CASE REPORT

X-linked Congenital Adrenal Hypoplasia with a Novel *NR0B1/DAX* Gene Mutation

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Background: The etiology of primary adrenal insufficiency has implications for further management of the condition. **Case characteristics**: A 5-year-old boy presented in adrenal crisis with glucocorticoid and mineralocorticoid deficiency. **Observation:** Investigations confirmed primary adrenal insufficiency and ruled out the common etiologies. Genetic testing identified a novel *NR0B1/DAX* gene mutation. **Message:** A genetic diagnosis in children with primary adrenal insufficiency is useful to provide genetic counselling.

Keywords: *Adrenal crisis, Hyponatemia, Diagnosis.*

Primary adrenal insufficiency is a life-threatening condition if not diagnosed promptly and requires lifelong glucocorticoid and mineralocorticoid replacement [1]. We wish to highlight the importance of investigating patients with primary adrenal insufficiency to reach an etiological diagnosis as it enables us to understand the evolution of the disease, permits follow-up of extra-adrenal manifestations and offers the option of genetic counselling to the extended family members. We report a boy with primary adrenal failure due to *X*-linked congenital adrenal hypoplasia secondary to a novel mutation.

Case Report

A 5-year-old Caucasian boy presented to an emergency department with increasing lethargy, nausea, vomiting, poor oral intake and weight loss of 3.5 kg over a period of one month. He was born at term to non-consanguineous parents, was not on any medications, and was vaccinated to date. There was no family history of sudden deaths, and adrenal or neurological disorders. He had two brothers, aged 10 years and 8 years, with no medical concerns. On examination, he was conscious and oriented but lethargic. He was afebrile with low volume pulses, cold clammy extremities with poor perfusion, reduced skin turgor, sunken eyes and dry mucous membranes with a pulse rate of 108/minute and BP of 90/60 mmHg. Normal saline bolus of 20 mL/kg was commenced to improve his circulatory status. Preliminary investigations revealed significant hyponatremia (Sodium 98 mmol/L) and hyperkalemia (Potassium 7.6 mmol/L). He had a compensated metabolic acidosis (pH 7.34, bicarbonate 13.1 mmol/L) with blood glucose of 60mg/dL. Emergent management of hyperkalemia was instituted with salbutamol nebulisation and intravenous calcium gluconate infusion. There were intermittent episodes of up-rolling of eyes, arching of back and slurring of speech. These symptomatic episodes of hyponatremia were treated with 3% sodium chloride infusion.

Adrenal pathology was strongly suspected and IV hydrocortisone 50mg was commenced and continued on maintenance doses. Sodium corrected from 98 to 112 mmol/L in the first 24 hours, and to 124 mmol/L in the next 24 hours. On further questioning, there was history of salt craving and increased tanning with hyperpigmentation on examination. He had no pubarche and was pre-pubertal with 2 cc testes bilaterally. His weight was 16.6 kg (*Z* score -1) and height was 108 cms (*Z* score 0). He was discharged home on day 6 on oral hydrocortisone 10 mg/m^2/day (4mg, 2mg, 2mg) and fludrocortisone at 50 mcg twice-a- day.

Investigations confirmed primary adrenal insufficiency with inappropriately low cortisol at the time of crisis (220; NR: >550mmol/L), elevated ACTH (325; NR: 2-10pmol/L) and low aldosterone (<50; NR 100-800pmol/L). 17-hydroxyprogesterone was normal (<0.2; NR: <3.5nmol/L) with a bone age of 6 years at chronological age of 5.1 years. Adrenal antibodies were negative. Quantiferon test for tuberculosis was negative and there was no evidence of EBV and CMV infections

on serology tests. MRI brain did not demonstrate abnormal signal in white matter and results of very long chain fatty acids (0.895; NR 0.550-1.150) were normal and ruled out *X*-linked adrenoleukodystrophy (X-ALD). Ultrasound of the abdomen revealed normal adrenal glands with no masses or haemorrhage. As there was no apparent cause for his adrenal insufficiency, *NR0B1* genetic testing was requested. Genomic DNA sequencing showed a hemizygous novel mutation - *p.Gln282*, *c.844C>T* in exon 1 of the *NR0B1* gene, which creates a premature stop codon resulting in a truncated protein or nonsense mediated RNA decay. The mother is an unaffected carrier and his two asymptomatic brothers did not carry the mutation.

At 7 years of age, his weight is 25.4 kg (Z score 0.5) and height is 121.9 cms (Z score 0) and remains stable on follow-up. Close monitoring of his pubertal status is maintained with a plan to commence on testosterone replacement, if spontaneous puberty fails to occur.

DISCUSSION

We report a 5-year-old boy who presented in adrenal crisis with glucocorticoid and mineralocorticoid deficiency in the absence of a family history and negative for the common causes of adrenal insufficiency. Though tuberculosis, fulminant infections and HIV are common etiologies in the developing world, congenital adrenal hyperplasia (CAH) and autoimmune adrenalitis are more prevalent in the developed world [1] and were ruled out in our patient. Investigations for X-ALD were also negative although this was strongly suspected in the male child presenting with adrenal insufficiency. Hsieh, *et al*. [2] evaluated the presentation of childhood adrenal insufficiency and only 3 of the 42 children did not have a definite diagnosis. As there was no apparent cause in our patient, *NR0B1* genetic testing was requested, which revealed a pathogenic mutation.

X-linked congenital adrenal hypoplasia accounts for half of adrenal failure in boys not caused by CAH, autoimmune disease, or X-ALD [3]. It is caused by inactivating mutations in *DAX1*/*NR0B1* (dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region on the X chromosome, gene 1/nuclear receptor subfamily 0, group B, member 1) [4]. DAX1 nuclear receptor is a transcriptional repressor of genes involved in steroidogenesis and plays an important role in adrenal development and function. Adrenal failure reflects a developmental abnormality in the transition of the foetal to adult zone. Most patients present with adrenal insufficiency in infancy; and the remainder present insidiously in childhood. Diagnosis may be delayed into adulthood as awareness of this condition is limited [5]. The gene is also expressed in hypothalamus, pituitary and testis and can lead to hypogonadotropic hypogonadism [6]. Testicular dysfunction affecting Sertoli cells can further contribute to infertility [7] with reduction in testosterone and inhibin B seen even in the pre-pubertal period [8]. This diagnosis has implications for monitoring our patient's puberty closely with the aim of commencing testosterone replacement if spontaneous puberty does not occur. Pubertal monitoring in the pre-pubertal period is also required as cases of transient precocious puberty have also been reported, the exact cause of which is not well elucidated [9]. Although there are not many cases reported in literature, the availability of genetic testing and the awareness of the impact that the diagnosis has on the management of the individual, should see an increase in the prevalence of this condition. In such cases, it is vital to extend screening to other family members to be able to identify asymptomatic adrenal insufficiency and possibly prevent sudden unexplained deaths.

This case highlights that *DAX* gene mutations should be sought in male patients with primary adrenal insufficiency after ruling out the more common etiologies as it has implications for the further management of the patient and extended family members.

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