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Case Report

Congenital Adrenal Hypoplasia the Importance of a Prenatal Suspicion

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Abstract

Background: Congenital Adrenal Hypoplasia (CAH) is a rare congenital X-linked disease, related to a mutation in the *NR0B1* gene. It is primarily characterized by adrenocortical hormone deficiency and hypogonadotropic hypogonadism. Our paper presents the clinical case of a newborn with a maternal history of known *NR0B1* gene mutation.

Case presentation: We present a case of a newborn male with a prenatal history of a mother with a previous abortion and a deceased newborn male child with an autopsy with diagnosis of ACH, her genetic prenatal study was positive for *NR0B1* mutation. The medical team had special attention on any early clinical manifestations. Pediatric endocrinology was aware of the birth. The patient had clinical and laboratory manifestations suggestive of congenital adrenal hypoplasia (hypoglycemia, hyperpigmented genitalia, hypocortisolism). Early steroids were started at 10 mg/m^2/SC IV, during the hospital admission he presented an infectious process treated with antibiotic and adjustment of the steroid dose, the patient was discharged with Prednisolone (33 mg/m^2/SC) and Fludrocortisone (0.1 mg/day) and follow up by pediatric endocrinology.

Conclusion: Prenatal genetic diagnosis of ACH may reduce morbimortality, warrants early hormone replacement, and enables the provision of genetic counseling to the family.

Keywords: Congenital adrenal hypoplasia; Hyperpigmentation; Hypoglycemia; Newborn; *NR0B1* protein

Introduction

Congenital Adrenal Hypoplasia (CAH) is a rare cause of congenital adrenal insufficiency and was first described by Sikl in 1948 [1]. It occurs in less than 1:12,500 live births and is an X-linked disorder caused by mutations in the *NR0B1* gene. This gene codes for the DAX-1 receptor (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1), which is an "orphan" nuclear receptor, as no specific ligand has been identified. One of the actions of DAX-1 is to activate target genes involved in the development and function of the Hypothalamic-Pituitary-Gonadal (HPG) axis [2,3].

AHC is primarily characterized by adrenocortical hormone deficiency and Hypogonadotropic Hypogonadism (HH) [4]. *NR0B1*-related congenital adrenal hypoplasia should be suspected in males with the clinical findings of X-linked Y (X-linked AHC) or Xp21 deletion and supportive laboratory and imaging findings. The initial clinical presentation is typically acute, especially in infants, with vomiting, feeding difficulty, dehydration, and shock caused by a salt-wasting episode. In some instances, hypoglycemia, frequently presenting with seizures or mineral corticoid deficiency, may be the presenting manifestation of adrenal insufficiency [4]. Lack of clinical suspicion of AHC may lead to misdiagnosis as Congenital Adrenal Hyperplasia (CAH), aldosterone deficiency, or Addison's disease, which may result in patients experiencing delays in treatment, as well as improperly medicated [5].

The diagnosis of Primary Adrenal Insufficiency (PAI) is traditionally based on low morning cortisol concentrations (measured in serum or plasma) and confirmed by low stimulated cortisol. In most cases, the diagnosis is highly likely if the cortisol is 140 nmol/L (5 g/dL) in combination with an ACTH concentration (measured in plasma) elevated more than 2-fold above the upper limit of the reference interval for the specific assay [6]. The diagnosis of *NR0B1*-related congenital adrenal hypoplasia is established in a male proband by detection of either a hemizygous pathogenic variant in *NR0B1* or a non-recurrent Xp21 deletion that includes *NR0B1* [1]. Making a specific genetic diagnosis allows for targeted treatment of the specific underlying hormonal defect (such as the need or not for continued mineral corticoid replacement) [7]. Early postnatal diagnosis may prevent severe hypoglycemia, Addisonian crisis and death [5].

