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M. T. Dotti
K. Plewnia
E. Cardaioli
L. Manneschi
A. Rufa
G. Alemà
A. Federico

A case of ethambutol-induced optic neuropathy harbouring the primary mitochondrial LHON mutation at nt 11778

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Sirs: Leber's hereditary optic neuropathy (LHON) is a maternally inherited form of acute central visual loss that occurs predominantly in healthy young men. Several mitochondrial point mutations associated with the disease have been described, but the pathogenetic link between the genetic defect, environmental factors and the disease is still poorly understood. The influence of several toxic, nutritional and genetic factors on onset and evolution of LHON has been debated [1, 3–5, 9]. Recent studies indicate the presence of primary point mutations that are pathogenetic and secondary mutations whose role is still unclear [5]. We report a case of ethambutol-induced optic neuropathy in a patient carrying the 11778 LHON mutation.

The patient is a 53-year-old man who had been healthy until the age of 51, when he developed pulmonary tuberculosis (TBC). He was treated with ethambutol (1500 mg/day) and isoniazid (200 mg/day) for 10 months, and streptomycin (1000 mg/day) for 1 month. After 8 months of therapy the patient developed a subacute bilateral visual loss diagnosed as toxic retrobulbar neuritis. The drug therapy was discontinued. The family history revealed that a maternal uncle, deceased at 60 years, had developed a severe, irreversible visual loss with subacute onset at the age of 20 years.

For further evaluation, the patient was admitted to our department. Neurological examination was normal except for the presence of mild bitemporal pallor of the optic discs, more evident in the right eye. Routine blood chemistry, creatine-kinase, aldolase, carnitine, lactic and pyruvic acid, vitamin E, vitamin B_{12}, folic acid levels and lysosomal enzymes were normal. Electromyogram (EMG), nerve conduction velocities, brainstem auditory evoked resfouces (BAERs) and electrocardiogram (ECG) were normal. Visual evoked potentials were severely reduced in the right eye and absent in the left eye. The best corrected visual acuity was 20/40 in the right and 8/200 in the left eye. Slight temporal pallor and circumpapillary microangiopathy, more evident in the left eye, were noted. Fluorescein angiography in the early phase demonstrated increased tortuosity of vessels around the disc without dye leakage.

Molecular analysis of mitochondrial DNA demonstrated a homoplasmic mutation at nt 11778. Other primary mutations at nt 3460 and nt 14484 [8] were absent. Two years after suspension of therapy, in spite of a subjective partial improvement, visual acuity was substantially unchanged. Visual evoked potientals did not show any recovery.

The 11778 mtDNA mutation is one of the so-called primary mutations and accounts for over 50% of LHON probands [5]. All studies to date have shown that recovery of bilateral optic neuropathy, when caused by the mt 11778 mutation, is exceptional [1, 8]. Although exclusively found in affected families, the presence of a primary LHON mutation does not necessarily imply that a patient will develop the disease [6–8].

Our patient developed bilateral optic neuropathy after 8 months of drug therapy for pulmonary tuberculosis. Ethambutol by itself can cause optic neuropathy, which is usually reversible after discontinuation of therapy. The development of visual loss is dosage-dependent; the dose received by the patient (20 mg/kg per day) is estimated to produce a risk of optic neuropathy lower than 5% [2]. The pathogenesis of LHON is still unclear, and several toxic, nutritional, autoimmune and genetic factors have been proposed as precipitating factors, presumably as additional stressors on an already compromised mitochondrial energy production system [1, 3, 4, 7, 9]. To our knowledge, an association between ethambutol therapy and Leber's optic neuropathy has not been described before.

In our patient, both ethambutol and the 11778 mutation have a role in the pathogenesis of optic neuropathy. It is difficult, at the moment, to determine which one was the primary trigger.

In conclusion, this case is an example of the interaction of exogenous toxic and genetic factors in the manifestation of clinical symptoms. It suggests that a full history and neurogenetic analysis may help in diagnosis and therapy.

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References

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