Diabetes and deafness; is it sufficient to screen for the mitochondrial 3243A>G mutation alone?

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Running title: Diagnostic strategies in diabetes and deafness.

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The m.3243A>G mitochondrial DNA mutation is well known to be associated with deafness and diabetes, and patients presenting with these clinical features are routinely screened for this mutation. We wanted to assess whether this is a suitable screening strategy. We retrospectively reviewed the clinical notes of 242 patients who had attended a specialist mitochondrial clinic in the preceding twenty five year period. Out of the total of 29 patients with mitochondrial disease presenting with deafness and diabetes, only 21 would have been correctly diagnosed by screening for the m.3243A>G mutation in blood or urine. Of the remaining eight patients, only six had other features suggestive of mitochondrial disease. We recommend that all patients presenting to diabetes clinics with the combination of deafness and diabetes be screened for the m.3243A>G mutation. In those patients in whom this test is negative we recommend referral to a specialist neuromuscular clinic for further investigation.

Research design and methods
The association between maternally inherited diabetes and deafness (MIDD) and mitochondrial DNA (mtDNA) mutations is well recognised (1,2). Several mutations have been associated with this phenotype, including the m.3243A>G (3) and m.14709T>C (4) point mutations. So strong is the association with the m.3243A>G mutation (thought to account for up to 1% of diabetes and 0.3% of deafness(5-7) ) that it has become common practice in diabetes clinics for patients presenting with the combination of diabetes and deafness to be screened for this mutation in either whole blood or urinary epithelial cells (8) . We wanted to assess whether this is a sensible investigation strategy in patients presenting in this way. Firstly, we wanted to assess how many patients with other mutations of the mitochondrial genome present with the combination of diabetes and deafness, who would potentially be missed in this screening strategy. Secondly, we wanted to see whether other clinical features of mitochondrial disease were present in these patients which might have provided additional clues as to the correct diagnosis (9) .

We retrospectively reviewed the clinical notes of 242 patients who had attended a specialist mitochondrial clinic in the preceding twenty five year period. All patients had proven mitochondrial disease on the basis of muscle histochemistry or mtDNA analysis. From this cohort we selected patients who were deaf at the time at which they presented with diabetes. Diabetes was defined according to WHO criteria (10). Deafness was defined clinically as hearing impairment not fully corrected with hearing aids. Audiometry was not deemed necessary as this is unlikely to have been performed at the time of presentation to a diabetes clinic.

Results
We found a total of 29 patients with mitochondrial disease who were deaf at the time of presentation with diabetes. 21 of these patients carried the m.3243A>G point mutation, the deafness having preceded the diabetes by a mean of 6.0 years. In addition, there were two patients with the m.12258C>A mutation, one
patient with the m.8344A>G mutation, four with single, large-scale mtDNA deletions and one with multiple mtDNA deletions secondary to an unknown nuclear genetic defect.

The clinical features of these eight patients who did not carry the m.3243A>G mutation are summarised in the table. The patient with m.8344A>G also had ptosis, dysarthria and cerebellar ataxia at the time of presentation with diabetes. One patient with the m.12258C>A mutation had no other clinical features, whereas the other had only mild constipation, fatigue and a mild dysarthria. Three of the patients with single mtDNA deletions had clear evidence of mitochondrial disease with ptosis, marked external ophthalmoplegia and clear dysarthria. However the fourth had only a history of mild fatigue in addition to deafness and diabetes. The patient with multiple mtDNA deletions also had ptosis and ophthalmoplegia.

Out of the total of 29 patients with mitochondrial disease presenting with deafness and diabetes, 21 would have been correctly diagnosed with mitochondrial disease by screening for the m.3243A>G mutation in blood or urine. The remaining eight patients would not have been detected by this screening strategy, underestimating the prevalence of diabetes and deafness due to mitochondrial DNA mutations. Six of these patients had other clear signs of mitochondrial disease. It is likely that these patients would have been referred for a neurological opinion and the correct diagnosis made. However, one patient with the m.12258C>A mutation and one with a single deletion had either no other features or only non-specific features (ie fatigue) which are unlikely to have alerted the assessing physician to the possibility of an alternative diagnosis.

Conclusions

We recommend that all patients presenting to diabetes clinics with the combination of deafness and diabetes be screened for the m.3243A>G mutation. Screening of urine is preferred as this has a greater sensitivity than either buccal mucosa or blood (8-11), is non-invasive and widely available. However, in those patients in whom this test is negative we recommend referral to a specialist neuromuscular clinic for further investigation, to ensure that patients harbouring other mtDNA mutations are correctly diagnosed.
References

<table>
<thead>
<tr>
<th>Mitochondrial DNA genotype</th>
<th>Percentage heteroplasmy in muscle</th>
<th>Years that deafness preceded diabetes</th>
<th>Clinical features at time of presentation with diabetes</th>
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<td>90</td>
<td>13</td>
<td>ptosis/ dysarthria/ ataxia</td>
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CPEO = chronic progressive external ophthalmoplegia
n/a not applicable
n/d not determined