Leber Hereditary Optic Neuropathy Mimicking Optic Neuritis

Abstract

Introduction: Leber hereditary optic neuropathy (LHON) is a rare case with an incidence of 1 : 31.000 – 50.000. This condition may mimic the optic neuritis. LHON is a maternally inherited genetic disorder that has been characterized as painless severe bilateral vision loss in young adult man.

Purpose: To report suspected LHON in young adult man

Case report : A 24 years old man came to Neuroophthalmology unit with a chief complaint painless blurred vision in both eyes with 1 month delay. He has family history with the same complaint. On ophthalmologic examination, visual acuity (VA) in the right eye was counting finger at 1 meter and VA in the left eye was counting finger at 2 meters. Intraocular pressure (IOP) on right eye was 13mmHg and IOP left eye was 14 mmHg. Eye movements were within normal limit on both eyes with orthotropia position. Light reflex were decreased on both eyes. Left eye showed dyschromatopsia and scotoma. Funduscopy on both eyes were within normal limit. Visual field examination showed cecocentral scotoma on both eyes. MRI showed no lesion. Patient diagnosed as suspected LHON and differential diagnosed with retrobulbar optic neuritis on both eyes. The management were metilprednisolon intravenous (IV), ranitidin IV, mecobalamine IV, calcium hydrogen phosphate dihydrate + cholecalciferol per oral (PO), and coenzym Q10 PO. Patient was planned to undergo genetic test, ANA test, IgG and IgM anti Toxoplasma. Prognosis quo ad vitam was ad bonam, quo ad functionam was dubia ad malam.

Conclusion: LHON is a rare maternal inherited mitochondrial disorder characterized as painless severe bilateral loss of vision in male adult. LHON may mimic optic neuritis. There is no effective therapy. The visual prognosis mostly poor but it depends on the mutation location.

I. Introduction

Mitochondrial diseases were once thought of as rare disorders and increasingly recognized as a common cause of neurologic and visual dysfunction. Disorders of mitochondrial DNA mutations demonstrate a maternal inheritance pattern. Ophthalmic manifestations are frequent among mitochondrial disorders and can result in retinopathy, ocular motility disorders, or optic neuropathy. Among the mitochondrial diseases, Leber hereditary optic neuropathy (LHON) is often considered a prototypical disorder.[1, 2]

Leber hereditary optic neuropathy (LHON) is the most common optic neuropathy caused by a primary mutation in mtDNA. Leber hereditary optic

neuropathy (LHON) is a maternally inherited genetic disorder that has been characterized as severe bilateral loss of vision. It has a minimum point prevalence of 1 in 31,000 in the northeast of England, 1 in 39,000 in the Netherlands, and 1 in 50,000 in Finland. Age of onset is typically between 10 and 30 years, but may range from 1 to 87 years. LHON affects 80-90% predominantly males. Most LHON patients are aware of a family member with LHON-compatible vision loss, although 40% deny a known family history. This case will report LHON in young adult man.[2–5]

II. Case Report

A 24 year old man came to neuroophthalmology unit at Cicendo National Eye Hospital on 18 December 2017 with a chief complaint gradually blurred vision on both eyes. His left eye vision blurred for 1 month. His right eye vision blurred for 2 months. There was no pain, headache, pain on eye movement, nausea, vomit, trauma, and flu like syndrome. He has no history of alcohol consumption, smoking, diabetes mellitus, nor hypertension. His mother, uncles, and cousin lost their vision at second decade with the same chief complaint.

