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Isolated Familial Adrenocorticotropin Deficiency: Prenatal Diagnosis by Maternal Plasma Estriol Assay

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We report on a brother and sister with adrenal insufficiency due to isolated adrenocorticotropin hormone deficiency discovered in the neonatal period. The first-born, a male infant, died; pathological findings suggested bilateral adrenal hypoplasia transmitted as an autosomal recessive trait. Plasma estriol levels were assayed during the mother's next pregnancy. The prenatal diagnosis allowed immediate and effective management of the second affected child. The supplementary evidence from the endocrine findings, unavailable on her brother, enabled us to make a diagnosis of isolated central ACTH deficiency. As the defect was found in infants of both sexes in the same family, it is in all likelihood transmitted as an autosomal recessive trait. We consider it important for genetic counselling to perform autopsies on all newborn infants whose death has no apparent cause. Maternal plasma estriol assays during pregnancy can help diagnose fetal adrenal insufficiency, whether the defect is central or adrenal.

Key words: adrenal insufficiency, pituitary gland, genetic counselling, autosomal recessive inheritance

INTRODUCTION

Isolated adrenocorticotropin hormone (ACTH) deficiency is rare, especially in children. To date, only two cases of familial occurrence have been reported [Ichiba and Goto, 1983]. Prenatal diagnosis by maternal plasma estriol assay has never been made in this condition. We report two new cases discovered in a brother and sister. Prenatal diagnosis was made during the second pregnancy.

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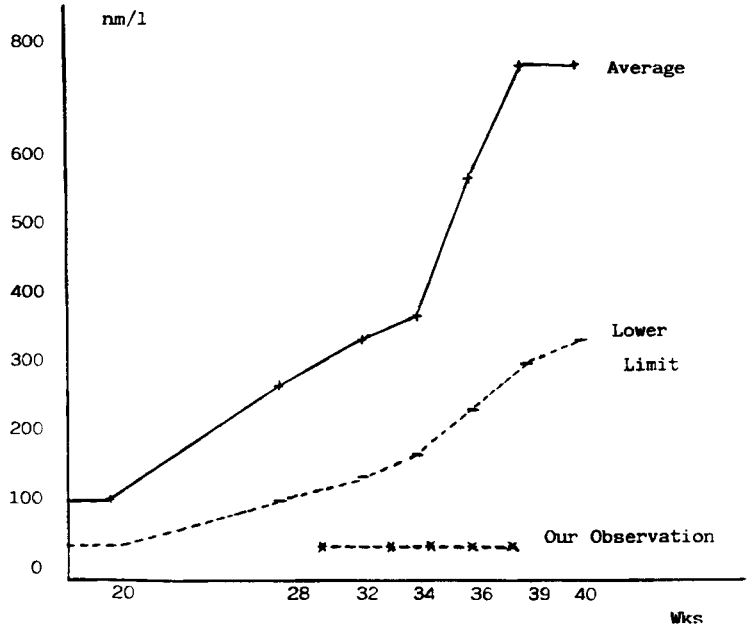

Fig. 1. Evolution of maternal plasma estriol levels (*) during the third trimester of pregnancy (according to the method of Scholler, 1980).

CLINICAL REPORTS

Patient 1

Patient 1, a male infant, was the first child of young, unrelated parents who were in good health; a previous pregnancy had ended in a spontaneous abortion. He was delivered vaginally at term and birth was uneventful. Birth weight was 3,250 g. The infant died suddenly at age 14 hours. At autopsy, bilateral hypoplasia of the adrenal glands was found. The three layers of the cortex were clearly distinct. Histological examination of the pituitary gland showed no abnormalities, and no other defect was noted. After study of the family history and the pathological findings we diagnosed hypoplasia of the adrenal glands, possibly transmitted as an autosomal recessive trait. The parents were informed that the risk of recurrence might be as high as one in four but that the condition could be treated. They were also told that it would be difficult to make a reliable prenatal diagnosis. Nevertheless, they decided on another pregnancy with the understanding that maternal plasma estriol levels would be monitored.

