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What are the characteristics and progression of visual field defects in patients with Leber hereditary optic neuropathy: a prospective single-centre study in China

Hong-Li Liu,[1] Jia-Jia Yuan,[1] Zhen Tian,[2] Xin Li,[2] Lin Song,[1] Bin Li[1,2]

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[1]Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Department of Ophthalmology, Taihe Hospital, Hubei University of Medicine, Shiyan, China

Correspondence to
Professor Bin Li;
libin-12@163.com

ABSTRACT

Objective To study the characteristics and progression of visual field defects in patients with Leber hereditary optic neuropathy.

Design Prospective study.

Setting 3-A-class hospital in China; single-centre study.

Participants From 100 patients diagnosed with Leber hereditary optic neuropathy, 80 (160 eyes; 68 men and 12 women; youngest patient, 6 years; oldest patient, 35 years) were recruited.

Exposure All patients were followed up for at least 12 months. Each patient underwent at least three visual field examinations. Patient groups 1–6 were created according to the time of visual field data acquisition. Patient group 7 included patients with a different onset of disease between eyes. Group 8 was composed of patients with a course of disease of 12–24 months when one of the examinations performed. Patients who performed the third examination made up patient group 9.

Primary outcome measures Prevalence of the different visual field defect types on the basis of severity in groups 1–6. Mean of the difference of visual function between eyes in group 7.

Result In groups 1–6, the prevalences of defects classified using Visual Field Index values were significantly different between groups 1 and 3. In group 7, with the prolongation of the course of the disease, the mean of the difference of visual function between eyes decreased. There was no significant correlation between age and the severity of visual field defect. There was significant correlation between visual acuity and the severity of visual field defect.

Conclusion Visual field defects in patients with Leber hereditary optic neuropathy (G11778A) may continuously progress within 6 months of disease development, and remain stable after 9 months. With the progression of the disease, the differences in visual function between eyes may decrease. The severity of visual field defect seems to be independent of age; however, could be related to visual acuity.

Trial registration number NCT03428178, NCT01267422.

Strengths and limitations of this study

- This study had a large sample size, and all visual field data were collected from patients with G11778A mutation.
- Each patient was followed up for ≥12 months and underwent at least three visual field examinations.
- The findings are expected to provide useful information for guiding gene therapy and developing a deeper understanding of Leber hereditary optic neuropathy, particularly in terms of disease course.
- We only examined the central 30° of the visual field in our patients.
- The use of a single visual field calculation method could have yielded suboptimal measurements because of individual differences or compensatory effects between different pathways in the visual system.

INTRODUCTION

Leber hereditary optic neuropathy (LHON) is an inherited mitochondrial disease characterised by bilateral, (sub) acute, painless vision loss. The G11778A mitochondrial DNA point mutation is most commonly associated with LHON.[1 2] Our study group and other researchers are conducting clinical trials to assess the safety and efficacy of gene therapy for LHON.[3 4] However, during the course of gene therapy for LHON, we found that determination of the optimal time window for treatment is very important.

Visual field examination is an important procedure for diagnosis, gene therapy, evaluation of treatment efficacy and follow-up observation in patients with LHON. In a previous study, we analysed the characteristics of different types of visual field defects in 32 patients with LHON[5]; however, the number of patients was small and detailed grading had not been possible.

In the present study, we used the semiquantitative visual field classification methods applied for patients with glaucoma based

on Visual Field Index (VFI) and mean deviation (MD) values to ensure thorough analysis of the relationship between the severity of visual field defects and the disease course. In addition, the characteristics of visual function in patients with a different onset of disease between eyes, and the relationship between the severity of visual field defect and age or visual acuity were analysed in detail. We used visual field data acquired at different points of time after vision loss to evaluate the characteristics and progression of visual field defects in patients with LHON and determine the optimal time window for treatment.

METHODS

Study subjects

In total, 160 eyes of 80 sporadic patients diagnosed with LHON (gene sequencing showed MTND4m.11778 G>A) between December 2016 and December 2017 were recruited for this study. All patients were followed up for at least 12 months, during which they underwent at least three visual field examinations. Inclusion criteria included: compliance with LHON diagnostic criteria (the symptoms and signs of patients were consistent with the clinical manifestations of LHON. Meanwhile, genetic testing showed MTND4m.11778 G>A); provided informed consent; voluntary participation; 6≤ age ≤60 years old; the time of referral. Exclusion criteria were: severe cardiopulmonary and renal dysfunction, cancer, bleeding disorders, acute infectious disease, high fever, high fever disease, pregnancy, heart disease and patients with mental disorders.[3]

