A toddler with Addison disease: a rare presentation of autoimmune polyglandular syndrome type 1

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Introduction

Autoimmune polyglandular syndrome type 1 (APS-1), also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, is a rare autosomal recessive condition characterized by multiple organ involvement and endocrinopathies which can lead to significant morbidity and mortality, if not diagnosed early. Individuals with APS-1 usually present with chronic mucocutaneous candidiasis (CMC) in infancy and subsequently develop hypoparathyroidism (HP) in early childhood and Addison Disease (AD) later in childhood[1,2]. We report a Sri Lankan boy with an atypical presentation of APS-1, presenting with AD and asymptomatic hypocalcaemia at the age of 1½ years with no evidence of CMC.

Case report

This child with healthy second-degree consanguineous parents presented at 18-months of age with vomiting, polyuria and polydipsia for 1 month, and weight loss of 1kg over six months. His birth, past medical and family history were unremarkable. He appeared unwell, dehydrated, and thin (weight 8.5kg [-2SD to -3SD]), and had severe hyponatraemia, hyperkalaemia and metabolic acidosis. His length (82cm [median to-1SD]), blood pressure and genital examination were normal, with no evidence of pallor, candidiasis or hyperpigmentation. He had high urinary sodium suggestive of renal salt wasting, elevated plasma renin activity with inappropriately low plasma aldosterone level indicative of aldosterone deficiency. Although his baseline cortisol was within normal range, he had elevated serum adrenocorticotrophic hormone (ACTH), and a short synacthen test showed an inadequate cortisol response upon stimulation, while serum 17 OHP was within normal limits. Further, he had low serum calcium, high serum phosphate and low parathyroid hormone levels with normal serum alkaline phosphatase, vitamin D, and magnesium levels, compatible with hypoparathyroidism. A summary of investigation results is given in Table 1. The combination of cortisol and aldosterone deficiency, together with hypoparathyroidism led to a clinical diagnosis of APS-I in this child. His hydration status and hyponatraemia were corrected with 0.9% sodium chloride, and he was commenced on long term therapy with hydrocortisone and fludrocortisone for adrenal insufficiency and calcitriol and calcium supplementation for hypoparathyroidism. Family education regarding the disease, need for stress dosing, long term management, and prognosis as well as genetic counselling regarding the risk of recurrence in future pregnancies were provided. He is under regular follow up and is currently 5½ years old with no new manifestations of APS-1 including candidiasis, type 1 diabetes or autoimmune thyroid diseases.

Discussion

APS-1 is due to loss of function mutations in the autoimmune regulator (AIRE) gene, with an incidence of 1 in 90,000-200,000[3]. It is associated with endocrinopathies and non-endocrine manifestations[3]. The clinical diagnosis of APS-1 is based on the classic triad of CMC, HP and AD[1]. Genetic analysis of the AIRE gene is technically time consuming and expensive, and diagnosis of APS-1 can be made on clinical grounds, based on the presence of two of the three main clinical manifestations[3]. It is recommended that any child or young adult with one disease component of APS should be examined for others[2,3]. AD was manifested as the first sign of APS-1 only in 5% of the patients[2]. The mean age of onset of AD in APS-1 is 11 years, youngest being reported at the age of 2 years[4]. Thus, our patient is one of the youngest reported patients to develop AD in APS-1.

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This child had several atypical features including early onset of AD without features of CMC or HP, as well as lack of hyperpigmentation. The early age of presentation led us to suspect congenital adrenal hyperplasia, and pseudo-hypoaldosteronism, which were excluded by a normal 17-OHP response to ACTH stimulation and low aldosterone level respectively. Adrenal gland damage in APS-1 typically begins in the zona glomerulosa and causes impaired mineralocorticoid secretion, with subsequent zona fasciculata involvement leading to three stages of hypocorticolism: 1) a subnormal cortisol response to synacthen test, 2) persistent ACTH increase, 3) decrease in basal cortisol level[4]. Lack of hyperpigmentation with normal baseline cortisol suggests that the child was in early stages of hypocorticolism. Further, asymptomatic hypoparathyroidism could be explained by the fact that untreated AD can mask the early stages of HP. Treatment of AD with adrenocortical hormone replacement therapy can induce hypocalcaemic seizures in patients with APS-1 with subclinical HP[4]. Thus, increased vigilance, early detection and treatment likely helped avert complications like symptomatic hypocalcaemia, hypoglycaemia and collapse in this child.

This case report presents an unusual presentation of APS 1 with early onset of adrenal crisis without the usual warning sign of APS-1 by mucocutaneous candidiasis, and highlights the importance of establishing the underlying aetiology in any child presenting with primary adrenal insufficiency. Individuals with APS-1 require lifelong screening for other manifestations and hormone replacement for endocrinopathies. Long-term follow-up with proper patient education and transition of care from paediatric to adult care services are other important aspects of management.

Table 1: ***Summary of investigation findings during initial presentation at 18-months-of-age***

Investigation	Result
Serum sodium (mmol/L)	120 (normal range 135-145)
Serum potassium (mmol/L)	5.8 (normal range 3.5-5.3)
pH	7.28 (normal range 7.35-7.45)
Serum osmolality (mosm/kg)	264 (normal range 275 -290)
Urine osmolality (mosm/kg)	221 (normal range 80-1200)
Plasma renin activity (ng/ml/h)	8.22 (normal range 0.6-4.1)
Plasma aldosterone (ng/dL)	2.0 (normal range 2-110)
Serum adrenocorticotrophic hormone (pg/mL)	158 (normal range 10-50)
Short Synacthen test - Cortisol response (nmol/L) 0 min (baseline) 30 min 60 min	 242 (normal range 140-690) 230 222 (normal range >550)
Serum calcium (mmol/L)	1.75 (normal range 2.2-2.7)
Serum phosphate (mmol/L)	2.52 (normal range 1.45-2.1)
Serum parathyroid hormone (pg/ml)	8.2 (normal range 14-72)

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