Mitochondrial mutation commonly associated with Leber's hereditary optic neuropathy observed in a patient with Wolfram syndrome (DIDMOAD)

D Pilz, O W J Quarrell, E W Jones

Abstract
DIDMOAD is usually considered an autosomal recessive condition, with wide phenotypic variation, but the possibility of mitochondrial mutations occurring in this condition has been considered. A 19 year old man presented with long standing diabetes mellitus, optic atrophy, and grand mal seizures. Further investigations showed unilateral sensorineural hearing loss and the most common mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy, which was inherited from his mother. This suggests the DIDMOAD phenotype is a mitochondrial disorder in some cases and is likely to have a heterogeneous aetiology.

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Case report
Our proband was a 19 year old man, who presented with a combination of diabetes mellitus, optic atrophy, and grand mal epilepsy. He is the son of non-consanguineous parents and has a healthy older brother. The extended family history is unremarkable.

At the age of 2 years he developed insulin dependent diabetes mellitus. His visual acuity was recorded as 6/9 in both eyes at the age of 9 years. Apart from his diabetes mellitus he remained generally well until the age of 14 years when he developed tonic-clonic seizures, which now occur mainly at night and are controlled with sodium valproate. Electroencephalograms performed in 1989 and 1991 showed excessive background slow activity, but no frank epileptic discharges.

Six months after developing the seizures he complained of blurred vision in both eyes. He was under regular follow up by an ophthalmologist and was known to have mild myopia. His vision deteriorated over the next few months, but apart from a markedly reduced visual acuity (from 6/12 to counting fingers on the right side and 6/5 to 6/60 on the left side within a year), other investigations, including a fluorescein angiogram and a cranial CT scan, were reported as normal. His symptoms persisted and a repeat CT scan was again normal, but visual evoked responses were absent in both eyes.

When re-examined four years after the onset of his visual disturbance, he was noted to have bilateral optic atrophy and large central scotomas. He is now registered as blind. A further cranial CT scan and an MRI scan were normal.

At this stage he was referred to the Genetic Department for consideration of the diagnosis of LHON. In view of the above history a diagnosis of DIDMOAD syndrome was also considered and an audiogram indicated unilateral sensorineural hearing loss in the high frequency range. He also had a water deprivation test which was normal. His islet cell antibodies were negative and HLA typing showed only one antigen commonly found in autoimmune diabetes mellitus, DR3. Respectively his fluorescein angiogram, which focused on diabetic retinopathy at the time, suggests the presence of some tortuous peripapillary vessels, which are an early and transient sign in LHON.

DNA analysis using amplification of the relevant part of mitochondrial DNA from

Sheffield Children's Hospital, Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN, UK
D Pilz
O W J Quarrell
Doncaster Royal Infirmary, Armthorpe Road, Doncaster, UK
E W Jones

Correspondence to
Dr Quarrell.

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Incidence of symptoms in DIDMOAD syndrome and our patient

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cremer et al (^a) (88 cases)</th>
<th>Dreyer et al (^a) (98 cases)</th>
<th>Present (%)</th>
<th>Mean age (y)</th>
<th>Present patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>98</td>
<td>100</td>
<td>7 (2-20)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>98</td>
<td>98</td>
<td>11 (4-22)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Abnormal audiogram</td>
<td>39</td>
<td>48</td>
<td>16 (3-32)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>32</td>
<td>35</td>
<td>14 (1-29)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>16</td>
<td>Not discussed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5</td>
<td></td>
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</tbody>
</table>

blood and digestion with SfaNI and MaeII\(^a\) showed the presence of the mitochondrial 11778 G to A point mutation. This was also present in his mother.

Discussion

This patient with diabetes mellitus, optic atrophy, sensorineural deafness, and epilepsy has the clinical phenotype of DIDMOAD syndrome and the absence of diabetes insipidus does not preclude the diagnosis (table). There are several possible explanations for the occurrence of the DIDMOAD phenotype in association with a mitochondrial point mutation commonly seen in LHON.

We think it is unlikely that the phenotype results solely from the mitochondrial mutation. The 11778 mutation has so far mainly been reported in families with optic atrophy alone. Cardiac pre-excitation syndromes\(^a\) and a multiple sclerosis-like illness in women\(^a\) have been reported with this mutation but, in general, extracocular manifestations are rare. These were reviewed by Newman et al\(^a\) and most appear to be fortuitous. It is possible that this is the case in our patient.

Mitochondrial mutations as a cause for diabetes mellitus are being increasingly discussed. Balinger et al\(^a\) pointed out that studies have shown increased maternal inheritance in patients with onset of diabetes mellitus at 25 years or older. They report a family showing maternal transmission of diabetes mellitus and deafness linked to a 10-4 kb deletion of the mtDNA in the affected members. Similarly, Rarond et al\(^a\) reported a point mutation of the mtDNA in a family with diabetes mellitus and deafness.

Wallace et al\(^a\) have discussed environmental stresses as a possible explanation for the variable expression of LHON. It is possible that our patient has autoimmune diabetes, which in combination with the LHON mutation accounts for the extended phenotype. The optic neuropathy seen in this patient was typical of LHON. The absence of islet cell antibodies 17 years after diagnosis and the presence of the HLA DR3 antigen does not allow us to diagnose or exclude autoimmune diabetes mellitus. In their review, Newman et al\(^a\) reported a family with multiple affected members; onset of visual problems was in their 30s, with the exception of a 9 year old girl whose early visual loss was associated with undiagnosed diabetes mellitus.

Finally, it is possible that the phenotype results from the combination of the 11778 mutation with an, as yet, undetected mutation elsewhere on the mitochondrial genome, or with a mutation of the nuclear genome in homo- or heterozygous form. With regard to the former, we are aware of a patient described as having the features of DIDMOAD in whom a 7-6 kb deletion of the mitochondrial genome was found.\(^a\)13 The features seen in that patient included diabetes mellitus, optic atrophy, retinitis pigmenteda, sensorineural deafness, and cerebellar ataxia, and also external ophthalmothers, extrapyramidal symptoms, mental retardation, and brittle hair, which are not normally associated with DIDMOAD but are well recognised in mitochondrial encephalomyopathy, which may be a better diagnostic label. The hypothesis of the combination of a mitochondrial mutation with a nuclear mutation has been postulated in some conditions. Jaber et al\(^a\) discussed the possible combination of an autosomal recessive mutation with a mitochondrial mutation in a large pedigree with sensorineural deafness. The inheritance of LHON is also subject to controversy in view of the excess of affected males, which cannot be explained by the mitochondrial mutation alone. This has led some authors\(^a\) to consider the possibility that LHON results from the combination of a mitochondrial mutation and an X linked visual loss susceptibility gene. The evidence for this remains inconclusive.\(^a\)

In conclusion, we suggest that mitochondrial mutations are sought in patients with the DIDMOAD phenotype and think that the aetiology of DIDMOAD should be considered as heterogeneous.

Since submission of this manuscript, Bu and Rotter\(^a\) have suggested that DIDMOAD may result from mutations in either the mitochondrial genome or nuclear genome and that, in the latter case, the nuclear defect interferes with mitochondrial function. Their hypothesis supports the conclusions of this case report.

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