A Case Report Survey (CRS) on the Natural History of Visual Acuity in Leber's Hereditary Optic Neuropathy (LHON)

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Introduction

Abstract

LHON is an inherited mitochondrial orphan disease leading to irreversible vision loss in the majority of patients. This survey reports the clinical course of vision loss and rates of spontaneous recovery based on a large retrospective case record survey (CRS).

Visual acuity data from 383 individual patients were collected under local ethics approval using a standardized report form. Detailed results for change of visual acuity with time since onset based on cross-sectional and longitudinal data are presented. The analyses confirm the expected rapid vision loss typically reaching nadir within less than 6 months. The time to recovery (off-to-on-chart or 2 lines on-chart) and proportion of patients with recovery from nadir varied with the associated mtDNA mutation. A total of 31.1% patients presented with spontaneous recovery (G11778A: 25%, G3460A: 50%, T14484C: 43%).

These data confirm the rapid and profound vision loss with mutation dependent rates of recovery. The vast majority of patients do not regain vision to below the treshold for legal blindness.

Background

LHON, the most common mitochondrial disorder, causes rapid vision loss generally leading to lifelong blindness with currently no approved treatment option (Yu-Wai-Man 2011, Sadun 2011, Newman 2012). The prevalence is 2–3 per 100,000 and typically otherwise healthy young men are affected. More than 90% of patients harbor one of three mitochondrial DNA mutations (G11778A, G3460A, T14484C) in the genes coding complex I of the respiratory chain. This genetic defect results in impaired cellular ATP synthesis. In the acute stage of the disease, within the first year of the initial onset of symptoms, the worsening in visual acuity (VA) is caused by dysfunction in retinal ganglion cells (RGCs) which leads to the development of a central scotoma and VA loss. Symptoms typically occur initially in one eye with the second eye following a similar course within weeks to months. It has been hypothesized that at an early stage the RGCs may still be viable although inactive (Howell 1998) presenting a window of opportunity for therapeutic intervention.

Promising outcomes for patients with LHON treated with idebenone have been reported in recent years in several publications (summarized by Gueven 2013) and were also demonstrated in a randomized, placebo controlled clinical trial (Klopstock 2011) as well as an open label Expanded Access Program (EAP) (Metz 2014). In the EAP, 24 of 48 patients with LHON (50%) and recent onset treated with Raxone (idebenone) experienced a clinically relevant and stable recovery in VA.

While in the natural course of the disease most patients present with irreversible vision loss, spontaneous partial or full recovery can occur and is reported in the literature from case series (Newman et al, 1991; Johns et al., 1992; Stone et al., 1992; Johns et al., 1993; Riordan-Eva et al., 1995; Macmillan et al., 1998; Mashima et al., 2000; Spruijt et al., 2006; Carelli et al., 2011). The analysis of incidence, magnitude and time to spontaneous recovery across the literature is limited however by factors such as differences in the definition of VA recovery, differences in the follow-up period as well as possible selection bias. Furthermore, these reports provide insufficient detail to allow conclusions on the "time to VA recovery", which is the critical parameter for comparison to treatment emergent VA recovery.

As is the case for orphan diseases in general, the availability of quantitative standardized natural history data in disease progression is limited but desirable in order to guide the design of clinical programs or as a reference for comparison of treatment effects as observed in open label studies. Therefore, in order to create more data on (i) the extent of VA loss at nadir and (ii) the extent and time-course of spontaneous clinically relevant recovery (sCRR) of VA observed during the natural course of disease, starting in May 2013, Santhera initiated this Case Record Survey.

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Methods

Conduct of the survey

This CRS was established as a collaboration between Santhera Pharmaceuticals and the European Vision Institute Clinical Research (EVICR.net). In addition, Santhera sought natural history data from LHON-treating centres participating in the EAP of Raxone® (idebenone) including a centre from the German Network for Mitochondrial Disorders (mitoNET).

