Introduction

Diffuse unilateral subacute neuroretinitis (DUSN) is a rare but sight-threatening inflammatory retinal condition caused by a nematode that invades the sub-retinal space.[1-15] The condition, originally termed "Unilateral Wipeout Syndrome" was first described by Gass in 1977, and later re-named by Gass and Scelfo in 1978.[11,15] DUSN tends to affect healthy, young adults in their second to third decade of life, with a higher incidence occurring in males.[8,10,15] Various nematodes have been implicated throughout the world, with the primary differences being their size and the animal from which they are derived, most notably dogs and raccoons.[12,15] The precise pathophysiology of DUSN is not entirely understood. The neuroretinitis is believed to occur due to a local immune reaction to toxic substances released by the nematode in the sub-retinal space, as well as by physical disruption of the retinal layers during nematode migration.[2,8,10,15] Interestingly, it is possible for the nematode to lie dormant in the retina for several years before reactivating and causing clinical manifestations again.[8]

The clinical presentation of DUSN varies from early to late stages of the condition. During the early stage, the patient may be asymptomatic or present with mild symptoms, such as blurring of vision. Initial presentation often shows minimal objective findings; most commonly, multiple gray-white retinal lesions.[15,17] In the subsequent stages, the patient typically presents with a complaint of unilateral, insidious, severe vision loss and a dense central or paracentral scotoma.[8,10,12] Upon examination, an afferent pupillary defect (APD), optic disc edema, progressive optic nerve atrophy, retinal vessel attenuation, focal and/or diffuse retinal pigment epithelium degeneration, and arterial sheathing will likely be present in the involved eye.[1,8] The late stage of this condition is visually devastating and permanent. The following case represents examination findings, diagnosis, and management of a patient with DUSN in the late stage.

Case Report

A 29-year-old Spanish speaking Hispanic male from Cuba presented with complaints of mild blur in the right eye (OD) and progressive central and peripheral vision loss in the left eye (OS) since his late teens. He described the vision loss in his left eye as a "blacked out" central region with significant peripheral blur. He denied any history of ocular trauma. The patient confirmed that he initially discovered his poor vision in his left eye when he was 19 years old at a military screening in Cuba. At that time, he was referred to an eye care specialist where he received an initial diagnosis of "nerve damage." A second eye care provider suspected previous "parasitic infection". The patient did not recall taking any prescribed oral anti-helminthic medication for the presumed parasitic infection. He reported that he had excellent vision in both eyes as a child. The patient indicated

that the reduced vision in his left eye had been long-standing and stable for several years.

The patient had never worn spectacles. His most recent eye examination was one year prior and no treatment was initiated at that time. His personal medical, family medical and family ocular histories were all unremarkable. He was not taking any ocular or systemic medications. He did not have any known allergies. He occasionally drank alcohol and smoked one pack of cigarettes per day. The patient's uncorrected visual acuities at distance were: 20/20 OD, light projection in all four quadrants (no improvement with pinhole) OS. Motilities were full and eye posture orthophoric with Hirschberg. Confrontation visual fields were full to finger counting OD and showed a central scotoma (using dynamic approach) with hand motion perception in the periphery OS (unable to make out fingers, but could see movement). Pupils measured 7mm OD and OS. The right pupil had a brisk reaction to light while the left pupil exhibited a sluggish reaction to light and a Grade 4 afferent pupillary defect (APD). Retinoscopy revealed: OD +0.25-1.00x170, OS +0.25-0.75x165. Best-corrected visual acuity (BCVA) in the right eye was 20/15 at distance and 20/20 at near with a manifest refraction of +0.75 -0.75x005; there was no improvement in visual acuity in the left eye.

Slit lamp examination of the anterior segment revealed Grade 1 meibomian gland dysfunction in both eyes, Grade 2 pingueculae nasal and temporal in both eyes, and small scattered opacities and vacuoles in the lens of the left eye. All other biomicroscopic findings were unremarkable and there were no signs of inflammation. Intraocular pressures (IOP) obtained by Goldmann tonometry were 12mm Hg OD and 13mm Hg OS. Dilated fundus examination was unremarkable in the right eye. Several findings were noted in the left eye: 4+ diffuse pallor of the optic nerve head (ONH), shallow optic cup (difficulty appreciating contour due to pallor), retinal nerve fiber layer (RNFL) defects, diffuse macular atrophy with scattered pigment clumping, and sclerotic and attenuated arterioles. Fundus photographs of the posterior poles were obtained (Figure 1A), as well as spectral-domain optical coherence tomography (SD-OCT) of the optic nerve and retinal nerve fiber layer, macula, and ganglion cell complex, which all had high signal strength scores.

