

Autoimmune Addison's disease and thyrotoxic thyroiditis presenting as encephalopathy in twins

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Abstract

An 11 year old boy who presented with neuropsychiatric symptoms including delirium and pronounced agitation was found to have simultaneous onset of autoimmune adrenocortical insufficiency and hyperthyroidism. His identical twin also had hyperthyroidism and six months later developed symptoms of adrenocortical insufficiency. In children presenting with neuropsychiatric symptoms, adrenal (or pituitary) and other endocrine disorders should be considered.

Acute encephalopathy in childhood is difficult to diagnose and manage. Metabolic causes account for up to 12% of acute encephalopathies but specific diagnosis is often delayed until empirical emergency measures have been taken. Adrenocortical insufficiency may present with acute encephalopathy, and there are neuropsychiatric features in other endocrine disorders.¹ The range includes apathy, fatigue, social withdrawal, true organic psychosis, and—in extreme cases—coma.

We present a case of intermittent encephalopathy in a twin who was found to have autoimmune adrenocortical insufficiency and hyperthyroidism. Hyperthyroidism and adrenocortical insufficiency were also detected in his HLA identical twin brother.

Case reports

TWIN I

A boy age 11·8 years presented with wheezing of acute onset. He was treated for asthma and improved on regular nebulised salbutamol, intravenous aminophylline, and hydrocortisone. Twenty four hours after admission he became disorientated and seemed to be hallucinating. Plasma sodium concentration was 129 mmol/l and blood glucose concentration was 10 mmol/l while an infusion of 0·18% saline in 4% dextrose was in progress. Eight hours later he was lucid and could not recall the events of the preceding night.

When he attended for follow up one month later his mother reported that since discharge he had been tired and lacked energy. He often felt nauseated, vomited intermittently, and had headaches and vague abdominal pain. He had had nightmares, episodes of uncontrollable sobbing, and he reported feeling as if 'he was floating'.

Seven weeks later he was readmitted because of vomiting and dehydration. He was disorientated, agitated, and aggressive. His temperature was 37·7°C and pulse 136/minute and thready in character. Blood pressure was 90/60 mm Hg.

No specific neurological abnormality was detected. Over the next four days his level of consciousness fluctuated with lucid intervals alternating with periods of disorientation, and he remained extremely agitated. There were no convulsions. Despite rehydration, his pulse rate remained raised and systolic blood pressure ranged from 120–150 mm Hg. He also had diarrhoea.

Management included rehydration with plasma followed by 0·45% dextrose saline and subsequently 0·18% dextrose saline, and correction of acidosis (pH 7·28, plasma bicarbonate concentration 13 mmol/l); 0·18% dextrose saline was continued for three days while the nausea and vomiting persisted.

Investigations showed: blood glucose on admission by stick test 1·8 mmol/l; plasma sodium concentration ranged between 130 and 138 mmol/l (on admission it was 133 mmol/l); and urea and creatinine returned to normal after rehydration. A random sample of urine contained sodium 52 mmol/l when the plasma sodium concentration was only 130 mmol/l. Plasma calcium was increased at 3·02 mmol/l (normal range 2·15–2·74), and phosphate was 1·38 mmol/l. Blood ammonia concentration was slightly raised at 80 μ mol/l (normal <70). Aspartate and alanine aminotransferase activities were increased to five to six times normal, but settled over the next few weeks. Screening for hepatitis A and B viruses was negative. The haemoglobin concentration was 114 g/l, white cell count $3\cdot3\times 10^9/l$ (differential count neutrophils 10%, lymphocytes 59%, eosinophils 18%, and monocytes 13%); the platelet count fell to $89\times 10^9/l$ and occasional burr cells were detected in the blood film. Toxicology screen was negative. Urinary porphyrins were increased to 832 mmol/l (normal <320). Screening for plasma and urinary amino acids and urinary organic acids was normal. An electroencephalogram showed generalised raised amplitude slow wave activity compatible with encephalopathy. A computed tomogram of the head was normal.

