Quality of Life in Patients with Leber Hereditary Optic Neuropathy

Matthew Anthony Kirkman,[1] *Alex Korsten,*[2] *Miriam Leonhardt,*[3] *Konstantin Dimitriadis,*[3] *Ireneaus F. De Coo,*[2] *Thomas Klopstock,*[3] *Philip G. Griffiths,*[1,4] *Gavin Hudson,*[1] *Patrick F. Chinnery,*[1,5] *and Patrick Yu-Wai-Man*[1,4]

Purpose. Leber hereditary optic neuropathy (LHON) is an inherited mitochondrial optic neuropathy characterized by bilateral, severe loss of central vision. In this study, the first formal assessment was conducted of visual disability in affected and unaffected individuals from molecularly confirmed LHON pedigrees.

Methods. Four hundred two LHON carriers—196 affected and 206 unaffected—from 125 genealogically distinct pedigrees were prospectively interviewed using the well-validated visual function index (VF-14) questionnaire: m.3460G>A (n = 71), m.11778G>A (n = 270), and m.14484T>C (n = 61).

Results. The mean age of onset of visual loss was 27.9 years (SD, 14.9) and mean disease duration was 15.5 years (SD, 15.4), with 74.5% of the affected subjects being men. The mean VF-14 score was 25.1 (SD, 20.8) in the affected patients, compared with 97.3 (SD, 7.1) in the unaffected carriers. Within the affected group, VF-14 score did not worsen with increasing disease duration and individuals with the m.14484T>C mutation had higher VF-14 scores compared with those in the m.3460G>A and m.11778G>A groups. Reading small print and reading a newspaper or book were the two VF-14 items that presented the greatest difficulty.

Conclusions. LHON has a severe negative impact on quality of life and has the worst VF-14 score when compared with other previously studied ophthalmic disorders. However, affected LHON carriers can be reassured that their level of visual impairment is unlikely to progress with time. The VF-14 questionnaire will be a useful tool for assessing the natural history of LHON and measuring outcome in future treatment trials. (*Invest Ophthalmol Vis Sci.* 2009;50:3112–3115) DOI:10.1167/iovs.08-3166

From the [1]Mitochondrial Research Group, The Medical School, and the [5]Institute of Human Genetics, Newcastle University, Newcastle-upon-Tyne, United Kingdom; the [2]Department of Child Neurology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, the Netherlands; the [3]Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University, Munich, Germany; and the [4]Department of Ophthalmology, Royal Victoria Infirmary, Newcastle-upon-Tyne, United Kingdom.

Supported by Ataxia (UK), the United Mitochondrial Diseases Foundation, and the European Union Research Framework Programme (EU FP) EU-Mitocombat (PFC). PYWM is an MRC Research Fellow and PFC is a Wellcome Trust Senior Fellow in Clinical Science.

Submitted for publication November 16, 2008; revised January 13, 2009; accepted May 4, 2009.

Disclosure: **M.A. Kirkman**, None; **A. Korsten**, None; **M. Leonhardt**, None; **K. Dimitriadis**, None; **I.F. De Coo**, None; **T. Klopstock**, None; **P.G. Griffiths**, None; **G. Hudson**, None; **P.F. Chinnery**, None; **P. Yu-Wai-Man**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Patrick Yu-Wai-Man, Mitochondrial Research Group, The Medical School, Newcastle University, Newcastle-upon-Tyne, NE2 4HH, UK; patrick.yu-wai-man@ncl.ac.uk.

Leber hereditary optic neuropathy (LHON; OMIM 535000; Online Mendelian Inheritance in Man; http://www.ncbi.nlm.nih.gov/Omim/ provided in the public domain by the National Center for Biotechnology Information, Bethesda, MD) is a mitochondrial genetic disease; more than 95% of cases arise from one of three point mutations in the mitochondrial genome: m.3460G>A, m.11778G>A, and m.14484T>C.[1–3] It preferentially affects young adults in the second and third decades of life and, among LHON carriers, males are five times more likely to be affected than are females. It is a common cause of inherited visual failure, affecting at least 1 in 30,000 individuals in the UK and 1 in 39,000 in the Netherlands, with an estimated carrier rate of 1 in 300.[4–6] Clinically, LHON is characterized by bilateral subacute loss of central vision as a result of focal degeneration of the retinal ganglion cell layer within the papillomacular bundle.[7] The visual prognosis is poor, and most patients remain severely visually impaired secondary to the marked reduction in visual acuity and the dense scotoma in their visual fields.