The SD-OCT macula thickness analysis (Figure 2A) showed relatively normal results in the right eye, with slight thickening of the inner retinal layers. There was diffuse macular thinning in the left eye, with abnormal shape and contour, and disruption of the RPE layer. The ganglion cell analysis (GCA; Figure 2B) supported the results of the macular thickness scan. The GCA results in the right eye were within normal limits, whereas the left eye showed diffuse thinning with an almost

non-existent ganglion cell layer. The instrument was unable to record numerical thickness values for the ganglion cell thickness in the left eye.

SD-OCT was also used to evaluate the ONH and RNFL of each eye (Figure 3). The results in the right eye were within normal limits, with an average RNFL thickness of 98 microns. The results in the left eye revealed severe neuro-retinal rim thinning and atrophy in all quadrants, with severe superior and inferior RNFL thinning and mild nasal RNFL thinning. The average RNFL thickness in the left eye was 46 microns.

The patient was diagnosed with hyperopic astigmatism in the right eye and a final prescription was released with a balance lens prescription for the left, with the recommendation of polycarbonate lenses for protection. He was counseled at that time about the atrophic changes in the left optic nerve and macular area, and that the specific diagnosis and cause of his vision loss in the left eye was unknown. He was educated on the importance of an annual dilated fundus examination (DFE) and recommended annual SD-OCT and fundus photos to monitor for progression of the condition. He was asked to return in 1 month for further evaluation, including electrophysiology, to further explore the etiology of the findings in the left eye. Fluorescein angiography may have proven to be useful, however, the patient was unable to pursue a retina specialist appointment due to financial restrictions.

The following differential diagnoses that were considered after the first visit included: unilateral retinitis pigmentosa, previous infectious retinochoroiditis, traumatic retinopathy, retinal vascular occlusion, compressive lesion, and DUSN. The patient's history of "optic nerve damage" and "parasitic infection," as well as the clinical signs and symptoms were most consistent with DUSN.

Additional Testing

The patient returned to undergo electrophysiology for his history of long-standing, insidious vision loss in the left eye. The patient had filled the spectacle prescription given to him at the previous visit and was wearing them full time. His VA with correction was 20/15- Snellen OD, 5/200 PRL 1 o'clock with the Feinbloom chart OS. His color vision was normal OD, and un-recordable OS. Pupil testing was consistent with results documented at the previous visit and additionally a neutral density 1.6 filter was used to neutralize the APD OS (needs 40x more light in left eye). All other findings were consistent with those obtained on the first visit.

Fundus photographs were taken with and without fundus autofluorescence (FAF) to better characterize the nature of the insult to the left eye, including evidence of

the nematode presence or tracking changes sometimes found in DUSN (Figure 1B). There was a serpiginous-appearing pattern of hyperpigmentation superficial to the macular atrophy OS, which may have been the result of long-standing presence of the nematode, however, no other evidence of parasitic tracking was noted upon examination of the fundus and photographs.

The dark-adapted full-field (flash) electroretinography (ERG) results were unremarkable in the right eye but showed a decreased b-wave in the left eye. Similarly, the photopic ERG b-wave response was relatively decreased in the left eye, consistent with the funduscopic and OCT findings, and suggestive of a more diffuse retinal dysfunction. Multi-focal ERG (mfERG) testing was also performed on each eye. The mfERG assesses responses from the retina in many subfields extending 60 degrees horizontally and 40 degrees vertically. The mfERG results in the right eye were well within normal limits, while the results in the left eye revealed that the majority of retinal responses from cone and cone bipolar cells were below normal in amplitude (>2SD below age-matched mean). The mfERG findings in the left eye indicated a more global adverse effect on cone and cone bipolar cell function despite the peripheral retina appearing normal on dilated fundus examination. It is likely that toxins released by the nematode, as well as the body's eosinophilic reaction to the toxins, contributed to a decrease in choriocapillaris function, producing a more diffuse effect on retinal function.[2,8,11,15] (Figure 4)

Visual-evoked potential (VEP) testing (Figure 5), which provides an objective index of central vision at the level of the visual cortex, showed normal amplitude and latency in the right eye and was unrecordable in the left eye, which is consistent with severe optic atrophy and loss of central visual function.

After this patient's follow up visit, his medical records were retrieved which revealed that his eosinophil count, tested 3 months prior when entering the United States as a refugee, was elevated (0.79 K/mcL). He was prescribed two tablets of Albendazole 200mg one time by mouth and Ivermectin 3mg four tablets a day for two days by mouth for treatment. It is unknown what parasite was responsible for the high eosinophilia count, however, the treatment would have remained the same. He did not recall receiving treatment for any parasitic infection prior to this instance. Additional serology testing may have proven to be useful to rule out conditions such as toxoplasmosis, however, we were only able to recommend testing through his refugee program.

