Visual Acuity Changes in Patients With Leber Congenital Amaurosis and Mutations in CEP290

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Objective: To evaluate changes in visual acuity (VA) over time in patients with Leber congenital amaurosis (LCA) and mutations in the CEP290 gene.

Methods: Visual acuity was determined at the initial and most recent visits of 43 patients with LCA and CEP290 mutations. The main outcome measures included the best-corrected VA at the initial and most recent visits, as well as the correlation between age and VA.

Results: At the initial visit, 14 patients had measurable chart VA in the better-seeing eye, 25 patients had nonmeasurable chart VA, and 4 young patients did not have VA assessed. At the most recent visit, 15 patients had measurable chart VA and 28 had nonmeasurable chart VA. The average interval between the 2 visits was 10.4 years (range, 2-47 years). For patients with measurable chart VA, the median logMAR value at the initial visit (0.75; range, 0.10-2.30) and at the most recent visit (0.70; range, 0.10-2.00) did not differ significantly (P > .05). There was no significant relationship between VA and age.

Conclusions: Patients with LCA and CEP290 mutations had a wide spectrum of VA that was not related to age or length of follow-up. Severe VA loss was observed in most, but not all, patients in the first decade. These data will help clinicians provide counseling on VA changes in patients with CEP290 mutations and could be of value for future treatment trials.

bloom, HOTV, and the Teller Acuity Cards. The best-corrected VA in the better-seeing eye at the initial visit was determined, and this eye was also used for analysis of VA at the follow-up visit. Some patients with hand motion (HM) or worse did not undergo refraction. All VA data were converted to logMAR for analysis. Patients who could only count fingers (CF), perceive HM, had only light perception (LP), or had no light perception (NLP) were assigned the values of 2.6, 2.7, 2.8, and 2.9, respectively. However, these data were analyzed separately because assigning numerical values to patients with very poor VA constitutes an ordinal scale of measurement and is somewhat arbitrary.

DATA COLLECTION

Databases from the following 7 centers were searched for patients with LCA and CEP290 mutations: the University of Illinois at Chicago, the Chicago Lighthouse for People Who Are Blind or Visually Impaired, the University of Iowa, McGill University Health Center, the Cole Eye Institute of the Cleveland Clinic, Oregon Health and Science University, and the University of Pennsylvania. To prevent possible duplication of patient entry into the study, patients’ dates of birth were compared across the data sets. Data identified from the records included sex, age at appearance of first visual symptom, age at the time of visit, presence or absence of a syndromic form of LCA, and mutation(s) in CEP290. In addition, VA, chart used to measure VA, refractive error, anterior segment findings, corneal abnormalities, lens changes, macular changes, and any systemic features were recorded. Informed consent was obtained from all participating patients or their legal guardians at the centers where they were examined. Approval was obtained from the institutional review boards at the participating centers, and the study was conducted in accordance with the Health Insurance Portability and Accountability Act and with the tenets of the Declaration of Helsinki.

RESULTS

The Table provides the subjects’ age at the initial visit, VA at the initial and most recent visits for each eye, the change in VA for each eye, and the duration of follow-up between the 2 visits for each of the 43 participants. Of the 43 patients, there were 19 females and 24 males. The mean (SD)
age at the initial visit was 12.7 (17.1) years (range, 2 months-57 years). The mean (SD) age at the most recent follow-up visit was 23.1 (17.2) years (range, 2-61 years). The average (SD) duration between the initial and most recent visits was 10.4 (10.7) years (range, 2-47 years).

A firm diagnosis, or a highly likely diagnosis, was determined prior to obtaining the results of genotyping. The most frequently observed mutation in our sample was c.2991 + 1655 A>G, with approximately 77% of our patients having this mutation on at least 1 allele. Approximately 21% of our patients were homozygous for this mutation.

Among the study cohort, 4 patients had keratoconus at the initial and most recent visits (patients 26, 35, 41, and 42) and 2 additional patients developed keratoconus during the follow-up period (patients 7 and 28). Seven patients had a cataract at the initial and most recent visits (patients 14, 16, 35, and 39-42), and 1 patient developed a cataract while being followed up (patient 30). When cataracts were present, they were most commonly of the posterior subcapsular type.