We present the case of a newborn with a maternal history of known *NR0B1* gene mutation and clinical manifestations suggestive of congenital adrenal hypoplasia. These findings led to an early diagnosis and timely treatment. Early genetic diagnosis of AHC may reduce morbimortality, warrants early hormone replacement, and enables the provision of genetic counseling to the family.

Case Presentation

We present a male newborn, born at 37.2 weeks of gestation, weighing 2,960 g, and measuring 47 cm. He is product of the third pregnancy, with the first pregnancy resulting in a miscarriage and the second pregnancy resulting in a full-term birth but with perinatal death at 15 days of life due to an adrenergic crisis. Following that event, the mother underwent studies and was found to have a heterozygous mutation in the *NR0B1* gene with the c1292 variant associated with congenital adrenal hypoplasia.

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The patient was born via c-section without complications during the first hours of life. However, at the nursery, during the initial physical examination, Hyperpigmentation of the genitals was observed, with the rest of the examination showing no abnormalities. A blood glucose test (glucometry) was requested at one and four hours of life, with readings of 72 mg/dL and 49 mg/dL, respectively. Despite early formula feeding for newborns, the glucometry levels remained below 50 mg/dL. After feeding, blood glucose was retested, and it was reported at 33 mg/dL, which was later corroborated with a blood count result of 41 mg/dL. There were no accompanying signs of hypoglycemia. He was transferred to the NICU for treatment of hypoglycemia.

Upon admission, a diagnostic approach was initiated due to the maternal history of being a carrier of the *NR0B1* gene. The reported ACTH (adrenocorticotropic hormone) level was 37 pg/mL (Reference value: 5 pg/mL to 57 pg/mL), 17- hydroxyprogesterone was 100 ng/dL (Reference value: < 630 ng/dL) and cortisol levels were less than 1 ug/dL (Reference value: 3.7 ug/dL to 19.4 ug/dL). Serum electrolyte levels were as follow: sodium 137.9 mEq/L (Reference value: 133 to 146), potassium 5.5 mEq/L (Reference value: 3.7 to 5.9), and chloride 111 mEq/L (Reference value: 98 to 113).

An MRI of the abdomen was performed in which the adrenal glands could not be delimited, abdominal ultrasound showed a decrease in size of the adrenal glands (6 mm right adrenal gland length and 4 mm left adrenal gland). Intravenous glucose and Hydrocortisone at 10 mg/m^2/SC were administered, resulting in an improvement in blood glucose levels to 73 mg/dl to 111 mg/dl. As no new episodes of hypoglycemia occurred, the hydrocortisone dose was reduced to 4.5 mg/m^2/SC at 48 hours of life. At 72 hours of life, intravenous glucose was discontinued, and the oral steroid was changed to Prednisolone at 30.8 mg/m^2/SC, while Fludrocortisone was started at 0.1 mg/day. On his fourth day of life, the patient presented intermittent fever for 24 hours, prompting laboratory studies that reported a C-reactive protein level of 3.87 mg/dl (Reference value: 0 mg/dl to 0.50 mg/dl) and a positive blood culture for Staphylococcus aureus MRSA (Treated with Vancomycin at 10mg/kg/dose for 10 days). After observing signs of systemic inflammatory response, steroid dosage was tripled, maintaining serum glucose levels at 84 mg/dl to 107 mg/dl. After completing the 7th day of antibiotic treatment, the steroid dose was progressively reduced until reaching a basal dose of Prednisolone at 33 mg/m^2/SC. Extended metabolic screening was performed with negative results, as well as cardiac and auditory screening without alterations. He was discharged home on his 17th day of life with treatment based on Prednisolone (33 mg/m^2/SC) and Fludrocortisone (0.1 mg/day). After his discharge home, the diagnosis of congenital adrenal hypoplasia was confirmed since the pathogenic variant c1292del was identified in the hemizygous state in the *NR0B1* gene within the Sanger sequencing test of the patient's genome. Our case was presented on the standard CARE Guidelines.

