OPEN ACCESS Freely available online

Hereditary Genetics: Current Research

ISSN: 2161-1041

Research Article

Leber Hereditary Optic Neuropathy: Visual Prognosis and Systemic Associations in Eastern Canada

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ABSTRACT

Leber hereditary optic neuropathy (LHON) is a mitochondrial disease which presents as a bilateral, sequential and painless central loss of vision. Around 90% of the cases are caused by 3 mutations: m.11778G>A (MT-ND4) (52-92% of cases), m.14484T>C (MT-ND6) (3-19% of cases) and m.3460G>A (MT-ND1) (1-33% of cases). Visual recovery is influenced by the mutation type involved. LHON can also be associated with cardiac and neurological manifestations. M.14484T>C (MT-ND6) is found only in 15% to 25% of cases worldwide but is responsible for 86% of all cases of LHON in French Canadian descendants. The goal of this retrospective study is to describe clinical ophthalmic and systemic manifestations, as well as the visual prognosis of LHON patients from Eastern Canada. Patient's files were reviewed in two Montreal hospitals. We have found 23 patient's files with a positive mutation for LHON. 87.0% had m.14484T>C (MT-ND6) and 13.0% had m.11778G>A (MT-ND4). No case of m.3460G>A (MT-ND1) was found in our patients. Visual recovery occurred in 23.7% of m.14484T>C (MT-ND6) and in 33.3% of m.11778G>A (MT-ND4). Final visual acuity varied from 20/20 to no light perception. Both cardiac and neurologic abnormalities were found. Our study confirms that m.14484T>C (MT-ND6) is the most prevalent in the province of Quebec, mostly inhabited by French Canadians. It is important to investigate these patients for cardiac and neurologic diseases, as both has been found in our patients.

Keywords: Optic neuropathy; Mitochondrial disease; Visual loss; Ophthalmology; Genetics

INTRODUCTION

Leber hereditary optic neuropathy (LHON) is a mitochondrial disease inherited by the mother and presents itself as a bilateral, sequential, painless loss of vision which leads to optic atrophy. It can affect people of all ages, but the disease manifests itself mostly in adolescents and young adults. It is believed that an oxidative stress is the cause of the optic neuropathy and can be triggered by tobacco and alcohol consumption [1-3]. On examination, a central or caecocentral scotomas are usually noted often in the presence of pseudo-edema of the optic nerve and peripapillary telangiectasias [4].

Many mitochondrial mutations linked to this disease have been discovered, but three of them are responsible for around 90% of the cases: mutations m.11778G>A in MT-ND4 (52-92% of cases), m.14484T>C in MT-ND6 (3-19% of cases) and m.3460G>A in MT-ND1 (1-33% of cases) [5]. Those mutations all involve genes encoding for complex 1 subunits of the mitochondrial respiratory chain [3]. Visual prognosis is influenced by the mutation type, as is the recovery after the initial visual loss. M.3460G>A (MT-ND1), m.11778G>A (MT-ND4) and m.14484T>C (MT-ND6) have a 15-25%, 4-25% and 37-64% recovery rate, respectively [6-9].

LHON is also associated with other systemic manifestations. Cardiac abnormalities may arise; cardiac arythmias and blocks as well as pre-excitation syndromes have all been reported [10-14]. Neurologic symptoms manifest themselves as peripheral neuropathies and white matter abnormalities mimicking multiple sclerosis [15,16].

Mutation m.14484T>C (MT-ND6) is found only in 15 to 25% of cases worldwide. In Canada, more specifically in French Canadian descendants, this is the main mutation found with a proportion

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Received: July 31, 2019, **Accepted:** September 19, 2019, **Published:** September 27, 2019

Citation: Chabot G, Rouleau J, El-Haffaf AZA, Ospina LHB (2019) Leber Hereditary Optic Neuropathy: Visual Prognosis and Systemic Associations in Eastern Canada. Hereditary Genet. 8:198. doi: 10. 24105/2161-1041.8.198

of 86% of all cases of LHON [10]. This mutation, being less prevalent worldwide than the others, has been less studied. Only one study has looked at demographic data and LHON familial risk of developing this disease in French Canadian patients [11]. To the best of our knowledge, no published study has examined the systemic associations of LHON in the Eastern part of Canada, where m.14484T>C (MT-ND6) is more prevalent. The goal of this study was to adequately describe m.14484T>C (MT-ND6) in this part of the world: its clinical manifestations, the visual prognosis and systemic associations in our population.