The patient's history, signs and symptoms, clinical appearance, electrophysiology testing and OCT results were consistent with DUSN. Because there was no direct

evidence of a retinal nematode, our diagnosis remains presumptive, though likely, given the pattern of visual loss, patient's geographic history, objective findings, and previous parasitic infection. The patient was educated on his condition at that visit and informed of the possibility of the nematode lying dormant in the retina. Due to the long-standing and apparent stable nature of his ocular condition, he was advised to return for a comprehensive eye examination, SD-OCT, and fundus photos in one year, unless he experienced any changes or worsening of his vision. He was encouraged to continue wearing his glasses (polycarbonate lenses) full time, in order to protect his right eye

Discussion

The pathogenesis of DUSN is not completely understood, but it is generally agreed that this condition, which is caused by a nematode in the subretinal space, results in destructive, irreversible vision loss. Two "types" of nematodes have been documented as being responsible for DUSN and may be distinguished based on size. The small nematodes, namely *Toxocara canis* and *Ancylostoma caninum*, more commonly responsible for DUSN, originate from dogs and tend to predominate in the southeastern United States, Caribbean, Brazil, Venezuela and northern South America.[1,8,12,15] The larger nematode, *Baylisacaris procyonis*, is a less common cause that originates from raccoons and tends to predominate in the northwestern United States, Europe, Japan and Brazil.[1,2,12,15] There have also been cases documented in Canada, China, and India with no predilection for nematode type.[8,12] The circle of life of these nematodes begins with dogs and raccoons acting as parasitic hosts, harboring larvae, which they can then shed as ova.[11-12] These ova are able to survive long-term in soil, are resistant to disinfectants and bleach, and may be accidentally ingested by young, healthy humans.[11,15]

Another mode of infestation involves the nematode penetrating intact skin, and then traveling through the blood stream to the lungs. The nematode may be expelled, then accidentally swallowed, ending up in the gastro-intestinal tract.[12] After ingestion, the nematode migrates outside of the intestinal wall and causes an eosinophilic reaction.[11] It is hypothesized that an over-action of the immune system during this eosinophilic response causes disruption to the choroid and retinal layers, affecting retinal blood supply.[11,15] It is also thought that the toxins that the nematode itself releases once it invades the retina damages the inner retinal layers.[2,8] During the early stage of DUSN, the patient may report symptoms such as unilateral mild vision loss, floaters, small central or paracentral scotoma, and/or ocular discomfort from intraocular inflammation.[16] Upon examination, a mild posterior uveitis, papillitis, clusters of multiple evanescent gray-white outer retinal lesions, mild APD, and/or focal chorioretinal scars may be present.[1,3,15-16] In the late stage, the patient will typically present with a complaint of unilateral insidious, severe vision

loss and a dense central or paracentral scotoma.[2,14-16] Upon examination, an APD, progressive optic atrophy, retinal vessel attenuation, focal and/or diffuse retinal pigment epithelium degeneration, and arterial sclerosis will likely be present, unilaterally.[2-3,13-16]

Differential diagnoses for DUSN differ for early versus later stage. In the early stage of the disease, differentials may include: vasculitis, multiple evanescent white dot syndrome (MEWDS), histoplasmosis, toxoplasmosis, syphilitic chorioretinitis, sarcoid retinopathy, and acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[2,8] In the late stage of the disease differentials may include: unilateral RP, past inflammatory conditions including toxoplasmosis, occlusive vascular disease, compressive lesion, and post-traumatic chorioretinopathy.[10] Electrophysiology is a useful method for differentiating several of these conditions from one another.[14,16] There was no evidence of active inflammation, as you may see with ocular toxoplasmosis. Ocular toxoplasmosis rarely occurs in an immunocompetent adult and the majority of congenital cases are bilateral, whereas this patient's findings presented unilaterally. Additionally, he had a large oval macular scar, not typical of ocular toxoplasmosis, and without evidence of adjacent scar or re-activated lesions. This patient had unilateral disc pallor and attenuation of the vessels, consistent with unilateral RP, however, absent were bone spicules or distinct areas of hyperpigmentation in the periphery. RP was ruled out because the photopic ERG results, though reduced, were not completely extinguished, as they would be in RP. The patient did not have any medical history of serious systemic infection at the time of evaluation. The patient underwent laboratory analysis for syphilis (RPR, VDRL, FTA) three months prior, which was negative, so syphilitic retinopathy was ruled out. A prior vascular occlusion could also have explained the attenuation and sheathing of the vessels, as well as ischemia of the RNFL and effects on the ERG b-waves because of disrupted or blocked blood flow to the retina at some point. No emboli or collateral vessels were present, and the macular atrophy did not fit with this diagnosis. A compressive lesion was of concern because of the unilateral disc pallor, however, the macular atrophy and other findings did not fit. Had the electrodiagnostic testing results been inconclusive, the patient would have been advised to undergo neuroimaging to rule out an orbital or intracranial lesion. Traumatic optic neuropathy and retinopathy were ruled out because the patient did not report any history of trauma, nor did he present with any other signs of trauma, such as unilateral cataract, iris damage, or choroidal rupture.

