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Diabetologia

Letters

Prevalence of maternally inherited diabetes and deafness in Australian diabetic subjects

Dear Sir,
Mutations of mitochondrial DNA (mtDNA) are a well described genetic cause of diabetes mellitus. Prevalence of the most common mutation at position 3243 in the tRNA for leucine of mtDNA has been reported in randomly selected subjects with Type II (non-insulin-dependent) diabetes mellitus from northern [1–3] and southern Europe [4] and Japan [5–7]. We report a study of prevalence of the A3243G $tRNA^{Leu(UUR)}$ and A8344G $tRNA^{Lys}$ mutations of mtDNA in Australian subjects, of mixed racial origin, with Type II diabetes referred to a hospital based outpatient clinic. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the local ethics committee. Subjects were determined as having Type II diabetes if they were initially treated with oral hypoglycaemic agents for a minimum of 12 months (if age of onset was over 30 years) and a minimum of 5 years (if age of onset was between 20 and 30 years). Subjects with an episode of ketoacidosis or who were less than 20 years old at the onset of diabetes were excluded.

Of the 208 consecutive diabetic subjects approached, 3 did not wish to participate. Patients answered a questionnaire, in conjunction with one of the investigators, including details of racial background, age of diagnosis of diabetes, diabetes therapy and family (maternal, paternal and sibling) history of diabetes and deafness. Patients were aware that the study was looking for a genetic cause of diabetes but were unaware of the maternal origin of the gene of interest. Hair follicle, lymphocyte or platelet samples or more than one of these were obtained and prepared for extraction of total DNA and mtDNA was amplified from this. Primers for the mtDNA region of interest for each mutation were used [8, 9] followed by restriction enzyme digestion and electrophoretic separation on agarose gel with ethidium bromide staining as described previously [8]. As little as 3% mutant mtDNA could be detected using this method. All tests included a positive and negative control and if possible both lymphocyte and hair follicle DNA were tested.

The majority of patients were of northern (57%) and southern (19%) European background. There were no Australian Aboriginals in the study. A history of diabetes in a first-degree relative was identified in 59% of subjects: 37.5% reported a mother with Type II diabetes, 19% reported a father with Type II diabetes and 3.5% reported both parents as having Type II diabetes. Of the study subjects 29% reported a hearing deficit and 16% reported a mother with a hearing deficit. In 4.5% of the subjects both the study subjects and their mother had a hearing deficit.

One patient of northern European descent was identified with the 3243 mutation giving a prevalence of less than 0.5% in unselected Australian Type II diabetic subjects. Both the study subject and his mother had a history of diabetes and deafness. No study subject was found to have the 8344 mutation. If Type II diabetic subjects were selected for a maternal and personal history of deafness and maternal or sibling history of diabetes, a 4% prevalence of the 3243 mutation was found. We believe the entry criteria chosen allowed for the relatively early age of onset of diabetes in maternal inheritance diabetes and deafness but the prevalence found is possibly an underestimation given that the 3243 mutation may result in Type I (insulin-dependent) or Type II diabetes [10]. The prevalence of the 3243 mutation in subjects with Type II diabetes in the present study is similar to the prevalence identified in the Netherlands [1]. A higher prevalence of 0.9–1.0% was identified in randomly selected Japanese diabetic populations [6, 7] and a lower prevalence of less than 0.2% was found in randomly selected British Type II diabetic subjects [2, 3].

We were able to successfully amplify mtDNA from hair follicles (in 88% of the samples) and from lymphocytes (in all subjects). Both tissues were found to contain the 3243 mutation in the affected study subjects. We conclude that screening for mtDNA mutations is worthwhile in Australian Type II diabetic subjects with at least two features in their history to suggest maternal inheritance diabetes and deafness. Initial screening could be done on hair follicle samples in the majority of patients without the need for blood collection.

Yours sincerely,
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Amylin innocent in essential hypertension?

Dear Sir,
It is increasingly apparent that the data linking the metabolic defects of insulin resistance with hypertension are associative rather than causal and that the precise nature of this relation has still not been explained. Long-term infusions of insulin both systemically [1] and intrarenally [2] have failed to increase blood pressure and patients with insulinomas were shown not to be hypertensive [3, 4]. It thus appears that hyperinsulinaemia in itself is unlikely to be directly responsible for increases in blood pressure.

After our identification that amylin (co-secreted with insulin from pancreatic beta cells) activated the renin-angiotensin system [5], we and others proposed that excess amylin action, likely to be present in hyperinsulinaemic patients, could be implicated in the pathogenesis of obesity-related hypertension. This hypothesis was supported by reports that patients with insulinoma did not over-secrete amylin [6] and were not characteristically hypertensive [3, 4]. In contrast, a patient with a tumour secreting an amylin-like substance had unexplained hypertension and subsequently died from cerebral haemorrhage [7].

We here report several lines of evidence that argue against the implication of excess amylin action in the pathogenesis of hypertension. Firstly, although the amylin antagonist AC625 blocked the effects of exogenous human amylin to stimulate renin secretion in humans, it had no effect, when infused for 4 days, on blood pressure in hyperamylinaemic subjects. Secondly, dogs made hyperinsulinaemic, hyperamylinaemic, hyper-reninaemic and hypertensive by fat-feeding, showed no effect after 1 week of continuous infusion of the potent amylin antagonist, AC253. Finally, in a 1-year study of 507 patients with Type II (non-insulin-dependent) diabetes mellitus (body mass 90.6 ± 18.2 kg; means ± SD), all of whom were treated with insulin and some three times daily with injections of the human amylin analogue, pramlintide, at doses (30, 75, 150 μg three times daily), plasma amylin activity was seen equal to or greater than that in hypertensive subjects (up to 50 pmol/l). There was no dose-related change in either systolic or diastolic blood pressures (Fig. 1).

The absence of effect of amylin, amylin agonists and amylin antagonists on blood pressure is surprising because of the action of other renin-angiotensin system-modulating agents (for example, renin inhibitors, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) on arterial pressure. It is possible that a theoretical propensity for amylin to promote sodium retention and hypertension through its activation of the renin-angiotensin system is countered by recently identified diuretic and natriuretic effects of amylin [8].

Yours sincerely,
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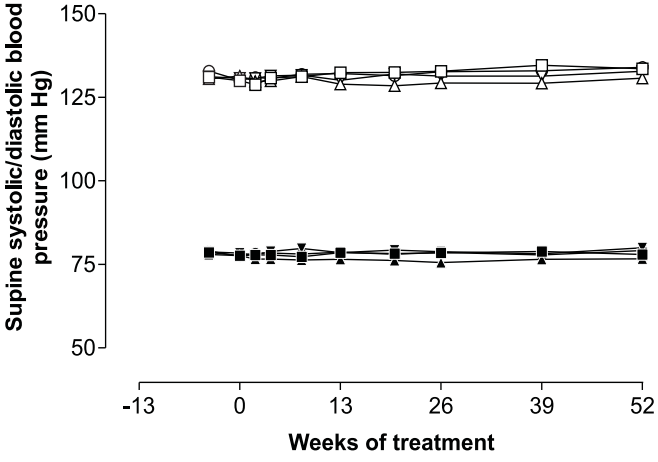

Fig. 1. Systolic pressures □ Placebo $n = 132$; △ 30 μg $n = 116$; ▽ 75 μg $n = 133$; ○ 150 μg $n = 126$. Diastolic pressures: ■ Placebo; ▲ 30 μg; ▼ 75 μg; ● 150 μg

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