# Leber Hereditary Optic Neuropathy Possibly Triggered by Exposure to Tire Fire

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**Abstract:** We report three members of one family, a mother and two daughters aged 4 and 7 years, who developed visual loss from Leber hereditary optic neuropathy within a 19-month period. All three had been exposed to smoke from two large rubber tire fires within the previous 24 months, suggesting the possibility of an epigenetic triggering factor.

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Leber hereditary optic neuropathy (LHON) is a maternally inherited form of acute or subacute loss of central vision due to death of retinal ganglion cells (RGCs) (1). It is variably expressed and typically affects young adult men at a much higher rate than women. The pathophysiology is usually dependent on one of three mitochondrial DNA (mtDNA) mutations at nucleotide positions 11778/ND4, 3460/ND1, and 14484/ND6 (2).

We report three female family members harboring the 11778 LHON mtDNA who developed visual loss within a short time period. All three had been exposed to smoke from two large rubber tire fires within the previous 24 months. Their young ages and gender add further to the suspicion of an environmental factor contributing to or triggering their visual loss.

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## CASE REPORTS

### Case 1

A 32-year-old woman (Fig. 1, V-2) presented to an ophthalmologist in September 1999 complaining of a 3-week history of painless visual loss in the right eye. A maternal grandmother (Fig. 1, III-2) and great-grandmother (Fig. 1, II-3) had become blind in their early 30s and a sister had bitemporal hemianopia (Fig. 1, V-3). The patient denied any use of alcohol or tobacco.

Best-corrected visual acuities were 20/80 in the right eye and 20/20 in the left eye. There was no relative afferent pupillary defect (RAPD), and color vision was

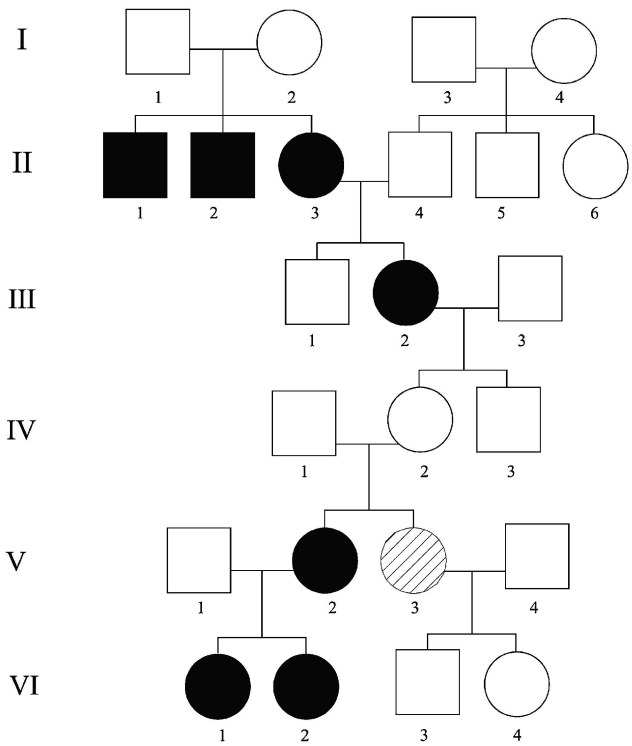


**FIG. 1.** Pedigree analysis of affected LHON family. *Squares* represent male family members and *circles* female family members. *Solid symbols* represent individuals with visual loss. The *shaded circle* (V-3) represents a possible affected woman who had bitemporal hemianopia.

