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Adrenal Insufficiency in Newborns with Congenital Diaphragmatic Hernia

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Abstract

Newborns with congenital diaphragmatic hernia frequently have catecholamine-unresponsive systemic hypotension and respiratory failure. We found that adrenal insufficiency frequently complicates the clinical course of infants with congenital diaphragmatic hernia and was associated with increased severity of illness.

Adrenal insufficiency (AI) is defined as the inadequate endogenous production of cortisol in response to an increased physiologic demand during periods of stress. AI and its association with vasopressor-resistant hypotension has been most widely studied in adult patients and older children.[1–3] However, AI may also complicate the clinical course of term infants with hypoxemic respiratory failure.[4] The potential role of AI in term newborns is poorly characterized, and in particular, there is little information available on the effects of AI in newborns with congenital diaphragmatic hernia (CDH). Moreover, studies examining adrenal insufficiency in newborns commonly depend on the adult literature for definitions of AI.

We have noted that respiratory failure and refractory systemic hypotension commonly complicates the early course of newborns with CDH. Therefore we suspected that AI could contribute to the severity of illness in these infants with CDH, who have a high risk of respiratory failure and hemodynamic instability leading to the use of extracorporeal membrane oxygenation (ECMO). We hypothesized that hypocortisolemia, as a marker of illness severity, would be associated with worse outcomes and impact the clinical course in infants with CDH.

Methods

We performed a retrospective cohort study using a database established to examine outcomes of outborn infants with congenital diaphragmatic hernia admitted to the Children's Hospital of Denver, a tertiary referral center for a 7-state region. Approval was obtained by the Colorado Institutional Review Board. The study period spanned the years January 1, 2002, to December 31, 2008. During this time period, 58 infants were admitted to The Children's Hospital with a diagnosis of CDH. We further limited the study population to those infants who were at least 35 weeks gestation, were admitted in the immediate neonatal period (<48 hours of age), and had not been treated with steroid supplementation before cortisol measurement.

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The primary outcome of our study was the finding of adrenal insufficiency during the infant's preoperative or immediate postoperative course (within 24 hours of surgery), which was considered to be the period of greatest stress.[3] Adrenal insufficiency was defined as a cortisol level <15 μg/dL, a threshold that has been used in numerous studies in the newborn and adult literature.[4,5] An infant was defined as being in the "low cortisol" group if a cortisol level was measured <15 μg/dL during the period of greatest stress and as being in the "high cortisol" group if the cortisol level remained ≥15 μg/dL during the period of greatest stress.

Other variables of interest included all cortisol levels measured during the patient's hospital stay, the timing of those levels, whether steroid supplementation was begun and over what time period, and whether supplementation was done before or after the lowest cortisol level. Other outcome measures included death, death or need for ECMO, length of time and type of ventilatory support needed, length of time and type of inotropic support needed, need for inhaled nitric oxide or pharmacologic paralysis, and hospital length of stay. Severity of illness measures included oxygenation index on admission and at its peak.

The diaphragmatic hernia was classified by its location (left or right), timing of surgery, patch repair versus primary closure, whether liver or stomach were in the defect at the time of surgery, polyhydramnios, and antenatal diagnosis. Demographic information included gestational age, birth weight, race/ethnicity, and other congenital anomaly or genetic diagnosis.

The data were analyzed with SAS 9.2 (SAS Institute, Cary, North Carolina). Differences between categorical and continuous variables were tested with the χ^2 tests and Kruskal-Wallis tests, respectively.

Results

Of the 58 infants with CDH admitted to the Children's Hospital, Denver, 6 infants were excluded for prematurity, 3 for admission after 48 hours, 7 were pretreated with steroids before their first cortisol level, and 8 did not have cortisol levels performed, leaving a study population of 34 infants.

Of the 34 infants included in the study, the overall survival rate was 73.5%, with survival rates in infants with isolated CDH of 84.6%. Eighty-two percent of the study population had cortisol levels <20 μg/dL, 67% had cortisol levels <15 μg/dL, and 65% had cortisol levels <10 μg/dL. When using a threshold level of <15 μg/dL to distinguish between "low" and "high" cortisol groups, the baseline cortisol level for the "low" cortisol group was performed at 0.9 ± 1.0 days, and the baseline cortisol level in the "high" cortisol group was performed at 0.7 ± 0.8 days ($P = .54$). An analysis of baseline cortisol levels showed that the "low" cortisol group had a mean value of 4.3 ± 2.7 μg/dL (median 3.7, range 1.0–11.0 μg/ dL), and the "high" cortisol group had a mean value of 20.0 ± 13.8 μg/dL (median 24.0, range 15.0–47.5; $P < .01$). All of the infants in the "low" cortisol group were given steroid supplementation and received treatment for 10.9 ± 7.0 days, and 71.4% of infants in the "high" cortisol group were treated with steroids, for a duration of 9.3 ± 7.0 days ($P = .45$).