Quality of life describes the social, emotional, and physical impact of illness from the patient's perspective, and it is increasingly used by health care professionals as a more comprehensive assessment tool, especially in the setting of chronic diseases.[8] Data on the impact of mitochondrial disorders on patient's quality of life are limited and no study has formally documented the level of visual handicap experienced by patients with LHON. The Visual Function Index (VF-14) was designed for the formal assessment of functional impairment in ocular diseases, and it is a widely used, well-validated tool that reliably quantifies an individual's ability to perform activities of daily living that are reliant on normal visual parameters. The VF-14 questionnaire was originally designed for patients undergoing cataract surgery,[9,10] but it has since been applied to other ophthalmic conditions, including amblyopia,[11] nystagmus,[12] age-related macular degeneration,[13] retinal disease,[14] myopia,[15] and corneal transplantation,[16] and has been administered to patients attending low-vision services.[17] We present the results of the first study to use the VF-14 questionnaire to assess visual function in a large, multicenter cohort of affected and unaffected LHON carriers known to harbor a primary pathogenic mutation.

Materials and Methods

Participants

The VF-14 questionnaire was conducted on 196 affected and 206 unaffected carriers (n = 402), from 125 genealogically distinct LHON pedigrees. These families were identified from clinical databases maintained by the Mitochondrial Research Group, Newcastle University (Newcastle-upon-Tyne; UK; n = 47), Erasmus Medical Center (Rotterdam, the Netherlands; n = 46), and Department of Neurology, Friedrich-Baur-Institute (Munich, Germany; n = 32). Affected LHON carriers were assessed by an experienced neurologist or ophthalmologist, and disease conversion was assigned on the basis of bilateral visual loss, the documentation of optic nerve dysfunction and the

presence of characteristic fundal abnormalities. In atypical cases, compressive, inflammatory, or infiltrative causes of a bilateral optic neuropathy were excluded with the relevant investigations, including neuroimaging. All LHON carriers harbored one of the three primary mitochondrial DNA (mtDNA) mutations—m.3460G>A (n = 71), m.11778G>A (n = 270), or m.14484T>C (n = 61)—and this finding was confirmed by molecular genetic testing involving direct mtDNA sequencing, restriction fragment length polymorphism analysis, or primer extension assay. With the exception of one Asian individual, all participants were white. Total disease duration for affected individuals was defined as the time from the first onset of visual symptoms to the telephone interview, and unaffected LHON carriers were used as the internal control. This study had the relevant institutional ethical approval and complied with the Declaration of Helsinki. Verbal informed consent was also obtained from each subject before proceeding with the questionnaire survey.

VF-14 Questionnaire

Study participants were interviewed via telephone by three investigators (MAK, AK, and ML) using the VF-14 questionnaire, which measures the ability of individuals to perform 14 vision-dependent activities of daily living and these are rated in terms of difficulty, with five possible scores for each question: 0 (unable to do), 1 (great deal of difficulty), 2 (moderate difficulty), 3 (little difficulty), and 4 (no difficulty). The interviewee was asked to give answers that incorporated the use of reading glasses but not visual aids. A question was not included if an activity was not performed by an individual for reasons unrelated to disease status. An average score was then generated from all the answered questions and multiplied by 25 to give a scale ranging from 0 (worst level) to 100 (best level) of visual function. A literature search was also performed to identify studies where the VF-14 questionnaire was used to assess functional visual impairment in other ophthalmic disorders.

Statistical Analysis

An independent-sample t-test was used to compare the VF-14 scores between affected and unaffected LHON carriers and for mutational subgroup analysis. Pearson's correlation coefficient was determined with commercial software (SPSS ver. 15; SPSS, Chicago, IL).