The gold standard for diagnosis of DUSN is localization of a nematode in the subretinal space.[1-16] The percentage of cases where a nematode is actually located varies in the literature, but the range tends to be between 25-50%; in other words, more than 50% of the time a nematode is not localized.[3,14] There are many tools

that optometrists can use to aid in the diagnosis of DUSN, including fundus autofluorescence (FAF) imaging, SD-OCT and ERG. FAF will show hyperautofluorescence in areas of poor functioning RPE and hypoautofluorescence in areas of RPE atrophy. SD-OCT in late DUSN will show diffuse full-thickness retinal thinning and RNFL thinning, with possible focal edema in areas where the nematode is present.[7,8] ERG may be normal to subnormal in the early stage, whereas late stage will reveal subnormal to severely decreased a- and b-waves (b>a).[8,17] Fluorescein angiography typically shows leakage of dye from the optic nerve and periphlebitis with minimal changes in the RPE during the early stage; whereas late stage will reveal a diffuse hypofluorescence and delayed retinal perfusion.[8] OCT angiography (OCTA) may prove to be useful in identifying areas of poor retinal perfusion, however, areas of leakage will not be visible. Lab testing may involve serological tests, peripheral blood smears, and stool tests, though they tend to be of little value.[8] ELISA with *Toxocara* excretory-secretory antigen (TES-Ag) may prove to be useful if *T. canis* is the culprit, though the most accurate results will come from aqueous fluid testing, rather than blood serum. Currently, there is not a serological test for *A. caninum* or *B. procyonis*, however, cerebrospinal fluid and serum may be tested for antibodies to the excretory-secretory antigens.[8,12]

Treatments options for DUSN are limited. Currently, laser photocoagulation is the treatment of choice in active cases for directly killing the nematode.[3,11,15] Oral anti-helminthic medications have been documented as showing only variable success because of their relative impermeability to the blood retinal barrier.[1] Corticosteroids may be useful in helping to control and decrease inflammation during the early stage of the condition. Vision improvement and prognosis depends on the stage of the condition at the time of treatment. Some studies have shown that despite treatment, the patient will continue to progress to the late stage of the disease, resulting in unilateral, permanent loss of vision.[4] Other reports have shown that upon successful, early treatment, photoreceptor anatomy and function, and ultimately vision, may be partially restored.[2] Overall, the long-term visual prognosis is variable.

Since effectiveness of oral anti-helminthic treatment for DUSN is inconsistent, it is possible that the causative nematode may be dormant but viable in the macular region of this patient. If the nematode is lying dormant, the possibility exists that it may become mobile again and cause further destruction. However, it is also possible that the oral-antihelminthic treatment that the patient received three months prior destroyed the nematode and that was why it could not be localized.

Conclusion

DUSN may cause devastating monocular vision loss in otherwise healthy individuals. In addition to classic findings of optic atrophy and arteriolar attenuation, our patient demonstrated unique degenerative macular changes. The combination of multimodal retinal and optic nerve imaging and selective electro-diagnostic testing proved invaluable in establishing the presumptive diagnosis of this rare condition.

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Figures/Captions

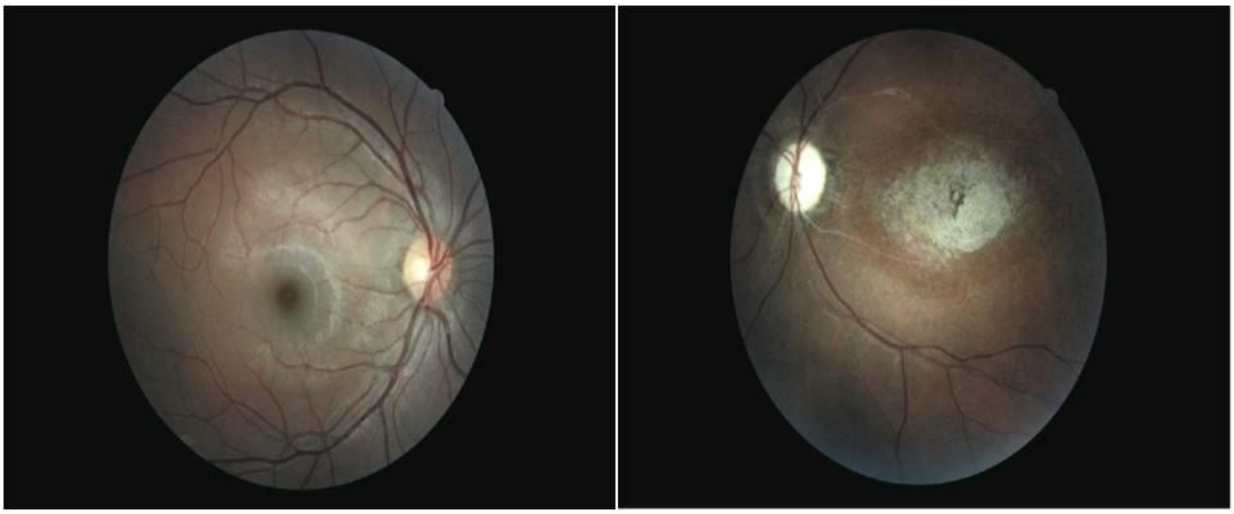

Figure 1A. Color fundus photos of the posterior poles. The right eye was within normal limits, however, the left eye showed diffuse 4+ optic nerve head pallor, sclerotic vessels, and a large macular atrophic scar with superficial pigment hyperplasia.

