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Adrenal Agenesis and X-Linked Adrenal Hypoplasia Congenita in A Toddler - A Case Report and Review of Literature

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Abstract: Adrenal agenesis (AA) and X-linked adrenal hypoplasia congenita are very rare anomalies. NROB/DAX-1 gene which is located on the X chromosome is associated with adrenal hypoplasia. Primary adrenal insufficiency and hypogonadotropic hypogonadism are the typical presentations. Here, we present a case of a two-year-old toddler who presented with hypoglycaemic convulsion, persistent hypotension, and generalised hyperpigmentation. His serum adrenocorticotropic hormone level was significantly raised while serum cortisol and 17- hydroxyprogesterone were within normal limits. Whole exome sequencing revealed a hemizygous single base pair deletion in exon 1 of the NROB1 gene located on the chromosome X (chrX:g.30308863del; Depth:84x) that results in a frameshift and premature truncation of the protein 95 amino acids downstream to codon 169 (p.Gly169AlafsTer95; ENST00000378970.5). He was diagnosed with adrenal agenesis and X-linked adrenal hypoplasia congenita. He was treated with oral steroid replacement therapy (hydrocortisone and fludrocortisone) and salt supplementation. On follow-up, hyperpigmentation was significantly decreased and growth was improved. This report emphasizes the importance of clinical vigilance and the role of genetic diagnosis in preventing severe adverse outcomes with primary adrenal insufficiency.

Keywords: *Adrenal hypoplasia congenita, NROB1, DAX1, primary adrenal insufficiency, X-linked AHC*

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1. Introduction

The adrenal gland was first described by Eustachius (1563), and its importance in life was recognised by the work of Thomas Addison (1855) and Brown-Sequard (1856) [1,2]. The adrenal cortex, gonads and kidneys are derived from components of the urogenital ridge; and at the end of the 9th week of gestation, the adrenal glands become completely encapsulated. Though, various genes (dosage-sensitive sex reversal (DAX-1/NROB1) and Steroidogenic factor 1 (SF1, NR5A1, also known as AD4BP) are known to play an important role in the development of adrenal glands, some unknown genes might be involved in the South Asian population [3]. Adrenal agenesis (AA) and/or adrenal hypoplasia are very rare anomalies and their real incidence is underestimated; as most of the cases are detected on autopsy. The estimated incidence of primary adrenal insufficiency is 10/100,000 person in the age group of 1-15 years among Finnish children [4]. X-linked adrenal hypoplasia congenita (AHC) was first reported in 1948 [6]. The incidence of AHC is approximately 1:12,000 live births. However, some researchers revealed a much lower incidence and it ranges from 1:140,000 to 1:1,200,000 children [6,7]. The onset of salt-losing syndrome is the key indicator of AHC. Primary adrenal insufficiency is the typical presentation in infancy and early childhood, while in later life it manifests as delayed or absent puberty due to hypogonadotropic hypogonadism. Lack of proper screening tests for AHC during the pre-symptomatic period is a matter of concern as well.

2. Case Report

A two-year-old male toddler was admitted to our institute with complaints of fever, vomiting, cough/common cold for three days and one episode of seizure on previous day. On further inquiry, mother gave history of loss of appetite/not gaining weight, salt craving and increased generalised blackish pigmentation of skin over a period of four to five months. He also had a history of intermittent febrile episodes. He was born of a non-consanguineous marriage (father age 44 years and mother age 31 years), third by birth order; of whom both the elder siblings were male and had complaints of hyperpigmentation, seizures, and febrile episodes and died at the age of six years and eight years respectively.

Detailed documentation about their diagnosis and cause of death was not available. On arrival to the emergency room, he was conscious (Glasgow Coma Scale 13/15), febrile (temperature 100.1^0F), with a heart rate of 176 beats per min. Peripheral pulses were regular, low volume and blood pressure was 90/48mmHg (10^{th}-25^{th} centile) without signs of respiratory distress with oxygen saturation of 99% on room air. He had mild pallor, signs of some dehydration, and generalised blackish hyperpigmentation all over the body, more on the trunk and back (Figure 1). His head was normal in size and shape without signs of meningeal irritation or signs of raised intracranial tension, and he had normal male external genitalia. He had no sign of dysmorphism except bilateral post axial polydactyly (Figure 2). His random blood sugar in the emergency room was 38mg/dl. The provisional diagnosis of acute febrile encephalopathy was considered and was treated with antibiotics, anticonvulsants and fluid resuscitation.

