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Case Report

A rare case of salt wasting type of Congenital Adrenal Hyperplasia with Turner Syndrome

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ABSTRACT

Combination of Congenital Adrenal Hyperplasia (CAH) with Turner Syndrome (TS) is rare. We report a 20-days old new born, born from second degree consanguineous marriage presented with refusal of feeds, vomiting and loose stools. On examination, ambiguous genitalia with presence of a 2.6 cm phallus, incomplete labial fusion, gonads not palpable and hyperpigmentation were noted. Laboratory findings revealed a classical type of CAH caused by 21-hydroxylase deficiency. Karyotyping showed a 45 X0[4] / 46 XX[16] pattern concluding mosaic TS. She was given hydrocortisone at a dose of 5 mg/m^2/day, fludrocortisone acetate in dose of 0.1mg/day, along with oral salt of 1 gm/day. At 8 months follow-up, the patient appeared to be in good health; her height was 69.3 cm [> 50th percentile] and her weight was 8.3 kg (> 50th percentile). System examinations turned out to be normal. The patient's electrolyte levels were normal and she was in good metabolic control. The findings of this particular patient show that routine karyotyping during investigation of patients with disorders of sexual differentiation (DSD) can help us to reveal TS. Additionally, signs of virilism have to be investigated at the time of diagnosis or during physical examinations for proper follow-up of TS cases.

Keywords: Congenital Adrenal Hyperplasia, Turner syndrome, Karyotyping, Disorders of Sexual Differentiation.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by enzyme defects in the steroidogenic pathways. 21-hydroxylase (21-OH) is the most common of these enzyme deficiencies and constitutes up to 95% of cases. The classical forms of 21-OH deficiency occur in about 1 in 14000 persons.[1]

Turner syndrome (TS) has problems such as short stature, skeletal abnormality, amenorrhea, lymphatic abnormalities, hearing loss, aortic coarctation or stenosis, renal abnormalities, thyroiditis, metabolic abnormalities such as carbohydrate intolerance, ovarian insufficiency, and infertility.[2] The occurrence of abnormalities in the sex chromosomal karyotype resulting in the loss of all or part of an X chromosome has been variously reported as 1:2000 to 1:5000 in live-born phenotypic females.[2,3] Diagnosis of CAH is tough in females with TS, because of sharing the common clinical features like short stature, amenorrhea, and infertility. Moreover, the combination of TS and classical CAH is rarely reported in literature.[4] In this article, we report a newborn patient who was diagnosed with CAH and TS concomitantly.

CASE HISTORY

A 20-days-old new born was brought to our NICU with the chief complaints of refusal of feeds, vomiting and loose stools. She was born from second degree consanguineous marriage at term to a 25-year-old G4 P3 L1 D3 mother through normal vaginal delivery. Birth weight was 3500 grams. On physical examination she was lethargic with sunken eyes, had dry oral mucosa, depressed anterior fontanels suggestive of dehydration, ambiguous genitalia (Figure-1), low hairline and pre auricular tag (Figure-2). Her weight was 2540 grams (3rd to 15th percentile), length 50 cm (50th percentile), and body surface area 0.18, head circumference was 33cm (50th percentile) and chest circumference 31 cm (50th percentile). Heart rate was 170/min, Capillary Refilling Time (CRT) > 3 seconds,

respiratory rate 44/minute, SpO2 92% on room air, and blood pressure 60/40 mm Hg. Rest of the systemic examination was normal.