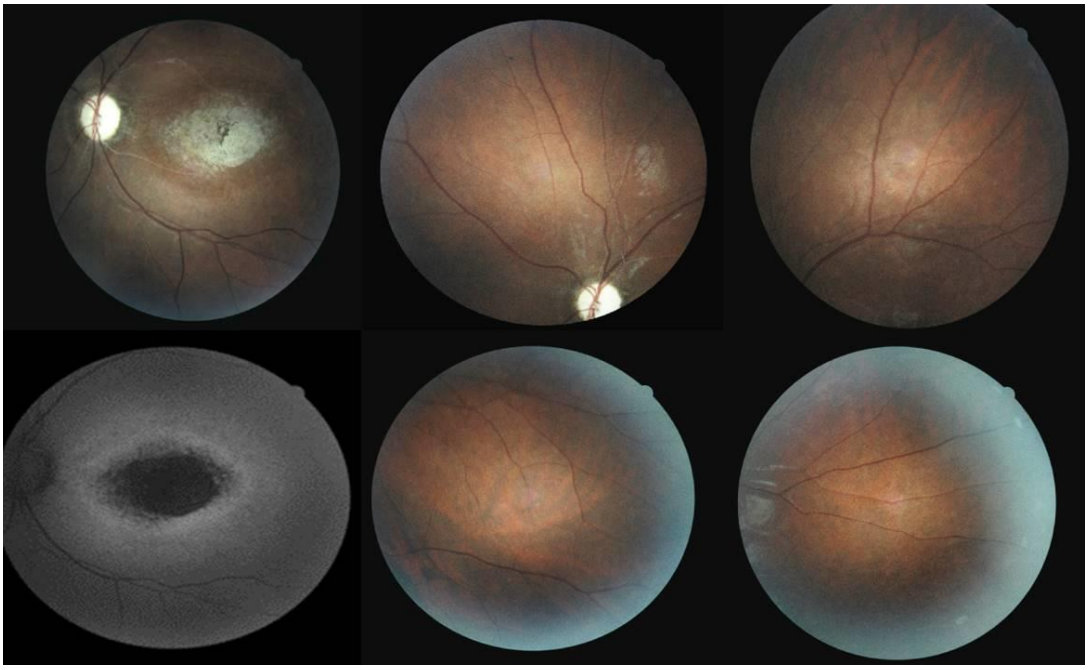

Figure 1B. Fundus photos of the periphery with and without fundus autofluorescence (FAF) taken to search for any evidence of the nematode or for tracking changes. Small linear areas of hypopigmentation were seen in the left eye which could be evidence of tracking, however, a nematode was not spotted.

