Association of adrenal insufficiency with insulin-dependent diabetes mellitus in a patient with inactivating mutations in nicotinamide nucleotide transhydrogenase: a phenocopy of the animal model

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We read with great interest the paper of Roucher-Boulez *et al.* in the July issue of the Journal reporting extra-adrenal phenotypes (i.e. gonadal, cardiac and thyroidal disorders) in a cohort of 18 patients with adrenal insufficiency due to nicotinamide nucleotide transhydrogenase (NNT) mutations (1). Indeed, NNT loss of function, which hampers NADPH production in mitochondria, was initially reported in families with familial isolated glucocorticoid deficiency (2). Yet, *Nnt* expression is severely reduced in pancreas of C57BL/6J mice due to a naturally occurring loss-of-function *Nnt* mutation in this strain. Consequently, C57BL/6J mice have reduced insulin secretion because of increased oxidative stress in pancreatic beta-cells (3). Here, we report a patient with NNT mutations who developed diabetes mellitus, thus recapitulating the *Nnt*-deficient C57BL/6J mouse phenotype (3).

A 12-month-old previously healthy boy was admitted with severe retro-pharyngeal cellulitis, causing airway obstruction, thrombosis of the left jugular vein, compression of the left carotid artery and associated infarction of the left parietal lobe. After treatment of the infection, anorexia and vomiting persisted, with a loss of 18% of body weight over a period of 6 weeks despite tube feeding. Serum sodium was low (126 mmol/L) and potassium was high (8.7 mmol/L). Serum cortisol was <22 nmol/L and ACTH (466 pmol/L) and renin (202 ng/L) were very high, confirming primary adrenal insufficiency. The patient responded rapidly to glucocorticoid and

mineralocorticoid replacement. We previously reported the patient as broadening the phenotype of NNT mutants to combined glucocorticoid and mineralocorticoid deficiencies (4). At 9.5 years, the patient presented with a two-week history of polyuria, polydipsia and weight loss. A glucose level of 42 mmol/L confirmed diabetes mellitus. There was no acidosis. Anti-GAD antibodies were slightly positive at 3.6 (normal <1), but anti-IA2 antibodies were negative. The patient is now 12 years old and requires 1 unit/kg/day of insulin to maintain good metabolic control.

The NNT mutations in this patient have already been described (patient #12 in Ref. (2)), as have the two heterozygous (biallelic) variants in the gene *ME3* revealed by exome sequencing, which may explain the combined glucocorticoid and mineralocorticoid deficiencies (4). The purpose of the present report is to add insulin-dependent diabetes mellitus to the phenotypic spectrum of patients carrying NNT mutations, consistent with findings in the animal model (3).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

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