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Case report

A neglected case of treatable genetic disorder

C. Rekha[1*], R. Paramaguru[2], Vimala sarojini[3], Dinisha Einstien[4], A. Prathiba[4]

[1]Assistant professor, Department of paediatrics, ACS medical college and hospital, Tamil Nadu, India
[2]Assistant civil surgeon, Department of paediatrics, Thiruvallor government hospital, Chennai, India
[3]Professor, Department of paediatrics, ACS medical college and hospital, Tamil Nadu, India
[4]Assistant professor, Department of pathology, ACS medical college and hospital, Tamil Nadu, India

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ABSTRACT

Congenital adrenal hyperplasia(CAH) is a autosomal recessive genetic disorder involving adrenal hormones resulting in excessive production of androgens and hence their effects. Here we report a case of CAH which was diagnosed very late but was treated successfully. 12 years old female child came to us with ambiguous genitalia. Examination showed praders stage 4 external genitalia. Evaluated further and confirmed as a case of classic type of simple virilising congenital adrenal hyperplasia due to 21 hydroxylase deficiency. She was successfully treated with steroids and surgical correction was also done. Now child has also attained menarche and on follow up at our pediatric out patient department.

Introduction

Congenital Adrenal Hyperplasia(CAH) is a autosomal recessive disorder involving steroidogenesis[1] in adrenal gland due to enzyme deficiencies, most common being 21 hydroxylase deficiency. This would lead to byproduct deficiency and accumulation of intermediate metabolites, thereby stimulating pituitary gland to produce more ACTH (AdrenoCortico Trophic Hormone). ACTH stimulates adrenal gland resulting in hyperplasia. The accumulated metabolites are the cause for symptoms in CAH, in addition to steroid deficiency. Hypothalamo-pituitary-Adrenal axis is essential for production and regulation of adrenal steroids. In CAH, when this axis is disturbed and the negative feedback is lostand hence would result in increased production of ACTH and CRH. Here we report a case of congenital adrenal hyperplasia who presented to our outpatient department with ambiguous genitalia.

Case report

12 years old female child shahida, came to our out patient department with complaints of abnormality of external genitalia and excessive growth of hair in private parts. Mother noticed the abnormal appearance of genitalia since birth. She was delivered in a PHC where, she was ensured that it is normal and as the child grows cliteromegaly would subside. When the child was three years old she was taken to a nearby hospital, from where she was referred to our hospital. But the child was brought here only after 9 years considering social stigma . No history of any antenatal drug intake. Neonatal history was uneventful. No history of similar complaints among family members. No history of any chronic drug intake in the child. She is developmentally and nutritionally normal for age. On examination, child had mild pallor. Systemic examination was normal. External genitalia examination was classified under prader's stage 4. No gonads were palpable externally. Excessive pubic hair was observed and hence classified under tanners stage 4. Started our workup with karyotyping and imaging of abdomen. 46 XX was identified. Mullerian structures were normal. No evidence of any intra abdominal testis. Blood electrolyte levels were normal. Suspecting 21 hydroxylase deficiency, 17 OHP levels were done.17- hydroxy progesterone levels were elevated more than 5 times normal(628 ng/l). ACTH stimulation test was not done as the 17OHP levels were elevated. Hence final diagnosis

[*]**Corresponding Author: Dr. C Rekha,** Assistant Professor, Department of Paediatrics, ACS Medical college and Hospital , India.

arrived as classic type of simple virilising congenital adrenal hyperplasia due to 21 hydroxylase deficiency.

Fig 1: Cliteromegaly, praders stage 4

Discussion

Adrenal gland enlargement in CAH was first described in 1865 by De Creuhio, an anatomist. Cortisol was used for its treatment first in the year 1950. Adrenal gland hyperplasia in CAH would result from increased an ACTH level which is produced as a feedback from pituitary due to steroid hormones deficiency. Deficiency of specific enzymes involved in steroidogenesis in the adrenal would result in lack of cortisol with or without aldosterone. This would also cause excessive production of precursors. These are then converted to androgens and would result in various clinical manifestations of the disease.

Most common enzyme deficiencies constituting CAH include-

1. 21-hydroxylase deficiency
2. 11-beta hydroxylase deficiency
3. 3-beta hydroxysteroid dehydrogenase deficiency
4. 17-alpha hydroxylase deficiency
5. 17,20 lyase deficiency
6. Congenital lipoid adrenal hyperplasia
7. P450 oxidoreductase deficiency

21-hydroxylase deficiency: This is the most common enzyme deficiency constituiting CAH. More than 90% of cases of CAH are due to this. 21-hydroxylase is the enzyme involved in the hydroxylation of progesterone and 17-hydroxyprogesterone to 11-deoxycorticosterone and 11-deoxycortisol. These intermediate metabolites are then converted to aldosterone and cortisol. Hence deficiency of 21-hydroxylase would result in both cortisol and aldosterone deficiency.