Patient 2

The mother of patient 1 became pregnant 2 years later. The course of the first 2 trimesters was normal. Chromosomes done on amniotic cells obtained by amniocentesis at 18 weeks of amenorrhea were normal: 46,XX. From week 30 of gestation, maternal plasma estriol assays were performed regularly [Scholler, 1980]. They showed a continuous fall in the levels, in the region of 30 nmol/l (Fig. 1), strongly indicating fetal adrenal insufficiency [Hensleigh et al, 1978; Oakey, 1984; Braunstein et al, 1976]. The infant was born by cesarean section after 38 weeks; birth weight was 3,370 g. She was immediately

transferred to the neonatal intensive care unit. During the first days of life, she suffered from mild respiratory distress as a result of amniotic aspiration and from jaundice due to a *Eschericia coli* sepsis. Hormone assays were done throughout the first days of life (Table I). We found low plasma cortisol levels but also very reduced levels of ACTH. Electrolyte composition of the blood was normal. Blood sugar levels were normal. Sodium excretion was slightly high, between 30 and 50 mEq/liter. Arterial pressure was normal for age. Abdominal echography showed a small left adrenal space (6 mm); the right space was not clearly defined. Sella turcica was normal on skull radiography.

Two problems arose in the following weeks. It became apparent that the jaundice was due to cholestasis. Echography and technetium radioisotopic scanning showed no obstruction. Needle biospy disclosed accumulation of biliary pigment in the liver cells and in the bile canaliculi. There was no hepatitis and no evidence of storage disease. At the same time, there was a general alteration of the infant's condition: she failed to thrive, she vomited frequently, and she tolerated fasting with difficulty, having hypoglycemia between 0.20 and 0.40 g/liter in the morning; she also had bouts of spontaneous bradycardia and reduced arterial pressure. Hypoglycemia was not accompanied by any rise in the plasma cortisol and ACTH levels (serum glucose 0.30 g/liter, cortisol 6 ng/ml, ACTH 16 pg/ml). We did two stimulation tests with exogenous corticotropin on days 15 and 45. On both occasions the increase in plasma cortisol levels was slight (Table II). We did a metopyrone test (30 g/kg) on day 40. Eight hours after sampling, the plasma levels of compound S had only increased from 0.5 to 1.20 ng/ml. Likewise, ACTH and cortisol levels only rose from 16 to 25 pg/ml and 6 to 14 ng/ml, respectively. Thyroid hormone levels were normal: T4-L: 14.8 pg/ml; thyroid stimulating hormone (TSH) level was normal at 6.1. μIU/ml. At 7 weeks the infant was treated with hydrocortisone (10 mg/day) and fludrocortisone (50 μg/day). As treatment continued her clinical state improved: hypoglycemia disappeared, blood pressure became normal, she gained weight steadily, and after a few weeks there was regression of the cholestatic jaundice. Assessment of hypothalamopituitary secreting capacity follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin hormone (PRL), and growth hormone (GH) was performed using a combined test: time 60, a single oral dose (1 mg/kg) of propranolol was given; time 0, I.V. administration of 250 μg of thyrotropin releasing hormone (TRH), 25 μg of luteinizing hormone releasing hormone (LHRH), I.M. administration of glucagon (1 mg). Hormone levels were determined at 60, 75, 90, 120, 150, 180 minutes after injection. Results were normal, and we diagnosed adrenal insufficiency of central origin due to isolated ACTH deficiency (Table III). At 4 1/2 months of age the infant's weight was 6,510 g and length 65 cm. Psychomotor development was normal. Monitoring of plasma cortisol levels (154 ng/ml) showed a satisfactory balance with hydrocortisone 7.5 mg/day and fludrocortisone 50 μg/day.

DISCUSSION

Very few cases are known where adrenal insufficiency due to ACTH deficiency was diagnosed in the neonatal period [Ichiba and Goto, 1983]. Our findings in patient 1 suggested hereditary adrenal hypoplasia. Normal adrenal architecture indicated transmission as an autosomal recessive trait rather than X-linked adrenal insufficiency.

In the second infant, adrenal insufficiency was suspected when echography showed small adrenals and also because from age 3 weeks she tolerated fasting with difficulty. The diagnosis was confirmed by the reduced plasma cortisol levels, particularly during attacks of hypoglycemia. We did not think it justified to do an insulin hypoglycemia test.

