmus, a clear image could not be obtained from the fovea of the left eye.)*

thickening and other ophthalmological findings associated with the disease are not observed in these patients, while horizontal nystagmus that worsens with horizontal gaze due to cerebellar dysfunction is a common finding.[6-8] More than 170 mutations associated with the disease have been reported, and it is thought that these genetic variations are responsible for the phenotypic differences observed among regions and patients where the disease is seen.[6]

It is thought that the loss of the foveal pit in ARSACS patients is secondary to thickening in RSLT, while it is now suggested that SACS mutations directly lead to abnormalities in prenatal foveal development and that foveal hypoplasia emerges as a distinct entity.[5,9] The absence of the foveal avascular zone is also considered a supportive finding for this idea and may provide insights into understanding the pathogenesis of the disease in the future.[9]

Foveal hypoplasia is defined as an ocular anomaly where the foveal pit is partially or completely underdeveloped, along with continuity of all neurosensory retina layers in the area expected to be the fovea. Abnormal development of the foveal pit is associated with the absence or underdevelopment of the foveal avascular zone. Major causes of foveal hypoplasia include albinism, aniridia, incontinentia pigmenti, achromatopsia, optic nerve hypoplasia, familial exudative vitreoretinopathy, congenital retinal macrovascular abnormalities, and Stickler syndrome.[10]

Many studies have been conducted on the increase in thickness of the peripapillary RSLT in ARSACS, and it has been shown that this finding does not lead to any visual symptoms or dysfunction in patients.[2,5,11] However,

it appears that there have not been enough studies focusing on the pathophysiology and effects of foveal hypoplasia, which could potentially cause visual dysfunction in these patients. In a study involving 29 ARSACS patients, it was observed that all patients had foveal hypoplasia, indicating that this finding is as specific to ARSACS as the peripapillary RSLT thickening.[5]

Thomas and colleagues classified foveal hypoplasia into stages 1-4 based on OCT findings, and it was revealed that advancing stages are associated with a decrease in visual acuity.[10] In previously reported cases of ARSACS with foveal hypoplasia, stages 1-2 of foveal hypoplasia were detected, and it was reported that there was no significant decrease in the visual acuity of the patients.[5,11,12] Our case comply with stage 4 foveal hypoplasia due to continuity of the inner retinal layers in the fovea, absence of the foveal pit, absence of elongation in the outer photoreceptor layer, and absence of expansion in the outer nuclear layer, this condition explains the patient's low visual acuity. Although ARSACS also affects the cerebral cortex and is associated with nystagmus, it should be kept in mind that advanced foveal hypoplasia may also be one of the causes of visual impairment in these patients.

REFERENCES

1. Garcia-Martin E, Pablo LE, Gazulla J, et al. Retinal segmentation as noninvasive technique to demonstrate hyperplasia in ataxia of Charlevoix-Saguenay. Invest Ophthalmol Vis Sci 2013;54:7137-7142. https://doi.org/10.1167/iovs.13-12726
2. Parkinson MH, Bartmann AP, Clayton LMS, et al. Optical coherence tomography in autosomal recessive spastic ataxia of Charlevoix-Saguenay. Brain 2018;141:989-999. https://doi.org/10.1093/brain/awy028
3. Garcia-Martin E, Pablo LE, Gazulla J, Polo V, Ferreras A, Larrosa JM. Retinal nerve fibre layer thickness in ARSACS: myelination or hypertrophy? Br J Ophthalmol 2013;97:238-241. https://doi.org/10.1136/bjophthalmol-2012-302309
4. Yu-Wai-Man P, Pyle A, Griffin H, Santibanez-Korev M, Horvath R, Chinnery PF. Abnormal retinal thickening is a common feature among patients with ARSACS-related phenotypes. Br J Ophthalmol 2014;98:711-713. https://doi.org/10.1136/bjophthalmol-2013-304534
5. Rezende Filho FM, Bremner F, Pedroso JL, et al. Retinal Architecture in Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS): Insights into Disease Pathogenesis and Biomarkers. Mov Disord 2021;36:2027-2035. https://doi.org/10.1002/mds.28612
6. Samanci B, Gokalp EE, Bilgic B, Gurvit H, Artan S, Hanagasi HA. A novel SACS p.Pro4154GlnfsTer20 mutation in a family with autosomal recessive spastic ataxia of Charlevoix-Saguenay. Neurol Sci 2021;42:2969-2973. https://doi.org/10.1007/s10072-021-05117-1
7. Sahin T, Karaarslan FT, Yilmaz R, Tekgül Ş, Başak AN, Akbostanci MC. Two cases of early-onset autosomal recessive spastic ataxia of Charlevoix-Saguenay diagnosed in adulthood. Clin Neurol Neurosurg 2021;201:106423. https://doi.org/10.1016/j.clineuro.2020.106423
8. Incecik F, Hergüner OM, Bisgin A. Autosomal-Recessive Spastic Ataxia of Charlevoix-Saguenay: A Turkish Child. J Pediatr Neurosci 2018;13:355-357. https://doi.org/10.4103/JPN.JPN_8_18
9. Douglas VP, Douglas KAA, Miller JB, Gaier ED. Absent Foveal Avascular Zone in Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. J Neuroophthalmol 2021;41:e166-e168. https://doi.org/10.1097/WNO.0000000000001050
10. Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? Ophthalmology 2011;118:1653-1660. https://doi.org/10.1016/j.ophtha.2011.01.028
11. Borruat FX, Holder GE, Bremner F. Inner Retinal Dysfunction in the Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. Front Neurol 2017;8:523. https://doi.org/10.3389/fneur.2017.00523
12. Shah CT, Ward TS, Matsumoto JA, Shildkrot Y. Foveal hypoplasia in autosomal recessive spastic ataxia of Charlevoix-Saguenay. J AAPOS 2016;20:81-83. https://doi.org/10.1016/j.jaapos.2015.10.007