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CASE REPORT

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Leber Hereditary Optic Neuropathy Associated with Bilateral Macular Holes

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ABSTRACT

Leber hereditary optic neuropathy (LHON) causes visual loss, predominantly in healthy young men. We recently examined a patient who previously had bilateral macular holes and subsequently developed LHON at 74 years of age. Although his central scotomas were initially attributed to the macular holes, his visual acuity declined following an initial improvement after operative closure of the macular holes; thus, other diagnoses, including LHON, were considered. Furthermore, macular optical coherence tomography (OCT) images remained unchanged in this time. A mitochondrial genetic analysis identified a 11778G→A mutation. From this case, we propose that LHON remains in the differential diagnosis even in older patients, as has previously been reported.

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Central scotoma; Leber hereditary optic neuropathy; macular hole

Introduction

Leber hereditary optic neuropathy (LHON) is a mitochondrial DNA-mediated disease that causes acute or sub-acute visual loss, predominantly in healthy young men (typically 18–35 years of age).[1] Cases of late-onset LHON have been reported—for instance, 11778G→A mutation in 50-,[2] 58-,[3] 59-,[4] 62-,[5] 63-,[6,7] 64-,[8] 67-,[9] 70-,[10,11] 72-,[12] 73-,[13] 75-,[14] 81-,[15] and 87-[16] year-old men, 14484T→C in 59-[5] and 81-[17] year-old men, and 3460G→A mutation in a 62-year-old woman[5] and in 75-[18] and 81-[19] year-old men. Onset in older age ranges increases the likelihood that the patients will previously have had other systemic[7,10] or eye[13] diseases, which can make the diagnosis of LHON more challenging. We recently examined a patient who developed LHON at the age of 74 years and previously had proliferative diabetic retinopathy and bilateral macular holes. His central scotomas were initially attributed to the macular holes.

Case presentation

In February 2014, a 74-year-old man presented with a central scotoma in his left eye. His family history was unremarkable; as far as he knew, none of his immediate relatives had a visual problem. He was a former smoker (up to 20 cigarettes/day until the age of 54). He had type 2 diabetes mellitus, complicated by proliferative diabetic retinopathy for which he had received bilateral photocoagulation (Figure 1A).

In December 2007, he was diagnosed with a macular hole in his right eye (Figure 2A), followed by his left eye in January 2013 (Figure 2B). The macular holes resulted in central scotomas and decreased his visual acuity to 15/100 in the right eye and 20/100 in the left eye. Both macular holes were closed by a combined vitrectomy with phacoemulsification: the right eye in December 25, 2007, and the left eye in February 14, 2013: his visual acuity subsequently improved to 20/40 in his right eye and 20/30 in his left eye on examination in August 2013 (Figure 2C).

The relapse of the central scotoma in his left eye (Figure 3A) was observed a year after the surgery and initially attributed to the macular hole. However, optical coherence tomography (OCT) images showed that the macular hole was still closed. Brain/orbital magnetic resonance imaging (MRI) failed to determine another cause of the scotoma. A 3-day course of intravenous methylprednisolone (1 g/day) followed by oral administration of

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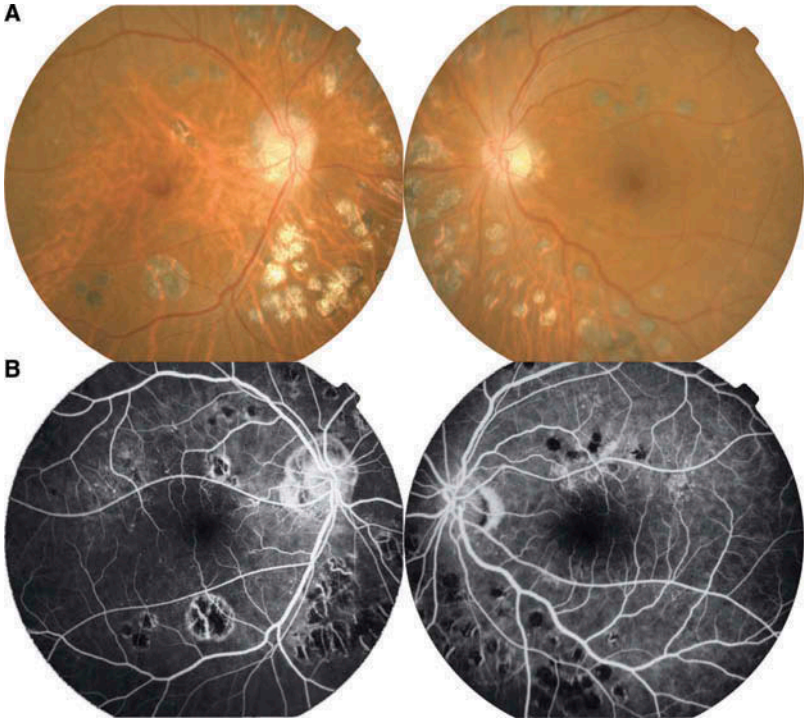

