

## BACKGROUND

- LHON (Leber's Hereditary Optic Neuropathy) is a rare orphan mitochondrial disease, maternally inherited, with an estimated prevalence  $\approx 1:30-40,000^3$ , and predominantly affecting males (80%), typically from 15 to 35 years of age.
- In  $\sim 90\%$  of cases, LHON is due to mutations in *ND1*, *ND4* or *ND6* genes which encode proteins of the respiratory chain Complex I (CI). Dysfunction of the mitochondrial respiratory chain CI is the direct cause of apoptotic death of retinal ganglion cells and atrophy of the optic nerve.
- The *ND4* G11778A mutation is responsible for the majority of cases ( $\sim 70\%$ ). All mutations have incomplete penetrance.<sup>4</sup>
- Vision loss manifests with acute to sub-acute decline in one eye, with rapid loss to nadir in days to weeks. 50% of patients have their 2<sup>nd</sup> eye clinically affected by LHON within  $\leq 8$  weeks of onset.
- Visual prognosis is very poor: between 75 and 98% of patients are reported to have final visual acuity of worse than 20/200, qualifying for legal blindness.<sup>5</sup>
- There is currently no approved treatment and no cure for LHON.

## PURPOSE

- Perceptions of affected patients with the *ND4* G11778A mutation and caregivers\* about the diagnostic process, the consequences of LHON on their respective lives and expectations around future treatments have not yet been surveyed.
- The aim of the present study was to gain a deeper qualitative understanding around these themes.

## METHODOLOGY

- 8 face-to-face exploratory qualitative focus groups took place in November 2014 in 4 countries - the USA, the UK, Germany and France.
- 1 separate group with LHON patients and 1 separate group with caregivers were set up in each country, all audio and video recorded for further analysis.
- 17 LHON patients with the *ND4* G11778A mutation in total were involved; 13 males and 4 females, aged between 18 and 67 years old.
- 17 caregivers whose relative(s) has/have LHON participated; 9 mothers, 3 wives, 2 husbands and 1 father.
- Each group was conducted in a viewing facility and led by an experienced, independent moderator to guarantee anonymity and confidentiality.
- A semi-structured discussion guide was used and the data collected was analyzed to determine key qualitative trends.

## CONCLUSIONS

- The findings highlight that disease awareness among physicians and referral pathways require improvements to lead to the relevant diagnosis more quickly.
- LHON strongly impacts patients and caregivers' lives as it affects activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.
- Increasing support to patients and caregivers would likely help both groups improve their quality of life.
- There is an urgent need for an effective drug improving LHON related visual failure to decrease dependency of patients and burden of caregivers.

