## SCIENTIFIC LETTER

# Cardiac abnormalities in patients with Leber's hereditary optic neuropathy

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Leber's hereditary optic neuropathy (LHON) is characterised by acute or subacute central visual loss[1] that typically occurs in early adult life. Three mitochondrial DNA (mtDNA) point mutations, 3460, 11778, and 14484, account for more than 90% of all LHON cases.[2] Cardiac involvement in LHON has been suspected ever since Leber's original 1871 report in which some patients with the disease complained of palpitations. The aim of this study was to determine the prevalence and nature of cardiac abnormalities in patients with LHON by systematically evaluating cardiac structure and function using echocardiography and adenosine testing.

## METHODS

The study population comprised 24 consecutive patients with LHON diagnosed at Queen Square Hospital, London. The diagnosis of LHON was based on characteristic clinical features of the disease and/or the presence of a primary LHON mutation.[3] Cardiovascular examination and investigation were performed at St George's Hospital, London. The investigation was approved by the local research ethics committee. All patients provided written informed consent before participation in the study.

Each patient underwent an initial clinical assessment and 12 lead ECG. ECG evidence of left ventricular hypertrophy was defined in accordance with Romhilt-Estes criteria. Ventricular pre-excitation was defined as a PR interval < 120 ms, QRS duration > 120 ms, and slurred onset of the QRS complex (δ wave). Ten patients gave informed written consent to undergo provocation testing with intravenous adenosine. During continuous ECG monitoring of leads II, aVF, V1, V4, V5, and V6, adenosine was administered via the right antecubital vein in 6 mg increments at 2–3 minute intervals. Administration was repeated until atrioventricular block or pre-excitation occurred. Left ventricular hypertrophy was defined as a left ventricular wall thickness of 15 mm or greater on two dimensional echocardiography. The peak instantaneous left ventricular outflow tract gradient was calculated using continuous wave Doppler and modified Bernoulli equation.

## RESULTS

Eleven patients from the same family carried the 3460 mtDNA mutation (table 1). Eight patients, including two siblings, carried the 11778 mtDNA mutation. The remaining five patients,

**Table 1** Clinical characteristics and study results for patients harbouring the 3460, 114480, and 11778 mtDNA mutations

| Patient | Age/ sex | MtDNA mutation | Cardiac symptoms | Echocardiography | | | | | ECG | | |
| | | | | LA (mm) | EDD (mm) | ESD (mm) | MLVWT (mm) | PAT | TWI | LVH | ST abnl |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 62/F | 3460 | – | 36 | 46 | 22 | 16 | ASH | + | + | + |
| 2 | 53/M | 3460 | – | 42 | 35 | 22 | 28 | CON | + | + | + |
| 3 | 53/M | 3460 | Syncope, angina, dyspnoea | 39 | 30 | 19 | 26 | CON | + | + | + |
| 4 | 58/F | 3460 | Syncope, angina, dyspnoea, palpitations | 38 | 36 | 23 | 15 | CON | + | + | + |
| 5 | 38/M | 3460 | Dyspnoea, palpitations | 25 | 53 | 32 | 17 | DIS | + | + | + |
| 6 | 36/F | 3460 | – | 31 | 42 | 24 | 10 | – | + | – | + |
| 7 | 33/F | 3460 | – | 30 | 46 | 30 | 9 | – | – | – | – |
| 8 | 24/M | 3460 | – | 38 | 48 | 29 | 11 | – | – | – | – |
| 9 | 31/M | 3460 | – | 38 | 47 | 39 | 10 | – | – | – | – |
| 10 | 34/F | 3460 | – | 31 | 44 | 29 | 10 | – | – | – | + |
| 11 | 32/M | 3460 | – | 39 | 50 | 32 | 11 | – | – | – | + |
| 12 | 42/M | 11778 | Dyspnoea, palpitations | 34 | 48 | 27 | 12 | – | – | + | + |
| 13 | 44/M | 11778 | Post-micturition syncope | 27 | 47 | 29 | 11 | – | + | + | + |
| 14 | 54/M | 11778 | Post-micturition syncope | 38 | 48 | 30 | 11 | – | – | + | – |
| 15 | 27/M | 11778 | – | 32 | 47 | 29 | 10 | – | – | – | – |
| 16 | 48/F | 11778 | Palpitations | 21 | 44 | 25 | 10 | – | – | – | – |
| 17 | 57/M | 11778 | – | 36 | 46 | 26 | 10 | – | – | – | – |
| 18 | 42/M | 11778 | – | 34 | 51 | 29 | 10 | – | + | – | + |
| 19 | 32/F | 11778 | – | 30 | 45 | 29 | 9 | – | + | – | – |
| 20 | 51/M | 14484 | Palpitations | 40 | 59 | 36 | 10 | – | – | + | + |
| 21 | 63/M | 14484 | – | 33 | 46 | 21 | 10 | – | – | – | – |
| 22 | 56/M | 14484 | – | 42 | 45 | 30 | 9 | – | – | – | – |
| 23 | 40/M | 14484 | Nil | 37 | 45 | 25 | 12 | – | – | – | – |
| 24 | 67/M | 14484 | Nil | 30 | 45 | 26 | 7 | – | – | – | – |

ASH, asymmetrical septal hypertrophy; CON, concentric hypertrophy; LVH, left ventricular hypertrophy; DI, distal hypertrophy; EDD, end diastolic diameter; ESD, end systolic diameter; MLVWT, maximal left ventricular wall thickness; LA, left atrium; PAT, pattern of left ventricular hypertrophy; ST abnl, ST segment abnormality; TWI, T wave inversion.

including two siblings, were affected with the 14484 mtDNA mutation.

