

Novel use of idebenone in Leber's hereditary optic neuropathy in Hong Kong

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ABSTRACT

We report a case of a young Chinese male presenting with sequential, painless, bilateral visual loss in Hong Kong. He was diagnosed to have Leber's hereditary optic neuropathy with genetic workup showing G11778A mutation with over 80% heteroplasmy. He was started on idebenone treatment 11 months after onset of the binocular disease. To our best knowledge, this is the first case of Leber's hereditary optic neuropathy treated with idebenone in Hong Kong. The recent evidence of the diagnosis and treatment of this devastating disease is reviewed.

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Introduction

Leber's hereditary optic neuropathy (LHON) is the commonest mitochondrial disease found to affect around 1 in 30 000 people in the first population-based clinical and molecular genetic study carried out in the UK.¹ It is characterised by sequential bilateral visual loss, optic nerve dysfunction, and retinal ganglion cell degeneration. Characteristic visual field defect in LHON includes either central or cecentral scotomas. Approximately 70% of patients were found to be young adults in the UK study. Over 20 mitochondrial DNA point mutations have been reported in LHON worldwide.² Around 95% of the LHON pedigree have one of the three mitochondrial DNA point mutations namely, G3460A, G11778A, and T14484C, which are responsible for coding of complex I subunits of the mitochondrial respiratory chain.

Case report

A 15-year-old Chinese male, with a history of congenital red-green colour blindness, presented with sudden blurring of right eye central vision in August 2011. He did not experience any ocular pain or photopsia. There was no family history of ocular or neurological diseases.

On admission, his visual acuity was 6/120 in the right eye and 6/6 in the left eye. Right-eye visual field examination showed central scotoma associated with right relative afferent papillary defect. Fundoscopy revealed right eye disc swelling without peripapillary haemorrhage or exudate (Fig

a). Neurological and cardiovascular examinations were normal.

Perimetry revealed right centrocecal scotoma. Computed tomography of brain and orbit with contrast showed normal eye globes and extra-ocular muscles but mildly thickened intra-orbital right optic nerve suggestive of right optic neuritis. Erythrocyte sedimentation rate and C-reactive protein were not elevated. Blood test for anti-nuclear antibody was negative. Serologies for toxoplasmosis, herpes virus, Lyme disease and syphilis as well as tuberculin test were negative. Visual evoked potential revealed prolonged P100 over the right eye compatible with optic neuropathy. Magnetic resonance imaging of the brain and orbit was unremarkable. The patient was diagnosed to have optic neuritis and recommended for steroid treatment according to Optic Neuritis Treatment Trial (ONTT).³ However, his parents declined the treatment due to the possible side-effects of steroids.

Two months later, the patient experienced sudden painless blurring of left eye central vision. Visual acuity was 6/60 in the left eye while it remained at 6/120 in the right eye. Cerebrospinal fluid examination revealed normal biochemistry and cell count, and was negative for oligoclonal bands. Serum folate and vitamin B12 levels were normal. He was started on an ONTT-recommended dose of intravenous methylprednisolone (1000 mg/day) for 3 days, followed by oral prednisolone (1 mg/kg/day) for 11 days. However, his visual function deteriorated despite treatment. In view of the atypical features of sequential visual bilateral optic neuritis without

香港首宗使用idebenone治療Leber遺傳性視神經病變病例

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本文報告香港一名年輕華籍男性病發時出現連續性的雙側視力喪失。病人未感痛楚，後被診斷患有Leber遺傳性視神經病變，基因測試顯示G11778A突變，並有八成為與異質體。病人發病後11個月開始接受idebenone治療。據我們所知，這是香港首宗使用idebenone治療遺傳性視神經病變的病例。本文回顧這種破壞力甚強的疾病最新的診斷和治療資料。