Patient groups

According to previous literature reports and clinical findings, the first 6 months after disease development constitute the acute or progressive phase, whereas the following 6 months constitute the chronic or optic nerve atrophy phase.[6 7] At 1 year after disease development, the status of the visual field stabilises.[8] Therefore, we created groups 1–6 according to the time of visual field data acquisition after vision loss: group 1, visual field data obtained within 1 month; group 2, visual field data obtained between 1 and 3 months; group 3, visual field data obtained between 3 and 6 months; group 4, visual field data obtained between 6 and 9 months; group 5, visual field data obtained between 9 and 12 months; and group 6, visual field data obtained between 12 and 24 months. All patients with a different onset of disease between eyes were included in patient group 7. Patient group 7 was divided into six subgroups according to the time of visual field data acquisition after vision loss: subgroup 1, visual field data obtained within 1 month; subgroup 2, visual field data obtained between 1 and 3 months; subgroup 3, visual field data obtained between 3 and 6 months; subgroup 4, visual field data obtained between 6 and 9 months; subgroup 5, visual field data obtained between 9 and 12 months; and subgroup 6, visual field data obtained between 12 and 24 months. Patient group 8 was composed of the patients with a course of disease of 12–24 months when one of the examinations performed. Patients who performed the third examination made up patients group 9.

Visual acuity examination

For best-corrected visual acuity examinations (BCVA, Star Kang Medical Technology, Wen Zhou, China), the distance between the visual acuity chart and the patient was 2.5 m. The time taken to read each optotype was not allowed to exceed 2 s. If the examination persisted for too long, the patient was instructed to close his/her eyes and rest them before further examination to avoid fatigue. Visual acuity examinations were carried out once every 10 min in triplicate. A mean value was taken for the final result. The logarithm of the minimum angle of resolution for the smallest optotype that was seen clearly by the patient was recorded to reflect their visual acuity.

Visual field examination

The 30-2 SITA-FAST program (HFAII740: Humphrey Field Analyzer II, Carl Zeiss Meditec, Dublin, California, USA) was used for standard automatic visual field examination of all participants. Under the guidance of an experienced physician, each subject underwent BCVA examination. Visual field testing is performed with vision correction in a dark room. A practice examination before the actual one was required for subjects undergoing visual field testing for the first time. Pupil dilation was performed for subjects with a pupil diameter <2.5 mm. The following parameters were used to inhibit mydriasis: stimulus cursor, III, white; stimulus cursor duration, 200 ms; background light intensity, 31.5 apostilb (ASB); and stimulus cursor intensity, 0.08–10 000 ASB.

The following parameters were recorded for all patients: fixation loss, false-positive rate, false-negative rate, MD, pattern SD and VFI. Patients with a fixation loss of >20% and a false-positive or false-negative rate of >15% were excluded.

Classification of visual field defects

Two trained evaluators classified the visual field defects according to VFI and MD values. A third trained evaluator made a decision in case of any disagreement between the two evaluators.

Classification based on VFI

The visual field defects were classified according to the University of São Paulo Glaucoma Visual Field Staging System (USP-GVFSS)[9]: early defect, VFI >91%; intermediate defect, 78%< VFI ≤91% and severe defect, VFI ≤78%.

Classification based on MD

The visual field defects were classified according to the Hodapp-Parrish-Anderson system (HPA)[10]: early defect, −6.00 dB <MD << −0.01 dB, when the defect degree (P) <5%, it is less than 18 points on the pattern deviation probability plots, or when p<1%, it is less than 10 points; moderate defect, −12.00 dB <MD << −6.01 dB,

when p<5%, p<37 points or when p<1%, p<20 points; and severe defect, MD << −12.01 dB, when p<5%, p≥37 points or when p<1%, p≥20 points.

Statistical analysis

All data are expressed as mean±SD. All statistical analyses were carried out using IBM SPSS statistics (SPSS V.22.0, SPSS Science). In patient groups 1–6, the ranked data non-parametric test was used for comparisons among multiple groups; a p<0.05 was considered statistically significant. While the multiple comparisons test was used for comparison between two groups, a corrected p<0.005 was considered statistically significant. In patient group 7, the mean of the difference values of VFI/MD between eyes in each subgroup was calculated. In patient groups 8 and 9, linear correlation tests were used to analyse the relationship between age or visual acuity and VFI/MD values.

