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CASE REPORT

Differentiating Leber Hereditary Optic Neuropathy from Normal-Tension Glaucoma

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ABSTRACT

Glaucoma is a neurodegenerative disorder characterized by thinning of neuroretinal rim, enlarged cup-to-disc ratio (CDR) and visual field damage. Although raised intraocular pressure is main risk factor for development of glaucoma, it can occur with consistently normal measurements in the intraocular pressure as normal tension glaucoma (NTG). Enlargement of CDR is a classical sign of glaucoma, but it can also result from non-glaucomatous optic neuropathies such as Leber hereditary optic neuropathy (LHON). We describe a case of LHON with increased CDR, discuss its differential diagnosis with NTG and highlight the reasons for misdiagnoses between these two entities.

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KEYWORDS

Differential diagnosis; Leber hereditary optic atrophy; low-tension glaucoma

Introduction

Glaucoma includes a heterogeneous group of disorders that features progressive optic neuropathy. It is characterised by the thinning of the neuroretinal rim of the optic disc, enlargement of the cup-to-disc ratio (CDR), and reduced thickness in the retinal nerve fibre layer (RNFL) associated with visual field defects.¹ Increased intraocular pressure (IOP) is the main risk factor for the development of glaucomatous optic neuropathy, although it may even occur at IOP levels consistently lower than 21 mm Hg and be classified as normal-tension glaucoma (NTG).²



CDRs above the normal distribution are not only seen in glaucomatous optic neuropathy. Some congenital abnormalities, such as megalopapilla and optic nerve coloboma, have CDRs greater than those in the general population. In addition, other non-glaucomatous optic neuropathies can develop increased CDRs, including arteritic anterior ischaemic optic neuropathy (AAION) and compressive optic neuropathy. Among the hereditary optic neuropathies, an

enlarged CDR is more common in dominant optic atrophy or Kjer's disease and, in some cases, Leber hereditary optic neuropathy (LHON).^{3,4}

In this report, we describe a case of LHON with an increased CDR and discuss its differential diagnosis with NTG.

Case report

A 25-year-old man of Asian ethnicity presented in March 2009 with complaints of progressive and painless diminution of vision in both eyes, greater in the right eye (OD). Two months previously he had sudden vision decrease in both eyes, simultaneously, with gradual worsening over time. Following the onset of symptoms, he began glaucoma treatment in Japan, where he lived, with topical travoprost once per day and dorzolamide twice per day. He denied any history of systemic or ophthalmologic comorbidities and did not report an increased IOP before the introduction of the eye drops. Three uncles and two male cousins had been diagnosed with visual impairments of unknown cause.

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Upon examination, this patient's best-corrected visual acuity (BCVA) was 20/200 in both eyes. The IOP was 14 mm Hg with travoprost eye drops once per day and dorzolamide eye drops twice a day, the anterior chamber angle was wide open, and there were no abnormalities seen with slit-lamp biomicroscopy in either eye. Corneal pachymetry was 545 μm in the right eye (OD) and 550 in the left eye (OS). Fundus examination showed diffuse optic disc pallor with an increased CDR in both eyes, whereas the remainder of the fundus appeared normal. The Humphrey Visual Field Analyzer program 24:2 full threshold visual field examination revealed a large diffuse reduction in sensibility, with discrete preservation of the sensibility in the nasal and inferior sectors. The optical coherence tomography (OCT) showed a diffuse decrease in the RNFL thickness of the optic disc.

The fundus finding of diffuse optic disc pallor, combined with the history of visual loss in relatives from the same family following a mitochondrial pattern, requested a genetic analysis of the mitochondrial DNA to evaluate the possibility of LHON. The presence of a G11778A mutation was confirmed via polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), using the *Sfa*NI enzyme, according to Johns and Neufeld.⁵

Based on the molecular genetic testing confirmation of LHON and the stability of the clinical findings, the anti-glaucomatous eye drop treatment was suspended. The IOP remained between 12 and 14 mm Hg, without any medication, with a unique peak of 20 mm Hg in a 24-hour tension curve. On

his last visit (May 2016), this patient was not using any topical or systemic medications. The ocular examination showed a BCVA of detection of hand movement (<20/1600), and the IOP was 12 mm Hg in both eyes. The dilated funduscopy revealed diffuse optic disc pallor and increased CDR, as seen previously (Figure 1). The visual field test and spectral-domain OCT (Spectralis) showed findings previously described (Figure 2).