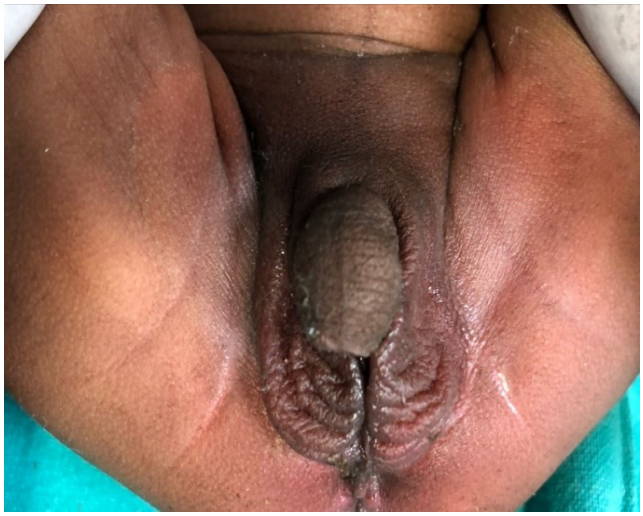


Figure-1: Ambiguous genitalia

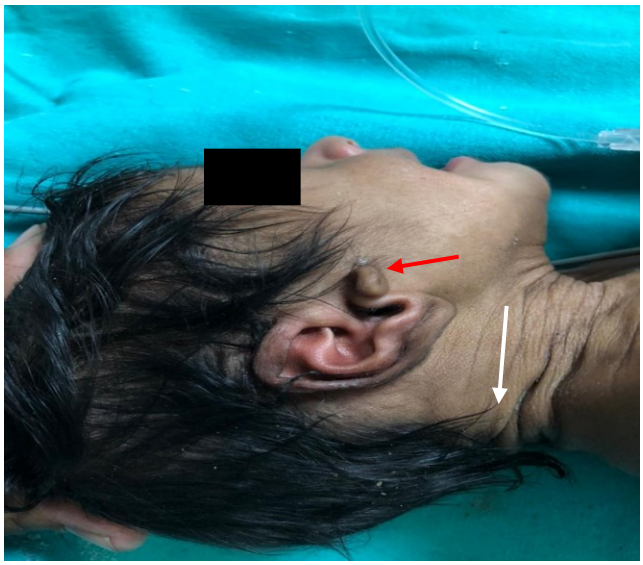
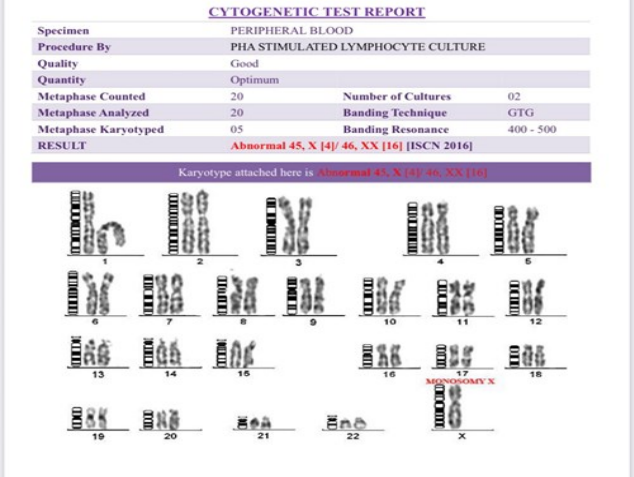


Figure-2: Low hair line (white arrow) & pre auricular tag (red arrow)

Investigations showed a positive septic screening with WBC 19140/cumm, CRP 25.5 ug/ml with normal urine analysis, renal and liver function tests. Biochemistry revealed a glucose level of 75 mg/dL, hyponatremia (Na^+ 122 mEq/L), hyperkalemia (K^+ 6.5 mEq/L), high 17-OH hydroxy progesterone (17.10 ng/dL). Cortisol was 4.3 µg/dL and testosterone 117.34 ng/dl. Pelvic ultrasonography demonstrated a uterus (17 X 8 mm), 21 hydroxylase enzyme assays revealed its deficiency and karyotyping was suggestive of abnormal 45 XO (Figure-3).

Treatment was started with injection Hydrocortisone at a dose of 100mg/m^2/day gradually tapered over next few days to a maintaining dose of 5mg/m^2/day. Tablet fludrocortisone 0.1mg/day was started on day 2 of starting hydrocortisone, oral salt 1gm/day and appropriate intravenous antibiotics were started with daily monitoring of blood sugar & serum electrolytes. After recovery from adrenal crisis and septicaemia, the patient was discharged on the 45th post-natal day. Diagnosis of CAH with salt-wasting crisis and turner syndrome was confirmed.

At the time of her last follow-up visit, when she was 8 months old, the patient appeared to be in good health; her height was 69.3 cm [> 50th percentile] and her weight was 8.3 kg (> 50th percentile). System examinations turned out to be normal. The patient's electrolyte levels were normal and she was in good metabolic control while taking hydrocortisone in dose of 5mg/m^2/day, fludrocortisone acetate 0.1 mg/day, along with oral salt of 1 gm/day.



CYTOGENETIC TEST REPORT

Specimen	PERIPHERAL BLOOD		
Procedure By	PHA STIMULATED LYMPHOCYTE CULTURE		
Quality	Good		
Quantity	Optimum		
Metaphase Counted	20	Number of Cultures	02
Metaphase Analyzed	20	Banding Technique	GTG
Metaphase Karyotyped	05	Banding Resonance	400 - 500
RESULT	Abnormal 45, X [4]/ 46, XX [16] [ISCN 2016]		

Karyotype attached here is Abnormal 45, X [4]/ 46, XX [16]