This CRS collected historically documented VA data from existing medical records in a completely anonymous manner for all patients with a genetically confirmed diagnosis of LHON and patients were not required to attend the clinic. No exclusion criteria were applied. The survey was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable local laws. For each patient, year of birth, gender, date of onset of first symptoms, specific mtDNA mutation, previous use of idebenone including start and stop date, all available VA test results from date of onset to start of CRS and the test method or eye chart used (e.g. ETDRS, Snellen, categorical VA assignment etc.) was recorded on a standardized Case Record Form (CRF). Overall data from 383 patients containing the results of 3128 VA assessments were collected between May 2013 and February 2014 and reported in this CRS **(Table 1)**.

Table 1: Centres Contributing Patient Data to this CRS (see Table 4)

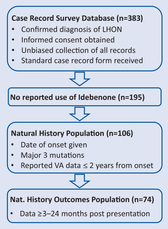
Source	Centre	Country	City	Patients
EVICR	s0006	France	Paris	40
EVICR	s0018	Belgium	Leuven	11
EVICR	s0020	Italy	Rome	14
EVICR	s0023	Slowenia	Ljubjana	5
EVICR	s0030	Denmark	Glostrup	90
EVICR	s0061	France	Bordeaux	1
EVICR	s0064	Italy	Bari	12
EVICR	s0067	Italy	Milan	121
EAP	s1001	Germany	Munich	76
EAP	s1002	Spain	Barcelona	11
EAP	s1003	USA	New York	2
Total				**383**

Database limitations and analysis populations

The reliability of historical longitudinal data could be affected by issues such as reporting of old assessments with a high degree of variability due to non-standardized procedures, uncertainties about the onset date as well as the predominant reporting of VA in Snellen notation (>90%) and its limitations particularly for low vision. Furthermore, as LHON is a disease with a very bad prognosis for VA, unless significant improvements occur, patients tend to be lost to follow-up which is reflected in the declining number of assessments with time since onset in the database. Where possible, strategies to mitigate the influence of these limitations (by e.g. raising data clarification queries to the centres) were implemented.

A number of filtering steps were implemented when defining the analysis populations **(Figure 1)**. The *Natural History Population* included all patients with no record of idebenone use, where one of the three major LHON-causative mutations was carried, where the date of onset of symptoms in the first affected eye was known and where the first assessment (Presentation) was available ≤24 months since onset. This population was used to establish the course of VA over time. The *Natural History Outcomes Population*, a sub-population of the *Natural History Population*, was identified from patients for which at least one assessment conducted ≥3–24 months after first presentation was available. This population was used to analyze clinically relevant recovery or worsening based on the VA outcome at the last available assessment within a 24 months follow-up period.

Figure 1: Definition of Patient Populations



Results

Natural history of disease progression

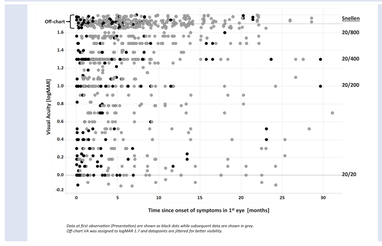
The demographics of the *Natural History Population* (n=106) is consistent with those reported properties for the general LHON population **(Table 2)**.

Table 2: Demographics Natural History Population (n=106)

Age at Onset [years]	mean (SD) median (range)	32.1 29.5	(15.4) (6–78)
Sex, N (%)	male	85	(80.2%)
	female	20	(18.9%)
	not given	1	(0.9%)
Mutation, N (%)	G11778A	78	(73.6%)
	G3460A	17	(16.0%)
	T14484C	11	(10.4%)
Age [years] at Presentation	mean (SD) median (range)	32.4 29.5	(15.5) (6–79)
Time since Onset [years] at Presentation	mean (SD) median (range)	0.3 0.2	(0.4) (0.0–1.9)
Best VA [logMAR] at Presentation	mean (SD) median (range)	0.75 0.78	(0.61) (–0.11–1.70)
VA of all eyes [logMAR] at Presentation	mean (SD) median (range)	1.03 1.28	(0.60) (–0.11–1.70)

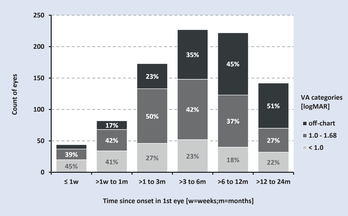
These patients provided VA data from 890 assessments which were used to assess VA change with time since onset **(Figure 2).** The number of available assessment decreases over time. Few data points are reported from patients with mild VA loss after 12 months of disease progression.