Figure 1. Fundus photographs in February 2014 (A) and fluorescein angiography in April 2014 (B).

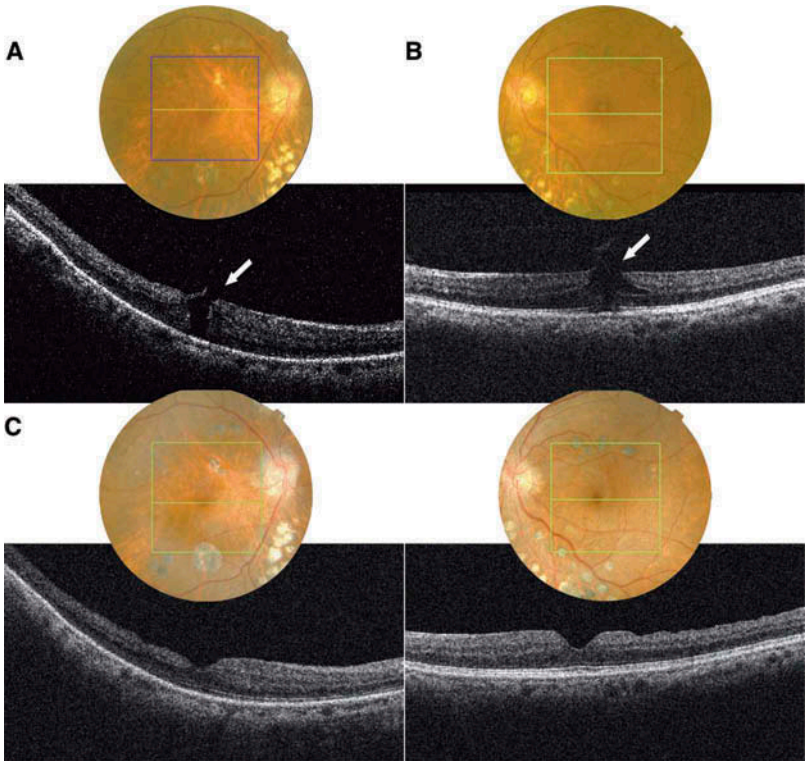

Figure 2. Optical coherence tomography images. (A) Stage 2 macular hole (arrow) in the right eye December 2007. (B) Stage 2 macular hole (arrow) in the left eye January 2013. (C) Bilateral macular holes were successfully closed after a combined vitrectomy/phacoemulsification, images taken in February 2013.