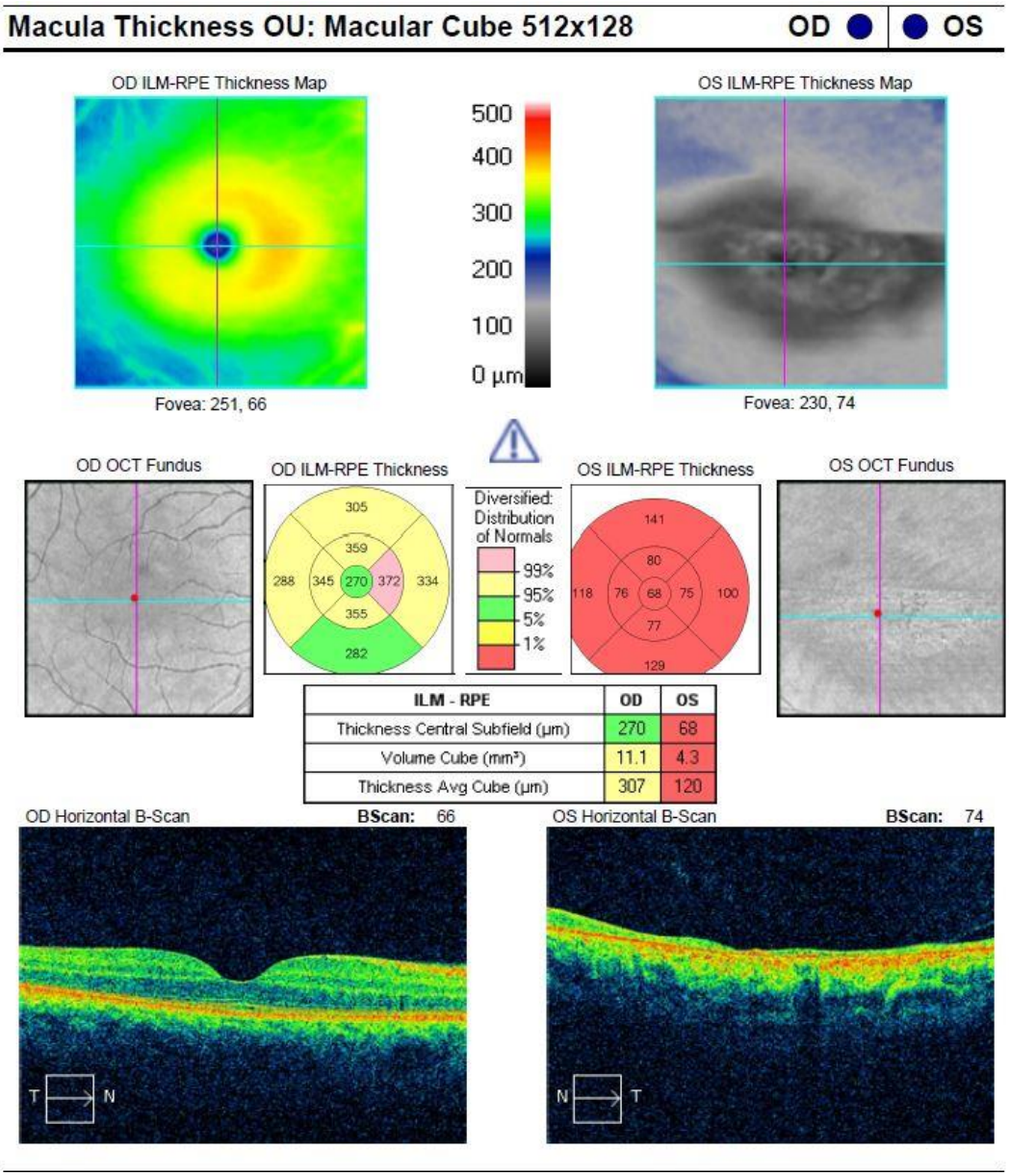

Figure 2A. Optical coherence tomography (OCT) of the maculas. There was normal foveal contour and slightly increased retinal thickness in the right eye, with diffuse thinning of all retinal layers and outer retina layer disruption in the macula of the left eye.