Patient and public involvement

Patients were involved in setting the research question and in the design of the study. During the feasibility stage, the priority of the research question, choice of outcome measures and methods of recruitment were informed by discussions with patients through in-person interviews and telephone surveys. No patients were asked for advice on the interpretation or writing up of results. The results of the research have been disseminated to the patient community through emails.

RESULTS

From 100 patients whose gene sequencing showed MTND4m.11778 G>A, in total, 160 eyes of 80 patients who underwent their first examination within 2 years of disease development were recruited for the three examinations. There were 68 men and 12 women, with the youngest patient aged 6 years and the oldest, aged 35 years.

Classification of visual field defects

After the exclusion of 17 patients lost to follow-up and the elimination of inaccurate data (according to reliability index of visual field data and the course of the disease), 271 visual field data were divided into six groups ultimately. Of the total data, 39 were included in group 1, 45 in group 2, 60 in group 3, 49 in group 4, 40 in group 5 and 38 in group 6.

The classification of visual field defects according to MD and VFI values in each group is shown in table 1. There was a significant difference in the prevalence of the different defect types based on severity among multiple groups ($p_{(VFI)}$=0.002≤0.05, $p_{(MD)}$=0.001≤0.05). When VFI was used for classification, there was a significant difference between groups 1 and 3 (p=0.001≤0.005), with no significant difference between adjacent groups. When MD was used for classification, there was a significant difference between groups 1 and 4 (p=0.000≤0.005), with no significant difference between adjacent groups (figure 1).

Characteristics of visual field defect between eyes

In total, 33 patients were included in group 7, with the maximum and minimum interval times of 33 months and 1 month, respectively. Eight data were included in subgroup 1, 8 in subgroup 2, 14 in subgroup 3, 13 in subgroup 4, 14 in subgroup 5, 16 in subgroup 6.

Mean of the difference of visual function between eyes according to MD and VFI values in each subgroup is shown in table 2. From subgroup 1 to subgroup 6, the mean of the difference based on VFI or MD values between eyes decreased (figure 2).

Table 1 Classification of visual field defects according to the mean deviation (MD) and Visual Field Index (VFI) values for patients with Leber hereditary optic neuropathy stratified into groups according to the time course of the disease

Classification of visual field defect	Type	Group 1, %	Group 2, %	Group 3, %	Group 4, %	Group 5, %	Group 6, %
VFI	1	11.11	4.88	2.00	0	0	0
	2	22.22	14.63	4.00	8.16	10.00	7.89
	3	66.67	80.49	94.00	91.84	90.00	92.11
MD	1	17.95	8.89	4.44	2.04	2.50	2.63
	2	28.21	17.78	20.00	10.20	17.50	7.89
	3	53.85	73.33	75.56	87.76	80.00	89.47

1: Early visual field defect.
2: Moderate/intermediate visual field defect.
3: Severe visual field defect.
Group 1: visual field data obtained within 1 month after vision loss.
Group 2: visual field data obtained between 1 and 3 months after vision loss.
Group 3: visual field data obtained between 3 and 6 months after vision loss.
Group 4: visual field data obtained between 6 and 9 months after vision loss.
Group 5: visual field data obtained between 9 and 12 months after vision loss.
Group 6: visual field data obtained between 12 and 24 months after vision loss.