Figure 2: Analysis of VA as a Function of Time since Onset for all Eyes



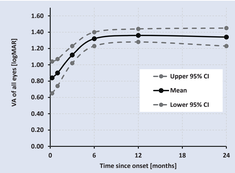
VA assessments for all eyes were grouped in various *windows* of time since onset and categories of residual visual acuity were defined **(Figure 3)**. The trend towards rapid and progressive worsening of VA with time becomes apparent with 45% of eyes assessed at 1 week with VA better than logMAR 1.0, whilst at 6 months this proportion had fallen to 23%. The number of eyes with off-chart VA increased from 16% at 1 week to 35% at 6 months and to 51% between 12 and 24 months after Onset.

Figure 3: Count of Eyes by VA Categories



A continuous trajectory connecting the mean VA observed with increasing time since onset using the same time windows as in Figure 3 is shown in **Figure 4.** LHON generally progresses rapidly, with substantial VA loss already at Presentation, worsening to a mean nadir of approximately logMAR 1.3 (Snellen 20/400) by 6 months after onset without general improvement thereafter (off-chart set to 1.7 logMAR). This course of rapid and permanent VA loss is in agreement with published literature (Newman et al., 1991; Riordan-Eva et al. 1995, Nikoskelainen et al., 1996).

Figure 4: Mean VA of all Eyes as Function of Time since Onset

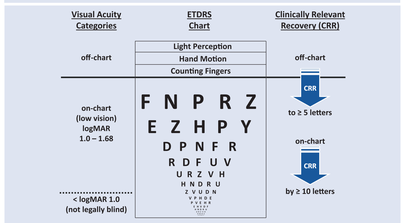


Spontaneous clinically relevant recovery (sCRR)

The classification of a sCRR **(Figure 5)** was restricted to patients presenting with VA improvement in at least one eye at the last available assessment using the following definitions (after Carelli et al., 2011; Barboni et al., 2005)

- For eyes with very severe vision loss and "off-chart" VA at nadir: improvement in VA sufficient to be able to read at least 5 letters (equivalent to one full line) on the ETDRS chart
- For eyes with "on-chart" VA at nadir: improvement in VA sufficient to be able to read at least 10 additional letters.

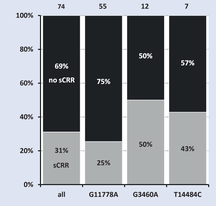
Figure 5: Definition of Clinically Relevant Recovery (CRR)



Spontaneous CRR was assessed for patients in the *Natural History Outcomes Population* (n=74) from whom at least 2 data points three months apart **(Figure 1)** were collected and comprised 774 data points in total. The demographic properties of this population were very similar to those of the *Natural History Population* (data not shown).

A total of 31.1% patients presented with sCRR. Analysis of the proportions of patients with sCRR by mtDNA mutation carried showed that higher proportions of sCRR were observed in patients carrying the G3460A (50.0%) and T14484C (42.9%) compared to patients carrying the G11778A mutation (25.5%) **(Figure 6)**. Since both the time since onset and the period over which VA was observed (Onset to outcome), can be expected to have affected the number of sCRR observed, these parameters were analyzed for all patients in the *Natural History Outcomes Population*. In the patients presenting with sCRR, the mean time from onset to sCRR was 9.9 months. For all patients, the mean time since onset at outcome was 14.9 months, and was slightly longer for patients presenting with sCRR compared to those without sCRR (17.3 and 13.8 months respectively). Analysis of the magnitude of the best sCRR observed for either eye in patients with sCRR revealed that the mean magnitude of sCRR was 39 letters, ranging from 32 letters in patients carrying the G11778A mtDNA mutation to 63 letters in patients carrying the T14484C mutation.