## ACKNOWLEDGEMENTS

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## REFERENCES

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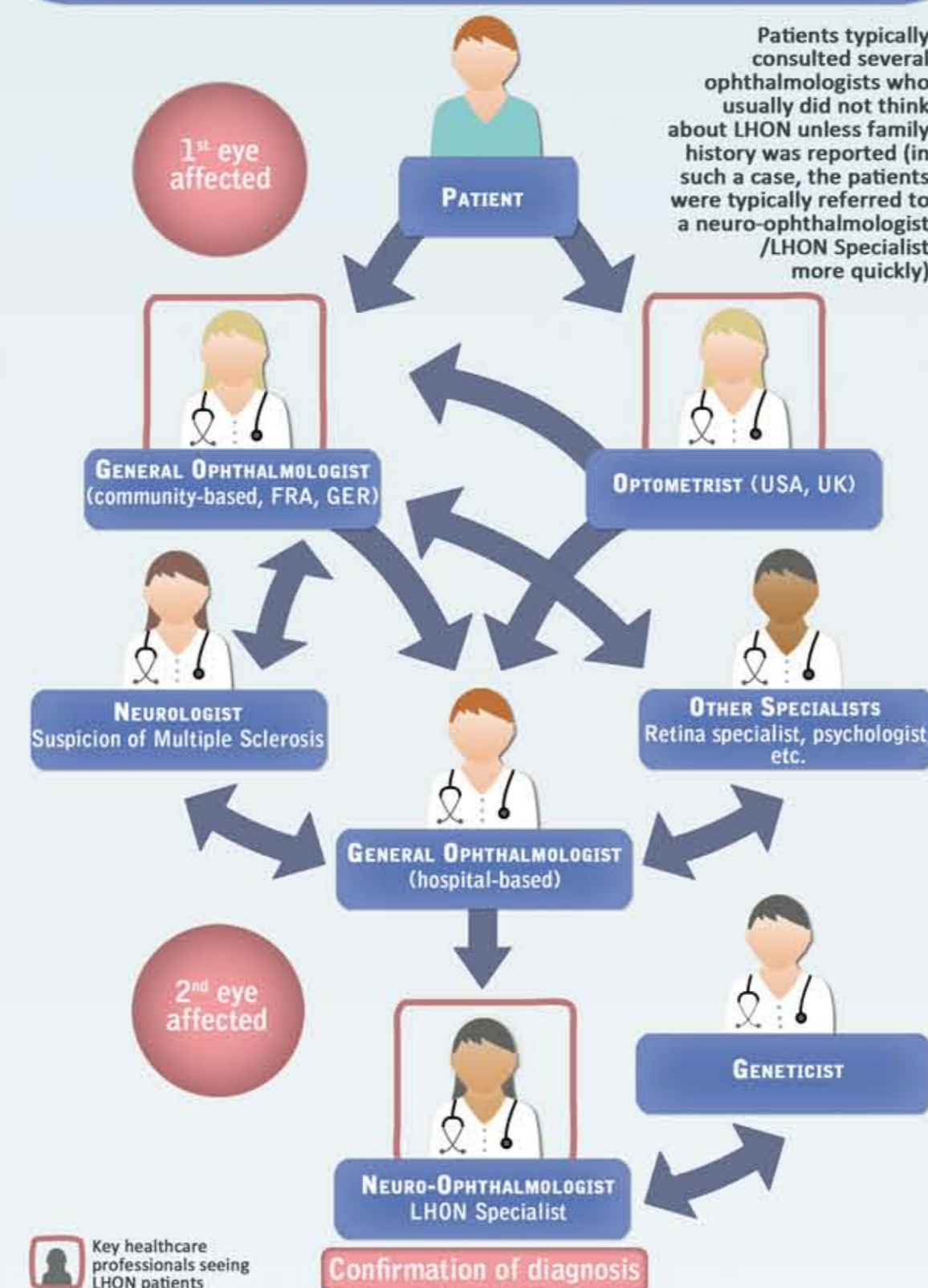
\* Caregivers: typically describe relatives or partners providing part or full time support to a patient. We acknowledge that most patients typically thrive for an as independent and autonomous life as possible and, in absence of a better word, we use this term here only reluctantly as patients might find the word 'caregiver' somewhat patronising or labelling.

## KEY FINDINGS

### Lengthy, worrisome, difficult journey before being diagnosed

- Patients first noticed a relatively quick, but progressive, blurred vision for one eye that they usually related to fatigue, worsening of eye deficiency or ageing; including some patients aware of LHON family history.
- When their vision did not improve, even deteriorated, and started affecting daily activities, patients worried more and usually first consulted an optometrist (USA, UK) or a community-based ophthalmologist (FRA, GER).
- After some visual tests, most patients were told the cause was unexplained, unclear or related to their lifestyle (e.g. smoking) - one was even misdiagnosed with a retina-related condition.
- Others were referred to a hospital-based ophthalmologist for further investigation, a few to a neurologist, leading for one patient to misdiagnosis of multiple sclerosis.
- Patients consulted between 2 and 7 different clinicians, often on their own initiative or pushed by relatives, before being finally referred to a LHON specialist, mainly when the 2nd eye became affected.
- After genetic testing, the LHON diagnosis was announced, devastating patients and caregivers who additionally learned that preventing vision loss progression or restoring vision was currently impossible.
- From the first symptoms, it took between 3 and 12 months to diagnosis; typically less time for patients with family history of LHON while more time for females and patients with onset after the age of 35.

### Typical diagnostic journey reported by LHON patients



Key healthcare professionals seeing LHON patients

## LHON strongly affects quality of life for both patients and caregivers

- All interviewed patients, including those recently diagnosed with some retained central vision, stress they feel locked in a world apart, often described as gloomy, shapeless, poorly colored if at all.
- This vision loss makes identification of people, objects and situations very complicated for them, requiring permanent attention and vigilance, often leading to a mental tiredness.



Patient, 20 y/o  
"It's like living in constant heavy mist."



Patient, 28 y/o  
"It's like having your two fists in front of your face and you are just able to see around."



Patient, 29 y/o  
"Like it's always very bad weather - grey and few colors."



Patient, 41 y/o  
"It's like walking around with a stocking over your head."



Patient, 56 y/o  
"It's like living in a pixelated world."



Patient, 67 y/o  
"It's like seeing the world in black, white and grey."

## LHON limits autonomy of patients

Several dimensions of the LHON patient's quality of life are negatively influenced by the condition, which generates dependency on others, including for patients who underwent rehabilitation and use visual aids.

