CASE REPORT

A Rare Cause of Primary Adrenal Insufficiency

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ABSTRACT

Adrenal hypoplasia congenita (AHC) is a rare inherited condition due to the failure of the adult zone of the adrenal cortex to develop despite normal development of its foetal counterpart. Affected patients are usually asymptomatic at birth but will present with clinical features of acute adrenal insufficiency during early infancy. It is clinically indistinguishable from the more common congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Here, we report a case of a one-month-old male infant with primary adrenal insufficiency (PAI) whose initial laboratory investigations revealed hyponatraemia and severe hyperkalaemia. The early onset of PAI with the absence of ambiguous genitalia and low baseline and adrenocorticotropic-stimulated 17-hydroxyprogesterone and undetectable dehydroepiandrosterone sulfate levels, suggest the possibility of AHC in this infant. Genetic analysis is crucial to confirm the diagnosis of this condition and to differentiate from CAH as their prognoses and management differ.

Keywords: Primary adrenal insufficiency, Adrenal hypoplasia congenita, Congenital adrenal hyperplasia

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INTRODUCTION

Adrenal hypoplasia congenita (AHC), a rare condition, is primarily inherited in an X-linked recessive pattern due to mutation of nuclear receptor subfamily 0 group B member 1 (NR0B1) gene that codes for the nuclear receptor protein, dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX1) (1). Disorders with adrenal hypoplasia are associated with reduced adrenocortical hormones (aldosterone, cortisol, androgens), regardless of the underlying genetic cause (1). In X-linked AHC, there is developmental failure of the adult zone of the adrenal cortex despite normal development of its foetal counterpart (1). Affected patients are usually asymptomatic at birth but will present with clinical features of acute adrenal insufficiency during early infancy (1). NR0B1 expression in the hypothalamus, pituitary and gonads also render the patient at risk of developing pubertal and fertility issues (1). While it does not change the immediate therapeutic approach, accurate molecular diagnosis can have important clinical implications for long term management as well as pursuing genetic counselling in affected families (1). Congenital adrenal hyperplasia (CAH) remains the most common aetiology of primary adrenal insufficiency (PAI) in children. However, other rare conditions should always be considered (2).

CASE REPORT

A one-month-old Indian male infant was referred from a district hospital to the emergency department of a tertiary hospital for failure to thrive and clinical suspicion of dehydration. The parents denied any history of illness, nor did the child have any behavioural changes such as irritability or lethargy.

The patient was born to a primigravida mother from a non-consanguineous marriage at full-term via an uncomplicated caesarean section performed due to foetal distress. His mother's antenatal history was uneventful, and no significant family history was noted. Upon review by the paediatric team at the emergency department, he was admitted for further evaluation and management. On admission, vital signs were in the normal range for age. He appeared small for his age, weighed 3.3 kg (between 3rd and 10th centile for age) and was 53 cm tall (10th centile). Examination of other systems was unremarkable. The clinical impression was consistent with mild dehydration in an otherwise healthy child.

Laboratory investigations, however, revealed hyponatraemia and severe hyperkalaemia. All other investigations were within normal range. Urinalysis was unremarkable with no significant bacteriuria on subsequent urine culture. C-reactive protein was not raised, and thyroid function test was appropriate for age (Table I).

Acute management of hyperkalaemia was initiated

Table I: Laboratory results

Test	Result	Unit	Reference Interval
Sodium	121	mmol/L	132 – 146
Potassium	7.1	mmol/L	3.5 – 5.5
Urea	6.6	mmol/L	3.2 – 8.2
Creatinine	18.8	umol/L	14 – 34
Hemoglobin	13.9	g/dL	10.7 – 17.1
Total white cell count	9.66	$X10^9$ L	5 – 20
Platelet	386	$X10^9$ L	150 – 400
Glucose	4.0	mmol/L	3.5 – 7.8
C-reactive protein	2.72	mg/L	< 5
Protein	66	g/L	57 – 82
Albumin	39	g/L	34 – 50
Globulin	27	g/L	23 – 32
Alkaline phosphatase	442	U/L	122 – 469
Alanine transaminase	30	U/L	10 – 49
Capillary blood gas:			
pH	7.40		7.35 – 7.45
pCO_2	39	mmHg	32 – 45
HCO_3	24	mmol/L	22 – 26
Cortisol AM	59.9	nmol/L	145.4 – 619.4
ACTH	278.0	pmol/L	< 10.2
17-OHP	2.8	nmol/L	1.03 – 14.12
Aldosterone	123.4	pmol/L	471 – 4272
Direct renin	123.20	mU/L	4.00 – 89.00
Testosterone	7.00	nmol/L	2.60 – 13.90
DHEAS	< 0.41	µmol/L	2.20 – 15.20
ACTH Stimulation Test:			
Cortisol (Peak level)	56.4	nmol/L	
17-OHP (Peak level)	1.6	nmol/L	
Karyotyping	46, XY		