Differences between the "low" and "high" cortisol groups are shown in Table I (available at www.jpeds.com). No significant differences were found between the 2 groups for gestational age, birth weight, sex, ethnicity, incidence of polyhydramnios, prenatal diagnosis, nor the existence of other anomalies.

When using <15 μg/dL to distinguish between the "low" and "high" cortisol groups, a greater number of infants in the "low" cortisol group had liver tissue in the defect, 68.4% compared with 28.6% ($P = .02$). No other significant differences are seen.

However, when using ≤ 15 μg/dL as the threshold, 1 patient was reclassified from the "high" to "low" cortisol group, and further differences became evident. Table II (available at www.jpeds.com) illustrates these differences in characteristics that define severity of illness between the "low" and "high" cortisol groups, with ≤ 15 μg/dL used as the cutoff. First, a significantly greater number of patients in the "low" cortisol group received steroid supplementation. More infants in the "low" cortisol group had liver identified in the defect, required epinephrine for vasopressor support, required high-frequency ventilation, and remained on inhaled nitric oxide for a longer period of time. No statistically significant differences were seen in survival or ECMO use in the 2 groups. Infants in the "low" cortisol group required a longer period of time to become stable for surgical repair, although this did not reach statistical significance.

Discussion

In this retrospective study of adrenal insufficiency in critically ill infants with CDH, we found that 67% of the study infants had a random stressed cortisol level < 15 μg/dL, commonly used as the threshold for relative adrenal insufficiency in the adult and neonatal literature.[4,5] Interestingly, we were able to show even greater differences in severity of illness when ≤ 15 μg/dL was used as a cutoff. Because the numbers in this study are small, classifying 1 patient as "low" instead of "high" had a marked impact on the results.

Using ≤ 15 μg/dL as the cutoff, infants in the "low" cortisol group demonstrated greater severity of illness, as these infants had liver tissue in the defect, increased number of days on inhaled nitric oxide, and a requirement for epinephrine and high-frequency ventilation. This suggests that use of a level of ≤ 15 μg/dL may provide greater sensitivity for this population. Because a large majority of the infants in both groups received steroid supplementation, this steroid treatment may have masked even greater disparities between the "high" and "low" groups, because treatment with cortisol would make the groups more similar.

Hydrocortisone supplementation has pharmacologic effects that improve hemodynamics; however, it is not as clear which infants warrant this treatment.[4,6,7] Major gaps exist in the literature regarding the exact criteria to define adrenal insufficiency, causing the incidence to vary depending on the definition used.[2] In addition, although some studies have examined adrenal insufficiency in term infants with respiratory failure or sepsis,[8,9] scant information is available on cortisol levels or adrenal insufficiency in infants with congenital diaphragmatic hernia.

Although a random stressed cortisol level of <15 μg/dL is commonly used to define adrenal insufficiency, wide variations persist in the literature regarding the threshold cortisol level that is adequate for stress,[2] and large studies determining serial cortisol levels in normal and sick newborns do not exist. In addition, caution must be exercised when interpreting a single cortisol value, because it is only 1 measure of the dynamic hypothalamic-pituitary-axis under stress.[10] Indeed, a limitation of our study was that cortisol measurements were not measured at standardized times.

Although several studies argue for the resulting change in cortisol level after the use of an adrenocorticotropic hormone (ACTH) stimulation test for the diagnosis of adrenal insufficiency,[1,11] others argue that using such a test, which was designed for use in an unstressed patient, is useless when the patient's stressful clinical condition serves as a stimulation test in its own right.[3] Indeed, Fernandez et al showed that stimulated cortisol

was no different in term and late preterm newborns despite increasing severity of illness.[8] In addition, the reproducibility of the ACTH stimulation test is also a concern.[12,13]

The mechanism of adrenal insufficiency in stressed newborns is unclear. Ng et al[14] used corticotrophin-releasing hormone to stimulate the entire hypothalamic-pituitary-adrenal axis in 137 very low– birth weight infants, divided into infants receiving inotropic support versus those who were not. Their results showed that the premature infants on inotropes had a greater response of ACTH, yet their adrenal gland was unable to counter with a corresponding increase in cortisol levels. They termed this faster maturation of the pituitary in relation to the adrenal gland as "transient adrenocortical insufficiency of the newborn." Although a similar study has not been replicated in term infants, Fernandez et al[8] did show low cortisol and low ACTH concentrations, but appropriate response to exogenous ACTH, in sick late preterm and term infants, suggesting secondary adrenal insufficiency, with a lack of adequate ACTH response during stress. Because we did not measure ACTH nor CRH concentrations in these infants with CDH, we were unable to clarify the mechanism.