Discussion

Usually, the diagnosis of glaucoma is based on progressive visual field detection (functional damage) associated with an enlarged CDR (structural damage). In addition, the presence of risk factors, such as ocular hypertension and family history, help make the diagnosis. However, the absence of ocular hypertension often prevents immediate confirmation of the diagnosis of glaucoma, taking it to the level of a suspected disease and requiring the detection of progression in structural or functional damage to confirm the diagnosis. In this situation, some patients with ocular hypertension can be detected during the assessment of diurnal tension curves, and other patients maintain statistically normal IOPs during the follow-up, leading to the diagnosis of NTG.^{1,2}

The difficulty in promptly diagnosing glaucoma is even greater because some non-glaucomatous optic neuropathies may present with an increased CDR and mimic NTG. The most common examples of these optic neuropathies are AAION and

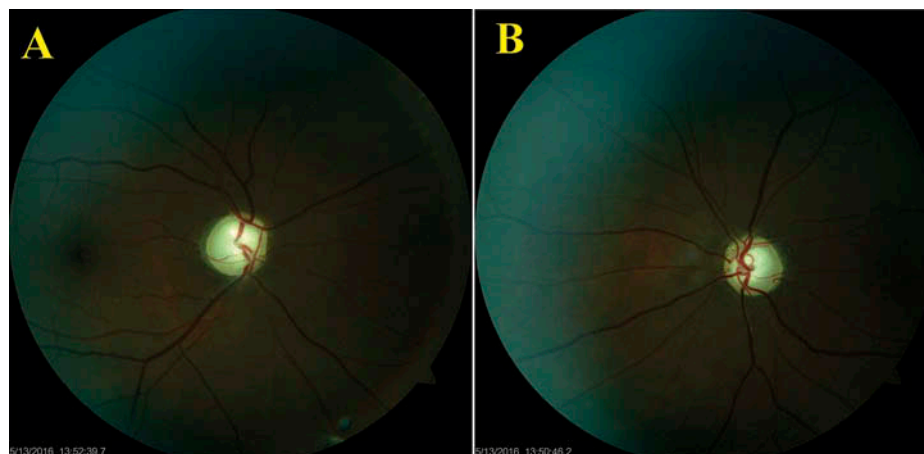


Figure 1. Fundus photographs showing optic discs with diffuse pallor and an increased cup-to-disc ratio in both eyes (A, right eye; B, left eye).