Three 3460 patients, four 11778 patients, and one 14484 patient had cardiac symptoms. Eight 3460 patients, five 11778 patients, and one 14484 patient had ECG abnormalities. Of the 11 patients with the 3460 mutation, five had myocardial hypertrophy (mean (SD) maximal wall thickness 20 (6) mm, range 16–28 mm). Myocardial hypertrophy was absent in patients with the 11778 and 14484 mutation. Unexplained left ventricular dilatation (end diastolic dimension 59 mm) was seen in one patient with the 14484 mutation. A history of sudden death was recorded in one member (in his 50s) of the family with the 3460 mutation. One patient, with a diagnosis of hypertrophic cardiomyopathy before this study, received a DDD pacemaker for sinus node dysfunction. No patient had evidence of ventricular pre-excitation at rest, or following adenosine provocation. There was no evidence of a skeletal myopathy in any of the patients studied.

## DISCUSSION

To the best of our knowledge, this study is the first report describing hypertrophic cardiomyopathy in patients with LHON. The pattern of cardiac hypertrophy was heterogeneous: three patients had concentric hypertrophy, one had asymmetric septal hypertrophy, and one had distal hypertrophy. Cardiac symptoms and isolated ECG abnormalities were also common, but in contrast to previous studies,[4] we were unable to demonstrate any evidence for ventricular pre-excitation. This may have been because of the small number of patients examined; however, other recent studies have also failed to demonstrate pre-excitation in patients with LHON.[5]

The fact that hypertrophic cardiomyopathy was observed in a single family of LHON patients with the 3460 mtDNA mutation could be explained by the co-inheritance of familial hypertrophic cardiomyopathy. Extensive screening for sarcomeric protein gene mutations that cause familial hypertrophic cardiomyopathy would be necessary to exclude this possibility, but several observations suggest that the cardiomyopathy was secondary to the 3460 mtDNA mutation; specifically the association between cardiomyopathy and other mitochondrial disorders, the presence of minor cardiac abnormalities in previous studies of patients with LHON, and the presence of 100% co-segregation of the 3460 mutation and cardiac disease.

The 3460, 11778, and 14484 mutations all alter the encoding of complex I, one of the five major protein complexes that make up the mitochondrial oxidative phosphorylation system. Complex I consists of over 40 protein subunits, seven of which (ND1-6, and ND4L) are encoded by mtDNA. The mtDNA encoded subunits are mainly intramembranous and are involved in interactions with ubiquinone and hydrogen ion transfer. The phenotypic heterogeneity with respect to cardiac involvement observed in this study may be explained in part by the different protein subunits that are affected by the 3460, 11778, and 14484 LHON mutations. The 3460 mutation occurs within the gene that encodes the ND1 protein subunit, causing the substitution of hydrophobic alanine for hydrophilic threonine in the $NH_2$ terminus of the polypeptide, which is rich in other hydrophobic residues. This mutation leads to a reduction in complex I dependent electron transfer activity and a 30–35% decrease in ATP synthesis. In contrast, the 11778 mutation which results in the substitution of histidine for arginine in the ND4 subunit does not appear to compromise electron transfer within the complex itself, but may disrupt interactions between the complex and NADH linked substrates. The 14484 mutation leads to the substitution of

valine for methionine in a poorly conserved region of the gene which codes for the *ND6* subunit. Although the pathogenic basis of the 14484 mutation has not been studied extensively, reductions in complex I activity and ATP synthesis have been reported. In the future a greater understanding of the genotype–phenotype relation in this condition may be obtained from assessment of the degree of mtDNA heteroplasmy in the myocardium.

The findings in this study suggest that patients with LHON should routinely undergo cardiac evaluation with echocardiography and ECG. The relation between individual mutations and cardiac disease, and the natural history of cardiac disease in LHON, warrant further study.

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**Erratum**
Schiele TM, *et al*. Clinical and angiographic acute and follow up results of intracoronary β brachytherapy in saphenous vein bypass grafts: a subgroup analysis of the multicentre European registry of intraluminal coronary β brachytherapy (RENO). *Heart* 2003;**89**:640-4.
Table 2 below was accidently omitted. The error is regretted.

**Table 2** Procedure related parameters per lesion

| | |
|---|---|
| Debulking | 0 (0%) |
| Use of cutting balloon | 10 (14.7%) |
| Nominal diameter of largest balloon used (mm) | 4.03 (3.77) |
| New stent implanted | 22 (32.4%) |
| Mean (SD) dose at 2 mm (Gy) | 20.1 (3.2) |
| 30 mm source train | 20 (29.4%) |
| 40 mm source train | 47 (69.1%) |
| 60 mm source train | 1 (1.5%) |
| Pullback manoeuvre | 17 (25.0%) |
| Fractionated treatment | 4 (5.9%) |
| Primary success | 62 (91.2%) |