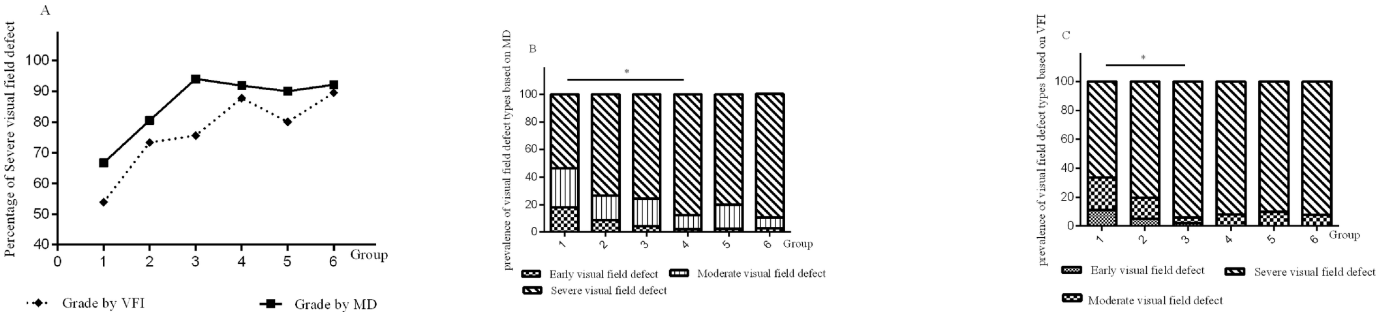

Figure 1 Progression of visual field defects in patients with Leber hereditary optic neuropathy. All patients are stratified into groups according to the time course of the disease. (A) Proportion of patients with severe visual field defects in the different groups. (B) Classification of visual field defects according to MD. The prevalence of the different defect types based on severity is significantly different between groups 1 and 4. There are no significant differences between adjacent groups. (C) Classification of visual field defects according to VFI. The prevalence of the different defect types based on severity is significantly different between groups 1 and 3. There are no significant differences between adjacent groups. Group 1: visual field data obtained within 1 month after vision loss. Group 2: visual field data obtained between 1 and 3 months after vision loss. Group 3: visual field data obtained between 3 and 6 months after vision loss. Group 4: visual field data obtained between 6 and 9 months after vision loss. Group 5: visual field data obtained between 9 and 12 months after vision loss. Group 6: visual field data obtained between 12 and 24 months after vision loss. MD, mean deviation; VFI, Visual Field Index. *There are significant differences.

Relationship between visual function and ages

Forty-two patients comprised the patient group 8, with the youngest patient aged 11 years and the oldest, aged 35 years. There was no significant correlation between the VFI or MD values and ages in patient group 8 ($p(VFI)=0.132>0.05$, $p(MD)=0.199>0.05$).

Correlation between visual acuity and visual field

Patient group 9 was composed of 66 patients. There were significant correlations among the changes in the VFI/MD and BCVA ($r(VFI)=-0.629$, $p(VFI)=0.000\leq0.05$, $r(MD)=-0.640$, $p(MD)=0.000\leq0.05$).

DISCUSSION

Based on the clinical characteristics of LHON (G11778A), the patient losses vision rapidly, even in a few days. However, visual field defects continuously progress to a stable state. How do the visual field defects progress? In this study, we found that the two classification methods yielded similar results. The magnitude of progression in adjacent 1-month and 1–3 months periods was not enough to yield a statistically significant difference, and there were no significant differences among the groups beyond 9 months. Thus, it appears that visual field defects continuously and rapidly progressed within the first 6 months after disease development and after 9 months, the defects had progressed to a stable state. This conclusion based on statistical analyses also matches that based on our longitudinal observations of obvious visual field defect progression at 1, 3 and 6 months in most patients, followed by stabilisation of the visual field at 6, 9 and 12 months. From the perspective of clinical significance, the severity of visual field defects reflects visual function, namely retinal ganglion cell (RGC) function, and it can be inferred that the number of RGCs rapidly decreases in the first 6 months after disease development and generally stabilises after 9 months, with stabilisation of RGC function between 6 and 9 months.

This disease progression pattern coincides with the findings of comprehensive visual electrophysiology for patients with LHON in a study by Majander A *et al*,[11] and the findings in nerve fibres in a study by Nikoskelainen *et al*.[12] It also corresponds to the previous staging system for LHON, where in the first 6 months following disease development constitute the acute or progressive phase and the next 6 months constitute the chronic or optic nerve

Table 2 Difference of visual function between eyes according to the mean deviation (MD) and Visual Field Index (VFI) values for patients with different onset of disease stratified into subgroups according to the time course of the disease in group 7

Mean of the difference	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5	Subgroup 6
VFI	41.00	16.00	16.77	8.86	9.00	10.56
MD	12.07	5.33	5.82	2.70	3.53	3.57

Subgroup 1: visual field data obtained within 1 month after vision loss.
Subgroup 2: visual field data obtained between 1 and 3 months after vision loss.
Subgroup 3: visual field data obtained between 3 and 6 months after vision loss.
Subgroup 4: visual field data obtained between 6 and 9 months after vision loss.
Subgroup 5: visual field data obtained between 9 and 12 months after vision loss.
Subgroup 6: visual field data obtained between 12 and 24 months after vision loss.

