Leber's Hereditary Optic Neuropathy

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Abstract

A case of Leber's hereditary optic neuropathy (LHON) in a healthy young man who presented with a slow progressive visual loss in one eye and later developed a visual loss in the other eye. There was no pre-existing symptom and no history of visual loss in other family members. Mitochondrial DNA mutation at 11778 was found in the patient and his uneffected mother and brother. Currently the availability of reliable molecular genetic testing has revolutionized the diagnosis of LHON. LHON is a maternal inherited disorder that causes bilateral visual loss, predominantly in young men. This disorder has been associated with point mutations in the mitochondrial genome which constitute the different clinical phenotypes and prognosis. Genetic counseling in families at risk is recommended.

Key word : Optic Neuropathy, Hereditary

CASE REPORT

An 18 year-old man presented with a slow progressive painless visual loss of the right eye. He had no pre-existing symptom. The visual acuity of the right eye was 20/70, with pinhole 20/70 and the left eye was 20/30, with pinhole 20/30. The anterior eye segment was unremarkable. The optic disc of the posterior eye segment of the right eye was more blurred than the left. He had colors defect and the amsler grid showed central scotoma in both eyes. He was treated at Chulalongkorn Hospital for the presumptive diagnosis of optic neuritis with steroids for 14 days but showed no improvement

Two weeks later he had decreased visual acuity of the left eye but no change in the right eye. The visual acuity of the right eye was 20/200, with pinhole 20/200 and the left eye was 20/200, with pinhole 20/200. The posterior eye segments showed

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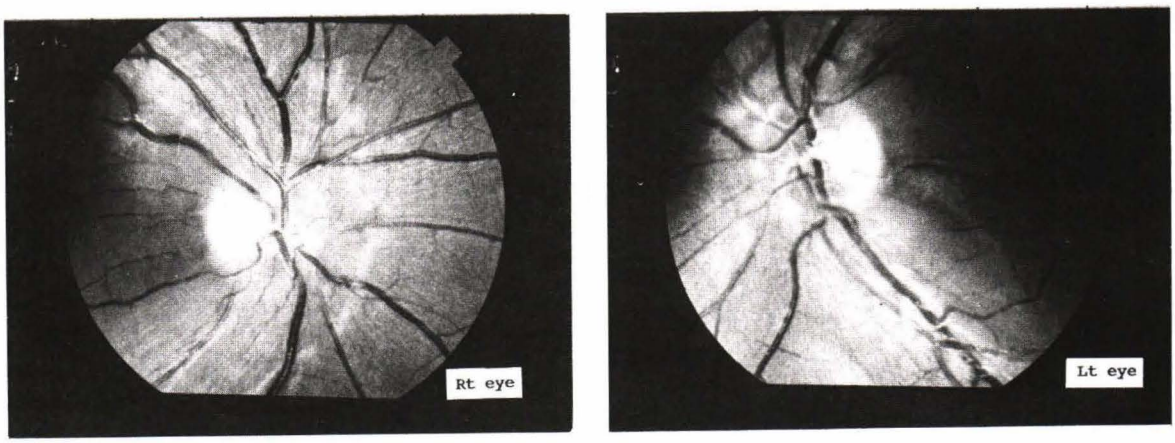

Fig. 1. Fundus ophthalmoscopic showed blurred optic discs of both eyes.