Results

Our LHON cohort had a mean age of onset of visual loss of 27.9 years (SD, 14.9) and a mean disease duration of 15.5 years (SD, 15.4). There was no statistically significant difference in the age of onset among the three primary LHON mutations, but in a minority of the 196 affected individuals, visual failure occurred after the age of 50 years (n = 18, 9.2%). Among the affected group, 74.5% were men (n = 146), with a male to female ratio of 2.9:1 (Table 1).

The mean VF-14 score for affected patients with LHON was 25.1 (SD, 20.8; range, 0–95), significantly lower than the mean VF-14 score of 97.3 (SD, 7.1; range, 25–100) for unaffected LHON carriers ($P < 0.0001$; Fig. 1A). Within the affected LHON group, patients with the m.14484T>C mutation had a significantly higher VF-14 score (mean, 44.2; SD, 25.7) compared with those carrying the m.3460G>A and m.11778G>A mutations (mean, 21.8; SD, 17.9; $P < 0.0001$; Fig. 1B), but there was no significant correlation between VF-14 score and disease duration ($r = 0.09$, $P = 0.210$). The mean VF-14 score was 23.4 (SD, 19.1; 95% confidence interval [CI], 14.7–32.1) among the 21 affected individuals with a disease duration of ≤1 year and 25.3 (SD, 21.0; 95% CI, 22.2–28.5) among the remaining 175 affected individuals with a disease duration of >1 year (P = 0.694). Reading small print and reading a newspaper or book were the two activities of daily living that caused the greatest subjective difficulty (Table 2).

Table 1. Characteristics of the Study Population

	Affected	Unaffected
Number of individuals		
m.11778G>A (%)	132 (67.3)	138 (67.0)
m.3460G>A (%)	35 (17.9)	36 (17.5)
m.14484T>C (%)	29 (14.8)	32 (15.5)
Total	196	206
Sex, n (%)		
Male	146 (74.5)	60 (29.1)
Female	50 (25.5)	146 (70.9)
Male/female ratio	2.9	0.4
Age, y		
Mean (SD)	43.3 (16.9)	47.8 (14.9)
Range	13–82	14–83
Disease duration, y		
Mean (SD)	15.5 (15.4)	—
VF-14 score		
Mean (SD)	25.1 (20.8)	97.3 (7.1)
Range	0–95	25–100

Discussion

Our LHON cohort is comparable with other published epidemiologic case series, with a predominance of the m.11778G>A mutation, most patients experiencing visual loss in their 20s, and male carriers having a higher risk of visual failure than female carriers. The male-to-female ratio of affected individuals was slightly lower than the ratios reported in previous LHON case series, where male carriers were on average five times more likely to be affected than female carriers.[7] This discrepancy is likely due to an ascertainment bias, with the recruitment of a proportionally larger number of affected females into this study. This is the first study where functional visual impairment has been documented in a large group of molecularly confirmed LHON families. Using the VF-14 questionnaire, our findings indicate that the visual deficits in this condition have a strong negative impact on the quality of life of LHON sufferers. Compared to previously studied inherited and acquired ophthalmic disorders,[9–17] LHON is associated with the worst mean VF-14 score, reflected by the fact that most of the patients with LHON interviewed in this study have been legally registered as visually impaired with the relevant social services (Table 3). Of interest, patients with the m.14484T>C mutation had higher VF-14 scores compared with those harboring the m.3460G>A and m.11778G>A mutations, which further supports the notion that this primary mutation carries a better prognosis for visual recovery.[18,19]

There are limited data on the long-term progression of visual function in LHON, and our findings do not suggest a worsening of VF-14 score with increasing disease duration. This is consistent with the personal observations made by Van Senus[21] in his extensive study of 352 patients with LHON from 27 large Dutch pedigrees. Although nearly half of his cohort experienced a drop in their socioeconomic status, most of the affected individuals readjusted to their new level of visual functioning within a few years of disease onset. This outcome is relevant for patient counseling. Affected LHON carriers can be reassured that their level of visual impairment is unlikely to progress with time, and with adequate visual and occupational rehabilitation, they can remain active members of society. However, it must be stressed that this is a preliminary observation that must be confirmed in prospective studies in which the VF-14 score is measured at different time points in the same individuals, with careful adjustments made for other possible causes of visual morbidity.