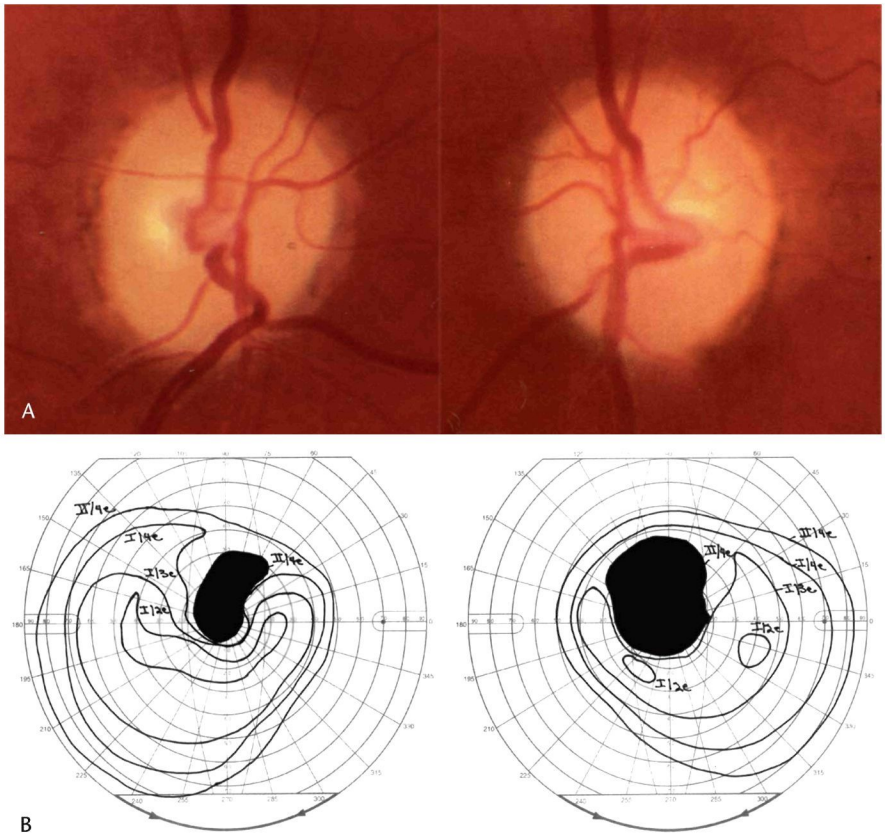


**FIG. 2.** Case 1. **A.** Fundus photographs in December 1999 show optic disc pallor in both eyes. **B.** Goldmann visual fields in December 1999 show central scotomas in both eyes.

intact. Humphrey visual field (HVF) testing revealed a paracentral defect in the right eye. Brain MRI was normal. Complete blood count (CBC), routine serum electrolyte levels, anti-nuclear antibodies (ANAs), erythrocyte sedimentation rate (ESR), fluorescent treponemal antibody absorption test (FT-ABS), and vitamin $B_{12}$ and folate levels were also normal.

The patient presented to the University of California (UC)–Davis Neuro-ophthalmology Clinic in December 1999. Visual acuities were 20/400 in both eyes. There was end-gaze jerk nystagmus with a mild upbeat nystagmus in both eyes. Ophthalmoscopic examination demonstrated optic disc pallor in both eyes (Fig. 2A). Dense central scotomas were noted in both eyes on Goldmann visual field (GVF) testing (Fig. 2B). Fluorescein angiography was unremarkable.

Mitochondrial DNA analysis performed on the patient's hair confirmed the diagnosis of LHON with a homoplasmic 11778/ND4 mutation. The patient began taking vitamins C and E and idebenone. In February 2000 visual acuities had worsened to counting fingers in both eyes. She had stopped using idebenone by April 2001. Four years later, visual acuities were still counting fingers in both eyes. Optic discs were markedly pale bilaterally.

## Case 2

The 7-year-old daughter of Case 1 (Fig. 1, VI-1) presented to an ophthalmologist in October 1999 complaining of difficulty reading. Visual acuities were 20/30 in both eyes. In February 2000, acuities were 20/200 in both eyes; optic disc hyperemia was noted in the right eye, but there was no RAPD.

She presented to the UC–Davis Neuro-Ophthalmology clinic in March 2000 with visual acuities of counting fingers in both eyes. Ophthalmoscopy revealed bilateral optic disc pallor, swelling of the inferior and superior nerve fiber layer, and nasal retinal telangiectasia in the right eye. Mild optic pallor and nerve fiber layer swelling were present nasally and superiorly with telangiectasia in the left eye (Fig. 3A).

Brain MRI was normal. The patient's hair contained a homoplasmic 11778/ND4 mutation. Visual evoked potentials revealed reduced amplitudes bilaterally. In January 2001, visual acuities had improved to 20/40 in both eyes and she was able to read. Goldmann visual field testing in May 2001 revealed central scotomas in both eyes (Fig. 3B). In April 2005, visual acuities had fallen to 20/150 in the right eye and 20/100 in the left eye. Marked optic disc pallor and end-gaze nystagmus were present in both eyes.