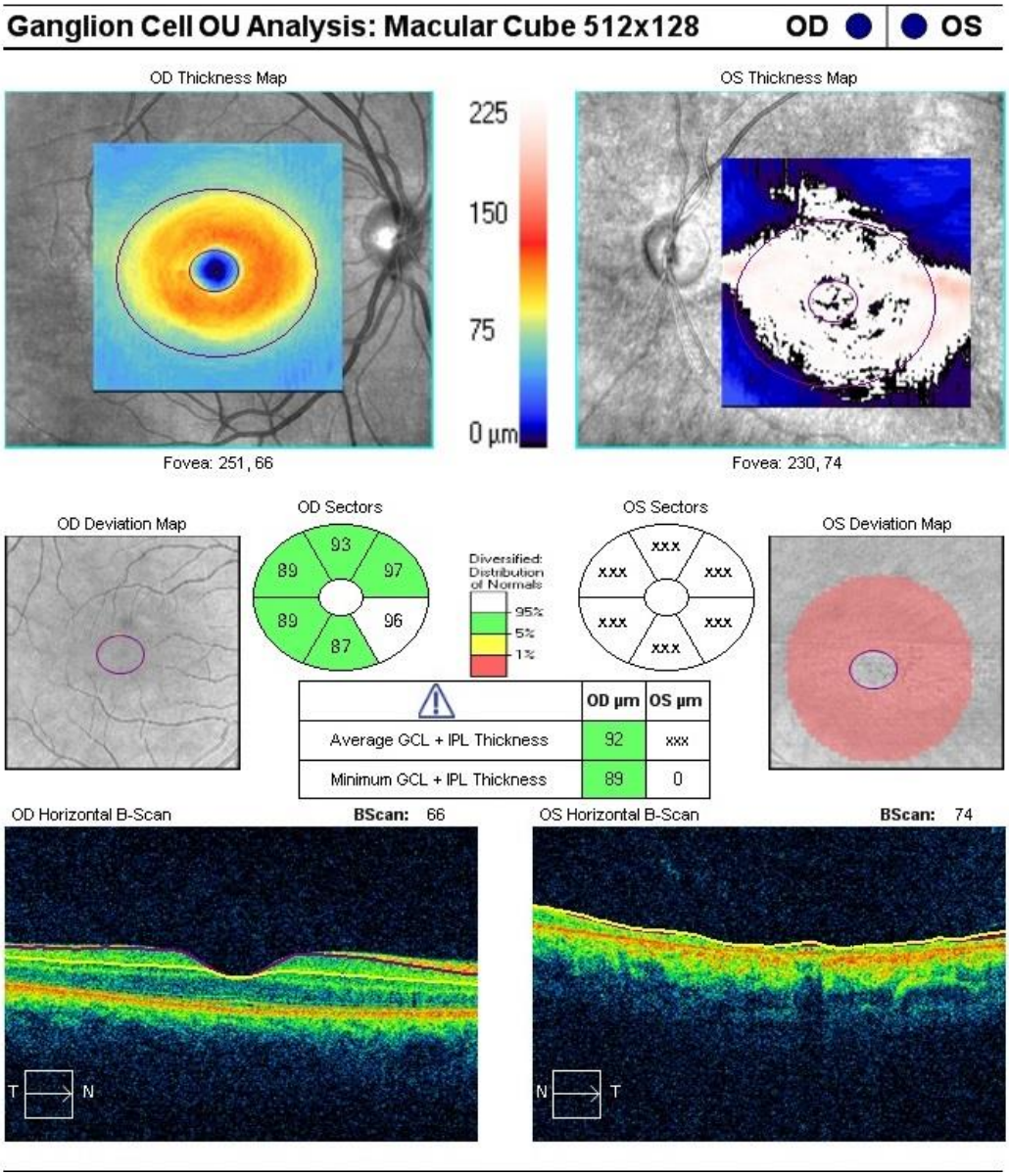

Figure 2B. Ganglion cell analysis (GCA). GCA results were normal in the right eye, however, revealed diffuse ganglion cell loss with unrecordable values in the macular region of the left eye.

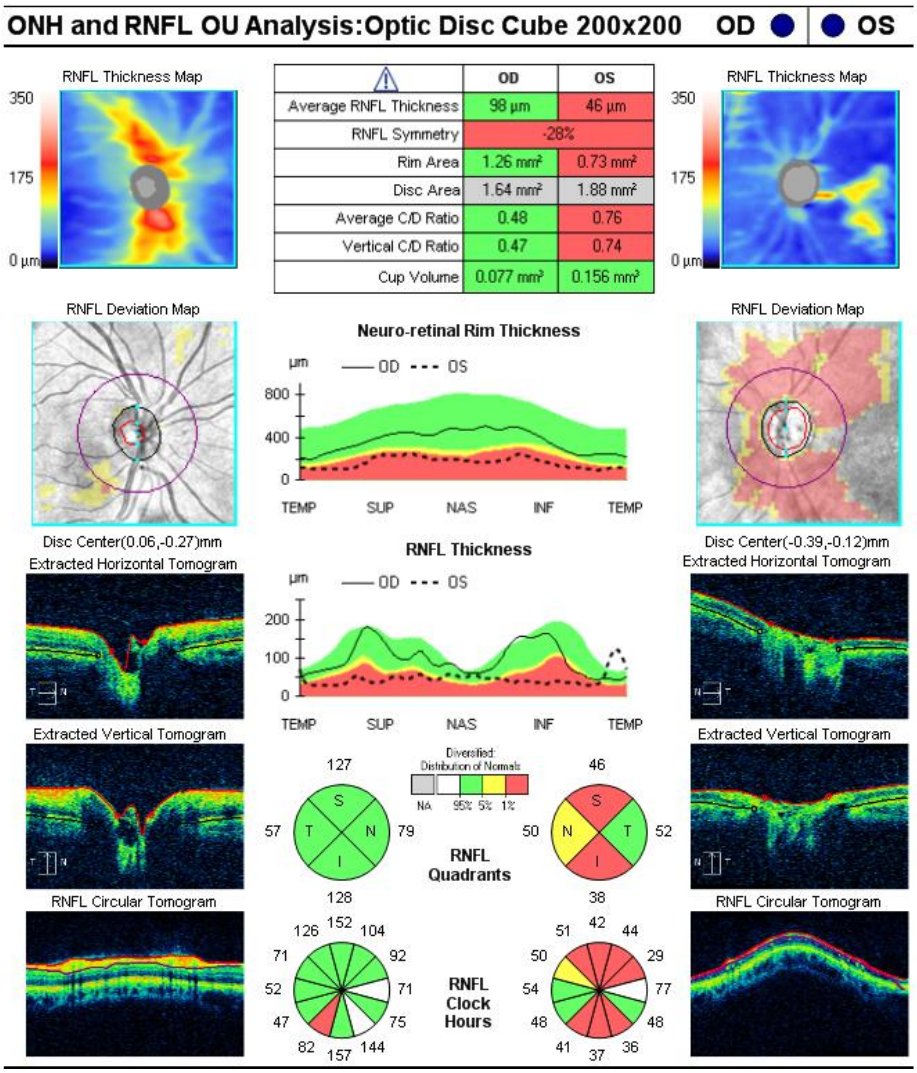

Figure 3. OCT of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). Results were within expected norms in the right eye, and showed diffuse neuro-retinal rim thinning and severe RNFL thinning superior and inferiorly, with mild RNFL thinning nasally.