alongside fluid administration to correct for hyponatraemia. Closer examination of the child revealed areas of hyperpigmentation, which was not readily noticeable due to his dark skin complexion. There was no dysmorphism and genital examination revealed normal male genitalia. A plausible diagnosis of salt-wasting CAH was then made based on the typical electrolyte deranged pattern and the appreciable skin pigmentation. Further tests revealed a low morning serum cortisol with raised plasma adrenocorticotropic hormone (ACTH), the combination of which were consistent with PAI. Serum 17-hydroxyprogesterone (17-OHP), however, was not raised suggesting that the adrenal insufficiency was unrelated to 21-hydroxylase deficiency (Table I).

Further studies demonstrated low aldosterone, raised direct renin and undetectable dehydroepiandrosterone sulfate (DHEAS) levels. ACTH stimulation tests showed blunted cortisol and 17-OHP responses. Testosterone concentration was within the age-specific reference range, and chromosomal karyotyping showed a normal male 46, XY. Laboratory investigations are detailed in Table I. Pelvic ultrasound conducted later did not reveal any sonographic evidence of extra-gonadal organs in the pelvis.

The patient responded well to hydrocortisone, fludrocortisone and sodium chloride and was followed-up at the paediatric endocrine outpatient clinic following discharge. A repeat ACTH stimulation test during his 3-month post discharge follow up visit revealed a similar biochemical profile. These findings prompted consideration of other alternative diagnoses, rather than CAH as was first hypothesised. More specific investigations such as genetic testing, however, are yet to be performed.

DISCUSSION

The early onset of PAI with the absence of ambiguous genitalia and low baseline and ACTH-stimulated 17-OHP with undetectable DHEAS levels suggest the possibility of AHC in this infant. Other differential diagnoses to consider include lipoid CAH, ACTH resistance, X-linked adrenoleukodystrophy (X-ALD) and destruction of the gland by autoimmune processes or by extrinsic causes (e.g., mechanical, infection) (2). In a boy of this age and with the history given, the last two can probably be ruled out.

AHC or also known as congenital adrenal hypoplasia is a rare condition that generally has an X-linked recessive inheritance but can be also inherited in an autosomal pattern (1). Regardless of the underlying genetic aetiology, deficiency of all adrenal steroid hormones is found in disorders associated with adrenal hypoplasia (1,2). AHC is commonly due to mutations or deletions of DAX1 (2). Although, studies have revealed that DAX1 is a repressor of gene transcription, its specific biological role remains unclear. Since DAX1 is thought to repress adrenal stem cell differentiation during organ development, loss of DAX1 would then lead to premature differentiation of progenitor cells into mature steroidogenic cells before progenitor cell number expansion can occur. This phenomenon may explain the early adrenal gland hyperfunction postnatally followed by declining function as the available pool of cells for renewal become depleted (1). DAX1 is also expressed in the hypothalamus, anterior pituitary and gonads. Hence, males with NR0B1 gene mutation will not only develop AHC, but at puberty, they may have impaired sexual development due to a combination of a primary defect in spermatogenesis and hypogonadotropic hypogonadism. This impairment is ensued by infertility (1,2). It has been estimated that approximately 50% of males with idiopathic PAI have NR0B1 mutations with more that 200 different mutations described. AHC is also seen with defects in steroidogenic factor 1 (SF-1), another nuclear receptor transcription factor but unlike DAX1 associated AHC, SF-1 deficiency is a rare cause of PAI (1).

