Diabetes and Deafness

Is it sufficient to screen for the mitochondrial 3243A>G mutation alone?

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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 special mitochondrial clinic in the preceding 25-year period. Of the total 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 with the combination of deafness and diabetes presenting to diabetes clinics 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 and mitochondrial DNA (mtDNA) mutations is well recognized (1,2). Several mutations have been associated with this phenotype, including the m.3243A>G (3) and m.14709T>C (4) point mutations. The association is so strong 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. First, we wanted to assess how many patients with other mutations of the mitochondrial genome present with the combination of diabetes and deafness would potentially be missed in this screening strategy. Second, we wanted to investigate whether other clinical features of mitochondrial disease that might provide additional clues as to the correct diagnosis were present in these patients (9).

We retrospectively reviewed the clinical notes of 242 patients who had attended a specialist mitochondrial clinic in the preceding 25-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 World Health Organization criteria (10). Deafness was clinically defined 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. Twenty-one of these patients carried the m.3243A>G point mutation, with deafness having preceded diabetes by a mean of 6.0 years. In addition, there were two patients with the m.12258C>A mutation, one 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 summarized in Table 1. 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.

Of the total 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 mtDNA 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 nonspecific features (i.e., fatigue) that 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

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Abbreviations: mtDNA, mitochondrial DNA.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical features of patients with diabetes and deafness not carrying the m.3243A>G mutation*

Mitochondrial DNA genotype	Percentage heteroplasmy in muscle	Years that deafness preceded diabetes	Clinical features at time of presentation with diabetes
m.8344A>G	90	13	Ptosis/dysarthria/ataxia
m.12258C>A	85	0	None
m.12258C>A	68	16	Mild constipation/dysarthria/fatigue
Single mtDNA deletion	ND	9	Ptosis/CPEO/dysarthria/ataxia
Single mtDNA deletion	50	12	Ptosis/CPEO/dysarthria/ataxia
Single mtDNA deletion	ND	15	Ptosis/dysarthria/mild ataxia
Single mtDNA deletion	10	4	Fatigue
Multiple mtDNA deletions	NA	3	Ptosis/CPEO/dysarthria/ataxia

CPEO, chronic progressive external ophthalmoplegia; NA, not applicable; ND, not determined.

mutation. Screening of urine is preferred, as this has a greater sensitivity than either buccal mucosa or blood (8–11), is noninvasive, and is 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 harboring other mtDNA mutations are correctly diagnosed.

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