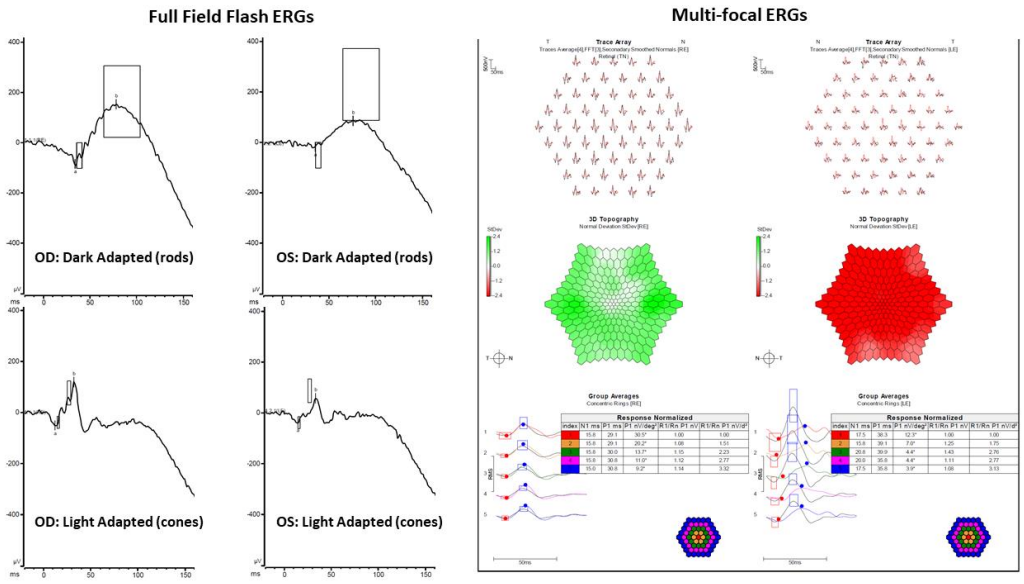

Figure 4. Full-field (flash) electroretinography (ERGs) and multi-focal electroretinography (mfERGs). Both dark-adapted (rod function) and light-adapted (cone function) flash ERGs are normal in the right eye but significantly decreased in the left eye. mfERGs, which assess cone and cone-bipolar cell function from multiple retinal sites, show robust, normal responses from the right eye while the left eye shows diffuse reduction in mfERG amplitudes and delayed latencies (upper traces: black from patient, red are norms, middle topography shows SDs from normal, green above, red below, lower traces and tables show mean responses from each color coded ring).

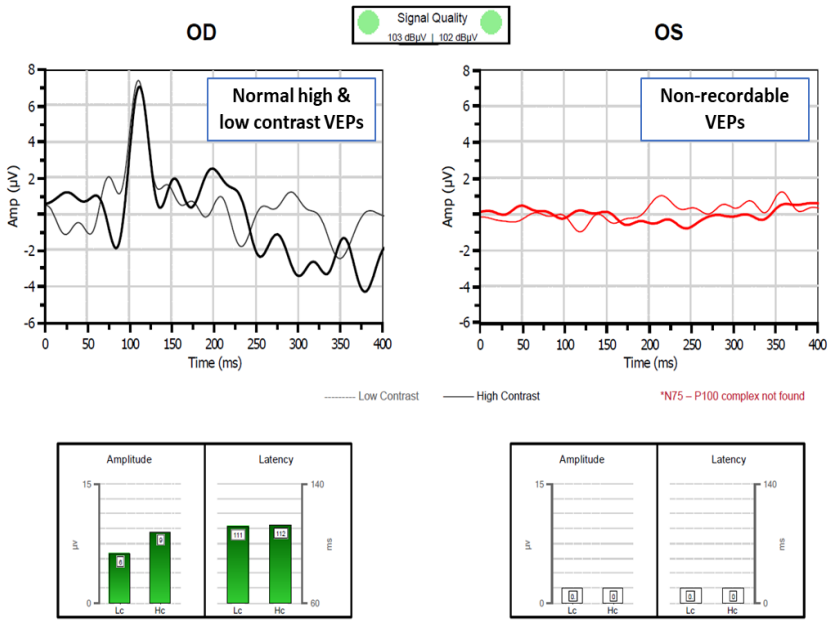

Figure 5. Visual Evoked Potential (VEP). Results were within normal limits in the right eye and unrecordable in the left eye, consistent with severe optic atrophy and loss of central vision.