He improved clinically after three days, and was discharged 10 days after admission. No cause for the encephalopathy was found.

He was readmitted three weeks later with vomiting, headache, abdominal pain, and polydipsia. He was not agitated or disorientated. Intravenous fluids were given to prevent dehydration and electrolyte imbalance.

Investigations to detect a possible metabolic defect were carried out, including search for porphyrins in the urine and (in view of the previously low plasma sodium) estimation of plasma cortisol concentration. When his mother was asked if she had noted any physical differ-

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Autoantibodies in family members

	Twin 1	Twin 2	Sister	Sister	Mother	Father
Age (years)	11.5	11.5	13	10	37	36
Gastric parietal	+	+	0	0	+	0
Adrenal	+	+	0	0	0	0
Nuclei speckled type	0	0	+	+	+	0
Thyroglobulin	+	+	0	0	0	Not measured
Thyroid peroxidase	+	+	0	0	0	Not measured
Thyroid stimulating hormone receptor (u/ml)	47.6 (strong positive)	8.2 (weak positive)	0	0	0	0

Mitochondrial, smooth muscle, and reticulin antibodies were not detected.

ence between the twins she volunteered the information that twin 1 had become pigmented. Although it had not initially been noticed, increased pigmentation of the palmar creases and the lower abdomen was present and was more striking when compared with his brother.

Primary adrenocortical insufficiency was diagnosed by a short tetracosactin (Synacthen) test (250 µg given intramuscularly) with plasma cortisol concentrations of 25 nmol/l at 0 minutes, 33 nmol/l at 30 minutes, and 32 nmol/l at 60 minutes. This was confirmed by a long Synacthen test (the baseline plasma cortisol concentration was 25 nmol/l and after three daily doses of Synacthen Depot 1 mg, 30 nmol/l). Plasma adrenocorticotrophic hormone (ACTH) concentration was 2000 ng/l (normal range 10–80). Ultrasound scan of the adrenal glands and plain abdominal radiograph were both normal. Bone age was 11–12 years (by the method of Greulich and Pyle).

At this stage he was noted to have tachycardia, warm extremities, lid lag, and slight diffuse enlargement of the thyroid gland, and he was fidgety. Thyroid function tests confirmed hyperthyroidism: thyroxine 230 nmol/l (60–140), triiodothyronine (T₃) 4.7 nmol/l (1.3–3.2), T₃ resin uptake 40% (25–34), free thyroxine index 92 (14–58), thyroid binding globulin 20 mg/l (17–28), and thyroid stimulating hormone (TSH) 0.1 µU/l (0.4–3.5).

Autoantibodies were detected against adrenal, gastric parietal, and thyroglobulin antigens, and thyroid peroxidase (table). TSH receptor antibody activity was 47.6 u/ml (strongly positive). Plasma B₁₂ concentrations were normal. HLA typing of twin 1 and his brother showed A:24, A:-, B:39, B:40, BW:6, DR:3, DR:4.

He was treated with oral hydrocortisone, fludrocortisone, and carbimazole, which resulted in considerable improvement in both behaviour and well being. He is no longer fidgety, and his performance in school has improved substantially both academically and in physical activity. His weight had increased from the 3rd to the 75th centile and height from the 25th to the 50th centile. A repeat electroencephalogram was normal.

TWIN 2

The second twin was examined about six months after the first twin had presented. He had tachycardia, warm extremities, and his mother described him as fidgety like his brother, and argumentative. He had slight diffuse enlargement of the thyroid and his weight

was on the 10th centile and height between the 25th and the 50th centile.

Thyroid function tests confirmed hyperthyroidism and a random plasma cortisol concentration was 180 nmol/l and plasma ACTH 270 ng/l. His autoantibody profile is shown in the table. TSH receptor antibody concentration was 8.2 u/ml (weak positive).