<b>ACTIVITIES OF DAILY LIVING</b> Total assistance needed at onset of disease, then partial due to rehabilitation and visual aids, especially for transport, administrative tasks, meals, or shopping.	<b>WORK</b> Patients of working age mention adjusted post for disabled people, reduced working hours and limited prospects of career progression. Even lower wages, work loss and early retirement for a few.
<b>EMOTIONAL FUNCTIONING</b> All patients report negative emotions due to LHON at the time of diagnosis and later: anxiety, frustration, sadness, depression, social withdrawal, panic, feeling of uselessness or guilt of being a burden to others.	<b>STUDIES</b> LHON patients, still at school or university at the time of diagnosis, say they had to reconsider studies, or their first job, in line with their vision loss instead of an orientation they would have otherwise chosen.
<b>RELATIONSHIPS WITH FAMILY</b> Closer relationship with the partner or parents, tending to turn more practical than sentimental, even oppressive for a few, sometimes generating tensions. Fear of not finding a partner or difficult to stay with one for the youngest.	<b>FINANCES</b> Some patients stress a decrease of work related revenues. Some of them purchased, at their own cost, visual aids or adapted electronic tools; in addition, non-reimbursed products in the U.S., U.K. and Germany.
<b>RELATIONSHIPS WITH OTHERS</b> Friends are seen less often, or are lost, due to self-withdrawal or patients' dependency on them. Since the patients' eyes appear normal, while behaving like those of the blind, this generates surprise, doubtfulness, distance, sometimes rejection from others.	<b>RECREATION</b> Discontinuation of most previous recreational activities such as: doing sports; going to the theatre or the cinema; reading a book; watching TV; playing videogames; doing gardening; or travelling in foreign countries.

## LHON generates burden for caregivers

Caregivers are strongly involved in the LHON's patient life and all had to fit their personal activities around the needs of the patient, some even had to completely sacrifice such activities to be able to support their loved one.

<b>ACTIVITIES OF DAILY LIVING</b> Partners, parents or even siblings sometimes have to dedicate more vigilance, time and efforts to the LHON patient for transport, administrative tasks, meals, shopping, or even dressing, often resulting in increased physical and mental tiredness.	<b>WORK</b> Most of the interviewed caregivers report that they kept their job, but some had to stop, adjust their work schedule or work part-time to find extra time to dedicate to the LHON patient.
<b>EMOTIONAL FUNCTIONING</b> Caregivers describe their situation as generating stress, anxiety, even depression for a few. They worry about how the patient is psychologically bearing the disease, what his/her future will be, especially partners who tend to avoid making plans for the future.	<b>FINANCES</b> Caregivers did not have a direct impact on their revenues due to LHON, except those who stopped working or reduced their hours significantly. A few in the US and UK mention the cost of travels and visits to physicians.
<b>RELATIONSHIPS</b> Closer relationship with the patient, especially for mothers as they feel guilty for having transmitted the disease and want to provide maximum help. A few report that as a result of the extra time dedicated to the patient, they take care less of the other children if any.	<b>RECREATION</b> Several caregivers stress they have little spare time for their personal relief. A few mothers report that, by solidarity with their LHON children, they even stopped doing activities their loved ones are not able to do, such as going to the cinema or reading a book.

## Expectations towards treatments relate to the restoration of some autonomy

- All patients and caregivers first wish for a cure. If that is not attainable, then a therapy should improve the vision enough to enable a minimal level of autonomy for patients, as well as less burden for caregivers.
- Enabling daily living activities, facilitating relationships with others in general and relatives in particular, plus being able to go back to previously abandoned recreational activities are the most expected benefits.
- The most hopeful respondents even wish to be able to drive again in the future, which would represent to them the symbol of a fully recovered autonomy.
- Some recently diagnosed patients also wish that a new drug should halt the progression of the vision loss or, even better, restore their initial vision if the medication is taken on time.
- Overall, interviewed respondents admit that just going from 'unable to do' to 'can do with difficulty' would be a big enough breakthrough for them to try out novel treatments.



Patient, 18 y/o  
"I would like to be able to play videogames again."



Patient, 28 y/o  
"I would like to take the plane alone, going to a capital alone, and visiting alone without being lost."



Patient, 21 y/o  
"To be able to recognise people right away would be nice so that I didn't have people coming up to me saying 'you walked right past me the other day without saying anything'."



Patient, 57 y/o  
"Be able to read slightly better and just being able to have generally just that little bit more independence."



Patient, 24 y/o  
"I think it would have to be miraculous to get to the stage of being able to drive."



Patient, 66 y/o  
"I would like to be able to do some shopping alone so that I would not mistake a can of cat food for a can of peas."