CASE REPORT

Optic Atrophy in End-Stage Giant Axonal Neuropathy: A Case Report

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ABSTRACT

A 32-year-old woman with a history of biopsy-proven giant axonal neuropathy (GAN) and no past ocular history presented after failing a vision-screening test conducted by her primary doctor. Bilateral optic atrophy was observed on fundus examination with cup-to-disc ratio of 0.7. Kinetic visual fields showed moderate constriction in both eyes. Optical coherence tomography (OCT) of the retinal nerve fibre layer (RNFL) exhibited diffuse thinning, a pattern atypical of glaucomatous or nutritional optic atrophy and most likely secondary to the optic atrophy associated with GAN. Serial OCT to monitor RNFL thickness may offer a non-invasive means of monitoring progression in GAN for future therapeutic studies.

Keywords: Giant axonal neuropathy, non-glaucomatous cupping, OCT, optic atrophy, retinal nerve fibre layer

INTRODUCTION

Giant axonal neuropathy (GAN) is a rare, inherited neurodegenerative condition associated with dense, defective neurofilament formation in axons. Due to its rarity, little is known regarding its incidence, much less its ocular phenotype. Here, we describe structural changes of the retinal nerve fibre layer documented with optical coherence tomography (OCT).

CASE REPORT

A 32-year-old Pakistani woman with history of GAN since childhood, confirmed by peripheral nerve biopsy, and no known past ocular history, presented after failing a vision-screening test conducted by her primary care physician. She had no known refractive error, nor did she notice a decline in vision. Evaluation 10 years prior to presentation revealed normal visual fields, extraocular movements, saccades, pursuit, and pupillary responses. Wheelchair-bound since

age 11, medical history included vocal cord paralysis, pharyngeal muscle weakness, respiratory muscle weakness requiring continuous positive airway pressure (CPAP), and gastrostomy tube placement for aspiration risk and poor oral intake. The patient denied any family history of ocular disease, although her brother was also diagnosed with GAN.

Examination revealed a young female with significant dysarthria and tightly kinked hair. Neurological examination showed diffuse motor weakness of distal extremities, decreased pinprick sensation distal to knees and wrists, and absent proprioception at toes and ankles. Deep tendon reflexes were absent. She was unable to fully extend her fingers, exhibiting a classic claw-shaped hand.

On ophthalmic examination, uncorrected visual acuity was 20/60 in the right eye and 20/40 in the left eye. Best-corrected visual acuity (BCVA) in the right eye was 20/25 with manifest refraction $-3.50 + 0.50 \times 104$, and in the left eye 20/25 with $-2.00 + 0.25 \times 115$. Nine of 10 Ishihara plates were identified with each eye. Visual fields were full

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FIGURE 1 (a) Fundus photographs depicting optic disc pallor. (b) Time-domain optical coherence tomography retinal nerve fibre layer assessment. Demonstrates nerve fibre layer loss bilaterally in all quadrants. Signal strength in the right eye was 9/10 and 7/10 in the left eye. RE = right eye; LE = left eye.

to confrontation and extraocular movements were full bilaterally. Central corneal thickness was 557 and 576 microns and intraocular pressures were 16 and 14 mm Hg in right and left eyes, respectively. Horizontal nystagmus worsened in lateral gaze, and saccades were mildly hypermetric. Slit-lamp examination revealed normal anterior segments. Optic disc pallor was present bilaterally with cup-to-disc ratio of 0.7 (Figure 1a).

OCT of the macula and optic nerve at the initial visit showed retinal nerve fibre layer (RNFL) thinning bilaterally (Figure 1b). Goldmann kinetic visual fields showed moderate constriction in both eyes (III-4e

isoptre 93 degrees in the right eye and 110 degrees in the left eye at the horizontal meridian).

Despite the patient's biopsy-proven diagnosis of GAN and its association with optic atrophy, we sought to rule out other causes of optic neuropathy. The lack of a caecocentral field defect, the timing of her visual changes, and diffuse RNFL loss suggested that her findings were less likely from malnutrition. Blood work revealed no evidence of macrocytic anaemia (haemoglobin 11.3 g/dL and mean corpuscular volume [MCV] 87.8 fL). Furthermore, the diffuse pattern of RNFL thinning in this young patient is atypical of glaucoma, which typically shows

preferential RNFL loss in the inferior and superior quadrants.

DISCUSSION

GAN, first identified in 1972,¹ affects the central and peripheral nervous systems.² The phenotype can vary considerably, likely secondary to its genetic heterogeneity.³ Patients commonly present with motor and sensory involvement, progressive weakness and hyporeflexia, nystagmus, ataxia, dysmetria, dysarthria, and tightly kinked hair. Most patients are confined to a wheelchair or deceased by the third decade of life.⁴

Pathologically, GAN is characterized by marked disorganization of the neurofilament network, and progressive axonal loss. Peripheral nerves are not clinically enlarged, but sural nerve biopsies exhibit giant axons and accumulations of neurofilaments and osmophilic aggregates.⁵ Diagnosis of GAN can be established by nerve conduction studies, brain magnetic resonance imaging (MRI), peripheral nerve biopsy, and molecular genetic testing. Nerve conduction studies show severely reduced compound motor action potentials and absent sensory nerve action potentials. Brain MRI typically depicts white matter abnormalities,⁶ and genetic testing for *GAN*, which encodes the protein gigaxonin, is available.⁷