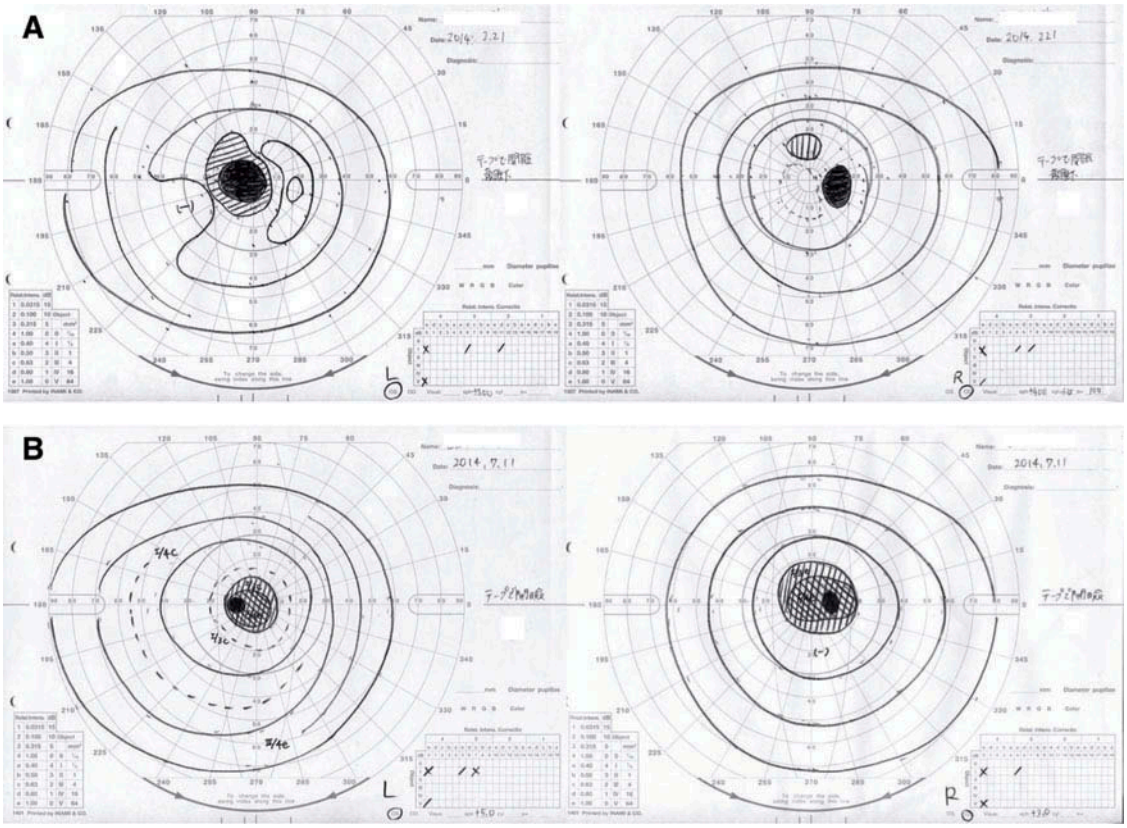

Figure 3. Goldmann visual field testings. (A) Central scotoma OS and an asymptomatic paracentral relative scotoma OD in February 2014. (B) Central scotomas OU in July 2014.

prednisolone had no effect except to increase his blood sugar level. Instead, he developed a similar central scotoma in his right eye in April 2014, 2 months after the onset in the left eye (Figure 3B). His visual acuity decreased to 20/500 in his right eye and 20/250 in his left eye. The treated macular holes remained unchanged throughout this time.

Fluoresein angiography, which had until then been withheld due to his renal condition, did not identify a pathogenic change in the fovea or the optic disc (Figure 1B). Neuromyelitis optica immunoglobulin G (NMO-IgG) was negative. Ultimately, we completed a workup for bilateral painless optic neuropathy, including mitochondrial genetic analysis, which revealed a 11778G→A mutation.

Discussion

A macular hole can be closed by vitrectomy, but it may have after-effects that could mask signs of other diseases. Although bilateral macular holes are relatively rare, as described in a recent study of 4507 cases with bilateral presentations in only 2.4% (108 patients),[20] they can potentially present with bilateral central scotomas. In this case, however, his visual acuity declined despite the initial improvement postoperatively and the unchanged macular OCT, all of which suggested an alternative aetiology. From this case, similar to previous reports,[3,6,7,9–11,13–17,19] we suggest that LHON be considered as a possible diagnosis even in older patients.

An onset of LHON can be not only associated with but also triggered by many factors, including diabetes,[11,21] optic neuritis,[22] anti-tuberculous medications,[10,23,24] antiretroviral therapy for human immunodeficiency virus,[25,26] carbon monoxide poisoning,[27] solvent exposure,[28] smoking,[1,11,14,29–31] trauma,[11,12,14,32,33] and even an increase in the intraocular pressure.[11,12] For example, a 58-year-old man had an onset of visual loss 1 year after an elevation in his intraocular pressures was first recorded, and a 11778G→A mutation was identified.[12] In our patient, a number of events, including an intraocular pressure fluctuation that was induced by the surgery, intraocular

tamponade, and postoperative posturing, might have induced the late onset of LHON.

