Our patient had an extensive SCC of the medial eyelid involving most of the surrounding structures, making us consider an alternative for surgical treatment. In our opinion, topical immunotherapy should be tried before opting for a surgical excision, especially in difficult areas such as medial canthus, fornix extension, and elderly patients with systemic comorbidities. It has been proven to provide better cosmetic and functional outcomes without additional local morbidities (such as flaps or grafts).

We also support the “treat with the cream first and see what’s left policy” of the SINS trial. Moreover, SCC is a more aggressive tumour that demands closer and longer-term follow-up compared to BCC. We believe that the skin of the eyelid, being the thinnest skin on the body, provides better and deeper penetration of Imiquimod cream compared to other areas.

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Optical coherence tomography-angiography in Wolfram syndrome: a mitochondrial etiology in disease pathophysiology

Wolfram syndrome (WS), also known by the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is an autosomal recessive, progressive neurodegenerative disease. Patients with WS characteristically present with early onset diabetes mellitus and optic atrophy in the first decade of life, diabetes insipidus and deafness in the second decade, and urinary tract with neurological complications in the third decade. WS has been shown to be associated with mutations in the WFS1 or CISD2 (WFS2) gene, probably leading to impaired calcium homeostasis and consequent widespread cellular apoptosis.

Optic atrophy is a constant and profound feature in WS, which commonly presents in patients as gradual visual acuity loss, colour vision insufficiency, and cecocentral scotomas on visual field (VF) examination. In addition, studies concerning WS neurophysiology have associated retinal ganglion cell (RGC) abnormalities with disease pathology. Such clinical features are shared in common with mitochondrial disorders such as Leber’s hereditary optic neuropathy (LHON) and suggest adjunctive etiologies involving mitochondrial dysfunction and mitochondrial DNA (mtDNA) in WS pathophysiology.

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OCT-angiography (OCT-A) makes the in vivo assessment of retinal and peripapillary blood supply in WS possible. Presently, our understanding of vascular involvement in WS pathogenesis is lacking and there remains a limited fund of knowledge of disease pathophysiology.

Given the shared clinical features between WS and well-known mitochondrial optic neuropathies, we sought to investigate the potential for overlapping patterns of vascular involvement. In this report, we evaluate, for the first time, the ONH and peripapillary microcirculation in correlation with VF and structural OCT in an adolescent patient affected by WS.

**CASE REPORT**

A 19-year-old female with a known history of WS, genetically confirmed for WFS1 gene mutation, had developed diabetes mellitus, hearing loss, and progressive vision loss bilaterally starting at age 12. Best-corrected visual acuities (BCVA) were 20/200 in the right eye and 20/300 in the left eye. Fundus examination revealed 2+ optic disc atrophy in the right eye and 3+ optic disc atrophy in the left. The patient had complete dyschromatopsia by Ishihara test plate testing. Humphrey visual field (HVF) showed generalized depression bilaterally. Structural OCT displayed dramatic loss of the retinal nerve fibre layer (RNFL), measuring 45 μm and 44 μm in the right and left eyes, respectively. The visual system of the patient was assessed by OCT-A in consideration of a complete neuro-ophthalmological examination including automated perimetry and OCT peripapillary retinal nerve fibre layer (RNFL) thickness. OCT images were obtained using Spectral Domain-OCT (Cirrus HD-OCT, V.6.0; Carl Zeiss Meditec, Inc., Dublin, Calif.). The scan size of the optic disc area was 6 mm x 6 mm and was divided into 4 layers comprising the optic nerve head (ONH), vitreous, radial peripapillary capillary (RPC), and choroid layers. Peripapillary and ONH vessel densities were evaluated. OCT-A scans illustrated a decrease in the vascular network of the ONH and RPC layers corresponding to the sectors of RNFL thinning, most pronounced in the temporal region (Fig. 1).

**DISCUSSION**

OCT-A examination of ONH and retinal microcirculation in WS demonstrates a vascular contribution to optic nerve pathophysiology. As a novel imaging modality, OCT-A has overcome some of the limitations associated with previous imaging technologies, providing high-resolution microcirculation maps and enhancing visualization of the optic disc and peripapillary capillary beds.

Previous WS studies in mice demonstrated that disruption of the WFS1 gene led to defective production of a transmembrane protein known as Wolframin, which has been shown to have a critical role in maintaining...
intracellular calcium homeostasis with specialized localization to the endoplasmic reticulum (ER), a cellular organelle forming an interconnected network of flattened, membrane-enclosed sacs of which there are two types, rough and smooth ER, with a diverse array of functions such as protein synthesis and lipid production, respectively. Given Wolframin’s ER localization and the resulting death of pancreatic beta cells as a consequence of WFS1 gene disruption as seen in mouse studies, studies have suggested that WS is primarily a disease of the ER. However, it is important to note that such animal findings may not be completely translatable to humans. Continued scientific investigation of this complex disease may reveal more than a single conclusive etiology. In addition, these animal studies solely addressed pancreatic involvement in WS without assessing involvement of the mitochondrion, the cell’s main source of energy in the form of adenosine triphosphate (ATP), which is used to fuel the wide spectrum of vital cellular activities. In turn, our current understanding of WS pathology remains incomplete, justifying the need to consider the potential for adjunctive etiologies for a disease comprised of an assortment of clinical features such as DIDMOAD.

