Paralysis as first manifestation of primary aldosteronism

Sir,

We have read with great interest the paper of Plouin et al. [1] about the trends in the prevalence of primary aldosteronism, aldosterone-producing adenomas and surgically correctable aldosterone-dependent hypertension. We would like to reiterate that primary aldosteronism occasionally presents with a dramatic clinical picture necessitating emergency therapy. An unusual case of a 31-year-old Caucasian female patient, who was admitted to hospital as an emergency case in complete paralysis of all four limbs, is reported. During the previous 4 months she had been complaining of fatigue, muscle weakness, cramps, polydipsia, polyuria and nocturia, but she had not visited a doctor. The night before the admission she went to bed without any additional symptoms and was woken up a few hours later by a severe headache and realized that she could not move her hands or legs. The clinical examination revealed flaccid paralysis of the hands and legs, blood pressure 200/115 mmHg and heart rate 124 beats/min. Serum potassium was 1.9 mEq/l, serum sodium 146 mEq/l, serum bicarbonate 32 mEq/l and 24 h urinary potassium excretion 58 mEq. The remaining routine laboratory tests were normal. The chest X-ray film showed cardiomegaly, the 12-lead electrocardiogram sinus tachycardia and the 2D-Doppler echocardiogram left ventricular hypertrophy. Plasma aldosterone (PA) was 92 ng/dl, plasma renin activity (PRA) was less than the lower limit of detection of our assay (0.35 ng/ml-1 h-1) and the plasma aldosterone/plasma renin activity ratio (ARR) was well above the cut-off level of 30 ng/dl/ml-1 h-1. The acute intravascular volume expansion with the intravenous administration of isotonic saline, at a rate of 500 ml/h for 4 h, showed autonomous aldosterone production (PA: pre = 97.9, after 2 h = 92.8, after 4 h = 116.6 ng/dl; PRA: pre = 0.06, 2 h = 0.06, 4 h = 0.04 ng/ml-1 h-1). The above results were considered diagnostic of primary aldosteronism. A computed tomography scan with fine cuts (2.5–3 mm) showed a nodule of 1.8 cm in diameter in the left adrenal and thickening of the right adrenal limbs. To investigate the possibility that the nodule could be a part of bilateral adrenal gland hyperplasia, adrenal venous sampling was performed. Adrenal vein cannulation disclosed a cortisol level in the left adrenal vein was 1.81, in the right one was 0.98 and the left/right ratio was 1.84, which is considered to be diagnostic of bilateral adrenal hyperplasia [2,3].

Intravenous potassium supplementation began immediately, leading to a rapid improvement of clinical symptoms. Spironolactone 100 mg t.d.s. was administered and in the following days normokalaemia was restored and blood pressure fell to normal levels. Potassium supplementation ceased and spironolactone was reduced gradually and was maintained at 25 mg t.d.s. After her discharge, the patient was followed as an outpatient and her general condition remained excellent with normal blood pressure 125/80 mmHg and serum potassium 4.2 mEq/l.

Hypokalaemia is usually well tolerated in otherwise healthy people, but it can be life-threatening when severe [4]. On the other hand, the clinical symptoms of primary aldosteronism are often absent or non-specific. Spontaneous hypokalaemia in a patient with hypertension is a strong indicator that primary aldosteronism is present. However, at least 20% of patients have a low normal potassium level. Aldosterone-induced renal potassium wasting is diminished by decreased sodium delivery to the distal nephron and some patients may have normal potassium levels, possibly because of self-selected dietary sodium restriction. As our patient was not aware of being hypertensive, she was apparently having a salt-free diet, which is the only possible cause of the excessive hypokalaemia. In addition, other hypertensive patients may have hypokalaemia as a result of diuretic therapy, liquorice ingestion, secondary aldosteronism or other syndromes associated with mineralocorticoid excess [5]. Hypokalaemic paralysis is more common in Asia, especially in China, and few cases have been reported in Western countries [6–8]. In conclusion, hypokalaemic paralysis may be due to different causes, but in combination with hypertension it may raise the suspicion of primary aldosteronism.

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Lack of evidence for the 1484insG variant at the 3′-UTR of the protein tyrosine phosphatase 1B (PTP1B) gene as a genetic determinant of diabetic nephropathy development in type 1 diabetic patients

