CONGENITAL ADRENAL HYPERPLASIA: A CASE REPORT

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Summary

Congenital adrenal hyperplasia (CAH) is rare condition with different presentations. The most important 'salt loosing' variant is a medical emergency. More than 90% of cases of congenital adrenal hyperplasia are caused by 21 α-hydroxylase deficiency (21αOH). Rather than cortisol, the adrenals produce excess sex hormone. Majority of patients cannot synthesize sufficient aldosterone. There is virilization of girls, rapid somatic growth with early epiphyseal fusion in both sexes and even life threatening hyponatremic dehydration. The present case presented on 5th postnatal day with unrecognized sex and repeated vomiting. The baby was hyperpigmented, dehydrated with ambiguous genitalia. Hyponatremic, hyperkalemic hypochloremic metabolic acidosis with normal renal profile was seen. Both adrenal glands were enlarged with presence of uterus. Serum cortisol level was low but testosterone level was very high. The newborn was treated as congenital adrenal hyperplasia with hydrocortisone, fludrocortisones, calcium gluconate and 10% dextrose in 0.45% NaCl solution. Significant clinical improvement was observed within a week in this case. The case was presented with a view to focus such rare medical emergency so that Pediatricians and Neonatologists could manage the problem timely.

Key words

Congenital adrenal hyperplasia; neonate; ambiguous genitalia; 21 α-hydroxylase deficiency.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of adrenal corticosteroid biosynthesis due to deficiency of a particular enzyme. The potential clinical effects occur due to either distal hormone deficiency or accumulation of proximal metabolite with abnormal production of a steroid whose biosynthesis is unaffected [1]. More than 90% of cases of congenital adrenal hyperplasia are caused by 21 α-hydroxylase deficiency (21α OH) [2,3].

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The fundamental defect among patients with CAH due to 21αOH deficiency is that they cannot adequately synthesize cortisol. Inefficient cortisol synthesis signals the hypothalamus and pituitary to increase CRH and ACTH, respectively. Consequently, the adrenal glands become hyperplastic. But rather than cortisol, the adrenals produce excess sex hormone precursors that do not require 21-hydroxylation for their synthesis. Once secreted, these hormones are further metabolized to active androgens—testosterone and dihydrotestosterone and to a lesser extent estrogens and estradiol. The net effect is prenatal virilization of girls and rapid somatic growth with early epiphyseal fusion in both sexes known as *'simple virilizing form'*. About three-quarters of patients cannot synthesize sufficient aldosterone to maintain sodium balance and are termed '*salt-losing forms'*. This predisposes them to episodically develop potentially life-threatening hyponatremic dehydration [4]. Besides this a '*nonclassic mild late onset forms'* of CAH may occur [5]. Deficiency of 11-β hydroxylase is found in 8-9% of patients with CAH [6,7]. Glucocorticoid synthesis remains impaired but, in this disorder deoxycorticosteron accumulates. Deoxycorticosteron and its metabolites have mineralocorticoid properties and may cause hypertension when they accumulate [6,8]. Prevalence of CAH due to 21αOH deficiency is 1 in 14000 worldwide but not known in our country [9]. Classic 11-β hydroxylase deficiency occurs in approximately one per 100,000 births and occurs more frequently in Moroccan Jews [10,11].

Etiology of CAH due to 21-OH deficiency is due to mutations in the CYP21A2 (CYP21B) gene [5]. The CYP21A2 gene for 21-hydroxylase enzyme (P450c21 enzyme) is located at 6p21.3 of endoplasmic reticulum [5,12]. The CYP21A2 gene is paired with a nonfunctional pseudogene CYP21A1P. Scores of abnormal alleles of CYP21A2 have been documented, most arising from recombination of homologous regions of CYP21A2 and CYP21A1P gene. Differences in residual enzyme activity of different alleles account for different degrees of severity of the condition [12]. Most patients with 'salt loss' have gene deletions or conversions that severely impair enzyme activity, whereas the 'late onset' form is an allelic variant with higher enzyme levels that are sufficient to maintain health and a normal phenotype in the newborn period [9]. Etiology of CAH due to other enzymes defect

involve genes at different locations of different chromosomes [5]. Congenital adrenal hyperplasia are rare conditions with different presentations. The most important 'salt loosing' variant is a medical emergency. Ethical issue in the management of 'virilized form' is not less. Clinicians may not update enough about this rare but critical condition. The case is reported to orient clinicians so that they may able to manage the problem timely.