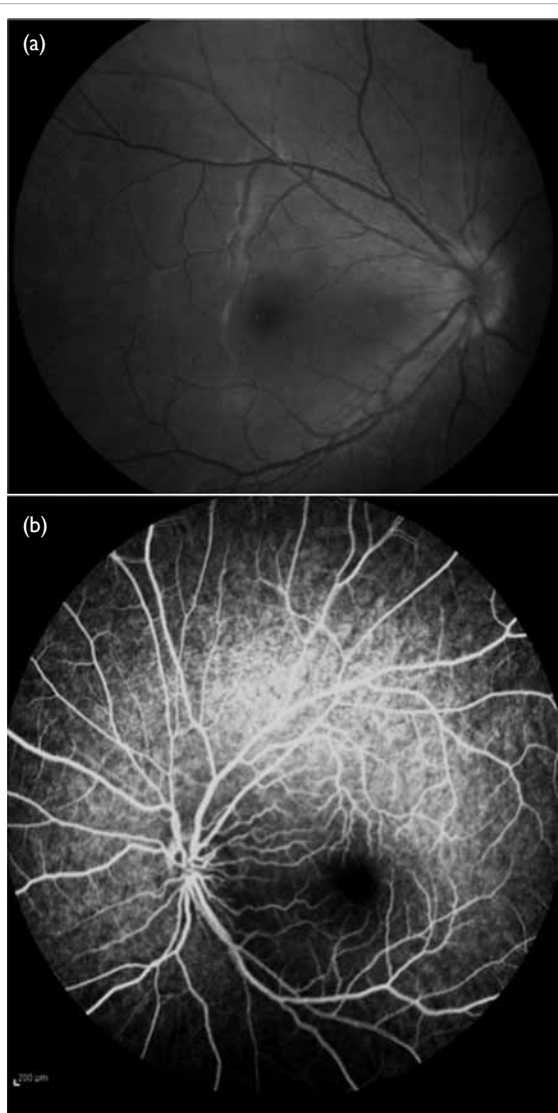


FIG. (a) Right optic disc swelling without haemorrhage or exudates. (b) Fundus fluorescein angiography of the left eye shows no leakage of optic disc head

recovery, LHON was suspected and confirmed by identification of mitochondrial DNA point mutation at 11778 guanine to adenine in the blood, with high mutant load heteroplasmy (over 80%). Fundus fluorescent angiography revealed left-disc telangiectatic vessels without optic disc head leakage compatible with typical angiographic features of LHON (Fig b).

He was then put on high-dose oral antioxidants (vitamin C 500 mg daily and co-enzyme Q10 ubiquinone). The medication was switched to idebenone 900 mg per day in divided doses when the drug became available in the hospital.

Six months after treatment with idebenone, his visual acuity remained static: 1/60 and 2/60 in the right and left eye, respectively. There were no side-effects related to the treatment. He gradually adapted to school life, with improvement in using Braille. Genetic study revealed the mother to be a LHON carrier (G11778A). His sister refused genetic testing due to the possible implications on future employment and academic considerations.

Discussion

Optic neuritis is an inflammatory disease of the optic nerve. It is the second commonest acquired optic nerve disorder in persons under 50 years old. The typical presenting symptom includes sudden visual loss with dyschromatopsia over several hours to days. This may be associated with dull retrobulbar pain which worsens with ocular movement. Symptoms can occur in both eyes either simultaneously or sequentially. A clinical diagnosis of optic neuritis may be made based on the following signs and symptoms: sudden visual loss with progression within 1 week, dyschromatopsia, pain on extra-ocular movement, no features of uveitis, and vision improvement beginning in 3 to 4 weeks.⁴ According to the findings in ONTT, 80% of patients with optic neuritis will improve within the first 3 weeks.⁵ Over 95% will regain visual acuity of at least 20/40, regardless of treatment options at 12 months' time from onset of symptoms.⁶ The initial presentation of our patient was similar to that of optic neuritis. However, failure of spontaneous recovery in the absence of other causes should alert the clinician to consider atypical optic neuritis. The differential diagnoses of atypical optic neuritis are listed in the Table. A detailed history and clinical examination helps to understand the underlying aetiology, which may be confirmed by relevant radiological, serological, bacteriological, electrophysiological, and molecular investigations.