Declaration of interest

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

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References

[1] Yen MY, Wei YH. Leber's hereditary optic neuropathy update review *Neuro-Ophthalmology* 2001;26:23–34.
[2] Mashima Y, Yamada K, Wakakura M, Kigasawa K, Kudoh J, Shimizu N, Oguchi Y. Spectrum of pathogenic mitochondrial DNA mutations and clinical features in Japanese families with Leber's hereditary optic neuropathy. *Curr Eye Res* 1998;17:403–408.
[3] Demidenko A, Vakili R, Eggenberger ER, Kaufman DI. Late onset Leber's hereditary optic neuropathy. *Neuro-Ophthalmology* 2008;32:41–42.
[4] Hotta Y, Fujiki K, Hayakawa M, Nakajima A, Kanai A, Mashima Y, Hiida Y, Shinoda K, Yamada K, Oguchi Y, Ishida M, Yaashima K, Wakakura M, Ishikawa S, Nakamura M, Sakai J, Yamamoto M, Hayashi T, Mitani I, Miyazaki S, Shimo-oku M, Imachi J, Kuniyoshi N, Nagataki S, Isashiki Y, Ohba N. Clinical features of Japanese Leber's hereditary optic neuropathy with 11778 mutation of mitochondrial DNA. *Jpn J Ophthalmol* 1995;39:96–108.
[5] Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* 1995;118:319–337.
[6] Borruat FX, Green WT, Graham EM, Sweeney MG, Morgan-Hughes JA, Sanders MD. Late onset Leber's optic neuropathy: a case confused with ischaemic optic neuropathy. *Br J Ophthalmol* 1992;76:571–573.
[7] Zoccolella S, Petruzzella V, Prascina F, Artuso L, Pacillo F, Dell'Aglio R, Avolio C, Delle Noci N, Attimonelli M, Specchio LM. Late-onset Leber hereditary optic neuropathy mimicking Susac's syndrome. *J Neurol* 2010;257:1999–2003.
[8] Edwards TL, Buttery RG, Mackey DA. Is second eye involvement in Leber's hereditary optic neuropathy due to retro-chiasmal spread of apoptosis. *Neuro-Ophthalmology* 2007;31:87–98.
[9] Goyal S, Riordan-Eva P, Coakes RL. Late onset of Leber's hereditary optic neuropathy precipitated by anaemia. *Eye (Lond)* 2004;18:1017–1018.
[10] Ikeda A, Ikeda T, Ikeda N, Kawakami Y, Mimura O. Leber's hereditary optic neuropathy precipitated by ethambutol. *Jpn J Ophthalmol* 2006;50:280–283.
[11] Pfeiffer ML, Hashemi N, Foroozan R, Lee AG. Late-onset Leber hereditary optic neuropathy. *Clin Exp Ophthalmol* 2013;41:690–693.
[12] Thouin A, Griffiths PG, Hudson G, Chinnery PF, Yu-Wai-Man P. Raised intraocular pressure as a potential risk factor for visual loss in Leber hereditary optic neuropathy. *PLoS ONE* 2013;8:e63446.
[13] Buchan JC, Ong C, Dabbs TR. Acute leber hereditary optic neuropathy in a 73-year-old man. *Eye (Lond)* 2007;21:859–860.
[14] Dimitriadis K, Leonhardt M, Yu-Wai-Man P, Kirkman M, Korsten A, De Coo IF, Chinnery P, Klopstock T. Leber's hereditary optic neuropathy with late disease onset: clinical and molecular characteristics of 20 patients. *Orphanet J Rare Dis* 2014;9:158.
[15] Decanini-Mancera A, Harrison AR, Lee MS. Another case of leber hereditary optic neuropathy in an octogenarian. *J Neuro-Ophthalmol* 2009;29:159–160.
[16] Giraudet S, Lamirel C, Amati-Bonneau P, Reynier P, Bonneau D, Miléa D, Cochereau I. Never too old to harbour a young man's disease? *Br J Ophthalmol* 2011;95:887–889.
[17] Shah VA, Randhawa S, Mizen T, Lee AG, Foroozan R. You're too old for that. *Surv Ophthalmol* 2008;53:403–410.
[18] Yu-Wai-Man P, Bateman DE, Hudson G, Griffiths PG, Chinnery PF. Leber hereditary optic neuropathy presenting in a 75-year-old man. *J Neuro-Ophthalmol* 2008;28:155.
[19] Dagi LR, Rizzo JF 3rd, Cestari DM. Leber hereditary optic neuropathy in an octogenarian. *J Neuro-Ophthalmol* 2008;28:156.
[20] Chang E, Garg P, Capone A Jr. Outcomes and predictive factors in bilateral macular holes. *Ophthalmology* 2013;120:1814–1819.
[21] DuBois LG, Feldon SE. Evidence for a metabolic trigger for Leber's hereditary optic neuropathy. A case report. *J Clin Neuroophthalmol* 1992;12:15–16.
[22] Wakakura M, Mogi A, Ichibe Y, Okada K, Hasebe H. Leber's hereditary optic neuropathy triggered by optic neuritis. *Neuro-Ophthalmology* 1996;16:337–341.
[23] De Marinis M. Optic neuropathy after treatment with anti-tuberculous drugs in a subject with Leber's hereditary optic neuropathy mutation. *J Neurol* 2001;248:818–819.
[24] Seo JH, Hwang JM, Park SS. Antituberculosis medication as a possible epigenetic factor of Leber's hereditary optic neuropathy. *Clin Exp Ophthalmol* 2010;38:363–366.
[25] Shaikh S, Ta C, Basham AA, Mansour S. Leber hereditary optic neuropathy associated with antiretroviral therapy for human immunodeficiency virus infection. *Am J Ophthalmol* 2001;131:143–145.