The effects of steroid supplementation in premature infants may be very different from term newborns with CDH, and these effects have been poorly studied in both groups. The decision to initiate steroid supplementation, however, may carry some risks for a poor neurodevelopmental outcome. As stated above, cortisol replacement has been shown to have positive inotropic effects for infants with vasopressor resistant hypotension. However, Ng et al[14] have postulated whether a period of adrenal quiescence is important to prevent excessive steroid exposure to the developing brain in premature infants. Indeed, Aucott et al[15] found that in a group of 350 intubated extremely low birthweight infants, infants who had high cortisol values (>90% or >62.8 μg/dL in that particular group of infants) had significantly higher rates of mortality, intraventricular hemorrhage, bowel perforation, and retinopathy of prematurity. The infants with low cortisol levels had no increased risk of morbidity or death. Further studies are needed in both premature and term infants to evaluate long-term neurodevelopment outcomes in those infants treated in the newborn period with hydrocortisone supplementation.

In summary, AI often complicates the course of infants with CDH. We found that low cortisol levels, in particular, ≤ 15 μg/dL, were associated with increased severity of illness. Infants with CDH and respiratory failure should be evaluated for AI early in their course of treatment. Treatment of AI with steroid supplementation in infants with CDH and its short- and long-term benefits should be further evaluated with a randomized controlled trial.

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Glossary

ACTH	Adrenocorticotropic hormone
AI	Adrenal insufficiency
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation

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Table I

Comparison of characteristics between low and high cortisol groups, with <15μg/dL as threshold

Demographics	Low cortisol (n = 20)	High cortisol (n = 14)	*P*
Gestational age (weeks) *	38.1 ± 1.7	38.5 ± 1.7	.48
Birth weight (grams) *	2933 ± 317	2931 ± 595	.77
Infant sex = male	15 (75.0%)	9 (69.2%)	.50
Ethnicity = Hispanic	12 (60.0%)	11 (78.6%)	.25
Polyhydramnios	2 (10.0%)	0	.50
Prenatal diagnosis	8 (40.0%)	6 (42.9%)	.87
Location of hernia = left-sided	17 (85.0%)	12 (85.7%)	1.00
Other anomalies †	4 (20.0%)	4 (28.6%)	.70

* Presented as Mean ± standard deviation.

† Other anomalies included: coarctation of the aorta, congenital cystic adenomatoid malformation, multicystic kidney with hydrops.

Table II

Comparison of severity of illness between low and high cortisol groups, with ≤ 15μg/dL as threshold

Severity of illness	Low cortisol (n = 21)	High cortisol (n = 13)	*P*
Survived	14 (66.7%)	11 (84.6%)	.25
Placed on ECMO	8 (38.1%)	4 (30.8%)	.66
Treated with steroid supplementation	21 (100%)	9 (69.2%)	.02
Days of life until surgery *	6.1 ± 3.8	3.8 ± 3.4	.06
Patch repair	14 (66.7%)	5 (38.5%)	.11
Liver tissue in defect	14 (70.0%)	3 (23.1%)	.01
Oxygenation index on admission *	30.1 ± 26.6	29.2 ± 48.4	.16
Highest oxygenation index *	36.3 ± 27.9	31.5 ± 47.7	.12
Days on mechanical ventilation *	25.0 ± 25.2	29.1 ± 70.0	.06
Required high-frequency ventilation	16 (76.2%)	5 (38.5%)	.03
Required inhaled nitric oxide	15 (71.4%)	5 (38.5%)	.06
Days on inhaled nitric oxide *	33.4 ± 56.2	25.2 ± 71.4	.04
Days on pressor support *	9.8 ± 6.5	6.8 ± 7.0	.10
Required dopamine	20 (95.2%)	11 (84.6%)	.29
Required epinephrine	14 (66.7%)	4 (30.8%)	.04
Required paralysis (Pancuronium)	15 (75.0%)	6 (46.2%)	.09
Pneumothorax	6 (28.6%)	1 (7.7%)	.21
Hospital length of stay *	47.2 ± 64.2	50.8 ± 75.1	.41

* Presented as mean ± standard deviation.