Patients with LHON experience devastating visual loss, typically worse than 20/200 in both eyes. At least 97% of patients will have sequential eye involvement within 1 year.⁷ Over 90% of patients harbour one of the three pathogenic mitochondrial

TABLE. Differential diagnoses of atypical optic neuritis

Differential diagnosis	Examples
Infiltrative diseases	Lymphoma, leukaemia
Tumours	Meningioma, optic nerve glioma, craniopharyngioma
Traumatic	Shearing injury
Toxins	Amiodarone, barbiturates, chloramphenicol, isoniazid, streptomycin, sulphonamides, ergot, penicillamine, quinine, digitalis, chlorpropamide, chemotherapy
Nutritional deficiency	Folic acid, vitamins B1, B2, B6, B12
Infections	Toxoplasmosis
Inflammatory	Multiple sclerosis, neuromyelitis optica
Ischaemic	Thromboembolism, migraine
Genetic	Leber's hereditary optic neuropathy, Wolfram syndrome, infantile Refsum disease
Hysteria	-

mutations (G3460A, G11778A, T14484C), which affect complex I of the mitochondrial respiratory chain.⁸ The pathogenesis of LHON involves a combination of decreased complex I-driven adenosine triphosphate production, increase in free radical production and, finally, retinal ganglion cell apoptosis.⁹ The most important prognostic factor for visual recovery is the mutation status. The T14484C mutation carries the best chance of some degree of visual improvement in 37% to 71% of patients, while the G11778A mutation is associated with only 4% chance of recovery.⁷

Kirkman et al¹⁰ suggested that visual loss occurs more often in smokers and people with high alcohol intake. It is essential to advise patients to avoid tobacco smoking, excessive alcohol intake, and medications that may have mitochondrial toxicity (eg aminoglycosides, metformin, statins), especially during the acute phase of visual loss. Directed therapies for mitochondrial disorders are very limited. To date, there is no effective treatment for LHON. The mainstay of management remains supportive, such as low visual aids to assist reading, communication, and employment.

Anecdotal reports have shown beneficial effects of idebenone, which is a short-chain benzoquinone structurally related to co-enzyme Q10. It is a potent antioxidant and inhibitor of lipid peroxidation. It facilitates mitochondrial electron flux in bypassing complex I.¹¹ In a retrospective open-label study involving 28 LHON patients, Mashima et al¹² reported significantly shortened onset of visual recovery (11.1 months vs 17.4 months; P=0.03) and shortened interval for recovery of vision to ≥ 0.3 (17.6 months vs 34.4 months; P=0.01) in the treated group versus the untreated group. Jancic¹³ administered idebenone to nine patients at 135 mg/day for up to 1 year. Three patients reported subjective improvement in visual acuity, one with monocular

disease showed arrest of progression of visual loss to the other eye, and four demonstrated improvement in visual evoked potential. Klopstock et al¹⁴ conducted a 24-week multicentre double-blind, randomised, placebo-controlled trial in 85 patients given idebenone at a dose of 900 mg/day. There was no significant difference in the overall group for best recovery of visual acuity. However, in the subgroup with discordant visual acuities at baseline (n=30), a significant trend for improvement in visual acuity was observed in the treated group. Idebenone was well tolerated with no adverse effect. In summary, current evidence suggests that idebenone is probably beneficial in the early-stage LHON patients with discordant visual acuities, and may help to shorten the interval of visual recovery.

In our patient, the static eye condition in the initial 6 weeks had prompted extensive diagnostic investigations including molecular study. However, the patient developed binocular involvement 2 months after onset of the symptoms. As idebenone was not available with the local pharmaceutical company, ordering of the drug from overseas had involved time and administrative process. The poor response of visual symptoms to idebenone might be explained by the late introduction of the treatment, in this case, 11 months after binocular involvement.

In our patient, the interval from disease onset till binocular involvement was only 2 months. Heightened physician awareness is important to identify this devastating condition during this interval, which may represent the golden window for initiation of idebenone to prevent sequential visual loss and hasten recovery. Molecular analysis for the three common mutations, which is available locally, aids definitive diagnosis, prognostication, and detection of presymptomatic family members. Those presymptomatic family members with positive mutation require lifelong surveillance,

lifestyle modification, and prompt intervention at disease onset.

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