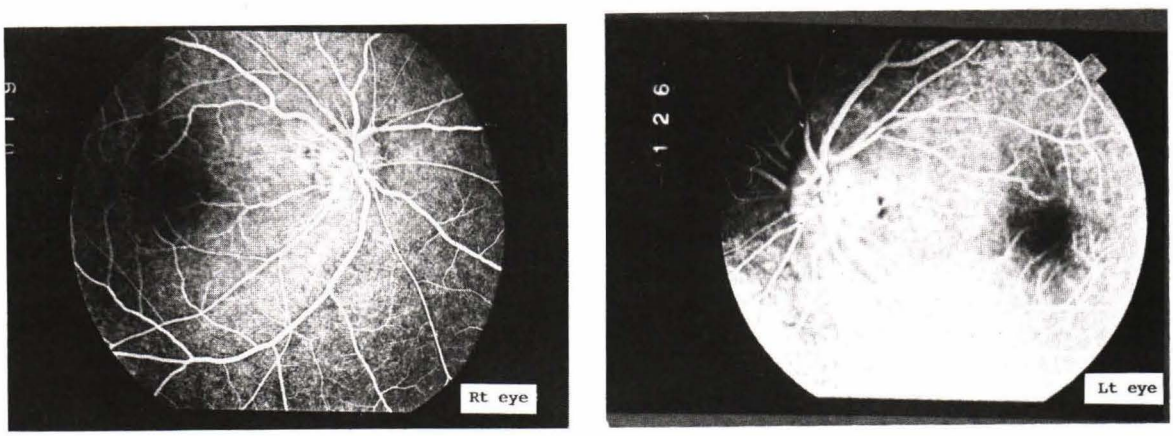

Fig. 2. Fundus fluorescein angiography (FFA) showed telangiectasia of both optic discs and no leakage of fluorescein.

(Fig. 1) optic discs blurred in both eyes. Fundus fluorescein angiography (FFA) revealed telangiectasia of both optic discs and there was no leakage (Fig. 2) Visual evoked potential (VEP) was axonopathy of both optic tracts and demyelinated of left the optic tract. (Table 1). Magnetic resonance imaging of the brain and orbit were unremarkable.

Leber's hereditary optic neuropathy (LHON) was most likely suspected and the patient underwent investigation for mitochondrial disease. Muscle biopsy was done at vastus lateralis muscle which showed non-specific muscle change. Electromyography (EMG) showed focal myopathy in both tensor fascia lata. Blood specimen for mitochon-

Table 1. Visual evoke potential (VEP) showed abnormal wave form and low amplitude of both eyes. Delay P100, N135 latency of the left eye.

Visual Evoked Potential	Latency (ms)			Amplitude (μV)	Wave form
	N75	P100	N135		
RT	53.4	105	153.6	3.7	Abnormal
LT	69	133.8	241.2	2.2	Abnormal

Negative wave = N Positive wave = P

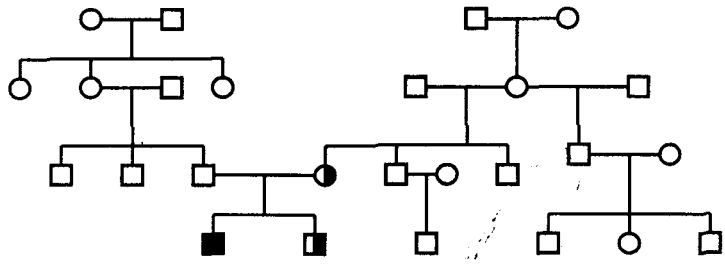

Fig. 3. Maternal lineage of a heteroplasmic 11778 LHON family. Affected individuals are indicated by blackened symbols.

drial DNA mutation screening showed heteroplasmy for the 11778 mutation (the coexistence of mutant and normal mitochondrial DNA within the same individual) in the patient, his uneffected mother and brother. Genetic counseling was given to the patient and family members. The family tree is shown (Fig. 3).

DISCUSSION

Each human cell contains hundreds of cytoplasmic mitochondria which contain a unique genetic material and provide energy require for cell maintenance and growth. The central nervous system, including eyes, has high energy requirements, thus, mitochondrial diseases have neurologic and opthalmic manifestations[1,2].

LHON is a disease caused by a maternal inherited defect in mitochondrial DNA, and was first described in 1871 as a hereditary optic neuropathy. The primary mutation (e.g. position 11778, 3460, 15257, 14484)[3] is more common for the disease, and the other mutations are called secondary mutations (e.g. position 15812)[1,4].

LHON is a disease of painless optic neuropathy in a healthy young person characterized by abrupt loss of central vision between the second and third decade of life[5,6]. Men are affected more than women[7], central vision progressively deteriorates over months, affecting one eye initially and the sequential eye within one year[1]. Visual loss ranges from 20/200 to hand movement or light perception, accompanied by central or cecocentral scotoma[5,8]. Color vision is affected early and is often severe[5].

