CONGENITAL ADRENAL HYPOPLASIA: A DISORDER FREQUENTLY MISSED

Nasir Abdallah Al Jurayyan, FRCP(C), FAAP; Mohammed Ahmed Abdullah, FRCP(Ed); Abdullah Soliman Al Herbish, FRCP(C), FAAP; Abdullah Mohammed Abo-Bakr, MSEd, FRCP(C)

Congenital adrenal hypoplasia is a rare disease which is known to cause severe salt wasting in the neonatal period. In this report, we describe three patients from two different families who were seen at King Khalid University Hospital, Riyadh, Saudi Arabia. All patients presented with classical clinical, biochemical, hormonal and radiological findings of congenital adrenal hypoplasia. To the best of our knowledge, no similar cases were reported from this part of the world. *Ann Saudi Med 1995;15(6):563-565.*

Congenital adrenal hypoplasia is a rare but not all that uncommon disease, causing a severe salt-wasting syndrome in the neonatal period.[1-6] Its incidence has been estimated to be one in 12,500 births and 0.19% to 0.26% of perinatal autopsies.[7-9] It is a hereditary disorder transmitted as an X-linked,[1-4,10,11] or rarely autosomal recessive.[12] Sporadic cases or those associated with other congenital anomalies have been reported.[6,7] Recognition of this life-threatening disease is, therefore, extremely important for appropriate therapeutic management.

In this report, we describe three cases of congenital adrenal hypoplasia from two different families who were seen at King Khalid University Hospital, Riyadh, Saudi Arabia. We would therefore like to draw the attention of the local pediatricians to this life-threatening but treatable condition, as similar cases could well have been missed.

Patients and Methods

Case records of all patients diagnosed as having congenital adrenal hypoplasia at King Khalid University Hospital were reviewed. All the cases were under the care of the authors. The criteria for diagnosis included clinical and biochemical evidence of salt wasting with low plasma cortisol and aldosterone associated with high plasma adrenocorticotropic hormone (ACTH) and renin activity. This was supported by history (including family history) and physical examination (including evidence of hyperpigmentation and phenotyping). Karyotyping was done on those patients showing female external genitalia. Hormonal investigations included plasma ACTH, cortisol, dehydroepiandrosterone sulfate, androstenedione, testosterone, 17-hydroxyprogesterone, aldosterone and plasma renin activity in addition to urinary electrolytes. While off therapy, rapid ACTH stimulation test using intravenous Cortrosyn 250 µg was done and blood was collected at 30, 60 and 90 minutes for cortisol and 17-OH progesterone, as described elsewhere.[13] Hormonal assays were done commercially by Bioscientia Laboratories, Germany.

From the Endocrine Division, Department of Pediatrics, College of Medicine, King Saud University (Drs. Al Jurayyan, Al Herbish, Abo-Bakr) and Department of Pediatrics, Security Forces Hospital (Dr. Abdullah), Riyadh.

Address reprint requests and correspondence to Dr. Al Jurayyan: Department of Pediatrics (39), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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Results

Summaries of the clinical presentation and hormonal investigations are shown in Tables 1 and 2 respectively.

Case 1. This male infant was the product of a full-term forceps delivery. Pregnancy was complicated by pre-eclamptic toxemia, which was treated with hydralazine. The parents were not consanguineous. Birth weight was 2.6 kg, height 52 cm and head circumference 38 cm. Apgar scores were 3 at one minute and 6 at five minutes. In view of prolonged rupture of membranes, the infant had septic screen and was started on antibiotics. Symptoms started at the age of 24 hours. Clinical and laboratory findings were suggestive of a salt-wasting syndrome with a blood pressure of 39/16 mmHg. He was therefore started on intravenous (IV) saline, hydrocortisone and DOCA after taking blood for hormone workup. He was discharged after stabilization and was maintained on hydrocortisone and Florinef. At six months of age, ACTH stimulation was done to confirm the diagnosis and revealed a blunted response. At seven and one-half years of age, the patient's growth has continued to follow the normal curve for age and his neurological development has been normal.