Distinguishing AHC from CAH is crucial because

their clinical course and prognosis differ, as well as the approach to steroid management and genetic counselling. 17-OHP levels are low in AHC, while high in CAH except in patients with a steroidogenic acute regulatory protein (StAR) gene defect (lipoid CAH) and 3β-hydroxysteroid dehydrogenase(3β-HSD) deficiency. However, unlike lipoid CAH and 3β-HSD deficiency, genital ambiguity is not a typical trait of DAX1 mutation. An important phenotypic feature of AHC is hypogonadotropic hypogonadism, manifesting as delayed puberty, impaired spermatogenesis or infertility (2). Hence, although only the adrenal gland may seem to be affected at diagnosis, careful evaluation of the pituitary and gonadal functions is needed in follow-up visits (1,2). Several case reports described typical cases of misdiagnosis in which boys who presented with salt-wasting in their neonatal period were diagnosed as CAH but were only discovered to have AHC later in life when their 17-OHP levels were persistently low or when manifestations of hypogonadism became apparent at follow up visits (4). NR0B1 mutational analysis should therefore be considered for our patient if alternative diagnosis is not established.

Another rare cause of PAI is ACTH resistance, often part of familial glucocorticoid deficiency (FGD) (2). Patients with FGD have high plasma ACTH and low cortisol levels that do not respond to exogenous ACTH stimulation, but the renin-angiotensin-aldosterone axis is typically well preserved (2), which makes ACTH resistance unlikely in the present case. X-ALD that also causes adrenocortical insufficiency due to toxic build-up of very long chain fatty acids (VLCFAs) in the adrenal gland is a X-linked disorder of peroxisomal fatty acid beta oxidation (2). It is caused by defective ATP Binding Cassette Subfamily D Member 1 (ABCD1) gene on chromosome X, which encodes the adrenoleukodystrophy protein (ALDP), a peroxisomal transmembrane protein through which VLCFAs move from the cytosol into the peroxisome. Mutations result in accumulation of VLCFAs in tissues throughout the body, with the myelin sheaths (central nervous system), Leydig cells (testes) and the adrenal glands being most severely affected (3). Its clinical manifestation is heterogeneous but a feature that differentiates X-ALD from other inherited neurodegenerative diseases is that at birth, patients are asymptomatic with neurological deficits never reported before the age of 2.5 years. However, PAI may develop during the first year of life, with the youngest reported patient being five months old (4). The early onset of PAI in our patient makes this condition less likely, but since the implications of late diagnosis are profound, it is essential to consider screening for X-ALD in this patient.

On another note, a compelling case reported by Mesut Parlak et al. highlighted the importance of weighing laboratory artefact when interpreting the steroid profile. He described a patient with 21-hydroxylase deficiency in which the baseline and ACTH-stimulated 17-OHP levels were markedly reduced, while the androgen levels were increased. The discordant results pointed to high-dose hook effect and a repeat analysis post-dilution revealed a markedly raised 17-OHP level, confirming this suspicion (5). Although less of a concern here given the concurrently low DHEAS, a call to the laboratory counterpart may prevent unnecessary investigations for this patient. There are a number of syndromes associated with adrenal dysgenesis and thus PAI (2), however they are not considered as part of the principal differential diagnosis as our patient lacks those syndromic features.

Although this patient responded well to treatment, genetic testing is essential at some stage in this patient's life considering the profound implications of some of the differential diagnosis of PAI. Parents of the patient should be thoroughly counseled and informed about the limitations of genetic testing, including likelihoods of uninformative results, and inability to predict the exact age of clinical manifestations or severity of symptoms of the said disease. Cascade screening of unaffected family members should also be offered as it may provide information about prognosis and treatment options.

CONCLUSION

In conclusion, this is a case of a one-month-old male infant with PAI, of whom clinical and biochemical profiles suggest the diagnosis of AHC. He continues to do well on replacement therapy, but genetic analysis is crucial to confirm the diagnosis of this condition that has significant implications for the patient, both prognostically and therapeutically. Furthermore, preventive measures can be considered for his family members with cascade screening.

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