Therefore, we postulate that WS pathophysiology may not be solely restricted to the ER, but may also include a mitochondrial-related etiology. Evidence for a mitochondrial-associated etiology was recently provided by our laboratory, demonstrating a striking similarity in the histopathological pattern of optic nerve atrophy between WS and LHON, an established mitochondrial optic neuropathy. In addition to the shared “mitochondrial pattern” of optic atrophy, our laboratory also demonstrated visual improvement in WS with idebenone therapy, a derivative of the coenzyme Q10 integral membrane protein of the mitochondrial respiratory chain used in the treatment of LHON. To further support an ER-mitochondrial association, an ultrastructural study by Marchi et al. demonstrated that these two organelles are closely connected as they join together at multiple contact sites to form specific domains, referred to as mitochondria-ER associated membranes (MAMs). Such close communication provides further insight on Wolframin’s critical role in facilitating calcium homeostasis via ER-mitochondrion interactions. In turn, Wolframin dysfunction may lead to impairment of these ER-mitochondrion-specific calcium exchanges, disturbing mitochondrial calcium regulation, and provoking apoptosis. Taken together, these findings do not propose a mitochondrial mutation, nor do they preclude ER-based etiologies for WS. These studies solely suggest a potential mitochondrial contribution to overall WS disease pathogenesis.

This report provides the first vascular assessment in an adolescent WS patient using OCT-A. Our findings revealed a significant reduction in the temporal ONH and peripapillary microvasculature. This pattern of vascular attenuation in the temporal area of the superficial plexus is consistent with the preferential involvement of the small axons comprising the papillo-macular bundle (PMB), a hallmark feature associated with well-established mitochondrial optic neuropathies such as LHON. With a small surface-to-volume ratio, these small axons are subject to high energy demands dependent on a hefty mitochondrial energy supply. The small PMB axons exhibit inefficient bioenergetics, rendering them as primary targets in mitochondrial optic neuropathies. The temporal involvement in WS is also consistent with the vascular attenuation patterns recently seen in OCT-A and laser speckle flowgraphy (LSFG) studies in dominant optic atrophy (DOA), another well-known mitochondrial optic neuropathy. Furthermore, striking similarities between WS and LHON were especially apparent in our OCT-A study with the demonstration of peripapillary telangiectatic blood vessels and vascular tortuosity (Fig. 1. B,E), a pathognomonic finding for LHON.

These OCT-A findings demonstrate the preferential involvement of the PMB in WS, which is consistent with the OCT-A findings in patients with well-established mitochondrial diseases such as LHON and DOA. This study further supports mitochondrial dysfunction as an important etiology involved in WS disease pathogenesis. Vascular involvement may supplement our understanding of WS pathophysiology, be useful in clinical practice for monitoring WS disease progression, and, ultimately, be useful as an outcome measure for the assessment of new and purported therapies. Zmyslowska et al. recently studied the value of serial RNFL thickness measurements to monitor the course of WS, demonstrating longitudinal RNFL thinning. Given the involvement of the superficial retinal vasculature in WS, it may be worthwhile to correlate serial vascular parameters as measured by angiography with serial structural RNFL changes as a function of disease duration. Such a study may provide further insight on the extent of vascular involvement in WS to further navigate therapeutic approaches. In addition, our previous demonstration of visual improvement with idebenone in a case of WS may warrant a prospective study using idebenone in patients with WS. While WS risk factors including smoking and excess alcohol consumption have not been definitively established, minimizing such exposures in WS patients seems prudent given a potential etiological overlap with mitochondrial optic neuropathies.

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Atypical presentation of primary Sjögren’s syndrome as optic neuritis

Sjögren’s syndrome (SS) is a chronic progressive autoimmune disease mainly affecting the exocrine secretory glands. The involvement of salivary and lacrimal glands by the disease process leads to dryness of the oral mucosa and the ocular surface respectively. It may be primary with an isolated involvement of the exocrine glands, or secondary to other underlying autoimmune diseases, but neurological associations in Sjögren’s syndrome are rare. 1–6 On the other hand, in atypical optic neuritis with subsequent unresponsiveness to treatment, a definitive diagnosis of the actual underlying disease process is always a challenge for a neuro-ophthalmologist. Here, we discuss the clinical course, evaluation, and management of an atypical presentation of primary Sjögren’s syndrome (pSS) as optic neuritis.

CASE DESCRIPTION

A 42-year-old woman presented to our outpatient department complaining of rapidly deteriorating visual acuity in the left eye for the past five days. Clinical history revealed associated peri-orbital pain; however, any relevant history for recent viral illness, trauma, or any other systemic diseases was absent. At presentation, the patient’s visual acuity was 20/20 and positive light perception with an inaccurate projection of rays in all quadrants in right and left eye respectively. The left eye had a relative afferent pupillary defect. The anterior chamber, optic nerve, and retinal examination were essentially within normal limits. In the right eye, best-corrected visual acuity was 20/20 and positive light perception with an inaccurate projection of rays in all quadrants. The patient had a very significant visual field deficit in the left eye, which was much less in the right eye.

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