Gigaxonin has been identified as a BTB-Kelch protein⁸ and found to be a substrate adaptor of the Cul-3-dependent E3 ubiquitin ligase.^{9–11} In the *GAN*-null mouse model, loss of gigaxonin results in impairment of the ubiquitin proteasome system and accumulation of cytoskeletal-associated proteins. These studies suggest a unique role for gigaxonin, linking cytoskeletal dynamics to the ubiquitin proteasome system by directing the degradation of proteins involved in the assembly, stability, and dynamics of microtubules.^{2,12–14}

If this process is disrupted by mutations in *GAN*, axonal neuropathy may well result from malfunctions in Schwann cells and oligodendrites, toxic accumulations of cytoskeletal association proteins, and/or simply alterations in microtubule organization and transport resulting in axonal degeneration.² Also, given the ubiquitous expression of gigaxonin,⁸ the vast amount of neurological signs and symptoms exhibited by affected patients is not surprising.

The patient presented here displayed signs of dysarthria, diffuse motor weakness, decreased sensation, absent deep tendon reflexes, spasticity, nystagmus, hypermetric saccades, and optic atrophy with bilateral cup-to-disc ratio of 0.7 and diffuse RNFL thinning on OCT. GAN was high on the differential diagnosis secondary to the patient's biopsy-proven diagnosis and its association with optic atrophy.¹⁵

Also, recent computed tomographic (CT) imaging of the patient's head demonstrated findings consistent with her known GAN diagnosis: diffuse cerebral and cerebellar volume loss and diffuse white matter hypoattenuation.⁷ Yet, other causes of optic neuropathy still had to be ruled out.

As discussed above, even though this patient had a gastrostomy tube for aspiration risk and poor oral intake, the lack of a caecocentral field defect, the absence of dyschromatopsia, and the diffuse RNFL loss suggested that her findings were less likely from malnutrition. In toxic/nutritional optic neuropathies, the OCT-measured RNFL shows preferential thinning temporally, which corresponds to the significant effects on the papillomacular fibres.^{16,17} In addition, blood work revealed no evidence of macrocytic anaemia, which would be expected if vitamin B₁₂ or folate were deficient.

Optic atrophy and cupping of the optic nerve head traditionally represent classic signs of glaucoma. However, non-glaucomatous optic neuropathies, such as GAN, may present with similar disc appearance.¹⁵ In glaucoma, RNFL loss tends to be most significant in the superior and inferior quadrants.¹⁸ This same pattern of loss has also been confirmed structurally with OCT.^{19–21} Recently, a study utilizing OCT to differentiate glaucomatous from non-glaucomatous optic nerve cupping found that the pattern of RNFL thinning in non-glaucomatous cupping was more diffuse than in glaucomatous cupping, with lower nasal and temporal thickness as well as lower macular thickness and volume.²² Hence, the bilateral optic nerve cupping observed in our patient is less typical of glaucomatous damage due to the diffuse RNFL thinning depicted on OCT (Figure 1b).

Interestingly, the study discussed above also found that patients with non-glaucomatous optic nerve cupping had better visual field mean deviation and pattern standard deviation than those with glaucomatous cupping.²² The patient presented here had relatively good BCVA and did not complain of a decline in vision. The moderate constriction in bilateral Goldmann kinetic visual fields with no evidence of arcuate scotomas corresponds accordingly and further illustrates the diffuse RNFL thinning. Yet, it seems discordance exists between the diffuse nature and degree of RNFL thinning observed on OCT and the visual acuity and fields. This dissociation may be explained by the subtle, relative sparing of the temporal fibres at 0 degree in both eyes (Figure 1b). Nonetheless, studies of non-glaucomatous optic neuropathies have previously demonstrated that RNFL loss extends beyond the visual field defect, that OCT can detect loss of axons prior to the presence of visual field defect, and that RNFL thinning corresponds with final visual acuity.^{23,24} Because of the subjective nature of visual field testing, OCT, especially spectral-domain OCT, would offer

further insights into structural changes and at an increased resolution, and therefore may be better suited for follow-up and estimation of visual prognosis in such patients.

A case series of four boys with GAN¹⁵ previously demonstrated consistent optic disc atrophy and nystagmus, documented with electrophysiological studies. Here, we demonstrate defects in the RNFL, providing structural evidence of optic neuropathy secondary to GAN. OCT is a non-invasive technique that provides a rapid and reproducible reconstruction of the retina that allows for objective analysis of the RNFL thickness. This measurement is of particular interest in optic neuropathies and neurological diseases in which there is progressive axonal loss. OCT is particularly promising in assessing axonal preservation in multiple sclerosis and is currently being investigated as a structural outcome measure in neuroprotection trials.^{25–27} With baseline measurements acquired, serial OCT of RNFL may also offer a non-invasive means of monitoring progression in GAN for future therapeutic studies.

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

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