RESEARCH METHODOLOGY

This is a descriptive retrospective study led from 2016 to 2017 in two Montreal hospitals (Centre Hospitalier de l'Université de Montréal and Centre Hospitalier Universitaire Ste-Justine). Pediatric and adult patients were included. Inclusion criteria were: LHON diagnosis confirmed by genetic testing and an available hospital file. The exclusion criterion was the presence of another disease causing a visual impairment. Patients with a LHON mutation were found by lists provided by the genetics department and the ophthalmologists. Each case was then reviewed, and the following information was recorded (if available): sex, age at the onset of visual loss, time between the first and second eye involvement, visual acuity at presentation, final visual acuity, length of follow-up period, visual fields during follow-up (mean deviation), smoking and alcohol consumption status and cardiac and neurological anomalies. A descriptive analysis was made with mean values calculation. This study was approved by CHUM institutional review board.

RESULTS

Genetic findings

Our hospital's laboratory uses a genetic panel to detect the three

Patient number	Visual acuity at presentation		Visual acuity at last follow-up		Length of follow-up (months)	Notes
	OD	OS	OD	OS		-
			m.11778G>A (MT-ND4)			
1	Hand motion (HM)	Count fingers (CF)	Light perception (LP)	CF	24	Anita-Harding syndrome treated with natalizumab
2	CF	CF	20/200	20/60	77	Visual recovery 12 months after the initial loss
3	20/25	20/40	20/40	20/60	131	-
			m.14484T>C (MT-ND6)			
4	CF	20/25	HM	CF	6	-
5	20/70	20/160	20/800	20/800	14	-
6	20/150	20/150	20/200	20/250	108	-
7	20/400	20/400	20/30	18/200	12	Visual recovery 16 months after initial loss
8	20/200	20/40	20/20	20/20	26	Visual recovery 12 months after initial loss
9	20/200	20/25	20/500	20/25	4	-
10	20/60	20/70	20/40	20/40	36	Visual recovery 15 months after initial loss
11	20/200	20/500	20/20	20/20	99	Visual recovery 84 months after initial loss
12	20/400	20/400	20/160	20/160	32	-
13	CF	CF	CF	CF	11	Peripheral neuropathy and chronic alcohol abuse
14	CF	CF	20/400	20/400	4	-
15	CF	CF	CF	CF	13	-
16	20/320	CF	CF	CF	82	Cardiac arrhythmia treated with sotalol
17	20/200	20/250	20/40	20/60	5	Visual recovery 25 months after initial recovery
18	HM	HM	CF	CF	7	-
19	20/400	20/160	20/640	20/500	7	-
20	CF	CF	20/500	20/400	30	-
21	CF	CF	20/200	20/200	81	Visual recovery 60 months after initial loss
22	CF	CF	CF	CF	8	-
23	CF	CF	CF	CF	97	-

Table 1: Visual acuity during follow-up.

m.14484T>C (MT-ND6)				
Patient number	MD at presentation		MD at final follow-up	
	OD	OS	OD	OS
14	-20.13	-18.31	-2.66	-5.45
16	-17.45	-12.09	-9.8	-14.95
17	-2.13	-4.28	-2.91	-3.51
18	-32.5	-31.8	-32.31	-29.36
19	-17.77	-15.18	-23.6	-27.15
20	-24.54	-21.43	-18.81	-20.29
22	-26.88	-31.62	-27.05	-31.58
23	-28.44	-26.42	-26.05	-27.16

Table 2: Visual field, Mean Deviation (MD) during follow-up.

main mutations causing LHON (m.11778G>A (MT-ND4), m.14484T>C (MT-ND6), m.3460G>A (MT-ND1)). We have found 23 patient's files with a positive mutation for LHON since 1997. To the best of our knowledge, none of them were related. 20 of them (87.0%) had m.14484T>C (MT-ND6) mutation and 3 (13.0%) had the G11778A mutation. No case of m.3460G>A (MT-ND1) was found in our patients. Biochemical tests directed at the respiratory chain's complex I activity were not done on any specimen. 14 patients (61%) were males and 9 (39%) were females. Age at the presentation of visual loss varied from 2 to 64 years old, with a mean age of 30 and a median of 36 years old. Active tobacco smoking was noted in 6 files (26%). 2 other participants mentioned heavy alcohol drinking: the first patient drank 40oz of vodka every week while the other one drank two bottles of wine daily.

Visual findings and prognosis

As seen in Table 1, visual acuity at presentation varied from 20/40 to hand motion. Visual acuity at the last visit also varied from 20/20 to light perception. Of the 3 patients with m.11778G>A (MT-ND4), 2 eyes presented visual recovery (2 Snellen lines or more), 3 eyes remained somewhat stable and 1 eye worsened (from hand motion to light perception).