Case

Baby of a consanguineous parent from Feni district was admitted in the ward of Neonatology of Chittagong Medical College Hospital (CMCH) on 8/11 /2012 at 5th postnatal day with unrecognized sex by parents and repeated vomiting for 1 day. Mother Mrs. Ferdous, 24 years old, primigravida was under regular antenatal check up. Her pregnancy was uneventful. She was immunized against tetanus as per schedule. At 38 weeks of her pregnancy she delivered a baby of unrecognized sex per vagina. History of prolong rupture membrane was absent and the baby cried immediately following delivery. Weight and length of baby was 2400g and 49cm respectively. Breast feeding was started within 1 hour of delivery. Feeding other than breast milk was not given. From 5th postnatal day the baby developed repeated vomiting. The infant became weak, was unable to suck breast properly. Guardians brought the infant to physician from where the baby was referred to CMCH without any medication. In CMCH, the baby looked hyper-pigmentated on whole body with increased pigmentation on and around external genitalia (Fig:-1). The newborn was mildly pale but not cyanosed. The infant was dehydrated but not icteric. Body temperature, respiratory rate and heart rate were within normal range. Auscultatory findings on chest and precordium were normal. Blood pressure was 70/40 mmHg. The baby was hypotonic and reflex activity was moderate. Umbilicus was normal and organomegaly was absent. The infant had ambiguous genitalia in the form of clitoromegaly with rugosity of fused labia majora (Fig:-2, 3). Testes were not palpable. Other systemic examination was normal. The case was suspected as congenital adrenal hyperplasia (21-hydroxylase deficiency) - salt losing variety.

Investigations of the infant revealed hemoglobin of 13.1 gm/dl. Septic screening, urine routine examination, blood sugar was normal and serum calcium was near normal. Serum electrolytes showed hyponatremia, hyperkalemia and hypochloremia (S. sodium = 128 mmol/L, S. Potassium =7 mmol/L, S. Chloride = 90 mmol/L). Arterial blood gas analysis showed metabolic acidosis (pH=7.30, PCO_2=17.7 mmHg, PO_2= 90.6 mmHg, HCO_3=16.0 meq/L, BE= -4.1 mmol/L). Renal profile was normal (S. creatinine = 0.7mg/dl and urea = 50mg/dl). An ultrasound of abdomen and pelvis showed both adrenal glands were enlarged (? hyperplasia) with presence of uterus (Fig:-4,5). Serum 17 hydroxy progesterone (17-HOP) level could not do due to lack of facility here. Serum cortisol level was low (4.9µg/dl) but testosterone level was very high (1400 ηg/dl). The newborn was treated with hydrocortisone (15 mg/m^2 area in 3 divided doses) and fludrocortisone (0.05 mg/day in single dose). Calcium gluconate, 10% dextrose in 0.45% NaCl solution, along with general measures were advised. Within 5 days of therapy there was significant clinical improvement of neonate but serum biochemistry returned to normal by further couples of days. Parents were counseled and the baby was discharged by 15th postnatal day.