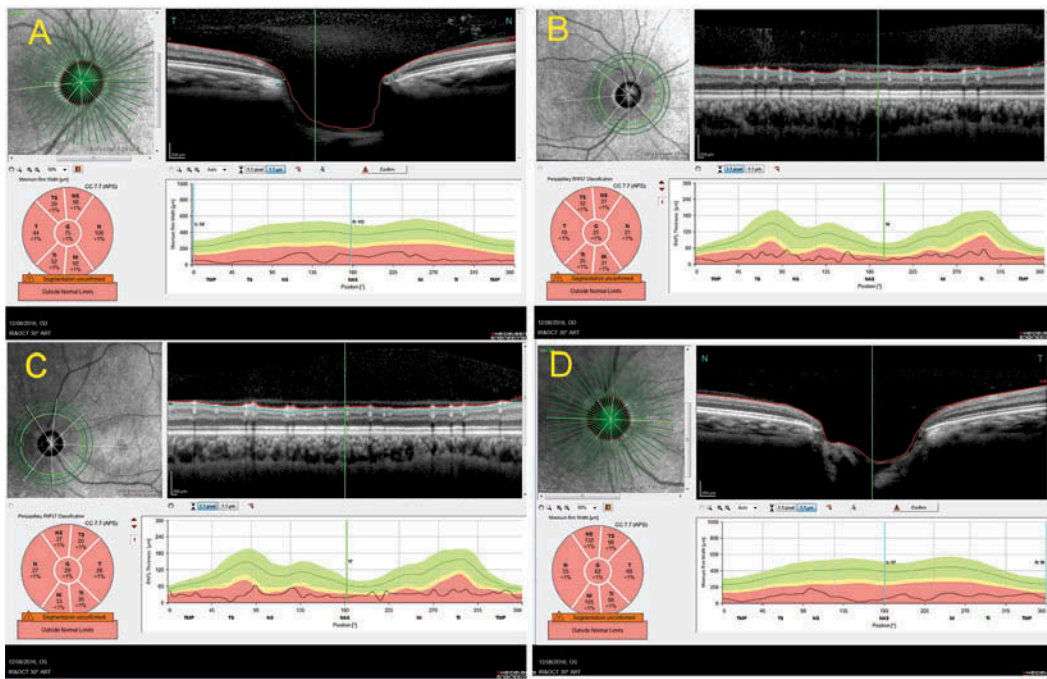


Figure 2. Spectral-domain optical coherence tomography (Spectralis) showing a reduced rim width (A, right eye; B, left eye) and a diffuse decrease in the peripapillary retinal nerve fibre layer thickness of the optic disc (C, right eye; D, left eye).

hereditary optic neuropathies, mainly dominant optic atrophy, but less frequently, LHON.^{3,4}

The association between NTG and LHON is rare, and cases of misdiagnoses between these entities have occasionally been reported in the literature.^{6–10} The reason for this confusion lies with the fact that optic discs at the atrophic stage of LHON exhibit glaucoma-like morphological changes, with enlarged CDRs.^{6–10} An evaluation of the optic disc nerve head with Heidelberg retinal tomography (HRT) has shown that in eyes with LHON, the disc area tended to be larger than that of the controls.¹¹ In addition, the cup area and cup-to-disc area ratio were significantly larger, and the rim area and rim volume were significantly smaller in those eyes with LHON, compared with the controls.¹¹ Mashima et al. reported that although the optic disc at the atrophic stage of LHON exhibited cupping similar to that in glaucoma, glaucomatous cups are deeper than LHON cups.¹² These authors also indicated that the main feature distinguishing the LHON discs from NTG discs was the pallor of the remaining neuroretinal rim. When pallor is present in the entire optic disc, it is strongly suggestive of LHON, whereas a glaucomatous disc usually shows localised or diffuse loss of the neuroretinal rim, without pallor.¹² The evaluation of the optic disc through spectral-domain OCT

(Spectralis), as performed in our patient, does not provide as much information about the structural parameters of the optic disc cup as HRT, although it was possible to see an enlarged CDR, with a diffuse loss of the neuroretinal rim.

The diagnosis of glaucoma with IOP within the normal statistical range is considered to be more prevalent than previously believed, and studies have shown that there is a higher incidence of NTG in the Asian population. Although structural damage to the optic disc in NTG is similar to that seen in eyes with a high IOP, findings such as small flame-shaped disc, haemorrhages, increased CDRs in flatter cups, and type β peripapillary atrophy suggest the diagnosis of NTG.^{1,2}

Our patient was probably first treated as a possible case of NTG due to an enlarged CDR, in the absence of raised IOP measurements. The diagnosis of NTG is a diagnosis by exclusion, but there are some risk factors associated with the disease, such as an age greater than 60 years old, female gender, and Asian ethnicity. In addition, some systemic diseases have been reported to occur concurrently with NTG, such as vascular disease, migraines, vasospasm, and immune-related diseases.^{1,2} In our patient, the only risk factor associated with NTG was Asian ethnicity, and during the entire follow-up period, there were no

structural features in the optic discs that were associated with NTG. The large amount of pallor of the remaining neuroretinal rim, together with a diffuse increase in the CDR in a shallow cup, highly suggested the diagnosis of non-glaucomatous optic neuropathy. In this case, the presence of a G11778A mutation confirmed the LHON diagnosis.

LHON is caused by mutations in the mitochondrial DNA that are located mainly in positions 11778, 3460, and 14484, which are responsible for mitochondrial oxidative phosphorylation.^{13–15} However, defects in the mitochondrial respiratory chain that suggest a similar pathogenesis for LHON and NTG have not been identified.^{12–14} Recent studies have shown the possible association of disorders in the mitochondrial respiratory chain in patients with primary open angle glaucoma (POAG), leading to an increase in its susceptibility.^{13–15} This finding would imply that both POAG and LHON could share, at least in part, a cumulative effect on oxidative stress, resulting in axonal damage and death of the retinal ganglion cells.^{13–15} Finally, the possibility of an organ-specific defect in mitochondrial function that justifies similar findings in the optic disk, such as an increase in the CDR, and a misdiagnosis between these two entities were not fully ruled out.¹⁶

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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