

Adrenal hypoplasia congenita: Delayed presentation of a rare cause of primary adrenal insufficiency

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Introduction

Majority of cases of primary adrenal insufficiency are due to congenital adrenal hyperplasia (CAH), adrenal hypoplasia congenita (AHC) being a rarer cause¹. Here, we report a patient with AHC who presented in pre-adolescent phase with recurrent episodes of dehydration, shock and severe hyperpigmentation.

Case Report

A developmentally normal 11 year old boy was referred from a peripheral hospital where he was admitted for recurrent episodes of vomiting, dehydration, abdominal pain, malaise, anorexia, growth retardation and increasing pigmentation over body for past 3-4 years. He had severe dehydration with shock requiring inotropic support. There were two similar episodes in the past year requiring hospitalization. Patient had distinct craving for salty diet. He was asymptomatic in the neonatal period and early childhood. One younger male sibling had died at the age of one year due to some neurological disorder (developmental delay with seizures). He was investigated at the All India Institute of Medical Science, New Delhi but parents could not recall the diagnosis and records were not available. There are two elder sisters who are apparently normal. There was no history of abortion, consanguinity or any significant family history.

On examination, he was wasted and stunted with weight for age (17.5 kg) and height for age (121 cm) below 3 SD as per World Health Organization

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(WHO) standards. He had diffuse hyperpigmentation all over the body predominantly at mucosal surfaces Such as lips, gums and buccal mucosa. He had infantile gonads and sexual maturity rating (SMR) stage I. His vital functions and other systemic examination were normal.

Total white blood cell count, liver function tests and renal function tests were within normal limits. Serum sodium (122 meq/L) was low, serum potassium (6.1 meq/L) high and random blood glucose (54 mg/dl) low. Basal serum cortisol level (0.208µg/dl) was low and the serum adrenocorticotrophic hormone (ACTH) level (1250pg/ml) high. ACTH stimulation test was done with an intravenous bolus (125µg) of ACTH (Synacthen) at 8 a.m. Both early morning cortisol at 8 am (0.625µg/dl) and 60 minutes (0.640µg/dl) after ACTH injection were low, suggestive of primary adrenal insufficiency. Serum levels of aldosterone, dehydroepiandrosterone sulphate (DHEAS) and 17-hydroxyprogesterone (17-OHP) were within the normal range for age ruling out CAH. Serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) were in the pre-pubertal range and serum testosterone was very low viz. 36.1 ng/dl (normal range 241-827 ng/dl). X-ray chest and ultrasonogram of abdomen were normal. Abdominal magnetic resonance imaging (MRI) revealed a very small triangular left adrenal gland (4-5mm) and short and thin single limb of right adrenal gland (1mm) suggestive of bilateral rudimentary adrenal glands. There was no obvious mass lesion, calcification or haemorrhage seen in bilateral adrenal glands. Serum lipid profile, serum creatine phosphokinase (CPK), human immunodeficiency virus (HIV), antinuclear antibody (ANA), MRI brain and karyotyping were normal.

Child was started on hydrocortisone 10-15mg/m²/day and fludrocortisone 0.1mg/day along with sodium supplementation (sodium chloride 1-2g/day) after which his electrolytes improved within a week and hyperpigmentation gradually disappeared. He did not have any further episodes of vomiting, dehydration or abdominal pain. His weight, height and general

wellbeing had improved markedly at the 2 year follow up. However, SMR stage 1 remained the same.

Discussion

AHC was first described by Sikl H³. Clinical signs and symptoms of AHC include that of adrenal insufficiency e.g. weight loss, vomiting, dehydration, malaise, muscle weakness, hyperpigmentation and biochemical findings characteristics of glucocorticoid and mineralocorticoid deficiency: hyponatraemia, hyperkalaemia and hypoglycaemia^{4,5}. The diagnosis of AHC, in our case was clinched by the typical clinical presentation with low serum cortisol, high serum ACTH, sub-optimal response on ACTH stimulation test, normal 17-OHP with rudimentary adrenal glands on MRI of adrenal glands.

Inheritance of AHC is commonly X-linked due to mutation or deletion of the DAX-1 gene and this form presents in early infancy². In this form, hypogonadotropic hypogonadism and progressive high frequency deafness commonly occur in adolescence^{6,7}. The rarer autosomal recessive type of AHC, which too is associated with hypogonadotropic hypogonadism, is due to a mutation or deletion of the gene encoding steroidogenic factor 1 on chromosome 9q33. Hypogonadotropic hypogonadism is clinically detected as pubertal delay and these patients may benefit from testosterone replacement^{5,6}. Index patient presented in SMR stage I and there was no pubertal growth in 2 years of follow up. LH and FSH were also in the pre-pubertal range suggesting hypogonadotropic hypogonadism. However, we will have to wait till 15 years before labelling it as hypogonadism. In our case there was no hearing deficit at presentation and during 2 year follow up.

A small number of patients with AHC, usually the autosomal recessive form, may present between 2-9 years of age⁸, when acquired causes of adrenal failure such as autoimmune/infections should be ruled out, as in our case where ANA, HIV and total blood count were all normal. DAX-1 mutations also occur in glycerol kinase deficiency and Duchenne muscular dystrophy^{9,10} which were excluded, as serum creatinine kinase and triglyceride levels were normal.

Anatomically, in the X-linked type there is hypoplasia of the adrenal cortex with preservation of the fetal zone. In the autosomal recessive type there is absence of the fetal zone and severe hypoplasia of the definitive adult adrenal zone^{1,4,5}. Rudimentary adrenal glands revealed on abdominal MRI, absence of hearing loss in the 2 year follow up and delayed

presentation indicates autosomal recessive form of AHC, but death of a male sibling and healthy female siblings suggest X linked form. The mutations and deletions associated with AHC could not be detected, Karyotyping was normal and FISH analysis could not be done¹¹.

The possibility of AHC should be considered in cases of adrenal insufficiency, not only in early infancy but also in the pre-adolescent age group as early recognition and treatment will improve the clinical outcome significantly. Long term monitoring of this patient is essential especially for hypogonadotropic hypogonadism and hearing deficits.

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