A male sibling of Case 1 died suddenly at home at the age of two weeks, following a presumed mild upper respiratory tract infection. Unfortunately, neither the

TABLE 1. *Summary of clinical presentation of the patients*

	1	2	3
Sex	M	M	F
Clinical presentation:	24 hours	5 days	4 weeks
Vomiting	–	–	+
Diarrhea	–	–	+
Dehydration	+	–	++
Lethargy	+	–	+
Poor feeding	+	–	+
Associated congenital anomalies	–	–	–
Skin hyperpigmentation	+	+	+
Hypoglycemia (B.S.<2.2mmol/L)	+	–	–
Hyponatremia (Na<130 mmol/L)	++(115)	+(130)	+(122)
Hyperkalemia (K>5.5 mmol/L)	++(8.1)	+(7.2)	+(7.2)
Serum BUN (mmol/L)	1.1	2	31
Serum creatinine (μmol/L)	35	53	329
Metabolic acidosis (HCO 3mmol/L)	+(16)	–(21)	+(15)
Urinary potassium (mmol/L)	16	21	18
Urinary sodium (mmol/L)	+(78)	++(140)	++(117)
Abdominal radiology			
Ultrasonography	*NK + NAG	NK + NAG	Adrenals not seen
CT Scan	NK + NAG	NK + NAG	Adrenals not seen
Chromosomes	–	–	XX

*NK=normal kidney; NAG=normal adrenal gland

TABLE 2. *Hormonal investigations at the time of presentation.*

Hormone	Normal Value	Case 1	Case 2	Case 3
Adrenocorticotrophin (ACTH) pg/ml	20-80	>250	164	>250
Cortisol μg/dl	1-24	1.8	3.4	1.9
Dehydroepiandrosterone Sulfate (μg/mL)	0.8-3.4	–	<0.1	<0.1
Androstenedione (ng/mL)	0.7-2.7	–	0.36	<0.15
Testosterone (ng/dL)				
(male)	up to 400	196	106	
(female)	<40			<10
17-hydroxyprogesterone (ng/mL) (Basal)	0.2-1.4	<0.2	<0.2	<0.2
Aldosterone (ng/dL)	5-60	<1	6.2	4.8
Plasma renin activity (ng/mL/hr)	<2*	>50	28	>50

obstetrician nor the treating pediatrician were aware of the previous family history; therefore, this child was discharged after birth without investigations or arrangement for follow-up. Most likely this child had a similar problem to Case 1.

Case 2. This is a male sibling of Case 1. Both the pediatrician and obstetrician were aware of the family history at this time. He was born after a full-term elective cesarean section with birth weight of 3.5 kg, height 51 cm and head circumference of 37.5 cm with normal Apgar scores. He had normal male genitalia with hyperpigmented skin. In view of the family history, he was kept under observation in the neonatal intensive care unit. Electrolyte abnormalities were first noticed on the fifth day, before any symptoms developed. After doing the relevant laboratory and radiological workup, the child was started and maintained on hydrocortisone and Florinef. Currently he is four and three-twelfths years old. His growth continues to follow the normal curve for age.

Case 3. This patient was the product of a full-term pregnancy, born by emergency cesarean section due to fetal distress. The parents were first-degree relatives. There was no history of neonatal deaths in this family; however, there is a history of multiple neonatal deaths in a maternal cousin's family. Birth weight was 2.4 kg, height 48 cm and head circumference 32 cm. She had normal femalegenitalia. The child was discharged in good condition on the seventh day. She became symptomatic at the age of four weeks with severe dehydration and weight dropping to 1.9 kg. Her blood pressure was 27/15 mmHg. In view of the salt-wasting picture on electrolyte workup and hyperpigmented skin, a provisional diagnosis of adrenal insufficiency was made and she was treated with IV fluids, Florinef and hydrocortisone after taking blood for hormonal workup. Ultrasound and computed tomography (CT) of the kidneys and adrenals revealed normal kidneys; however, the adrenals were not visualized. CT scan of the brain was normal. ACTH stimulation test at nine months of age revealed a blunted response. The child is currently five years old and her growth has continued to follow the normal curve for age on hydrocortisone and Florinef. Her neurological development has also been normal.