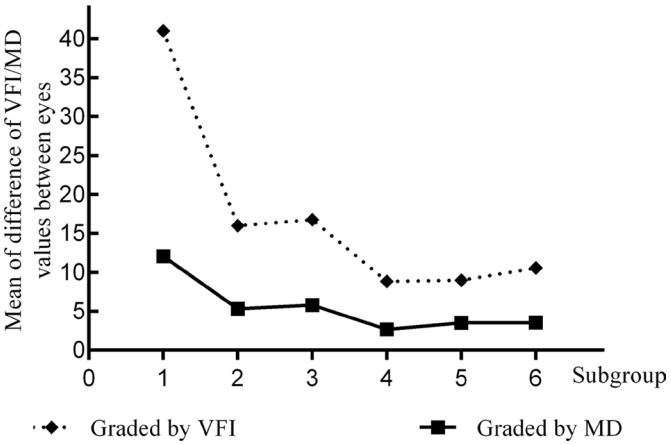

Figure 2 Progression of visual field defects between eyes in patients with different onset of disease.Patient group 7 is stratified into subgroups according to the time course of the disease. Subgroup 1: visual field data obtained within 1 month after vision loss. Subgroup 2: visual field data obtained between 1 and 3 months after vision loss. Subgroup 3: visual field data obtained between 3 and 6 months after vision loss. Subgroup 4: visual field data obtained between 6 and 9 months after vision loss. Subgroup 5: visual field data obtained between 9 and 12 months after vision loss. Subgroup 6: visual field data obtained between 12 and 24 months after vision loss. MD, mean deviation; VFI, Visual Field Index.

atrophy phase. In addition, in the result of the classification of visual field defects section, we can find a puzzling phenomenon in group 3: when the USP-GVFSS index was used, 94% of data scored to severe visual defect, while when the HPA score was taken into account, 20% of the data scored to moderate visual defect. The creation of this phenomenon is the different criteria for groups 1–6 and the good situation of visual field defect in some patients. For example, some visual field reports belong to severe defect based on VFI (VFI ≤78%); however, when based on MD, these reports belong to moderate defect (−12.00 dB <MD << −6.01 dB).

The characteristics of visual field defects have also been studied by many other researchers. Wakakura M studied early-stage visual field defects in nine patients with LHON,[13] while Ran analysed the morphological characteristics of visual field defects in 32 patients with LHON. Newman *et al* closely observed visual field defect progression from the early asymptomatic stage to complete vision loss as an endpoint in nine patients with LHON.[14] However, the number of cases in these studies was small, and not all patients had the G11778A mutation, so an accurate classification of the severity of defects was not possible. For instance, LHON strikes first one eye and that the second eye becomes involved within a 2–4 months period. How do the visual field defects progress in these patients? In our present study, we found that irrespective of the values (VFI or MD) used, mean of the difference between eyes decreased with the course of the disease. In other words, along with the progression of the disease, differences of visual function between eyes decreased in patients withdifferent times of onset of the disease. In addition, we found the severity of visual field defect was independent of age, but related to visual acuity when the visual function remains stable.

The present study has some limitations. First, we examined the central 30° of the visual field in our patients. However, patients with LHON have visual field defects covering a wide area, most of which rapidly progress to severe diffuse defects.[15] Second, the use of a single visual field calculation method could have yielded suboptimal measurements because of individual differences or compensatory effects between different pathways in the visual system.

Currently, gene therapy for LHON is safe and effective, but individual variations in the treatment efficacy are very large. Therefore, an optimal time window for gene therapy is of great significance. Previous studies have found that, in the early stages of LHON, the status of RGCs is unstable and nerve fibres are swollen.[6 8] Balducci *et al* proposed a time window of 6 months after disease development for gene therapy.[6] From our studies, we conclude that RGCs are in a state of deterioration for the first 6 months after disease development and gradually stabilise at 6–9 months. Accordingly, we propose that gene therapy should be ideally performed within the first 6 months after disease development. In other words, gene therapy should be performed when visual field defects are in the progressive stage in order to mitigate optic nerve damage to the greatest extent and achieve better recovery and outcomes.

CONCLUSION

First, our findings suggest that visual field defects in patients with LHON (G11778A) may continuously progress within 6 months, tend to stabilise between 6 and 9 months, and remain stable after 9 months. Administration of gene therapy within 6 months of disease development could prevent progressive injury to the optic nerve. Second, along with the progression of the disease, differences of visual function between eyes decreased in patients with different times of onset of the disease. Third, the severity of visual field defects was not related to age, however, is correlated with visual acuity. The findings provide useful information for guiding gene therapy and developing a deeper understanding of LHON, particularly in terms of the disease course.

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Contributors BL designed the experiments and obtained funding. H-LL and J-JY collected the data; LS performed the visual field examination. ZT and XL analysed the data. H-LL drafted the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Obtained.

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