Of those with m.14484T>C (MT-ND6), 11 eyes (27%) experienced a visual recovery of 2 Snellen lines or more, 23 eyes (57%) were somewhat stable and 6 eyes (15%) suffered from a worse visual acuity at the last visit. Time elapsed between the moment of visual loss and the identification of improvement either by the patient or in the follow-up exams varied from 12 to 84 months, as seen in Table 1. 9 cases had documented Humphrey visual fields at the time of the visual loss and at a later follow-up. All of them showed a central or caecocentral scotoma. Results of variation of mean deviation between first and last exam are shown in Table 2.

Time before contralateral visual loss was noted only in 6 files. The mean value was 1.5 months. Of the 6 patients with worsened visual acuity, no active consumption of alcohol and tobacco was noted in 4 of them. There was no mention in the files for the other two. Of the 7 patients who recovered at least 2 Snellen lines of visual acuity, three of them were active smokers.

Systemic associations

3/23 patients with cardiac abnormalities were found, all in patients with m.14484T>C (MT-ND6). One patient was found to have a first-degree atrioventricular block on the EKG. The second one had sinusal bradycardia with auricular extrasystoles. The third one was known for a cardiac arythmia (type of arythmia not specified in the file as the patient was followed by an outside cardiologist) and was already treated with sotalol. No pre-excitatory syndrome was found in any of our patients. None of them had a pacemaker.

2/23 of our patients had neurologic symptoms. The first one, with m.14484T>C (MT-ND6), was followed by a neurologist for a peripheral neuropathy which has been attributed to chronic alcohol abuse prior to the LHON diagnosis. The second one, who had m.11778G>A (MT-ND4), was a young woman with white matter lesions on the cerebral MRI mimicking multiple sclerosis and was treated with natalizumab.

DISCUSSION

Our results show an unusual high prevalence of 87.0% of m.14484T>C (MT-ND6) compared to previous studies [1-4]. This study confirms a higher prevalence of m.14484T>C (MT-ND6) in the French-Canadian population and this result is similar to what has been found precedently [5-10]. This confirms the founder effect in this part of Canada. There was very few cases of m.11778G>A (MT-ND4) in our study and there was no recorded case of m.3460G>A (MT-ND1). Mutation prevalence was the same in the adult and pediatric population.

Visual recovery in our study was different of the actual published literature. M.14484T>C (MT-ND6) is known to have the best visual prognosis with 37 to 58% of individuals experiencing visual recovery [8-10]. We found a lower rate of visual recovery of 27% for that mutation. It may be explained by our definition of visual recovery (an improvement of two Snellen lines). If we take in consideration every eye who have experienced any amount of visual improvement, our recovery rate goes up to 40%. The high incidence of visual recovery in our patients with m.11778G>A (MT-ND4) compared with the literature may not be real because of our small sample size.

Tobacco smoking and alcohol consumption have both been associated with worse visual prognosis and with onset of visual loss in individuals with LHON mutation, although none of them have been proven to be causal [11,12]. A European study has shown that penetrance of vision loss was higher in heavy smoker [13-16]. However, our study has not shown such a correlation, with only 26% of patients who were active smokers. To our knowledge, no participant with worsening visual acuity was actively smoking at the time of vision loss.

Concerning visual fields, it is interesting that there was no strong correlation between visual acuity recovery and the mean deviation change. For example, one patient visual acuity was 20/200 at presentation and 20/40 at final follow-up for his right eye and went from 20/250 to 20/60 for his left eye. In the same follow-up period, his mean deviation stayed almost the same in both eye. If truly there is no coherency between visual field and visual acuity recovery, one explanation for the visual improvement may be the training of eccentric fixation. Once again, visual field data was limited and was not available for all patients, so this may be biased. As expected, we found some cardiac and neurologic diseases associated with LHON. No cardiac anomaly was found in patient with m.11778G>A (MT-ND4), but the sample size was small. One

patient with a neurologic disease was found in each of the mutation group. No case of associated deafness was noted, even in children.

CONCLUSION

LHON is a debilitating disease causing a vision loss that can be profound. Our study has confirmed that m.14484T>C (MT-ND6) is the most prevalent in the province of Quebec, mostly inhabited by French Canadians. Half of our patients with this mutation experienced some form of visual recovery. Finally, it is important for clinicians to remember to counsel patients and their families about the genetics of LHON. Other family members and children of affected females may be screened if desired. It might be prudent to discourage tobacco and alcohol consumption, as both could be linked with the onset of the optic neuropathy.1-2 As previously described in the literature, physicians should ask about neurological symptoms and investigate for cardiac disease with an EKG for every confirmed case of LHON.

ACKNOWLEDGEMENT

Authors would like to thank Marie-Catherine Tessier for her support with administrative tasks.

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