Sir,
Insulin resistance (IR) is likely to precede and to play a role in diabetic nephropathy (DN) in both type 1 (T1D) [1] and type 2 diabetes [2]. IR and DN may also share common genetic determinants [3–6]. The gene encoding PTP1B, a tyrosine phosphatase which inhibits insulin signalling, is an excellent candidate for IR and related disorders. We recently have identified a 1484insG variation in the 3′-untranslated region (UTR) of the gene which stabilizes PTP1B mRNA and associates with IR in the general population [7]. Our aim was to verify whether the PTP1B 1484insG variant [as evaluated by polymerase chain reaction (PCR) and SacII enzyme digestion] plays a role in the development of DN in patients with T1D. In a case–control study, 288 European patients with T1D were enrolled. There were 170 patients with microalbuminuria [albumin excretion rate (AER) = 30–300 mg/24h or albumin/creatinine ratio (ACR) = 2.5 males/3.5 females, 30 mg/mmol on two or more consecutive occasions] or persistent proteinuria (AER > 300 mg/24 h or ACR > 30 mg/mmol or a urine sample dipstick positive for protein on two or more consecutive occasions). There were 118 controls (i.e. no DN after ≥15 years since diabetes onset). Of the whole cohort, 186 subjects (65%) were recruited in Italy and the remainder in the UK. Cases and controls were of similar age (42.7 ± 11 vs 44.2 ± 13 years), gender distribution (103 males/67 females vs 64 males/54 females) and duration of diabetes (25.9 ± 10 vs 25.6 ± 9 years) but different HbA1c (8.6 ± 1.7 vs 7.9 ± 1.6%, P < 0.01) and plasma creatinine (118 ± 79 vs 79 ± 13 μmol, P < 0.01) levels. The PTP1B 1484insG genotype and allele frequencies were in Hardy–Weinberg equilibrium. The frequency of the less common 1484insG allele was similar in cases and controls (0.06 and 0.07; χ² = 0.38, P = 0.5). Similar data in terms of genotype and allele frequencies in both cases and controls were also observed when Italian and British cohorts were analysed separately (data not shown).

Data obtained in this first cohort were replicated in a second, more ethnically homogeneous, cohort recruited from Tuscany, Italy: 104 cases and 109 controls of similar age (37 ± 10 vs 37 ± 11 years), gender distribution (44 males/65 females vs 45 males/59 females), duration of diabetes (23.2 ± 7 vs 21.9 ± 8 years) and frequency of the 1484insG variant (0.04 and 0.04; χ² = 1.52, P = 0.2). When the two cohorts were pooled and analysed together, carriers of the 1484insG variant did not show an increased risk of having DN; rather the risk tended to be reduced (age- and gender-adjusted odds ratio = 0.69, 95% confidence interval = 0.34–1.4, P = 0.3). In addition, the 1484insG variant was distributed similarly between patients with micro- (n = 124) or macroalbuminuria (n = 150) (data not shown). In a subset of 80 patients of the first cohort reported here, we have retrospective information on the rate of decline of the glomerular filtration rate (GFR; as derived by the Cockcroft-Gault formula), whose median value was 4.4 ml/min/year (range 1.3–16.6). Also in this case, no statistical difference in GFR decline was observed between patients carrying (n = 8) or not carrying (n = 72) the 1484insG variant (3.2 ml/min/year, range 1.4–11.7 vs 4.7 ml/min/year, range −3.8 to 16.6; P = 0.9). The low number of patients carrying the 1484insG variant does not allow us to draw a firm conclusion about a possible role for this variant in the rate of diabetic nephropathy progression, and indicates the need for a larger study to obtain insight into this specific issue.

Our study clearly indicates, therefore, the lack of association of the 1484insG variation in the PTP1B gene with the risk of developing DN in patients with TID. Although a negative case–control study may be the consequence of insufficient statistical power, we believe this possibility is unlikely in our case. In fact, the number of patients we have studied is at least comparable with that of other major studies in this field (reviewed in [8]). Given a genotype frequency of the PTP1B 1484insG of 15% in the general population [7] and assuming the same frequency in control patients, the two cohorts pooled and analysed together have a power of 80% (P = 0.05) to detect twice as high a risk of developing DN in patients carrying the gene variant. A similar risk has been reported for other genetic determinants of DN (as indicated in [5,6,8]). In addition, data replication in two different cohorts minimizes the risk of a false-negative result due to population stratification bias. Overall, we believe, therefore, that the possibility of a false-negative result in our study is very unlikely. Our finding adds complexity to the potential relationship between IR genes and DN, indicating that not all functional genetic variations affecting insulin sensitivity play a role in DN development. An additional functional single nucleotide polymorphism (SNP) in the PTP1B gene (a missense SNP, P387L) has been identified recently and associated with type 2 diabetes among Caucasians [9]. However, no association was observed with IR, making the relevance of this observation to DN uncertain. In addition, due its extremely low frequency (i.e. ~1% in the general population), the possibility that it may exert a relevant and detectable population-attributable risk of DN is trivial.

In conclusion, the 1484insG variant of the PTP1B gene, which increases the susceptibility to IR in the general population, is unlikely to play a role in modulating the risk of developing DN in patients with TID. Whether this variant plays a role in other aspects or stages of DN pathophysiology as reported for other IR genes, including time to development since diabetes onset [10] or rate of disease progression [3,4] once the complication is established, is currently unknown and cannot be answered by our present study design. Further prospective and larger studies may clarify this issue.

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