Affected individuals reported the greatest level of difficulty with reading small print, newspapers, or books, which is not

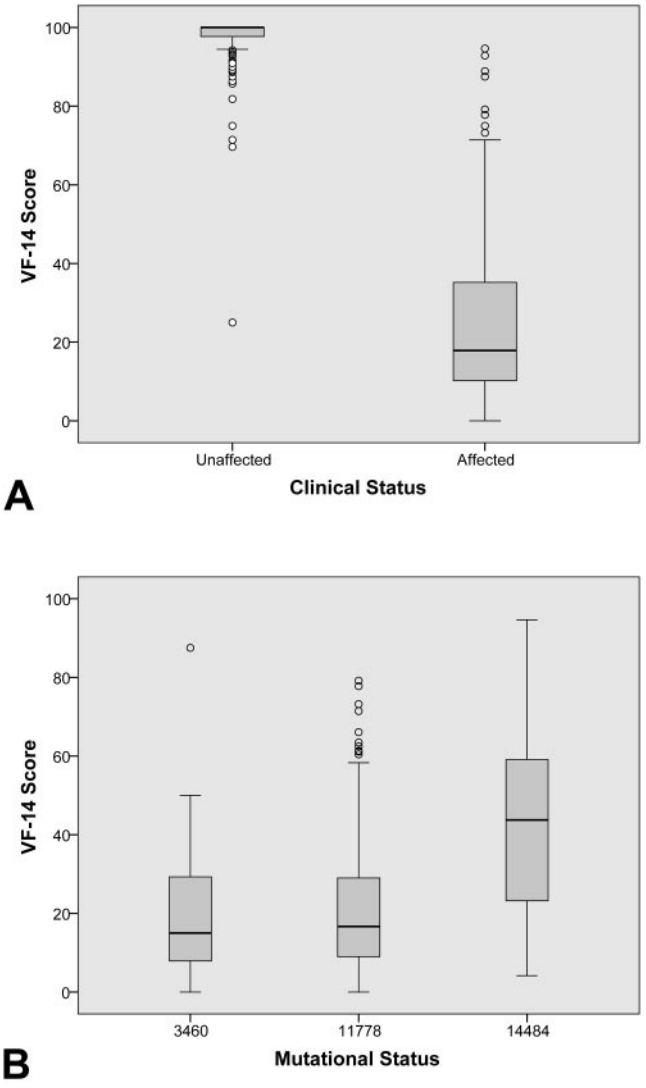

FIGURE 1. Box plot of VF-14 scores (**A**) for affected and unaffected LHON carriers and (**B**) for affected patients with LHON subdivided by mutational status. The *whiskers* represent the 95% CI; (○) outliers; *midline*, median VF-14 score; *box endlines*: the upper and lower quartiles, with the vertical length of the boxes indicating the interquartile range.

TABLE 3. Mean VF-14 Score in LHON Compared with Other Ophthalmic Conditions

Ophthalmic Condition	Mean VF-14	Reference
Amblyopia	79	11
Myopia	91	15
Age-related macular degeneration	89	13
Retinal diseases	84	14
Cataract surgery		10
Preoperative	73	
Postoperative	91	
Precorneal graft	72–76	16
CPEO	72	20
Nystagmus		12
Adults	55	
Children (child's assessment)	69	
Children (parent's assessment)	73	
Low vision services	54–62	17
LHON	25	This study

surprising, given that LHON results in a dense central or centrocecal scotoma involving the 10° around fixation. Although these patients use eccentric fixation to a certain extent, this adaptation is not helpful with standard-sized letters. These two VF-14 questions may therefore represent the most sensitive markers for assessing the level of functional disability in LHON and would offer a quick screening tool that could be applied in a busy clinical setting.