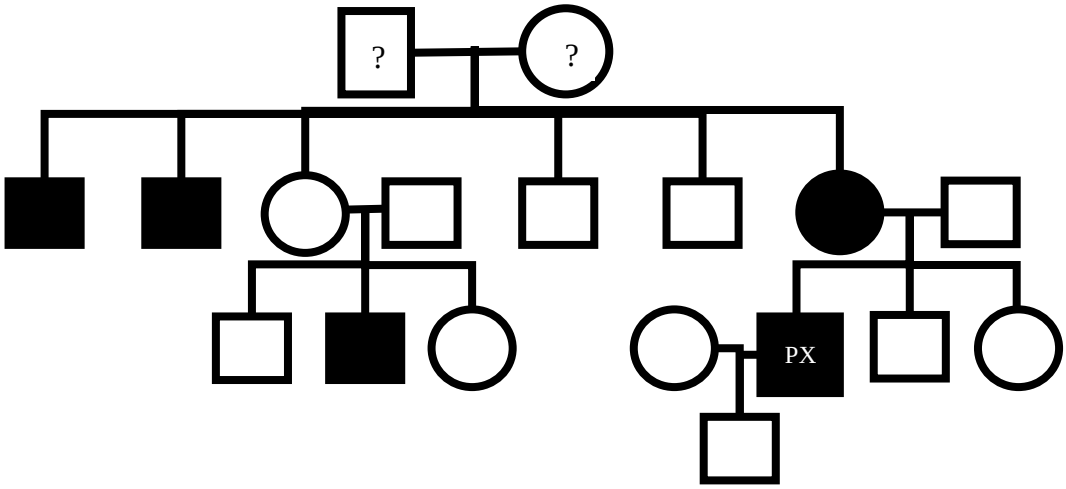

Figure 1. Patient's Pedigree
? = unknown history; Px = Patient
● = female with visual loss; ■ = male with visual loss

Consciousness was compos mentis, heart pulse 90 x/minute, respiration 18x/minute, blood pressure 110/70 mmHg, temperature 36 ^{o}C. On ophthalmologic examination, visual acuity on his right eye was counting finger at 1 meter and visual acuity on his left eye was counting finger at 2 meters. Intraocular pressure (IOP) on his right eye was 13mmHg and IOP on his left eye was 14 mmHg. Eye movements were full on both eyes with orthotropia position. Anterior segment on both eyes were within normal limit with exception light reflex decreased on both eyes. The test for color vision, Amsler grid, and contrast sensitivity on right eye cannot be evaluated. On the left eye, color vision test using Ishihara plate was demoplate (+), Amsler grid showed scotoma (+) on central and no metamorphopsia, contrast sensitivity test result was 1,25%. The posterior segment examination was within normal limit.

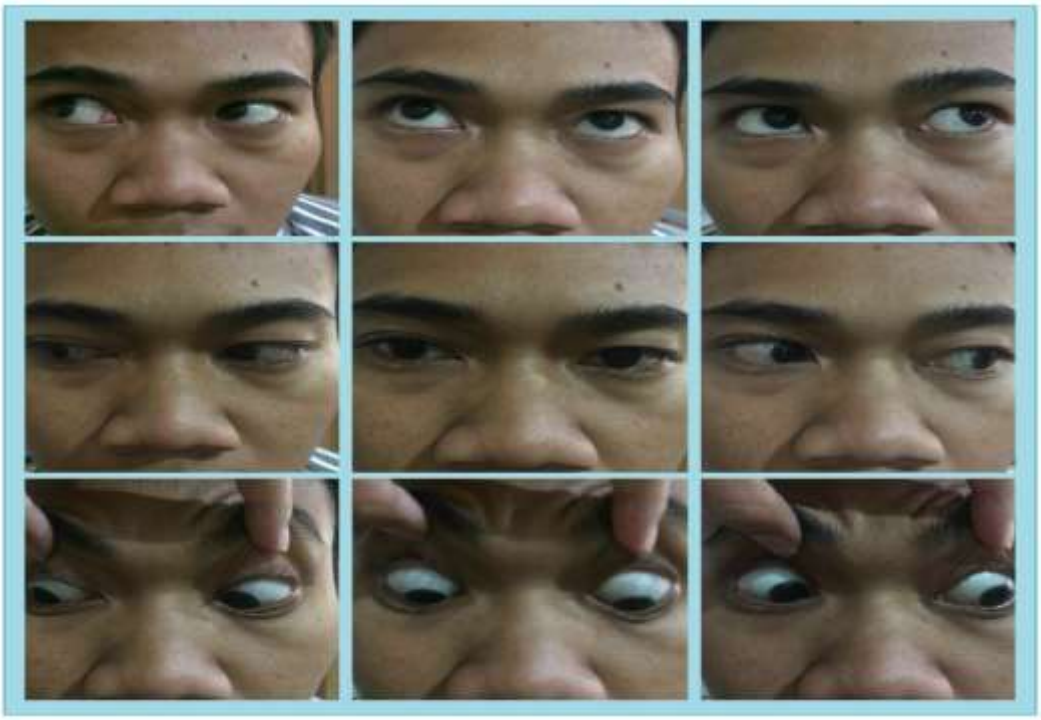

Figure 2. Eye movement was within normal limit.

