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Repeating ACTH Stimulation Test Is Necessary to Diagnose ACTH Deficiency in Neonatal Hypopituitarism With Initial False Negative Result

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Introduction

Low-dose 1-μg adrenocorticotropic hormone (ACTH) stimulation test has generally been the test of choice to evaluate adrenocortical function in neonates with suspected ACTH deficiency. There are limited data about its sensitivity in diagnosing central adrenal insufficiency in this age group. We urge caution interpreting cortisol results in the neonatal period and to maintain a high degree of suspicion for false negative testing.

Case Presentation

Case 1

A term female infant was evaluated at age 9 days for hypernatremia and diagnosed with diabetes insipidus, optic nerve hypoplasia, and septo-optic dysplasia. Pituitary testing showed normal thyroid function (free T4 1.1 ng/dL, thyroid-stimulating hormone [TSH] 2.52 μIU/mL) and peak cortisol of 36.2 μg/dL (defined as normal >18 μg/dL) on a low-dose 1-μg ACTH stimulation test.[1] The infant was later admitted at age 2 months for jaundice and hypoglycemia. Repeat ACTH stimulation test showed baseline cortisol <1 μg/dL, with low peak cortisol of 8.6 μg/dL (see Table 1). Repeat thyroid tests showed borderline low free T4 of 0.7 ng/dL (normal 0.7-1.8) and TSH of 3.4 μIU/mL. Growth hormone was 5.8 ng/mL at the time of hypoglycemia. She was then started on hydrocortisone, followed by levothyroxine and growth hormone replacement.

Case 2

A term female infant was evaluated at age 10 days for persistent hypoglycemia. A low-dose 1-μg ACTH stimulation test revealed a baseline cortisol of 10.9 μg/dL with peak cortisol of 29.6 μg/dL. Thyroid function testing at age 8 days showed free T4 0.6 ng/dL and TSH 4.43 μIU/mL. Growth hormone level was 2.8 ng/mL at the time of hypoglycemia. Levothyroxine and growth hormone replacement were started. A brain magnetic resonance imaging scan revealed pituitary hypoplasia with tiny pituitary stalk and ectopic pituitary bright spot, confirming diagnosis of congenital hypopituitarism. Scheduled repeat morning cortisol was <1 μg/dL at age 21 days. Repeat ACTH stimulation test performed at age 22 days showed a baseline cortisol of 2.5 μg/dL and low peak cortisol of 11 μg/dL. The patient was then started on hydrocortisone, in addition to the levothyroxine and growth hormone.

Discussion

In these 2 cases, a robust cortisol response on initial ACTH stimulation test obtained on 9 to 10 days of life provided a falsely reassuring assessment of the hypothalamic–pituitary–adrenal axis. Repeat testing showed an inadequate cortisol response, necessitating adrenal replacement therapy. One possible mechanism for this phenomenon is due to adequate adrenal reserve that produces a high cortisol response to exogenous ACTH during the immediate postnatal period. How infants with congenital ACTH deficiency may transiently possess adequate adrenal reserve may be explained by the following brief review of normal fetal gland development.

In the normal fetus, the majority of fetal corticotropin releasing hormone (CRH) is derived from the placenta.[2] In studies by Sirianni et al using human fetal adrenal

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Table 1. ACTH Stimulation Test Results (1 µg Cosyntropin).

	Patient 1	Patient 2
Age at first ACTH stimulation test	9 days	10 days
Baseline cortisol[a]	2.8	10.9
Stimulated cortisol[a] 20 minutes	36.2	26.9
Stimulated cortisol[a] 40 minutes	27.1	29.6
Baseline ACTH[b]	N/A	11
Age at second ACTH stimulation test	2 months	3 weeks
Baseline cortisol[a]	<1	2.5
Stimulated cortisol[a] 20 minutes	8.7	11
Stimulated cortisol[a] 40 minutes	8.3	11
Stimulated cortisol[a] 60 minutes	N/A	5.9
Baseline ACTH[b]	26	N/A

Abbreviation: ACTH, adrenocorticotropic hormone.
[a]Cortisol levels in µg/dL.
[b]Normal ACTH 6-48 pg/mL.

samples taken from the definitive and transitional zones, placental CRH directly induces transcription of fetal adrenal steroidogenic enzymes and cortisol production.[3] In contrast to the mature adrenal, in the fetus a positive feedback loop increases both cortisol and CRH concentrations.[2,4] CRH levels therefore increase in the third trimester. Cortisol and dehydroepiandrosterone sulfate (DHEAS) levels also increase late in gestation and may affect the timing of parturition. DHEAS is converted into estrogen, which may promote myometrial contractility.[3,4] Cortisol is important later in gestation because it promotes organ development, including lung maturation in the fetus.[5] CRH binding protein levels decrease in both the mother and fetus in late gestation, leading to increases in free cortisol.[3] This creates a feed-forward loop of increasing cortisol and CRH until delivery. The fetal adrenal gland weighs the same as the adult adrenal gland at birth, underscoring its importance to fetal development and parturition.[4]

In contrast to the mature adrenal, fetal ACTH levels decrease as the fetal adrenal increases in size during advanced pregnancy in normal fetus.[5] This indicates that ACTH is not the primary stimulator of adrenal development in utero and points to the importance of placental CRH. Additionally, maternal ACTH does not cross the placental–fetal blood barrier.[6,7] Cortisol crosses the placental barrier, but is partially degraded by 11-β-hydroxysteroid dehydrogenase enzyme, type 2.[8] About one third of variations in fetal cortisol levels are attributable to maternal cortisol.[2]

After birth, the fetal zone of the adrenal that produces DHEAS during pregnancy undergoes involution.[3,9] Cortisol is produced in the transitional zone, which is believed to give rise to the postnatal zona fasciculate.[10]

In newborns with congenital hypopituitarism with ACTH deficiency, there is a normal upregulation of fetal steroidogenic enzymes secondary to placental CRH stimulation, leading to fetal adrenal maturation and steroidogenesis, including cortisol production. This would give rise to adequate adrenal reserve, allowing a temporary normal cortisol response to synthetic ACTH injection after birth. After a period of lack of stimulation by pituitary ACTH deficiency (and withdrawal of placental CRH stimulation), the cortisol-producing zona fasciculata is unable to respond normally. This leads to low cortisol response on a repeat ACTH stimulation testing, which was seen as early as 3 weeks of age in Case 2. This report raises awareness of falsely normal adrenal function testing during postnatal period in infants with congenital hypopituitarism. Clinicians should have high index of suspicion for ACTH deficiency even after a normal initial ACTH stimulation test in infants with other pituitary hormone deficiencies or ongoing hypoglycemia despite growth hormone replacement. This report highlights the importance of repeating ACTH stimulation testing within 3 to 4 weeks after initial testing for timely diagnosis of secondary adrenal insufficiency.

Declaration of Conflicting Interests

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