Figure 6: Count and Percentage of Patients with Spontaneous Clinically Relevant Recovery (sCRR) in the Natural History Outcomes Population (n=74)



Spontaneous stabilization of visual acuity

LHON patients suffer from rapid, worsening in their VA typically leading to VA logMAR >1.0 (Snellen 20/200) within 12 months from initial onset of symptoms (Newman et al., 1991; Riordan-Eva et al. 1995, Nikoskelainen et al., 1996). The proportion of patients with good residual VA at Presentation in whom this residual VA is preserved over time was analyzed and revealed that from the 47 patients within the *Natural History Outcomes Population* who presented with VA logMAR <1.0 (i.e. not legally blind), 14.9% had maintained VA logMAR <1.0 at the last follow-up visit within 24 months from Presentation (Outcome) **(Table 3)**. The proportion of such patients was lowest in patients carrying the G11778A mtDNA mutation.

Table 3: Patients presenting with VA < 1.0 logMAR (n=47) in whom this VA was maintained at Outcome

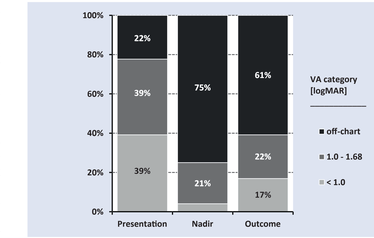
		at Presentation	at Outcome	
All patients	N %	**47**	7	14.9%
Mutation	G11778A	**36**	4	11.1%
	G3460A	**6**	1	16.7%
	T14484C	**5**	2	40.0%

Overall visual acuity outcomes

The natural course of LHON as observed in the *Natural History Population* in this CRS is presented in **Figures 3 and 4**. This presentation of the data yields however no information on the proportions of patients within the on- or off-chart VA categories at important clinical milestones (Presentation, Nadir and Outcome). This is now shown in **Figure 7**.

The mean time since Onset at Presentation was 3-4 months but at Presentation only 39% of eyes were not already legally blind (logMAR <1.0). On the other hand, 96% of eyes were legally blind at nadir typically after 6 months. At the same time, whilst the VA of only 22% of eyes had already deteriorated to off-chart VA at Presentation, 75% had reached this level of VA at their nadir. Furthermore, 83% of eyes for which data is available were legally blind at Outcome. Overall these findings confirm previous results that LHON patients experience rapid and severe vision loss between presentation and nadir. Whilst some degree of VA recovery is possible post-nadir, VA remains very severely affected with the great majority of patients remaining legally blind.

Figure 7: Analysis by VA Category for Eyes at Presentation, Nadir and Outcome in the Natural History Outcomes Population (n=148)



Discussion

The objective of this Case Record Survey was to establish the clinical course of vision loss and recovery in patients with LHON.

The medical records of 383 individuals with LHON were collected in this CRS. Loss of patients to long-term follow-up, the reliability of historic, longitudinal data due to case follow-up and unusual outcomes reporting bias as well as methodological and technical challenges associated with Snellen and ETDRS VA assessment comparisons were anticipated in this CRS. Where possible, strategies to mitigate the influence of these factors were implemented.

The clinical course of LHON in the 106 patients qualifying for inclusion in the *Natural History Population* was established from 890 individual VA observations collected up to 24 months after the reported date of onset of symptoms. When plotted against the time since Onset, the VA data from these records showed the very rapid loss of VA characteristic of LHON with over 50% of eyes deteriorating to the threshold for legal blindness within 1 week of Onset, increasing to over 70% within 3 months. By 12 months, over 80% of patients eyes were legally blind. VA loss was not commonly recovered, and in the 142 observations available at between 12 and 24 months of Onset, 78% of eyes remained legally blind.