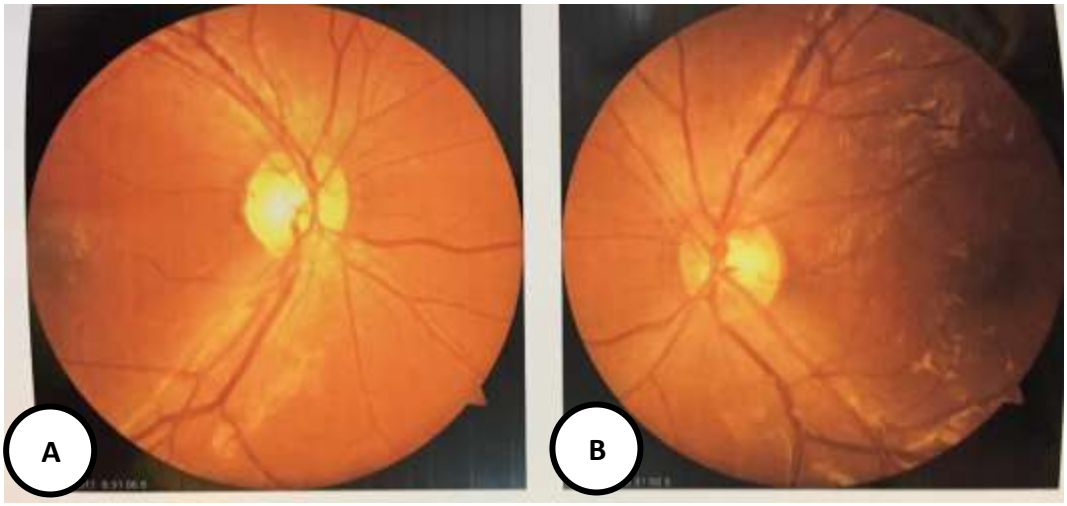

Figure 3. Fundus Photography
(A) Right eye revealed normal papil ; (B) Left eye revealed normal papil

His Humphrey visual field 30-2 examination on 17 November 2017 showed cecocentral scotoma on both eyes. Magnetic Resonance Imaging (MRI) showed bilateral optic neuritis. MRI showed no mass, compression, nor any lesion on the brain.

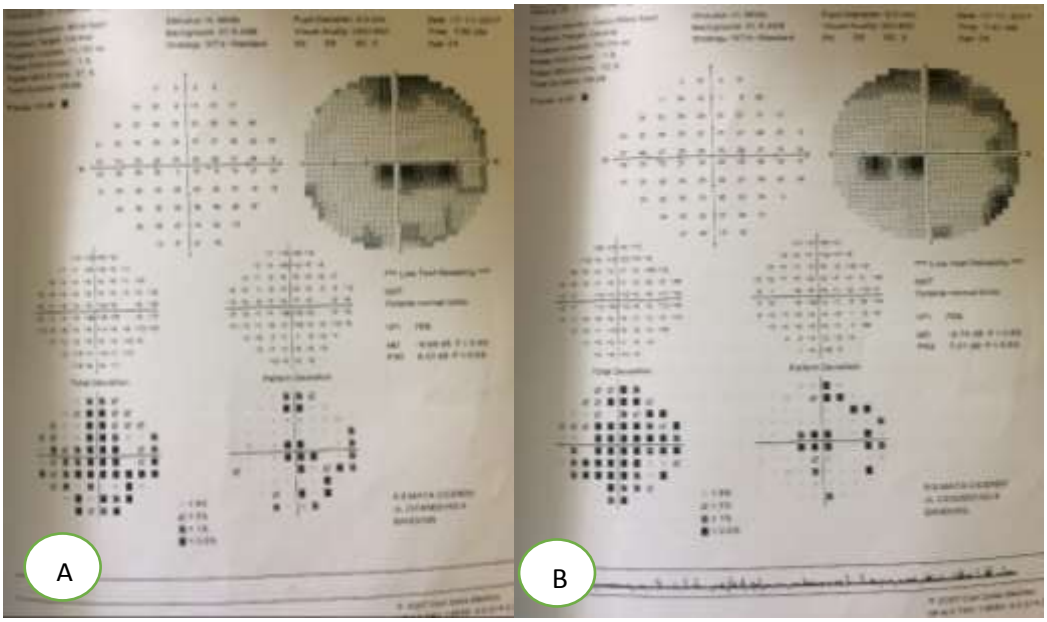

Figure 4. Humphrey visual field 30-2
(A) right eye visual field showed cecocentral scotoma
;(B) left eye visual field showed cecocentral scotoma