Discussion

Congenital adrenal hypoplasia, first described by Sikl[1] in 1948, is a life-threatening disease, usually manifested very early in life or even at birth with dehydration, poor feeding, failure to thrive, vomiting or diarrhea.[1-6] The earliest biochemical abnormality is hyperkalemia, hyponatremia, and metabolic acidosis.[3,4] The patients described here all presented within four weeks with this picture. The finding of low plasma cortisol and aldosterone levels associated with high plasma renin activity and ACTH proved normal pituitary function and served as the best parameters to document primary adrenal failure and excluded isolated mineralocorticoid deficiency or renal disease. All these findings were documented in our patients. If patients with normal-appearing male genitalia are found to have normal 17-hydroxyprogesterone levels, either basal or after dynamic studies, the ACTH stimulation test (as shown in Cases 1 and 2) is enough to exclude

congenital adrenal hyperplasia due to 21-hydroxylase deficiency,[3] a disease which is more prevalent in the region.[14,15] However, in patients with apparently normal female genitalia, chromosomal studies should be performed to exclude the diagnosis of congenital lipoid adrenal hyperplasia in males.[3,16] In females, it is difficult to distinguish this disease from congenital adrenal hypoplasia,[3,4,16] as the clinical and biochemical findings are exactly the same. However, the finding of very small or absent adrenals, as in patient 3, suggests congenital adrenal hypoplasia rather than congenital lipoid adrenal hyperplasia, which is usually associated with large adrenals laden with lipid.[3]

The presence of three male siblings with congenital adrenal hypoplasia in this series, whose parents are both well and nonconsanguineous, is a further confirmation of the X-linked recessive inheritance.[1-4,10,11,17] The presence of multiple neonatal deaths in first-degree relatives of the other patient is suggestive of the autosomal recessive inheritance[12] of this disease; however, it cannot confirm it.

The causes of the condition are several and their pathogenesis is not well understood.[4-17] Two different and distinct forms have been described: the miniature and cytomegalic forms.[3,4] In the miniature form, the adrenals have normal structure but are extremely small; this form is usually associated with cerebral malformations and can be sporadic or autosomal recessive. In the cytomegalic form, an X-linked disease, the normal adrenal architecture is replaced by large vacuolated cells resembling those of the provisional zone of the fetal adrenal cortex. This form is usually associated with hypogonadotropic hypogonadism[18,19] and rarely may be associated with glycerol kinase deficiency and congenital dystrophic myopathy, which has recently been described in association with deletion of the X-chromosome.[20,21]

Treatment entails replacement of deficient adrenal cortical hormones. A regimen of oral hydrocortisone, 15 to 20 mg/m^2/day divided in two to three doses, along with mineralocorticoid, 9 α-fluorocortisone (Florinef) in a dose of 0.05 to 0.2 mg/day, has proven to be efficient.[3] The adequacy of treatment is monitored by observation of physical growth, reduced hyperpigmentation, absence of hypotension and weakness, and normalization of electrolytes and plasma renin activity.[3]

In the past, most of the reported patients died early in infancy;[1-9] however, with the improvement in the diagnostic means, including antenatal diagnosis,[8,22] appropriate and early treatment has resulted in a better outcome.[3,19]

In conclusion, congenital adrenal hypoplasia can be a life-threatening disease. For early recognition and appropriate management, it should be included in the differential diagnosis of infants presenting with salt-wasting syndrome.

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