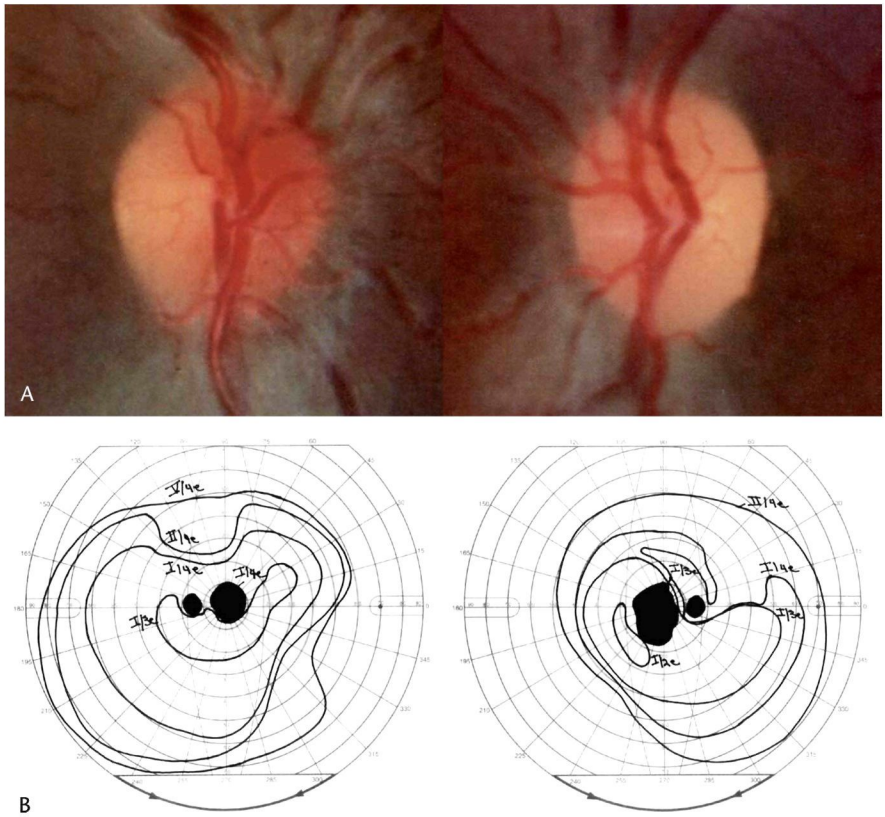

**FIG. 3.** Case 2. **A.** Fundus photographs in March 2000 show optic disc pallor, nerve fiber layer swelling, and nasal telangiectasia in both eyes. **B.** Goldmann visual fields in September 2001 show central scotomas in both eyes.

## Case 3

The 4-year-old daughter of Case 1 (Fig. 1, VI-2) presented to an ophthalmologist in April 2001 with a 2-week history of visual difficulty. On our examination in May 2001, visual acuities were 20/60 in both eyes by single pictures. There was no RAPD. End-gaze horizontal nystagmus was present in both eyes. Mild temporal optic disc pallor temporally was present in both eyes, and there was nerve fiber layer swelling in the right eye (Fig. 4A).

Brain MRI was normal. Hair sampling was positive for the homoplasmic 11778/ND4 LHON mutation.

By September 2001, the patient's vision had fallen to 20/100 in both eyes and by July 2004 to 20/400 in both eyes. GVF testing revealed central scotomas bilaterally (Fig. 4B). In April 2005, visual acuities were 20/400 in the right eye and 20/150 in the left eye.

## Northern California Rubber Tire Fires

Case 1 reported that two large fires involving rubber tire pits sparked by lightning had occurred near the family home. The first fire occurred on August 8, 1998, approximately 1 year before onset of symptoms in Case 1 (Fig. 5). This fire originated approximately 3 miles from the family's residence and consumed 2.5 million tires, producing a 2,500 m smoke plume and leaving a thick layer of ash in their yard. The family recounted smelling fumes from the fire for one year. On September 22, 1999, a second tire pit fire was sparked by lightning about 20 miles from the family's home. This fire consumed 5 million tires and a pool of pyrolytic oil until it was extinguished on October 27, 1999. Environmental Protection Agency (EPA) reports from this second fire indicated increased levels of carbon soot (close to 200 $\mu g/m^3$; the seasonal norm is 5–8 $\mu g/m^3$) as well as other potential toxins during this episode.