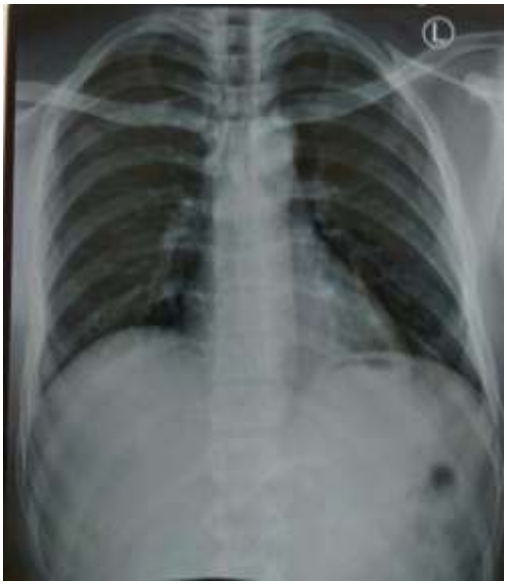

Figure 5. Rontgen thorax was within normal limit

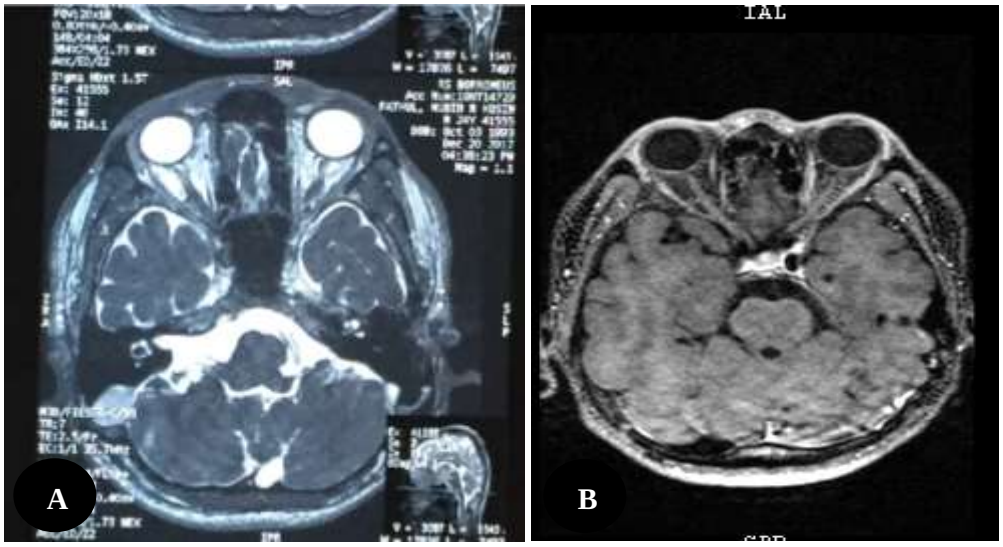

Figure 6. MRI brain showed bilateral acute optic neuritis.
A. MRI brain with contrast showed hyperintens on DWI (Diffusion Weighted Imaging);
B. B. MRI brain post contrast showed enchancement in bilateral opric nerve

Patient was diagnosed as suspected Leber hereditary optic neuropathy (LHON) and differential diagnosed (dd/) with retrobulbar optic neuritis on both eyes. The therapy of this patient was metilprednisolon 4 x 250 mg intra venous (IV), ranitidin 2 x 50 mg IV, mecobalamine 1 x 500mg IV, calcium hydrogen phosphate

dihydrate + cholecalciferol 3x1 tablet per oral (PO), and coenzym Q10 200mg tablet PO. Patient was planned to undergo genetic test, ANA test, IgG and IgM anti Toxoplasma. Prognosis quo ad vitam was ad bonam, quo ad functionam was dubia ad malam.

III. Discussion

Leber hereditary optic neuropathy (LHON) is an inherited disorder caused by mutations in mitochondrial DNA (mtDNA). LHON 80% - 90% in most pedigrees affects boys and men age 10–30 years but may occur earlier or later in life. Women may account for 10%–20% of cases. Affected females are more likely to have affected children than unaffected female carriers. [5–9]

In this case, the patient is 24 years old man who has uncle, cousin, and mother with symptomatic visual loss which onset at second decade. Most of his relatives with the same chief complaint were male at second decade. The patient's mother was affected females which is account for 10-20% of cases.