During his hospital stay, he had no repeat episodes of seizure, and he symptomatically improved; however, he had persistent hypotension, which was fluid responsive. His hemogram was within the normal limit except for anaemia (Hb 9.4gm%, white blood cell counts 8500/cumm and platelets 3.19 lac/cumm). The malarial parasite was not detected on peripheral smear examination and the "C" reactive protein was within normal limit. His cerebrospinal fluid biochemistry and microscopy did not reveal significant findings. Liver function, blood gas analysis, and blood/cerebrospinal fluid /urine cultures were negative. Renal function tests were within the normal limits except for persistently low serum sodium and high urinary sodium on multiple occasions. Serum calcium, magnesium and phosphorus were within normal reference range. He had persistent hypoglycemia which was transiently corrected by intravenous 10% glucose solution. Hormonal assessment was as mentioned below; serum adrenocorticotropic hormone level was significantly raised to 1825.0 pg/ml (reference range 10-46pg/ml, done on immulite), serum cortisol 5.140 mcg/dl (reference range 5.0-25.0 mcg/dl), and 17 hydroxyprogesterone 0.16 ng/ml were within normal limits. Among his radiological investigations, magnetic resonance imaging of the brain and two-dimensional echocardiography did not reveal any abnormalities while ultrasonography of the abdomen was suggestive of cholelithiasis without cholecystitis. On further evaluation, contrast enhanced computed tomography of the abdomen revealed a hypoplastic band-like adrenal gland over the left side and an absent right adrenal gland (Figure 3). Whole exome sequencing was done which revealed a hemizygous single base pair deletion in exon 1 of the NROB1 gene located on the chromosome X (chrX:g.30308863del; Depth:84x) that results in a frameshift and premature truncation of the protein 95 amino acids downstream to codon 169 (p.Gly169AlafsTer95; ENST00000378970.5). Hence, a diagnosis of X-linked Adrenal Hypoplasia Congenita was made and he was started on oral steroid replacement therapy (hydrocortisone and fludrocortisone) and salt supplementation. Gradually, his symptoms subsided, his appetite improved and he was discharged after one week of hospitalisation. On outpatient follow up, hyperpigmentation was significantly decreased (Figure 4), with increased appetite and he was gaining weight adequately.

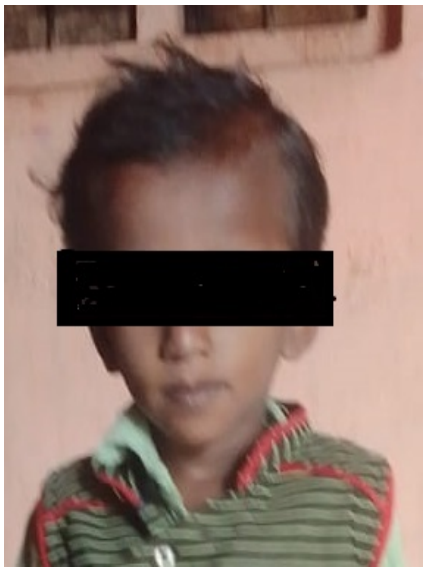

Figure 1. Showing generalised hyperpigmentation

Figure 2. Post axial polydactyly of the upper limb

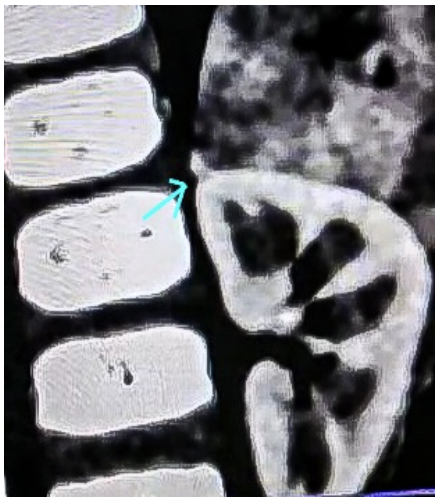

Figure 3. Contrast enhanced computed tomography of the abdomen showing hypoplastic band-like left adrenal gland (blue arrow)

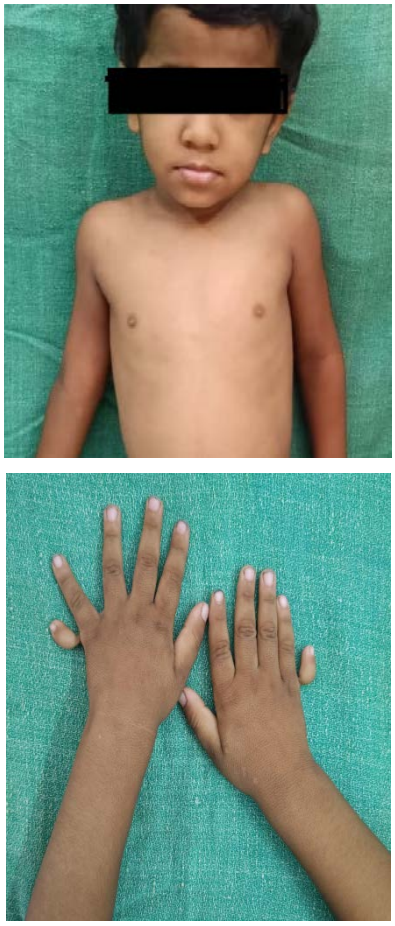

Figure 4. Improvement in hyperpigmentation after treatment

3. Discussion

Although, congenital adrenal hyperplasia (CAH) is the most common cause of primary adrenal insufficiency, AA and AHC are very rarely associated with adrenal insufficiency. The bilateral absence of adrenal gland is not compatible with post-natal life without lifelong hormonal replacement. D'Arcy et al reported bilateral adrenal agenesis in a suspected foetus with hydrops fetalis on post-mortem examination after termination of pregnancy [8]. Sethuraman et al studied five cases of AA on post-mortem examination. Respiratory distress was the commonest clinical presentation among the live births while anomalies of the kidneys, lungs, spleen, and blood vessels were associated with two of the cases without gonadal abnormalities and maternal diabetes was associated with one of the cases [9]. In our case, we noted agenesis of the right adrenal gland and hypoplastic cord like structure of the left adrenal gland without any other organ anomalies or dysmorphism except bilateral postaxial polydactyly.

