

Case Report

A Rare Occurrence of Central Precocious Puberty in Adrenal Hypoplasia Congenita

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Abstract

AHC (X-linked adrenal hypoplasia congenita) is a rare cause of adrenal insufficiency due to mutations in the DAX1 gene. It traditionally causes hypogonadotropic hypogonadism. We present a boy with AHC presenting with primary adrenal insufficiency at age of 1 ½ months and developing central precocious puberty (CPP) at 7 months. Common perception with DAX1 mutation is hypogonadism. Therefore, precocious puberty in an infant with adrenal insufficiency and in whom CAH is ruled out may deter the physician from further investigating the aetiology of primary adrenal insufficiency. Knowledge of such an uncommon presentation may guide the physician to test for DAX1 gene. This also gives a better insight into our understanding of the DAX-1 gene.

Keywords: Central, Nuclear Receptor DAX-1, Precocious Puberty, X-linked Adrenal Hypoplasia Congenita.

INTRODUCTION

X-linked adrenal hypoplasia congenita (AHC) is a disorder which presents as a life-threatening adrenal crisis in infancy. AHC usually causes delayed puberty. There are very few case reports describing children with DAX1 mutation presenting with precocious puberty- which is predominantly gonadotropin independent. We present a rare occurrence of central precocious puberty in an infant with primary adrenal insufficiency due to DAX1 mutation. The literature search yielded only 5 cases reported with DAX1 mutation and central precocious puberty.

CASE REPORT

A 1 ½ month old boy was brought with complaints of persistent vomiting for 15 days and failure to thrive. He had dark pigmentation of skin and was dehydrated. This child weighed 2.7 kg at birth and had a weight of 3.0kg (-3.87 SDS) and length 53cm (-1.88 SDS) at the time of presentation. Blood investigations

showed hyponatremia (115meq/L) and hyperkalaemia (8.9meq/L) but renal functions were within normal limits.

With a provisional diagnosis of primary adrenal insufficiency, he was further investigated. Basal cortisol level was 9.58microgram/dl which did not rise after synacthen stimulation (stimulated values of 7.58 microgram/dl). ACTH level was high at 355pg/ml (Normal 0-46 pg/ml). 17-OH Progesterone level was normal i.e. 1.61ng/ml (pre-synacthen) and 2.17ng/ml (post synacthen) which ruled out congenital adrenal hyperplasia (CAH) due to 21 alpha hydroxylase deficiency. With a provisional diagnosis of primary adrenal insufficiency, he was treated with hydrocortisone and fludrocortisone replacement. Serial growth monitoring showed adequate gain in weight and decrease in the pigmentation.

At 7 months of age, parents noticed the development of pubic hair. His height and weight were 74cm (1.86 SDS) and 10.5kg (2 SDS) respectively. He was found to have a testicular volume of 4 ml and stretched penile length of 5cm with Tanner stage 2 of pubic hair. There was no history of



exogenous androgen exposure. The bone age was 1 year 3 months at the chronological age of 9 months. Basal FSH, LH and testosterone levels were 1.87mIU/ml (0.58-2.4mIU/ml), 1.14mIU/ml (0.81.3mIU/ml) and 150.50ng/dl (prepubertal level <30 ng/dl) respectively. After GnRH agonist (leuprolide) stimulation, peak LH and FSH were 10.62mIU/ml and 6.21mIU/ml respectively, thus confirming central precocious puberty.

DAX1 gene sequencing was done which showed a single nucleotide variant in exon 1 of DAX1/NROB1 gene which caused methionine to lysine amino acid substitution at position 296. This was found to be disease causing by Mutation Taster bioinformatics prediction analysis. (c.887T>A p.Met296Lys-Variant).

Parents were advised on GnRH analogue therapy for precocious puberty, however due to financial constraints they refused.