LHON caused by maternally inherited mitochondrial DNA point mutations, most frequently (50–90%) at nucleotide position 11778 in the *MT-ND4* gene. This type mutation is the poorest visual outcome and the least chance of spontaneous recovery. Another less common mutation at the 3460 or 14484 locations. 31% to 89% of European, North American, and Australian LHON pedigrees have the 11778 mutation, greater than 90% of Asian LHON patients are 11778 positive. [5–7,10,11]

In this case, patient's mother was affected females. She inherited the mitochondrial mutation to her son. This patient is Asian, the most probable is 11778 mutation according to demographic finding. However, the genetic test gives the definite result.

LHON usually presents as painless, acute visual loss begins simultaneously in both eyes (25-50%) or initially in one eye followed by visual loss in fellow eye within days, weeks, months or very rarely years later (50-75%). Median delay of visual loss between both eyes is 6–8 weeks. The majority of individuals progress

to a visual acuity of 20/200 or worse. The earliest visual field abnormality is a central or cecocentral visual field impairment due to preferential involvement of the papillomacular bundle. Dyschromatopsia is common and usually parallels the degree of visual acuity loss. [2,6,7,10]

This patient complains painless visual loss in right eye then followed by left eye in 1 month delay. The visual acuity on the right eye was counting finger at 1 meter and left eye was counting finger at 2 meters. Visual field on both eyes were cecocentral visual field impairment. This patient also has dyschromatopsia parallels to his visual acuity.

Relative afferent pupillary defect (RAPD) can occur in cases of asymmetric bilateral or monocular vision loss. In this case, pupillary light reflexes were decreased in both eye symmetrically so RAPD cannot be evaluated. [2,6,9,10]

The classic fundus appearance triad of LHON are hyperemia and elevation of the optic disc with thickening of the peripapillary retina; peripapillary telangiectasia; and tortuosity of the medium-sized retinal arterioles. Fundus examination in 20-40% of cases can appear normal in the active stage of vision loss. In this case, the fundus appearance showed normal appearance. Normal fundus appearance could be found in LHON and retrobulbar optic neuritis. [2,7,10]

Differential diagnosis includes optic neuritis, compressive optic neuropathy, and infiltrative optic neuropathy. LHON may mimic optic neuritis, clinically and on MRI. Both conditions tend to affect young adults in the second to fourth decades with abrupt visual loss. MRI in LHON may demonstrate optic nerve enhancement similar in appearance to optic neuritis. [2,7]

In this case, patient was young adult in the second decade with painless vision loss on both eyes. These findings could be found in optic neuritis and LHON. MRI in this case showed bilateral optic neuritis. Genetic testing to look for the three common causative mutations. Mitochondrial testing for the most common mutations is commercially available, but results may take several weeks. This patient was suggested to undergo genetic testing because it may confirm the diagnosis, permit genetic counseling, and provide information about prognosis.

This patient also suggested to undergo ANA test , IgG and IgM anti Toxoplasma to find the cause of optic neuritis. [2,7,9,11,12]

Attempts to treat or prevent the acute phase of visual loss with systemic steroids, hydroxocobalamin, or cyanide antagonists are ineffective. Other therapies tried are naturally occurring cofactors involved in mitochondrial metabolism or agents with antioxidant capabilities, including coenzyme Q10, idebenone (an analog of coenzyme Q), succinate, vitamin K1, vitamin K3, vitamin C, thiamine, and vitamin B2. Smoking and excessive alcohol consumption should be discouraged, theoretically in order to minimize mitochondrial stress.[6,7,9,10,13,14]

This patient therapy were metilprednisolon 4 x 250 mg intra venous (IV), ranitidin 2 x 50 mg IV, mecobalamine 1 x 500mg IV, calcium hydrogen phosphate dihydrate + cholecalciferol 3x1 tablet per oral (PO), and coenzym Q10 200 mg tablet PO. Although steroid and mecobalamine are ineffective, the patient was given steroid and mecobalamine because the differential diagnose was optic neuritis. He was given coenzym Q10 as antioxidant in mitochondrial. This patient has no history of smoking and alcohol consumption.