At the initial visit, patients had various degrees of macular changes including 32 patients with a normal or blunted foveal reflex, 9 with retinal pigment epithelial pigmentary changes, and 2 with atrophic-appearing macular lesions. At the most recent visit, 33 patients had a normal or blunted foveal reflex, 2 had retinal pigment epithelial pigmentary changes, 5 had a bull’s eye macular lesion, and 3 had an atrophic-appearing macular lesion. Only 1 patient (patient 9) showed cystoid macular edema on spectral-domain optical coherence tomography; the cystoid macular edema was detected only at the most recent follow-up visit.

The distribution of VA among the patients is given in Figure 1. For patients with measurable chart VA, the median logMAR value at the initial visit in the better-seeing eye was 0.75 (range, 0.10-2.30). While the median logMAR VA at the most recent visit was 0.70 (range, 0.10-2.00). There was no statistically significant difference in median VA between visits for the 13 patients who had measurable chart VA at both visits (Wilcoxon signed rank test; P = .94).

As illustrated in Figure 2, 2 patients with measurable chart acuity at the initial visit had a loss in VA of more than a factor of 2 between the initial and most recent visits. This magnitude of VA change, a logMAR change of more than a factor of 2, was used as a criterion to evaluate VA changes during the follow-up period, consistent with previous studies. One patient with measurable chart VA had an improvement of more than a factor of 2. None of the patients with nonmeasurable chart acuity had more than a 2-level decrease in visual function (eg, from CF to LP or HM to NLP) between the initial and most recent visits. Patient 1 (the youngest patient) improved from NLP to CF, but this change is likely attributable to the difficulty of assessing visual function in very young children. For all patients, the modal change in VA was 0 logMAR.

Figure 3 shows the change in logMAR VA as a function of the duration of follow-up. The dashed lines in Figure 3 define a factor of 2 change in VA and data points falling within the dashed lines had less than a factor of 2 change. Nearly all of the patients had less than a factor of 2 change in VA. The 2 outliers shown in Figure 3 are patients 20 and 22, who had changes of 1.2 logMAR to LP and HM to 0.7 logMAR, respectively. Additionally, changes in VA were not significantly related to the duration of follow-up (r = −0.32; P > .05).

Figure 4 plots VA as a function of the patient’s age at the initial visit and most recent visit. There was a wide range of VA values for all age ranges, with no overall tendency for VA to become better or worse with age. The correlation between logMAR VA and age was not significant at either the initial visit (r = 0.00; P > .05) or the most recent visit (r = −0.14; P > .05).

Severely reduced VA, beginning in the first decade of life, was observed in most of this cohort, which constitutes a sizeable proportion of patients with LCA with CEP290 mutations from large retinal degeneration centers within...
the United States and Canada. At the time of presentation, 64% of the patients were classified as CF or worse in the better-seeing eye. Similar results were observed by Perrault et al,7 who examined 47 patients with CEP290 mutations and found that most patients had a severe and early reduction in VA. However, den Hollander et al6 found variable visual function in 4 affected siblings, ranging from LP to a VA of 20/80. Neither of these studies6,7 reported follow-up data; therefore, an evaluation of changes in VA over time is not possible based on these studies.

The severity of the CEP290 phenotype resulted in a relatively small number of patients with measureable chart acuity, which may require some caution when generalizing to a larger population of these patients. Nevertheless, 10 of the 14 patients with measurable VA at the first visit had a change in VA measured at the most recent visit of less than a factor of 2. Of the 13 patients with measurable chart acuity at both visits, the Snellen chart was used in 8 patients and the Early Treatment of Diabetic Retinopathy Study chart was used in 2 patients. Visual acuity was measured with different charts at the initial and most recent visits in only 1 patient. Consequently, the use of different charts for VA measurement cannot explain the relatively constant VA over time.

Of the 25 patients with nonmeasurable chart acuity, only 2 lost additional visual function between the initial visit and follow-up, with patient 4 decreasing from CF to LP and patient 13 decreasing from CF to HM. Eleven patients with nonmeasurable chart acuity gained at least 1 level of visual function during the follow-up. However, these presumed changes in visual function in patients with nonmeasurable chart acuity are difficult to interpret.

In conclusion, the data obtained from this study showed a substantial spectrum of VA abnormalities among patients with LCA and CEP290 mutations. A severe loss of VA was found in most, but not all, of the patients. There was no clinically significant additional loss of VA during the course of follow-up and we found no clinically significant relationship between age and VA, consistent with previous work.16,17 It will be of interest to continue to follow these patients, particularly those with measurable chart VA, to verify that VA remains stable over time. The present data will aid clinicians in counseling patients with CEP290 mutations about their visual prognosis, and the results may also be of value in patient selection for future treatment trials.
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REFERENCES