TABLE I. Hormonal Levels in Patient 2 Measured From Day 1 to Day 45 of Life

Hormone	Hormone level at age (days)								Mean ± SEM (or normal range) in a one-day-old infant
	1	3	6	8	12	25	40	45	
Cortisol (ng/ml)	17	18	10	11	5	23	6	5	68 (12.5–298)[a]
ACTH (pg/ml)	12	15	15	18	15	13	16	15	143 ± 7[b]
Androstenedione (ng/ml)	0.46	0.16	0.20	—	—	—	0.15	0.12	0.64 (0.27–0.99)[a]
Aldosterone (ng/ml)	2.77	6.81	5.10	—	—	—	—	—	2.51 (1.20–8.51)[a]
Compound S (ng/ml)	0.2	0.4	0.2	—	—	—	0.5	0.2	4.06 (1.52–18.7)[a]
DHA sulfate (ng/ml)	155	483	155	—	—	—	172	155	139 (20–411)[a]
Plasma renin (ng/ml)	5.6	>16	>16	>32	—	—	16	10.3	24.8 ± 8.4[b]
Urine cortisol (nmol/24 h)	—	<5	<10	<10	—	—	—	<10	–

[a]Sippel et al., 1980.
[b]Winters et al., 1974.

TABLE II. Tests With Exogenous Corticotropin "Synacthene" Cortisol Levels (ng/ml)

	HO	HO + 30 min	HO + 60 min
Day 15	12	27	31
Day 45	5	12	12

TABLE III. Basal and Stimulated Serum Levels of Pituitary Hormones

	Basal level	Maximum level after stimulation
LH m(IU/ml)	2.4	4.5
FSH (mIU/ml)	6.4	18.2
Prolactine (μIU/ml)	854	2548
TSH (μIU/ml)	2.2	9.5
GH (ng/ml)	7.8	21.3

The very low levels of plasma ACTH observed generally, and especially during the attacks of hypoglycemia when cortisol levels were also low, were indicative of a central defect. Both Carey [1985] and Ichiba and Goto [1983] carried out prolonged ACTH stimulation testing and provided additional evidence for a central defect. We did two short stimulation tests with exogenous corticotropin, but the increase in the cortisol levels were slight. The changes in compound S and ACTH levels observed during testing with metopyrone were not significant. Had corticotropin releasing hormone (CRH) been available we should have attempted to assess whether the deficiency could be localized to the hypothalamus or the pituitary [Carey, 1985]. This defect is very likely isolated, given the results of the study of the other hypothalamo-pituitary functions and the clinical evolution after replacement with just hydrocortisone and fludrocortisone.

The clinical manifestations of the illness can appear during the first years of life [Stacpoole et al, 1982; Lucking and Willig, 1975; Hung and Migeon, 1968; Aynsley-Green et al, 1978] or later [Aynsley-Green et al, 1978; Cleveland et al, 1960; Odell et al, 1960] but may also occur very early, as in the case of our first patient, who died at age 14 hours. In the two cases reported by Ichiba and Gotto [1983] the infants also had hypoglycemia in the neonatal period: one died at age 5 months and the other was admitted to hospital at 20 days with seizures. The association of neonatal cholestasis and hypoglycemic episodes, while not establishing whether the defect is central or adrenal, is, as illustrated in our second case report, a good indication of cortisol deficiency [Leblanc et al, 1981; De luca et al, 1986]. The autopsy of the first infant showed adrenal hypoplasia as the cause of death. As a result we were able to make a prenatal diagnosis in the subsequent pregnancy. In the interests of genetic counselling, we suggest that autopsies be made on all newborn infants who die under unexplained circumstances. Maternal plasma estriol assays during pregnancy can be invaluable since a decrease in levels indicates fetal adrenal insufficiency, whether its origin is central or adrenal [Hensleigh et al, 1978]. It is essential to make a prenatal diagnosis to achieve effective management of these newborn infants. Adrenal insufficiencies are usually asymptomatic during the first days of life. The genetic evidence strongly suggests that this deficiency, observed in a brother and sister and not in their parents, is transmitted as an autosomal recessive trait. The observations of Ichiba and Goto [1983], who reported the case of two affected sisters, are consistent with this mode of transmission.

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