Classification

21-hydroxylase deficiency may be of two types-

1. Classical
2. Non-classical

Classical type is again reclassified into

1. Salt wasting
2. Simple virilizing

Classical type- Incidence of classical type is about 1 in 15,000 to 20,000 birth. Of the both varieties of classical type, salt wasting is the most common type which constitutes 70% of the total case. Both cortisol and aldosterone are deficient and hence would result in salt wasting crisis, if not identified and treated early.

Non-classical type: Non-classical variety has a prevalence of 1 in 1000. Hence it appears to be most common but goes undiagnosed in many. Amount of enzyme activity that is retained ranges from 20% to 60%, based on which the characteristics may vary.

Clinical features:

Salt-wasters: Presentation may take even up to 1 to 2 weeks of life. Newborn may present with recurrent vomiting causing dehydration and hypotension. Other markers were hypoglycemia and dyselectrolytemia in the form of high potassium and low sodium levels. If not recognized and started on steroids it would result in shock and death. Female babies have ambiguous genitalia at birth. Other clinical features may include hyperpigmentation in both male and female babies.

Simple-virilizers: Only presentation may be ambiguous genitalia in girl babies. Hyperpigmentation may or may not be associated. Male babies present with hyperpigmentation and penile enlargement which may be missed in many. Pseudoprecocious puberty may be there in some males.

Non-classical type: Female babies may have normal genitalia at birth. They may later have precocious pubarche. Other mild symptoms like acne and hirsutism may be there. They may also remain asymptomatic.

Hormonal changes: The step which is blocked in this is the conversion of 17OHP and progesterone to aldosterone and cortisol. Hence it results in the accumulation of 17OHP. Further stimulating the production of ACTH, which would again try to increase steroidogenesis? Since there is a block, the precursors would accumulate and hence producing high levels of 17-hydroxyprogesterone. These are then shunted to androgen synthesis. As early as 8 to 10 weeks of gestation fetus would be affected because of androgen excess. Female babies have clitoromegaly with or without labial fusion which is more severe in salt wasters. Growth may be affected in most of these kids.[2]

Diagnosis: Blood 17-hydroxyprogesterone levels would be elevated and it should be measured in the morning hours. Levels more than 240 nmol/l in suspected case is considered diagnostic of 21 hydroxylase deficiency. The levels of 17OHP are lower in simple virilizing than salt wasting type.ACTH stimulation can be done for doubtful cases where following stimulation, 17 OHP levels are measured at 30 and 60 minute interval and plotted on normogram. Blood electrolytes show hyperkalemia and hyponatremia. Acidosis with hypoglycemia may or may not be associated. Serum cortisol may be low but it is of low diagnostic value. Karyotyping and ultrasonogram of abdomen should be done to rule out other causes of ambiguous genitalia.

Management: Replacement with deficient steroids is the mainstay in the treatment of congenital adrenal hyperplasia. This replaced steroidswill breakdown the feedback and production of adrenocorticotropic hormone decrease[3]. Drug of choice is hydrocortisone because it is regarded to have minimal growth suppressing effects.[4] In the neonatal period as high as 20 mg/m2/day may be needed and this should be tapered slowly to a dose of 10-15 mg/m2/day during infancy. Fludrocortisone replacement should be done for all patients with salt wasting type. Initially started at high doses 0.1 to 0.3 mg daily and should be tapered to 0.05-0.1 mg daily. Even for simple virilizers fludrocortisone is found to be beneficial.

Surgical management: For severe clitoromegaly, Partial excision of corporal bodies and Vaginoplastysould be done. urogenital sinus corrective surgery may be needed in some patients and this is usually followed by a revision surgery at adolescence period.[5]

Follow up

All the three kids were started on replacement steroids and clitroplasty with vaginoplasty were done. They were all followed up with regular checkup of 17OHP levels. With treatment they improved well. Advised to come for regular follow up at our endocrinology opd. Baby shahida has attained her menarche about 4 months after starting treatment.

Conclusion

CAH is a condition which should be diagnosed as early as possible to prevent both morbidity and mortality for the same. Treatment should be started immediately after diagnosis and followed up regularly. Frequent monitoring of height[6,7], weight and BMI is essential for all patients with CAH irrespective of the type of disease, for better outcomes[8].Based on the clinical findings and hormonal assays, steroid dose levels should be modified regularly

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