Adrenal hypoplasia can be primary, because of an intrinsic defect during differentiation of the foetal adrenal gland, or secondary, due to pituitary or hypothalamic dysfunction leading to reduced adrenal stimulus [10]. The first case of congenital adrenal hypoplasia was reported by Sikl in a 33-day old infant who presented with failure to gain weight and bronzing of the skin. Muscatelli et al (1994) revealed that the DAX-1 gene is responsible for X-linked AHC in 12 unrelated individuals whereas in four sporadic cases and in a familial case, a point mutation was not found; suggesting genetic heterogeneity or differential expression of the DAX1gene [11].

Although, AHC typically manifests in infancy and in early childhood as primary adrenal insufficiency, the onset of salt-losing syndrome is a key indicator. Kyariakakis et al reported two new adult-onset X-linked adrenal hypoplasia cases who presented with adrenal insufficiency and azoospermia due to a missense mutation of the DAX-1 gene [12]. Similarly, delayed-onset AHC and hypogonadotropic hypogonadism due to a novel mutation in the DAX-1 gene is described by Liu et al [13]. The associated clinical presentation of AHC depends on the DAX-1 gene mutation and its expression. Various associated congenital anomalies like central diabetes insipidus and schwannoma with a frameshift mutation in the DAX-1 gene (c543delA), Duchenne muscular dystrophy and glycerol kinase deficiency, hypospadias, and micropenis are reported by various authors in X-linked congenital adrenal hypoplasia [14-17]. Isolated hypoaldosteronism as the first sign of X-linked AHC due to a novel mutation in the NR0B1/DAX1 gene is reported by Iughetti et al [18]. In our case, there were no structural anomalies except bilateral postaxial polydactyly.

Our case presented with seizures associated with fever, generalised hyperpigmentation, persistent hypotension and hyponatremia. A similar type of presentation was noted by Park et al in a four-day-old female newborn with congenital AA, Chatterjee et al in four boys and a girl from India, and Zheng et al reported hyperpigmentation in 90%, vomiting/diarrhoea in 48%, failure to thrive in 31% and convulsion in 17% of cases of X-linked AHC at onset [3,19,20]. Similarly, Flint et al and Amer et al observed poor feeding, failure to thrive, and salt wasting with low sodium in early infancy [21,22].

In this case, whole exome sequencing revealed a hemizygous single base pair deletion in Exon 1 of the NROB1 gene located on the chromosome X (chrX:g.30308863del; Depth:84x) that results in a frameshift and premature truncation of the protein 95 amino acids downstream to codon 169 (p.Gly169AlafsTer95; ENST00000378970.5). More than 200 mutations were reported in the NROB1 gene. Reutens et al reported nonsense mutations in three cases that introduce a stop codon and frameshift mutations in the other three cases. [23]. Suthiworachai C et al described six patients with classic phenotypes with early-onset adrenal failure, and they noted *DAX1* mutations in all patients, among which there were three novel mutations and three known mutations They also reported that the *DAX1* mutants had lower levels of repressor activity on the *StAR* gene promoter compared with the wild-type DAX-1 protein [24]. Esquiaveto-Aun et al recently reported a novel and deleterious deletion–insertion–inversion–deletion complex rearrangement sorted in the 5′-3′ direction. It was a nonrecurrent rearrangement that had not yet been described. It may involve a repair mechanism known as nonhomologous end-joining (NHEJ), which joins two ends of DNA in an imprecise manner, generating an “information scar,” represented herein by the 37 bp insertion on the NROB1 gene of an adopted boy who was reported to have the onset of an adrenal crisis at

two weeks of age, requiring replacement therapy with mineralocorticoids and glucocorticoids for four months [25]. Abe et al described that the genetic panel analyses for AHC-related genes in first-born male neonates having failure to thrive and systemic subcutaneous hyperpigmentation with AHC showed the hemizygous variant of the *NROB1* gene [26].

4. Conclusion

Maintaining a high index of suspicion in children presenting with symptoms such as hypoglycemic convulsions, hypotension, and failure to thrive is imperative for early diagnosis of primary adrenal insufficiency. Early genetic diagnosis is essential in reducing adverse outcomes and can provide vital information for family planning and management. This report emphasizes the importance of clinical vigilance and the role of genetic diagnosis in preventing severe adverse outcomes with primary adrenal insufficiency.

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