## DISCUSSION

Our report of this LHON pedigree is remarkable in that the 3 female members of one family were all affected within a 19-month period. Two large tire fires had subjected all 3 patients to high and prolonged levels of several air pollutants within 2 years of development of visual loss, suggesting that epigenetic factors might have contributed to its development.

Visual loss in female patients with LHON usually occurs later than in male patients (3). These 3 patients are remarkable in that they are all female, and 2 of them suffered visual loss at an unusually young age. Although Case 3 is not the youngest reported patient to develop visual loss in LHON (she may be the youngest female patient to be reported) (4–7), her young age warrants

 

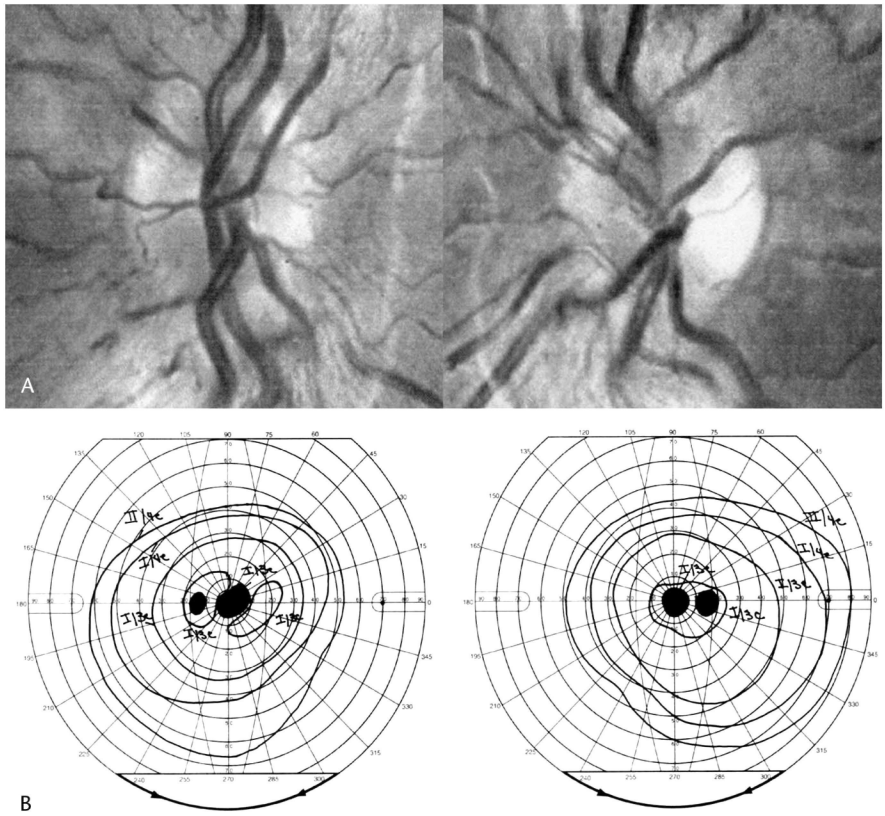


**FIG. 4.** Case 3. **A.** Fundus photographs in May 2001 show mild temporal optic disc pallor and nerve fiber layer swelling in both eyes. **B.** Goldmann visual fields in September 2004 show central scotomas in both eyes.

investigation into epigenetic factors. Moreover, all 3 patients suffered visual loss over a relatively short period of time (19 months) that followed prolonged exposure to potentially toxic substances.

The pathophysiology of LHON is complex. In recent years, much attention has focused on complex I dysfunction due to the LHON pathogenic mutations (1,8). Cellular models have shown 2 main pathologic consequences of the mutation consisting of a reduction of complex I-driven ATP synthesis (9) and a chronic increase of reactive oxidative species (ROS) production (10,11). Although the exact link between biochemical dysfunction and the massive wave of apoptosis of retinal ganglion cells (RGCs) is not completely understood in vivo, the most recent studies demonstrate that there is an increased predisposition of LHON cybrids to undergo apoptosis through a mitochondrial failure in vitro (12,13). Excess ROS production increases the expression of aldose reductase and allows its potentially toxic enzymatic products to accumulate and activate the apoptotic cascade in LHON cybrids (12). In this context, any further insult to mitochondrial function, such as further ROS exposure or inhibition of respiratory function due to environmental toxic exposure, may trigger the fatal wave of apoptotic death in