On follow up at 3 years of age, testicular volume, pubic hair and penile length had not progressed. His height was 97cms(0.42SDS) and weight was 16.2kg(1.06SDS). His basal FSH, LH and testosterone levels at 3 years were 1.36mIU/ml, 0.72mIU/ml and 147.34 ng/dl respectively. ACTH levels were 28.5pg/ml (0-46pg/ml) indicating the adequacy of steroid replacement.

On follow up at 4 years 6 months of age, bone age corresponded to the chronological age of 4years 6 months. Basal FSH was 1.03 mIU/ml, LH was 0.17 mIU/ml with a testosterone of 13.54 ng/dl. These results indicated that central precocious puberty had not progressed and had spontaneously burnt out.

DISCUSSION

Patients with AHC develop severe salt wasting with glucocorticoid and mineralocorticoid insufficiency mostly in infancy due to adrenal failure. The adrenal failure reflects a developmental abnormality where the fetal zone of adrenal cortex fails to get transitioned into an adult zone¹. AHC is caused by mutation in DAX 1 gene. DAX1 belongs to the orphan nuclear receptor. Unlike other nuclear receptors it also does not have zinc finger DNA binding motifs.

CAH being the closest differential of AHC, should be differentiated from it. Both conditions present with adrenal crisis. CAH patients may develop precocious puberty whereas AHC is traditionally associated with hypogonadotropic

hypogonadism (HHG) which refers to hypogonadism at central level due to gonadotropin deficiency. Mutations in the DAX1 gene which causes this disorder leads to absence of development of the permanent zone of adrenal cortex. DAX 1 encodes a nuclear receptor that is expressed in embryonic stem cells, steroidogenic tissues (gonads, adrenals), ventromedial hypothalamus and pituitary gonadotropes. Mutations in DAX1 is traditionally associated with (HHG)¹. Our case is interesting because AHC presented with CPP at 7 months of age. This is unique and diametrically opposite to the traditional case series presented by Muscatelli et al where there was integral association of HHG with AHC². The exact mechanism of HHG is not known however hypothesized to involve combined and variable deficiency of hypothalamic.

GnRH secretion or decreased responsiveness of pituitary to hypothalamic GnRH resulting in low LH, FSH and testosterone. However, Wittenberg³ described 4 male cousins with X linked AHC who had varying degrees of virilisation, but their response to LHRH was prepubertal indicating gonadotropin independent precocious puberty.

The first confirmed case of DAX1 mutation with AHC and central precocious puberty was reported by Kah Yin Loke et al in a 6-year-old Chinese patient with Duchenne muscular dystrophy due to non-contiguous gene deletion of DAX1, glycerol kinase and dystrophin gene. The mechanism of central precocious puberty was not clear. Possibly there may be loss of one or more transcription factors which suppresses puberty encoding genes which may also lie in the X chromosome in close proximity to DAX1 and dystrophin genes⁴. Recently central precocious puberty in a patient with X linked AHC and Xp21 contiguous gene deletion syndrome was reported by Ji Won Koh et al.⁵

The phenotypic expression of AHC varies; most presenting in adrenal crises during infancy and very few after infancy. One patient reported is to have presented as late as 28 years.

Similarly, most of the patients present with HHG barring a very few who present with precocious puberty. This phenotypic heterogeneity of AHC may be due to multiple factors including compensation from other genes, epigenetic or non-genetic factors and modulation of DAX1 localization function in the foetal adrenal gland by components of extracellular matrix and hormones such as ACTH¹.

Katsumata et al reported the first association of X-linked AHC with presumed central precocious

puberty in 1997. At the age of 6 months, he developed pubic hair, and at 1 year and 3 months of age, his mean testicular volume increased to 3.5 ml. He was presumed to have central precocious puberty, based on the increased urinary excretion of gonadotropins and testosterone⁶. GnRH stimulation tests were not done.

Though traditional textbook teaching is occurrence of HHG in DAX-1 mutation, it is important for an astute physician to be aware of a very rare opposite occurrence i.e. precocious puberty. This case report and extensive research has helped us shed some new light on this disease.

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