The rate of spontaneous clinically relevant recovery in VA was defined prospectively by a stringent definition. Overall, 31.1% of patients and 24.3% of eyes presented with sCRR and the rates of sCRR varied with the LHON-associated mtDNA mutation carried (25.5% G11778A; 50% G3460A and 42.9% T14484C of patients presented with sCRR). Whilst the observations of sCRR in the G3460A or T14484C mutation carrying patients were based on very small numbers (6/12 and 3/7 respectively), the findings are broadly comparable to the rates of sCRR reported in the literature.

Taking the clinical course of VA loss and recovery into consideration, the overall outcomes for patients in the *Natural History Outcomes Population* was assessed by comparing the proportions of patients in VA categories at important clinical milestones of disease progression in LHON (Presentation, Nadir and Outcome), again indicating rapid VA loss and limited recovery.

Overall, the findings of this CRS are in agreement with those reported previously for the natural history of LHON, albeit from a small number of case series. This suggests that despite the limitations of this CRS, the findings are to be considered representative of the natural history of LHON.

The availability of such datasets as collected in this CRS for LHON are of particular importance in the context of orphan diseases where clinical and regulatory progress can be hindered by lack of insight into the natural course of the disease. In the orphan drug sector with limitations in the ability to run placebo controlled trials, a natural history comparator group pre- or post-approval may be requested by regulatory agencies. The collaborative effort of pharmaceutical companies with treating physicians and clinical and research networks such as the German Network for Mitochondrial Disorders (mitoNET) and the European Vision Institute Clinical Research Network (EVICR) network provides an example on how to access medical data for the better understanding of the natural history of orphan diseases.

Acknowledgements and References

The authors like to thank all the physicians providing data **(Table 4)** and the patients for giving their consent to use those data for analysis. We would also like to thank AIBILI (Association for Innovation and Biomedical Research on Light and Image) who were responsible for the project management for the EVICR centres. The EVICR CRS is registered under ClinicalTrials.gov with the identifier NCT01892943.

Table 4: List of participating physicians

Program	Name	Site ID	Institution	Location
EVICR	Dr. S. Mohand-Said	0006	CHNO des Quinze-Vingts	Paris, France
EVICR	Dr. W. Spileers	0018	University Hospitals Leuven	Leuven, Belgium
EVICR	Dr. V. Parisi	0020	Fondazione G.B. Bietti	Rome, Italy
EVICR	Dr. M. Hawlina	0023	University Eye Clinic	Ljubljana, Slovenia
EVICR	Dr. M. Larsen	0030	Glostrup Hospital	Glostrup, Denmark
EVICR	Dr. M.Rougier	0061	CHU Hôpitaux de Bordeaux	Bordeaux, France
EVICR	Dr. S. Guerriero	0064	University of Bari	Bari, Italy
EVICR	Dr. M.Cascavilla	0067	San Raffaele Hospital	Segrate, Italy
EAP mitoNET	Dr. C. Gallenmüller	1001	Friedrich-Baur- Institut, LMU	Munich, Germany
EAP	Dr. J. Arruga	1002	Institut Català de Retina	Barcelona, Spain
EAP	Dr. R. Banik	1003	NY Eye and Ear Infirmary	New York, NY, USA

EVICR : European Vision Institute Clinical Research
EAP: Expanded Access Program (Santhera)
mitoNET: German Network for Mitochondrial Disorders

Conflict of Interest

G. Metz, N. Coppard, D. Petraki and T. Meier are regular employees of Santhera Pharmaceuticals (Liestal, Switzerland). T. Klopstock has been serving on the scientific advisory board for Santhera Pharmaceuticals and has received speaker honoraria and travel costs from Santhera Pharmaceuticals. José-Alain Sahel is a founder and consultant for Pixium Vision and GenSight Biologics, and a consultant for Sanofi-fovea and Genesignal.

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