A Case of Congenital Lipoid Adrenal Hyperplasia

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Case Report

ABSTRACT

Lipoid congenital adrenal hyperplasia (lipoid CAH), a rare disorder of steroid biosynthesis, is the most severe form of CAH. In this disorder the synthesis of glucocorticoids, mineralocorticoids and sex steroids is impaired which result in adrenal failure, severe salt wasting crisis and hyperpigmentation in phenotypical female infants irrespective of genetic sex. In this report, we presented a 28-day-old phenotypic female infant, which referred with lethargy, failure to thrive and electrolyte abnormalities. Considering the clinical and biochemical findings, lipoid CAH was diagnosed and replacement therapy with standard doses of glucocorticoid and mineralocorticoid and sodium chloride was initiated. During follow-up, she had good clinical condition, but at 6 years of age, she refers with hypertension and adrenal insufficiency because of arbitrary drug discontinuation by mother. In ultrasonography an abdominal mass (the testicles) was reported. Chromosome study showed 46XY pattern. Orchiectomy was performed. We recommended that in cases with clinical presentation of adrenal insufficiency if there is not the facility to determine the karyotype, repeated ultrasonography perform during follow-up. In addition, investigating the genetic bases of the disorder would help us to determine the pathogenesis of lipoid CAH in our community. It would be helpful in prenatal diagnosis and treatment of the disorder to prevent its related comorbidities.

Key words: 46XY, failure to thrive, lipoid congenital adrenal hyperplasia

INTRODUCTION

Lipoid congenital adrenal hyperplasia (lipoid CAH), a rare disorder of steroid biosynthesis, is the most severe form of congenital adrenal hyperplasia (CAH).In this disorder the synthesis of all adrenal and gonadal steroid hormones is impaired due to a molecular defect in the steroidogenic acute regulatory protein. It is inherited as an autosomal recessive disease. It represent in two classic and nonclassic forms.[1]

In classic form, patients present with life-threatening adrenal insufficiency and salt wasting, during the first months of life. They develop female external genitalia in both human karyotypes

due to impaired gonadal steroid synthesis. In nonclassic form which recognized recently, patients represent with a phenotype of late onset adrenal insufficiency with only mild or minimally disordered sexual development.[2,3]

Lipoid CAH as an inherited endocrine disorder was first described by Prader and colleagues in 1955.[4] Thereafter, it largely overlooked in several studies for many years. The achievement of mentioned studies in accordance with understanding of adrenal steroidogenesis and genetic evaluation of patients with lipoid CAH led to understanding the molecular pathophysiology of this disorder. Accordingly mutation in two genes encoding cytochrome P450scc (cholesterol side chain cleavage enzyme) and steroidogenic acute regulatory protein (StAR) are the causes of the disorder. However, the frequency of lipoid CAH due to StAR gene mutation is higher than P450scc.[5,6]

The true incidence of lipoid CAH is not determined yet, but evidences suggest its higher prevalence among Japanese, Korean and Palestinian ancestry.[7] In Iran two case of documented lipoid CAH were reported with different presentation.[8,9] In this report we present a case of 46XY lipoid CAH.

CASE REPORT

A 28-day-old phenotypic female infant was admitted to pediatric endocrinology clinic of Al-Zahra Hospital, affiliated to Isfahan University of Medical Sciences, because of poor weight gain and lethargy.

She was a full-term infant with a birth weight of 3250 gr (50th percentile), length of 51 cm (50th percentile) and head circumference of 34 cm (50th percentile).The patient had no perinatal problem. She was the 1st child of nonconsanguineous parents.

At the time of admission, she was lethargic without history of vomiting or diarrhea.

There was not any familial history of similar presentation or features endocrine disease.

She had no history of drug consumption except vitamin A+D.

Physical examination

She was lethargic, had depressed fontanele. She had mild dehydration and decreased skin turgor.

In skin examination, she had mild hyperpigmentation, including oral cavity.

External genitalia seemed normal female type with no ambiguity. There was not any abdominal or inguinal mass in abdominal examination.

Her body weight, length and head circumference were 2900, 51 cm and 33.5 cm, all of them were beneath the 5th percentiles.

Her blood pressure was 60/40 mmHg, respiratory rate was 39/min, pulse rate was 112/min and body temperature was 37.1°C.

Laboratory findings

The initial biochemical examinations were as follows; serum sodium, 129 meq/lit(N:135-145) ; serum potassium, 6.1 meq/lit (N: 3.5-5.5);blood sugar, 45 mg/dl; blood urea nitrogen, 73 mg/dl; serum creatinine, 0.5 mg/dL; C-reactive protein ,negative; blood culture, negative. The results of venous blood gas were as follows; pH: 7.3 HCO_3=11.9 mmol/L, PCO_2= 35 mmHg which represented metabolic acidosis.

The results of hormonal tests were as follows; Cortisol: 0.2 µg/dl, ACTH: >1000 pg/ml, 17 OHP: 0.3 ng/ml.

Radiological findings

Ultrasonographic examination revealed small hypoplastic uterus (6*7*3 ml) or atretic ovaries and adrenal glands had normal sizes.

Clinical Course and Follow-up

First, the patient hydrated with normal saline. Thereafter, considering hyponatremia, hyperkalemia, metabolic acidosis and decreased cortisol level and increased ACTH level, lipoid CAH was diagnosed and replacement therapy with standard doses of glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) and sodium chloride was initiated.

After replacement therapy, electrolyte abnormalities were corrected during first week and the patient was discharged from hospital with good clinical condition.