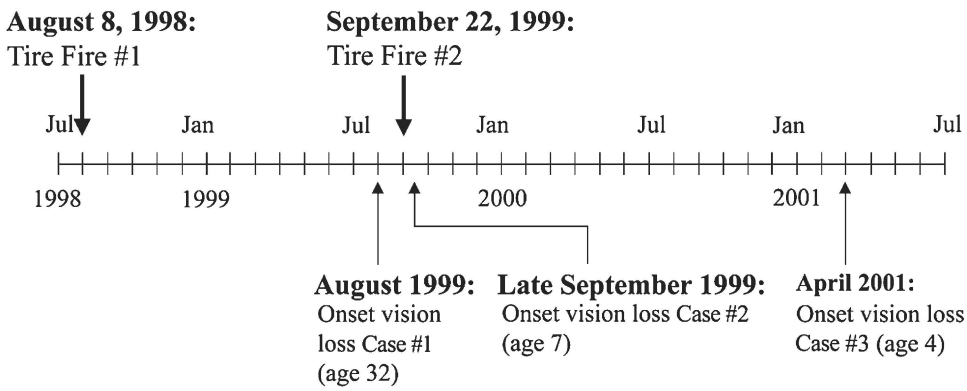


**FIG. 5.** Timeline indicating the relationship of visual loss in each patient to the two tire fires.

RGCs characteristic of the subacute/acute optic neuropathy in LHON. Studies with LHON cybrid technology have already demonstrated a link between these types of environmental triggers and a preferential up-regulation of transcriptional products involved in electron transport and ATP synthesis (12).

The description of the toxins polluting the air provided by the EPA was too long and general to be of much use in understanding what the 3 patients had been breathing, nor were serum samples from the patients analyzed for toxicology. However, the remarkable combination of sudden high penetrance in three female patients at very widespread ages, with 2 of them certainly out of the usual range for LHON onset, strongly suggests that environmental factors played a major role in these patients.

We are aware of a similar circumstance in Italy, where a 36-year-old woman, her 31-year-old brother, and her 13- and 17-year-old male children became affected with LHON within 2 years from September 2000 to December 2002. All were also found to be homoplasmic for the same 11778/ND4 mutation (ML Valentino, P Barboni, and V Carelli, personal communication). Having lived together in the same house in a rural area of Southern Italy, the only common environmental exposure was a wood-burning stove in their house that produced much smoke.

Traces of cyanide are commonly found in cigarette smoke, and carbon monoxide is a component of carbon-fire and wood-fire smoke. Smoke has previously been reported to be a possible environmental risk factor, including exposure through firefighting (14). Cyanide and carbon monoxide found in smoke have been shown to inhibit cytochrome *c* oxidase (complex IV) and may play a role in lowering the threshold of an unstable mitochondrial respiratory function such as that of unaffected carriers of LHON mutations.

Our hypothesis that ROS exposure may have also contributed to the pathogenesis of LHON expression in this family is controversial. Previous case-controlled studies (15,16) and the results from a large Brazilian pedigree of LHON (17) highlighted the role of epigenetic factors, most notably heavy tobacco and alcohol consumption, as risk factors for developing blindness in LHON. However, the results of another case-controlled study suggested that neither smoking nor alcohol consumption were risk factors for visual loss in individuals harboring the LHON-associated mitochondrial mutations (18). In that study, (18) investigators had evaluated the effects of tobacco and alcohol on visual loss in multiple LHON probands and their siblings through questionnaire analysis. Only 56% of questionnaires were returned for analysis. Therefore, the investigators' conclusions may have been subject to a selection bias.

During the preparation of this manuscript, the 16-year-old nephew of Case 1 (Fig. 1, VI-3) presented to our clinic in February 2006, complaining of decreased vision in the right eye. Visual acuity was 20/400 in the right eye and 20/20 in the left eye. Funduscopic examination revealed temporal pallor of the optic disc right eye. Two months later, visual acuities were 20/400 in both eyes. There was temporal pallor in both optic discs, and Humphrey visual fields revealed dense central scotomas bilaterally. Brain MRI was normal. The patient had the LHON 11778 mutation. His parents disclosed that they had used a wood-burning stove as the primary source of heat in their residence for the past 16 years.

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