He was treated with carbimazole, and his mother was instructed to give him hydrocortisone during infections. As with his brother, the symptoms of hyperthyroidism responded promptly. Six months later (12 months after his brother's initial presentation) he developed symptoms of sweating and lightheadedness in the morning. A short Synacthen test (250 µg) showed a poor response as follows: plasma cortisol 299 nmol/l at 0 minutes, 286 nmol/l at 30 minutes, and 299 nmol/l at 60 minutes. He was started on regular hydrocortisone and fludrocortisone, and made a prompt and excellent response like his brother.

FAMILY

The autoantibody profiles of the mother, father, and two sisters aged 13 and 10 years are shown in the table. Thyroid function and random plasma cortisol concentrations were within normal limits for all subjects. Short Synacthen tests (250 µg) were carried out on the two sisters and were normal.

Discussion

The neuropsychiatric symptoms of twin 1 caused a considerable diagnostic problem and delay in diagnosis. We presume that the symptoms were caused by a combination of adrenocortical insufficiency and hyperthyroidism. In adrenocortical insufficiency correction of electrolyte imbalance alone does not result in improvement in the psychiatric symptoms.¹ We initially presumed that the hyponatraemia was caused by inappropriate secretion of antidiuretic hormone associated with a metabolic or encephalopathic disorder. It was probably exacerbated by our giving intravenous fluids of inappropriately low tonicity and was also presumably responsible for the electroencephalographic abnormalities indicating cerebral oedema. During his second admission other findings compatible with adrenocortical insufficiency were hypoglycaemia, hypercalcaemia, an increased proportion of eosinophils in the differential white cell count, and diarrhoea. The raised plasma aminotransferase activities, and

ammonia concentrations and the presence of porphyrins in the urine may have been the result of transient liver dysfunction associated with hypoglycaemia, electrolyte imbalance, or hypovolaemia. The diarrhoea may also have been related to the hyperthyroidism.

These twins have autoimmune polyglandular syndrome type II, which has two or more of the following: adrenal insufficiency, hyperthyroidism or primary hypothyroidism, insulin-dependent diabetes mellitus, primary hypogonadism, myasthenia gravis, and coeliac disease.² There may also be vitiligo, alopecia, and pernicious anaemia. It is associated with HLA-B8, DR3, the peak incidence occurs at ages 20–60 years, and multiple generations may be affected. In contrast, the main features of type I polyglandular syndrome are hypoparathyroidism, mucocutaneous candidiasis, and adrenal insufficiency, with hypothyroidism occurring in a small proportion of cases. There is no HLA association, it usually presents in infancy or childhood, and siblings are commonly affected. In children with type II syndrome the combination of hyperthyroidism and adrenocortical insufficiency is rare.

Hyperthyroidism may develop before or after the onset of adrenocortical insufficiency,³ but the simultaneous occurrence of the two conditions is rare at any age.^{3–5} When thyroid and adrenal disorders coexist the onset of hyperthyroidism may precipitate latent adrenocortical insufficiency. Conversely, when there is hypothyroidism, thyroid function may improve after glucocorticoid replacement.

Adrenal insufficiency should be considered in any child presenting with neuropsychiatric symptoms. All children presenting with neuropsychiatric symptoms should have their blood glucose measured and if hypoglycaemia is found blood should be taken for plasma insulin, cortisol, and growth hormone concentrations before correction of the hypoglycaemia. Persistent tachycardia after electrolyte and fluid correction in autoimmune Addison's disease should suggest the presence of hyperthyroidism. Patients with adrenocortical deficiency should have thyroid function tested and a fasting glucose concentration estimated, whether or not symptoms of thyroid disease or diabetes mellitus are present.

Ideally relatives should have a history taken and a physical examination, and measurements of glucose (fasting), plasma thyroxine, and cortisol concentrations and an autoantibody screen every three to five years, especially between the ages 20 and 60 years.²

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