She recommended referring for follow up. During follow-up, she had good clinical condition, with normal laboratory results except for 17 OHP which was lower during the period.

At 6-years old, the patient referred with high blood pressure and adrenal insufficiency because of arbitrary drug discontinuation by mother. Renal

Doppler ultrasonography and scan was performed which was normal. Regarding the recommendation of pediatric nephrologist fludrocortisone and sodium chloride was discontinued and treatment continued with hydrocortisone . Ultrasonography revealed the testicles in the abdominal cavity and uterus was not detected in pelvis. Orchiectomy was performed. Chromosome study showed 46XY pattern.

On her most recent visit at the age of 6 years, the patient had no hyperpigmentation. Her height was 110 cm (10-25th percentile), weight 23 kg (75-90th percentile). Her last laboratory tests results were as follows; Na: 142 mmol/l, K: 4.5 mmol/l ,17OHP: 0.1 ng/ml, ACTH: 22 pg/ml, Renin:50.8 pg/ml, Aldosterone: 105 pg/ml.

DISCUSSION

In this report we present a case of 46XY male infant with lipoid CAH from Iran-Isfahan with classic presentation of the disease. In this disorder the synthesis of glucocorticoids, mineralocorticoids and sex steroids is impaired. The consequences are adrenal and gonadal insufficiencies due to impairment of steroid synthesis. The signs of mentioned impairments are adrenal failure, severe salt wasting crisis and hyperpigmentation in phenotypical female infants irrespective of genetic sex. Gonadal impairment lead to development of a female phenotype in 46XY subjects due to destruction of Leydig cell and impairment of testosterone biosynthesis. Severe forms of lipoid CAH is fatal if it is not diagnosed and treated. Patients with lipoid CAH could have normal mental and physical development in the case of timely replacement treatment.[10]

Though mutations in two genes, P450 and StAR are the underlying causes of the disorder, but evidences from different studies in patients with lipoid CAH from various ethnic and genetic backgrounds suggest that mutations of StAR gene are responsible for most if not all cases of the disorder.[11]

Several cases of lipoid CAH with a spectrum of clinical presentation have been reported worldwide.

Gonzalez *et al.* in Chile reported a 2-month-old female patient with 46XY karyotype , who referred with growth failure, convulsions, dehydration, hypoglycemia, hyponatremia, hypotension, and severe hyperpigmentation. Likewise our reported case, in laboratory results they reported; high ACTH and undetectable or low serum cortisol, 17OHprogesterone, 17OH-pregnenolone, and aldosterone.[12]

In Iran, Amirhakimi and colleagues have reported a 2-year-old phenotypic female with lipoid CAH.[8] Recently another case of lipoid CAH with cholestasis was reported by Khodadad *et al.* in Tehran.[9]

Lipoid CAH has a spectrum of clinical manifestations which reported in many studies as the results of different mutations of StAR gene such as; neonatal hyponatremia, hyperkalemia, dehydration and female external genitalia which were reported in our case also. In our case mentioned presentation was reported at 28 days of life, whereas some studied reported that in some cases vomiting, dehydration, hypotension, growth failure and electrolyte abnormalities presented within two weeks after birth. It seems that except for genital phenotype which is similar in both sexes, the clinical manifestations, age of onset and the severity of lipoid CAH varied significantly in different cases.[13]

Previous studies indicated that in some cases of lipoid CAH, androgen action during early or late period of gestation would reflect by minor labial fusion or clitorimegaly. In our reported case, there was not such a presentation.[14]

Corticotropin hypersecretion result in hyperpigmentation in this group of patients which occurs in two-thirds of patients with lipoid CAH. It was reported in our cases also.[14]

Glucocorticoid deficiency results in hypoglycemia which occurs in one-fourth of affected infants.[14] The reported case had hypoglycemia.

For unknown reasons the serum 17OHP was low during treatment. Although in previous reports there were cases with elevated ACTH and renin even during treatment with high doses of glucocorticoid and mineralocorticoids,[15] but there was not similar report with low 17OHP likewise our case. So the reason should be investigated in future studies.

Massive adrenal enlargement consider as classic sign of lipoid CAH, but it is not pathognomic for the disorder and small or normal size of adrenal gland have been reported in some cases.[16] According to the

findings of some reports in this field, normal-sized adrenal gland, which was seen in our case too, could not exclude the diagnosis of lipoid CAH but it could be suggestive for P450scc deficiency or nonclassic form of the disorder.[17,18] Considering that clinical presentation of the patient is related to the classic form of the disease, it is suggested that the patient may have P450scc deficiency. However, this suggestion could not be conclusive, because genetic study was not performed in our case.

The limitation of current report is that we did not perform genetic study. In addition considering that the karyotype study was not performed early, during the first manifestation of the disease and the ultrasonography failed to detect the testicles in the first evaluation of the patient due to small size or technical errors, we recommended that in cases with clinical presentation of adrenal insufficiency if there is not the facility to determine the karyotype, repeated ultrasonography perform during follow up. However, studies indicated that the findings of ultrasonography, CT scan and MRI and familiarity with these methods would be useful in appropriate diagnosis and management of lipoid CAH, even during the first week of life.[19]

In sum, though the disorder is rare in our community, but it seems that investigating the genetic bases of the disorder would help us to determine the pathogenesis of lipoid CAH in our community. In addition, it would be helpful in prenatal diagnosis and treatment of the disorder to prevent its related comorbidities regarding to both its life-threatening adrenal insufficiency and salt wasting and gonadal impairment.

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