The fundus ophthalmoscopic findings at onset of visual loss are variable and classic appearances are circumpapillary telangiectatic microangiopathy, prominent vascular tortuousity of disc surface, swelling of nerve fiber layer around the disc (pseudoedema)[1,6,9] absence of leakage telangiectatic vessels and fine arteriovenous shunt-like vessels within peripapillary retina on fundus fluorescein angiography (FFA)[5,8,10] eventually becoming optic atrophy[5]. The majority of patients with LHON have only visual symptoms and signs, but a few patients may have cardiac conduction defect [6,7] or neurologic abnormality[5,6,8,11].

From the history, fundus ophthalmoscopic and fundus fluorescein angiography (FFA) findings above we can differentiate LHON from other optic neuropathy, to make a definite diagnosis of LHON we should have mitochondrial DNA mutation screening (molecular genetic testing)[3].

Coenzym Q10, a nature cofactor necessary for normal mitochondrial energy production, was used in this case for prophylaxis of visual loss in the second eye and preventing visual loss in male family members at risk[1,8]. The result was not encouraging. To prevent other potential stress on mitochondrial energy production the patient and the family members at risk for LHON should avoid tobacco, alcohol and environmental toxins[1,3,8].

In four primary common mitochondrial DNA mutations, the 11778 mutation is the most common one and has a very poor prognosis for significant visual recovery[1,4] but the 14484 mutation which is the second most common has the best prognosis for recovery. (about 10 fold better than 11778 mutation)[1,4]. Patients with 3460 mutation which has a better prognosis for visual acuity than the 11778 mutation[12] are likely to have a family history of visual loss, a high incidence of tobacco and alcoholic abuse (tobacco and alcohol are risk factors for visual acuity loss), and metabolic disor-

ders (DM, hyperlipidemia). Environmental factors may play a role in the pathogenesis of LHON(1). Patients with 15257 mutation have a better outcome for visual recovery but higher neurological involvement, particularly spinal cord and peripheral nerve (1). Mutation analysis in the mitochondria genes has an implication in family counseling, risk factor assessment and prognosis for visual recovery. Genetic counseling is strongly recommended in families at risk(1,13).

This is the first reported case of the patient and his uneffected mother and brother which the mitochondrial DNA mutation at the 11778 position were found in Thailand.

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รายงานผู้ป่วยโรค Leber's hereditary optic neuropathy (LHON) 1 ราย ผู้ป่วยรายนี้เป็นชายอายุน้อย มาด้วยอาการตามัวด้านหนึ่ง แล้วมีอาการตามัวอีกด้านหนึ่งตามมาในระยะต่อมาโดยไม่มีอาการใดนำมาก่อนและไม่มีประวัติในครอบครัว และภายหลังตรวจพบ mitochondrial DNA mutation ตำแหน่งที่ 11778 ในตัวผู้ป่วย ในมารดาและน้องชายของผู้ป่วย

ในปัจจุบันการตรวจทาง molecular genetic testing ได้นำมาใช้ในการวินิจฉัยโรค LHON ซึ่งโรคนี้เป็นโรคที่ถ่ายทอดทางพันธุกรรมโดยผ่านทางมารดาทำให้เกิดตามัวได้ทั้ง 2 ข้าง มักพบในผู้ชายที่มีอายุน้อย ความผิดปกตินี้เกิดจาก point mutations ของ mitochondrial genome ซึ่งแต่ละตำแหน่งจะมีลักษณะการแสดงออกของโรคและการพยากรณ์โรคที่แตกต่างกัน

การให้คำแนะนำปรึกษาทางพันธุศาสตร์แก่ครอบครัวที่มีอัตราเสี่ยงในการเกิดโรคมีประโยชน์อย่างยิ่งต่อตัวผู้ป่วยและสมาชิกในครอบครัว

คำสำคัญ : ภาวะประสาทตาเสื่อม, เหตุพันธุกรรม

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