The only other study to assess the visual impact of a mitochondrial disorder was performed on individuals with chronic progressive external ophthalmoplegia (CPEO), which is present in up to 20% of patients with an underlying mitochondrial genetic defect and typically presents with ptosis and the progressive limitation of eye movements.[20] Similar to LHON, reading small print was also identified as one of the most difficult tasks among patients with CPEO, implying that significant impairment in reading ability could be a prevalent deficit among patients with other mitochondrial diseases. The VF-14 questionnaire is a well-validated quality of life scale with high internal consistency[9] and strong test–retest reliability,[22] and it is highly responsive to change.[23,24] It provides a more accurate picture of the true level of visual handicap than the measurement of single visual parameters, such as visual acuity, or more generic quality-of-life scales such as the SF-36.[14,22–24] Easy and quick to administer, the VF-14 questionnaire could therefore be used for patient assessment in conjunction with the recently developed Newcastle Mitochondrial Disease Adult Scale (NMDAS), a semiquantitative rating scale used to monitor a

TABLE 2. VF-14 Responses among Affected LHON Carriers

Question (Number of patients applicable)	Extent of Difficulty (%)				
	None	Little	Moderate	Great Deal	Unable to Do
Reading small print (196)	1.5	2.0	3.6	7.7	85.2
Reading a newspaper or book (196)	2.0	1.5	5.1	9.7	81.6
Writing checks or filling out forms (192)	4.7	1.0	7.8	19.3	67.2
Reading signs (195)	2.1	3.1	8.7	21.0	65.1
Doing handiwork (147)	3.4	5.4	15.0	29.3	46.9
Recognizing people (196)	3.6	4.6	8.2	38.8	44.9
Playing board games (131)	11.5	4.6	17.6	22.1	44.3
Reading a large print publication (194)	10.8	7.7	7.7	36.6	37.1
Playing sports (130)	23.8	5.4	15.4	21.5	33.8
Watching television (194)	5.2	4.1	12.9	53.1	24.7
Seeing steps or curbs or stairs (196)	9.2	12.2	20.4	37.8	20.4
Cooking (178)	23.0	16.9	27.0	21.3	11.8

The VF-14 items are ranked from highest to lowest based on the proportion of affected LHON patients reporting "unable to do."

patient's disease status in relation to other organ systems commonly involved in mitochondrial diseases.[25]

We have demonstrated the applicability of the VF-14 questionnaire in LHON, and it should be incorporated into prospective studies documenting the natural history of this disorder. It will also undoubtedly be a useful outcome measure to investigate the treatment effect of possible therapeutic agents in future LHON trials. LHON is one of the commonest primary mtDNA disorders, and it is the most frequent inherited optic neuropathy encountered in neuro-ophthalmological practice.[26] Our study confirms the significant visual impairment caused by LHON, which affects a predominantly young and otherwise healthy population, and highlights the urgent need to develop effective treatment strategies, which are currently lacking.

Acknowledgments

The authors thank the Dutch patients' association "De LOA-contactgroep" (Eindhoven) for their contribution and all the LHON families who kindly took part in this survey.