Figure-3: Karyotyping

DISCUSSION

This rare combination of TS with CAH was first described by del Arbol et al. in 1983.[5] So far, ten cases with both TS and CAH caused by 21-OH deficiency have been reported in the literature.[1-3,5-11] First reported case was of an 8-year-old girl, with 45,X/46,X,Xq karyotype, a 2.5 cm phallus, and a hormonal profile which was consistent with non-classical CAH. In 1985, Montemayor-Jauregui et al reported a 23-year-old female patient having primary amenorrhea, 3 cm phallus, hirsutism, and 45,X/46XX chromosome pattern.[6] This case was diagnosed being CAH following the detection of high levels of 17-ketosteroids in the 24-hour urine sample. The hormonal profile later returned to normal and menarche commenced after giving prednisolone treatment. A 16.9-year-old female patient with 45,X0 karyotype with cliteromegaly is the third case of this unusual combination, which was reported in 1992 by Larizza et al.[7] In 1997, Maciel-Guerra et al had published a

one-year-old patient having 3 cm phallus, penoscrotal hypospadias, and 45X0/46XX karyotype, diagnosed as CAH, and who, during the newborn period, was evaluated as male, had non palpable gonads with penoscrotal hypospadias, and experienced three adrenal crises.[3] Cohen et al also reported a case of 28-year-old female patient known to have TS and who was diagnosed having CAH during the oocyte donation process.[8] In 2005, Atabek et al reported a patient from Turkey, having ambiguous genitalia at birth, and being diagnosed as a case of TS at the age of one year, by detection of the 45,X/46XX karyotype.[4] Presenting for evaluation of signs of pubarche, the genital examination of this patient at the age of 4 years revealed Prader stage 3, bone age of 8 years, and basal and stimulated 17-OHP levels consistent with a diagnosis of the simple virilizing form of CAH.

A study conducted on 52 Italian TS cases and their relatives, showed that the basal and stimulated serum 17-OHP levels were found to be much higher compared to those in normal controls, and similar hormonal data were also found in the relatives of these patients.[7] These data were considered to be related to increased adrenal sensitivity to ACTH or to changes in metabolic clearance rate of 17-OHP, as observed in obese patients. However, HLA antigen and haplotype frequencies in the patients and their relatives had a similar distribution in Italian families with 21-OH deficiency. According to the results generated from this study, the frequency of 21-OH deficiency carriers in TS patients was remarkably higher (21.6%) compared to that of the general Italian population. Mantovani et al also reported that the frequencies of both abnormal 17-OHP response to ACTH stimulation test and CYP21 gene mutation carriers were prominently higher in patients with TS than in healthy controls.[9] They speculated that while more than 90% of conceptions with 45X0 karyotype would normally result in spontaneous abortion, certain endocrine signals originating from embryos with decreased 21-OH activities could lead to relaxation of maternal screening, and so provide survival advantage for heterozygote patients with 21-OH deficiencies.

Concomitant existence of TS and CAH can be associated with some problems. First of all, the diagnosis becomes difficult due to the presence of few common features like short stature, infertility, and amenorrhea.[4] Our case showed features of adrenal crisis during the newborn period, and during investigation, she was diagnosed as having CAH, but later as TS following routine karyotype analysis. Considering the fact that mean age of TS diagnosis is 10-11 years, diagnosis of patients with common clinical features may be delayed until this age, particularly when signs of virilism are not as prominent as in our case. In addition to the classical 45X0 chromosomal structure observed in TS, the karyotype may show a wide spectrum, and the X and Y chromosomes may be accompanied by mosaic monosomy. Virilism can also be observed in TS patients having a Y chromosome. These patients not only present with adrenal crisis and shock but also carry the risk for developing a malignant gonadal tumor.[3] Our patient had the mosaic form of TS and presented with features of virilism. However, she had no Y chromosome. Her elevated levels of 17-OHP and 21 hydroxylase enzyme deficiency clearly established a diagnosis of the classical form of 21-OH deficiency. Another problem of the TS and CAH combination is developing short stature. Inadequacy in hormone replacement therapy or overtreatment of CAH can cause final short stature. However, in TS, there is a tendency for progressive deviation from normal height percentile caused by retarded bone age along with decrease in the growth rate. The final heights of patients having concomitant TS and CAH has a tendency to deteriorate due to the presence of both diseases.[3] While it is possible to obtain good results in those CAH patients that are treated with careful clinical and laboratory follow-up in TS, growth hormone (GH) treatment initiated at supra physiological doses during an early age can also lead to acceptable increases in height, despite the absence of GH deficiency.[4] Optimal treatment of TS with GH is suggested to be initiated at an early age (before age 4 years), and high doses are recommended particularly during the first year of treatment.[10]

In conclusion, the findings in this patient show that routine karyotyping done during investigations of patients presenting with adrenal crisis and ambiguous genitalia or with a diagnosis of CAH may reveal the concomitant presence of TS. Also, signs of virilism have to be investigated at the time of diagnosis or during the follow-up of patients with TS.

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