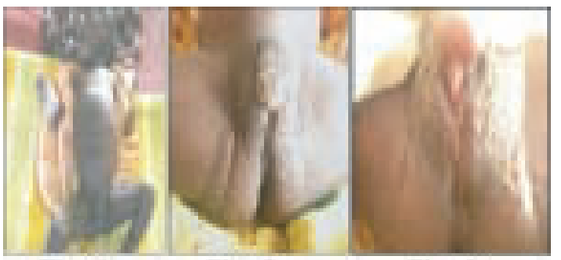

Fig : 1 Fig : 2 Fig : 3

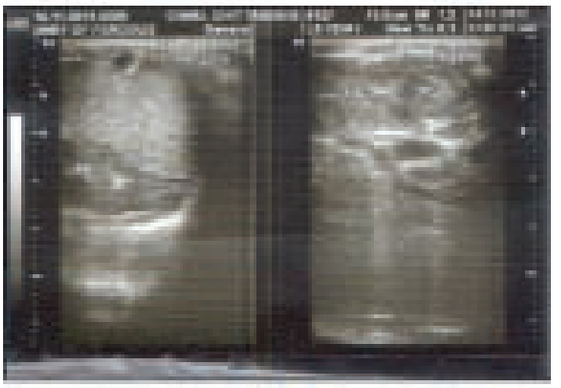

Fig : 4 USG showing big sized adrenals.

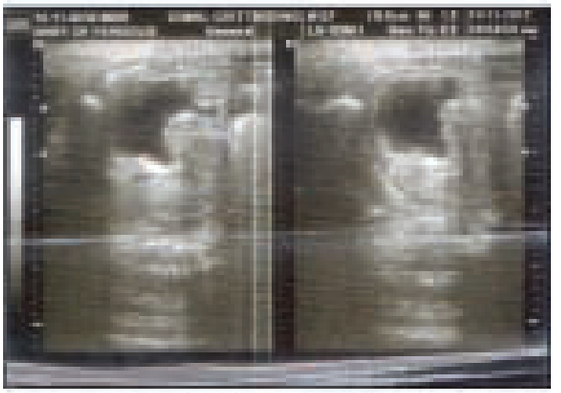

Fig : 5 USG showing uterus.

Discussion

Virilization is the hallmark of 21-OH deficiency. Genetic heterogeneity of this condition results in *'classic (severe)'* and *'nonclassic (mild)'* forms[5]. The severe classic form is characterized by marked overproduction of adrenal androgens. Virilization of the affected female fetus begins. This ranges from enlargement of clitoris with or without partial fusion of the labioscrotal folds, to complete fusion of the folds with appearance of a penile urethra (Fig-2). The affected female infant has normal ovaries, fallopian tubes, and uterus. Upper third of the vagina is normal, but a urogenital sinus may be present distally with one opening on the perineum (Fig-3). Increased pigmentation of skin creases and genitalia due to increased ACTH may alert clinician to the presence of adrenal insufficiency [5].

In classic 21-OH deficiency, inadequate hydroxylation of progesterone to 11-deoxycorticosterone results in aldosterone deficiency, and a salt-wasting crisis may occur [5,13]. Urinary sodium concentrations may exceed 50mEq/L. The infant cannot maintain blood volume; hyponatremic dehydration begins to develop by the end of first week of life. Potassium and acid excretion are impaired leading to hyperkalemia and metabolic acidosis gradually. Ability to maintain circulation is further limited by the effect of cortisol deficiency. The early symptom is poor weight gain, but most infants with severe CAH develop vomiting, severe dehydration, and shock by the second or third week of life which may lead to death of infant if not treated properly [12].

Objective of treatment is to achieve normal growth, pubertal development, sexual function, and fertility. Glucocorticoids are administered to decrease ACTH secretion. It suppresses hyperplastic adrenal gland, stop overproduction of adrenal androgens, thereby preventing progressive virilization. A variety of glucocorticoids (hydrocortisone, prednisone, dexamethasone) with dosage schedules have been used. Salt-losing crisis should be treated with high doses of hydrocortisone (50 to 100 mg/m^2/day in 3-4 divided doses) in addition to intravenous fluids to correct sodium and water depletion. Glucose infusion is needed in presence of hypoglycemia. With correction of electrolyte and fluid depletion and resolution of the adrenal crisis, glucocorticoid dose can be tapered, oral fluids begun, and intravenous fluid is discontinued. Maintenance therapy for classic 21-OH deficiency is oral hydrocortisone (10 to 20 mg/m^2/day) in 3 divided doses. Some clinicians prefer intramuscular cortisone acetate 15 to 20 mg every 3 days for first 2 years of life.