References

1. Harding AE, Sweeney MG, Govan GG, Riordan-Eva P. Pedigree analysis in Leber hereditary optic neuropathy families with a pathogenic mtDNA mutation. *Am J Hum Genet.* 1995;57(1):77–86.
2. Newman NJ, Biousse V. Hereditary optic neuropathies. *Eye.* 2004; 18(11):1144–1160.
3. Mackey DA, Oostra RJ, Rosenberg T, et al. Primary pathogenic mtDNA mutations in multigeneration pedigrees with Leber hereditary optic neuropathy. *Am J Hum Genet.* 1996;59(2):481–485.
4. Man PYW, Griffiths PG, Brown DT, Howell N, Turnbull DM, Chinnery PF. The epidemiology of Leber hereditary optic neuropathy in the North East of England. *Am J Hum Genet.* 2003;72(2): 333–339.
5. Elliott HR, Samuels DC, Eden JA, Relton CL, Chinnery PF. Pathogenic mitochondrial DNA mutations are common in the general population. *Am J Hum Genet.* 2008;83(2):254–260.
6. Spruijt L, Kolbach DN, de Coo R, et al. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. *Am J Ophthalmol.* 2006;141(4):676–682.
7. Man PY, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. *J Med Genet.* 2002;39(3):162–169.
8. Higginson IJ, Carr AJ. Measuring quality of life: using quality of life measures in the clinical setting. *BMJ.* 2001;322(7297):1297–1300.
9. Steinberg EP, Tielsen JM, Schien OD, et al. The VF-14: an index of functional impairment in patients with cataract. *Arch Ophthalmol.* 1994;112(5):630–638.
10. Norregaard JC, Bernth-Petersen P, Alonso J, Andersen TF, Anderson GF. Visual functional outcomes of cataract surgery in the United States, Canada, Denmark, and Spain: report of the International Cataract Surgery Outcomes Study. *J Cataract Refract Surg.* 2003;29(11):2135–2142.
11. Sabri K, Knapp CM, Thompson JR, Gottlob I. The VF-14 and psychological impact of amblyopia and strabismus. *Invest Ophthalmol Vis Sci.* 2006;47(10):4386–4392.
12. Pilling RF, Thompson JR, Gottlob I. Social and visual function in nystagmus. *Br J Ophthalmol.* 2005;89(10):1278–1281.
13. Mackenzie PJ, Chang TS, Scott IU, et al. Assessment of vision-related function in patients with age-related macular degeneration. *Ophthalmology.* 2002;109(4):720–729.
14. Linder M, Chang TS, Scott IU, et al. Validity of the visual function index (VF-14) in patients with retinal disease. *Arch Ophthalmol.* 1999;117(12):1611–1616.
15. Rose K, Harper R, Tromans C, et al. Quality of life in myopia. *Br J Ophthalmol.* 2000;84(9):1031–1034.
16. Boisjoly H, Grosset J, Fontaine N, et al. The VF-14 index of functional visual improvement in candidates for corneal graft. *Am J Ophthalmol.* 2002;134(2):166–171.
17. Scott IU, Smiddy WE, Schiffman J, Feuer WJ, Pappas CJ. Quality of life of low vision patients and the impact of low vision services. *Am J Ophthalmol.* 1999;128(1):54–62.
18. Kerrison JB, Newman NJ. Clinical spectrum of Leber's hereditary optic neuropathy. *Clin Neurosci.* 1997;4(5):295–301.
19. Nakamura M, Yamamoto M. Variable pattern of visual recovery of Leber's hereditary optic neuropathy. *Br J Ophthalmol.* 2000;84(5): 534–535.
20. Yu Wai Man CY, Smith T, Chinnery PF, Turnbull DM, Griffiths PG. Assessment of visual function in chronic progressive external ophthalmoplegia. *Eye.* 2006;20(5):564–568.
21. Van Senus AHC. Leber's disease in the Netherlands. *Doc Ophthalmol.* 1963;17:1–163.
22. Steinberg EP, Tielsch JM, Schein OD, et al. National study of cataract surgery outcomes: variation in 4-month postoperative outcomes as reflected in multiple outcome measures (comment). *Ophthalmology.* 1994;101(6):1131–1140; discussion 1140–1141.
23. Alonso J, Espallargues M, Andersen TF, et al. International applicability of the VF-14. An index of visual function in patients with cataracts. *Ophthalmology.* 1997;104(5):799–807.
24. Cassard SD, Patrick DL, Damiano AM, et al. Reproducibility and responsiveness of the VF-14. An index of functional impairment in patients with cataracts. *Arch Ophthalmol.* 1995;113(12):1508–1513.
25. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. *Neurology.* 2006;66(12):1932–1934.
26. Schaefer AM, McFarland R, Blakely EL, et al. Prevalence of mitochondrial DNA disease in adults. *Ann Neurol.* 2008;63(1):35–39.