[26] Mackey DA, Fingert JH, Luzhansky JZ, McCluskey PJ, Howell N, Hall AJ, Pierce AB, Hoy JF. Leber's hereditary optic neuropathy triggered by antiretroviral therapy for human immunodeficiency virus. *Eye (Lond)* 2003;17:312–317.

[27] Hwang JM, Park HW. Carbon monoxide poisoning as an epigenetic factor for Leber's hereditary optic neuropathy. *Korean J Ophthalmol* 1996;10:122–123.

[28] Carelli V, Franceschini F, Venturi S, Barboni P, Savini G, Barbieri G, Pirro E, La Morgia C, Valentino ML, Zanardi F, Violante FS, Mattioli S. Grand rounds: could occupational exposure to n-hexane and other solvents precipitate visual failure in leber hereditary optic neuropathy? *Environ Health Perspect* 2007;115:113–115.

[29] Tsao K, Aitken PA, Johns DR. Smoking as an aetiological factor in a pedigree with Leber's hereditary optic neuropathy. *Br J Ophthalmol* 1999;83:577–581.

[30] Kerrison JB, Miller NR, Hsu F, Beaty TH, Maumenee IH, Smith KH, Savino PJ, Stone EM, Newman NJ. A case-control study of tobacco and alcohol consumption in Leber hereditary optic neuropathy. *Am J Ophthalmol* 2000;130:803–812.

[31] Kirkman MA, Yu-Wai-Man P, Korsten A, Leonhardt M, Dimitriadis K, De Coo IF, Klopstock T, Chinnery PF. Gene-environment interactions in Leber hereditary optic neuropathy. *Brain* 2009;132:2317–2326.

[32] Redmill B, Mutamba A, Tandon M. Leber's hereditary optic neuropathy following trauma. *Eye (Lond)* 2001;15:544–547.

[33] Nagai A, Nakamura M, Kusuhara S, Kanamori A, Negi A. Unilateral manifestation of Leber's hereditary optic neuropathy after blunt ocular trauma. *Jpn J Ophthalmol* 2005;49:65–67.