Discussion

Congenital adrenal hypoplasia is a X- linked rare congenital entity, caused by different mutations that plays an important role in the development of the endocrine gland. This disorder causes primary adrenal insufficiency because the cortisol synthesis is impaired. The incidence is not well established due to a lack of diagnosis and documentation of cases; despite this, it is estimated that 1 in every 12,500 births have the disease [8].

There are different mutations that can cause congenital adrenal hypoplasia, like alterations in X- linked adrenal hypoplasia, Steroidogenic factor-1 related (NR5A1/SF-1), IMAGe syndrome (CDKN1C), IMAGe- like syndrome (POLE1), MIRAGE syndrome (SAMD9), SERKAL syndrome (WNT4) and the idiopathic causes. In this case we focus on the X-linked adrenal hypoplasia (*NR0B1*/DAX-1). DAX-1 is a nuclear receptor, first described in 1994, that regulates adrenal development and function. It is involved in the steroidogenic pathway and the hypothalamic-pituitary-gonadal axis, so the loss of function modifies this whole axis. One of the notable things in the case is the prenatal suspicion as only a small number of patients with a family history received timely genetic testing and were diagnosed when the symptoms first occurred [8-10].

AHC predominantly affects males, and women are carriers of the gene mutation. X-linked congenital adrenal hypoplasia has an acute onset of primary adrenal insufficiency, presenting as glucocorticoid and mineral corticoid deficiency. Most of the symptoms begin at 3 weeks of life when maternal steroids stop having an effect on the newborn, and the hypothalamic-pituitary-gland axis starts functioning on its own. The patient we present exhibited Hyperpigmentation on the genitals and was diagnosed with hypoglycemia on the first day of life as indicated by glucometry reports. Patients typically debut with a salt-losing crisis, hypoglycemia, Hyponatremia, hyporeactivity or lethargy, nausea, vomiting, poor feeding, and skin Hyperpigmentation. They can also experience a prolonged period of jaundice. During puberty, most patients develop hypogonadotropic hypogonadism, leading to an interrupted normal pubertal development [11].

Since the clinical manifestations are not specific, the diagnosis of congenital adrenal hypoplasia may go unnoticed. Electrolyte imbalances, hypoglycemia, and skin Hyperpigmentation should raise diagnostic suspicion. Laboratory studies should be conducted, where low cortisol levels, high ACTH levels are expected with a decreased 17-hydroxyprogesterone, altered plasma-renin activity and aldosterone are expected, indicating mineral corticoid deficiency. Genetic studies should be performed to complement the diagnosis, such as Karyotype, Fluorescent In Situ Hybridization (FISH), or microarray analysis, which may reveal the gene deletion involving DAX1. Reaching a genetic diagnosis is fundamental in the early stages of the disease because it provides the medical team with insights into what to expect and how to avoid various complications that could lead to fatal outcomes. Prenatal diagnosis is possible with an amniocentesis, but in our case, it was not performed and would not have changed the prognosis or patient management. Although prenatal genetic diagnostic is the best approach, some cases have reported screening through maternal estriol in the second trimesters of pregnancy suspicion is based on the fact that estriol originates from DHEA synthesized in the fetal glands [5-12].

Therapy is started by stabilizing the patient, to maintain normal glucose levels and ensure proper hydration with balanced electrolyte levels in the serum. Then, glucocorticoid replacement and mineral corticoid replacement should be carried out, and the doses are adjusted depending on the patient's response.

The detection of affected family members that have gene mutations can be essential to improve the newborn's survival rate. It can help doctors to be prepared of what to expect and treat them promptly after birth. This disease can be lethal if the treatment is initiated late. At this time, technology is improving so the detection of these mutations could be more accessible.

Conclusion

AHR is a rare x-linked genetic condition. The prenatal genetic diagnosis provides important information to the medical team to be able to make an early clinical suspicion which will benefit the patients to have an early intervention and avoid complications. The early use of steroids is essential for disease management, and we need to consider modifying the steroid dose to stress doses in case of infection events.

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