The visual prognosis in LHON is poor. Most patients suffer permanent bilateral visual loss with a final VA of counting finger at 6 meters or less. However, recovery of central vision may occasionally occur after visual deterioration. Spontaneous visual improvement in patients with LHON, 4–30% usually occurs about 1 to 2 years later depending on the mutation. Recovery usually is bilateral and symmetric, and once it occurs, recurrent visual loss is extremely rare. Spontaneous visual recovery is more common in patients with the 14484 mutation, with a partial recovery rate of 37%–58%. The 11778 mutation has the lowest partial with recovery rate 4%. Patients with the 3460 mutation have an intermediate prognosis, with an approximate 20% partial recovery rate. Earlier age of onset (younger than 20 years), a subacute time course of vision loss, and a larger optic disc are all associated with a better visual prognosis. This patient has visual acuity less than counting finger at 6 meters and onset of the visual loss was 24 year, this may cause poor prognosis. However, further follow up in this patient is required. [2,6,7]

IV. Conclusion

LHON is a rare maternal inherited mitochondrial disorder characterized as painless severe bilateral loss of vision in male adult. LHON may mimic optic neuritis. There is no effective therapy. The visual prognosis mostly poor but it depends on the mutation location.

References

1. Wiggs JL. Molecular Genetics of Selected Ocular Disorders. In : Yanoff M, Duker J S, editor. Ophthalmology. 4th Edition. Philadelphia: Elsevier; 2014. p.9-14
2. Meyerson C, Van Stavern G, McClelland C. Leber hereditary optic neuropathy: current perspectives. Clin Ophthalmol Auckl NZ. 2015 Jun 26;9:1165–76.
3. Peragallo JH, Biousse V, Newman NJ. Hereditary optic neuropathies. In: Taylor and Hoyt's Pediatric Ophthalmology and Strabismus. 5th ed. Philadelphia, PA; 2017. p. 581–91.
4. Hwang TJ, Karanjia R, Moraes-Filho MN,Gale J, Tran JS, Chu ER, Solange R. Salomao SR, et al. Natural History of Conversion of Leber's Hereditary Optic Neuropathy. Ophthalmology 2017;124:843- 50. [cited 2018 Jan 27]; Available from: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S016164201630848X
5. Chen JJ, Brodsky MC. Presymptomatic Visual Loss in Leber Hereditary Optic Neuropathy: A Therapeutic Window of Opportunity? Ophthalmology. 2017 Jun;124(6):755–6.
6. Miller NR, Subramanian PS, Patel VR. Walsh and Hoyt's Clinical Neuro-Ophthalmology The Essentials. 3rd Edition. Philadelphia: Wolters Kluwer; 2016. p. 382-95
7. Foroozan R, Bhatti MT, Falardeau J, Gordon LK, Lee MS, Subramanian PS, Kawasaki A. Basic and Clinical Science Course Section 5 : Neuro-Ophthalmology. 2015th–2016th ed. New York: American Academy of Ophthalmology
8. Forrester JV, Dick AD, McMenamin PG, Roberts F, Pearlman E. The Eye: Basic Sciences in Practice. 4th edition. Philadelphia: Elsevier; 2016. p. 156
9. Liu GT, Volpe NJ, & Galetta SL. Neuro-Ophthalmology: Diagnosis and Management. 2nd edition. Philadelphia: Elsevier Inc; 2010. p.126-9
10. Bowling B. Kanski's Clinical Ophthalmology. 8th edition. Philadelphia: Elsevier; 2016. 773-849 p.
11. Barboni P,Savini G, Wang MY. Optical Coherence Tomography in Neuro-Ophthalmology. In : Yanoff M, Duker J S, editor. Ophthalmology. 4th Edition. Philadelphia: Elsevier Inc; 2014. 858-5 p.
12. Manfready RA, Hedges TR, Mendoza-Santiesteban CE. Structural and functional degeneration of retinal nerves in sibling carriers of a Leber's hereditary optic neuropathy mutation. Can J Ophthalmol J Can Ophtalmol [Internet]. 2017 Aug [cited 2018 Jan 27]; Available from: http://dx.doi.org/10.1016/j.jcjo.2017.05.010
13. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, et al. Gene Therapy for Leber Hereditary Optic Neuropathy. Ophthalmology. 2016 Mar;123(3):558–70.
14. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, et al. Gene Therapy for Leber Hereditary Optic Neuropathy : Initial Results.

Ophthalmology 2016;123:558-70. [cited 2018 Jan 27]; Available from: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0161642017304955