Patients with disturbed electrolyte regulation (salt-wasting) also require a mineralocorticoid and sodium supplementation [5]. Fludrocortisone acetate (usually 0.05 to 0.1 mg daily irrespective of body size) is the drug of choice. Some also recommend sodium supplementation (1 to 5 mEq/kg/day) [13]. Increased doses of glucocorticoid are indicated during periods of stress [5,13]. The protocol for monitoring patients varies. Serum 17-OHP, androstenedione, testosterone, and plasma renin activity, preferably measured at 7:30 AM to 8:30 AM, prior to morning medication, provide indices of control. Surgical treatment on genitalia of infant depends on degree of virilization. Initial surgery most often is performed within first year of life; later revision may be necessary [5]. Counselling of the parents is the crucial part of management of CAH. Management of such condition needs multidisciplinary involvement.

Presentations and laboratory findings of the present newborn infant correlate to CAH of 'salt loosing type'. The infant was attended earlier than many other cases with vomiting, dehydration and virilized external genitalia [1,4,5]. Her whole body was darkly pigmented but the external genital was darker. Such dark pigmentation on whole body was not reported in many other CAH cases [1-5,7,9-12]. The newborn responded well with recommended medical treatment.

Conclusion

Congenital adrenal hyperplasia (CAH) is a rare disorder of adrenal corticosteroid biosynthesis. The 'salt loosing' variant is a medical emergency. Prompt treatment is essential to save the life of neonate. Management of such condition needs multidisciplinary involvement. Surgical treatment on genitalia of infant depends on degree of virilization. Counseling of parents with follow-up is crucial part of management of CAH.

Disclosure

All the authors declared no competing interest.

References

1. Shah I, Amit. Congenital Adrenal Hyperplasia. Pediatric Oncall 2004; 1(5):16.

2. White PC, Speiser PN. Congenital Adrenal Hyperplasia due to 21- Hydroxylase deficiency. Endocr Rev 2000;21:245.

3. Speiser PW, White PC. Congenital Adrenal Hyperplasia. N. Engl J Med 2003; 349:776.

4. Perrin C.W & Phyllis W.S. Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Endocrine Reviews 2000; 21(3): 245–291.

5. Levine LS. Congenital Adrenal Hyperplasia. Pediatrics in Review2000;21(5):159-171.
ases and Drugs New York.USA.Lange; 2004;5:329.

6. New MI. Genetic disorders of Adrenal hormone synthesis. Horm Res.1992; 37(suppl 3):22–33.

7. White PC, Speiser PW. Steroid 11 beta-Hydroxylase deficiency and related disorders. Endocrinol Metab Clin North Am. 1994; 23:325–339.

8. Auchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. Endocrinol Metab Clin North Am 2001; 30:101-119.

9. Cheetham T. Endocrine disorders. In. Rennie JM editor. Roberton's Textbook of Neonatology, China: Elsevier Churchill Livingstone; 2005;4:886.

10. Deaton MA, Glorioso JE, Mclean DB. Congenital Adrenal Hyperplasia: Not Really a Zebra. Am FAM Physician. 1999; 59(5):1190-1196.

11. White PC, Curnow KM, Pascoe L. Disorders of steroid 11b Hydroxylase isozymes. Endocr Rev 1994;15:421–438.

12. Trakakis E, Loghis C, Kassanos D. Congenital Adrenal Hyperplasia because of 21-Hydroxylase deficiency. A genetic disorder of interest to obstetricians and gynecologists. Obstet Gynecol Surv 2009; 64 (3): 177–189.

13. Gomella TL. Neonatology*: Management,* Procedures, On-Call Problems, Diseases and Drugs New York.USA.Lange; 2004;5:329.