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EDITORIAL

The challenge of defining relative adrenal insufficiency

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Defining relative adrenal insufficiency in preterm infants remains a significant challenge for neonatologists. The phenomenon of relative adrenal insufficiency in adults and children has been well described, with normal basal levels of cortisol, yet inadequate response to stress as documented by a blunted response to adrenocorticotropin hormone (ACTH) stimulation.[1–3] In preterm infants, numerous confounding factors make the definition more elusive. Preterm infants developmentally may have low basal cortisol levels in the absence of symptomatology,[4] and it is less clear what constitutes an appropriate stress response in the face of an acute illness, such as respiratory distress syndrome or sepsis.[5,6] Similarly, many of the symptoms of relative adrenal insufficiency, such as hypotension and electrolyte abnormalities, are common in this population, with many possible underlying etiologies.

In the paper by Hochwald *et al.*,[7] the authors approach this dilemma by performing an ACTH stimulation test shortly after birth to obtain cortisol values in preterm infants 29 weeks and less with varying degrees of illness. They used the symptom of hypotension as a clinical marker to differentiate those infants at highest risk for relative adrenal insufficiency, and thus define an inadequate response to ACTH in the face of clinical symptoms. Using this higher risk population to establish reasonable cut points for response to ACTH provides important data specifically relevant to this unique population. Although the authors acknowledge that hypotension is multifactorial and may or may not be due to relative adrenal insufficiency, the methodology allows a narrowing of the population to symptomatic infants where the definition is most relevant. A concern has previously been raised for attempting to base a definition of relative adrenal insufficiency on cortisol values obtained shortly after birth owing to the potential for suppression of the hypothalamic–pituitary–adrenal axis from maternal steroid administration.[8,9] The population presented in this study has predominantly been exposed to prenatal steroids (over 90% in both groups), allowing for a realistic evaluation comparable to the dilemma confronted by clinicians. Clearly, there is an advantage to an early diagnosis of relative adrenal insufficiency to allow appropriate clinical decision making, as shown in this study by approximately one third of the infants receiving inotropes in the first 24 h of life.

Other authors have used hypotension as a potential marker for relative adrenal insufficiency. Ng *et al.*[10] examined ACTH stimulation tests on day 7 and day 14 of life, and found that infants with a low response to ACTH on day 7 were more likely to require inotropic therapy in the first 2 weeks of life. Basal cortisol levels alone were as predictive as the post ACTH stimulation cortisol results. Although Ng was able to document that an abnormal cortisol response was predictive of need for inotropic support, the information was clinically not timely as much of the need for inotropic therapy preceded the timing of the testing. In a multicenter trial of prophylaxis of relative adrenal insufficiency in extremely low birth weight infants, where infants were randomized to receive hydrocortisone therapy for the first 2 weeks of life, there was no difference in the need for inotropic support or the subsequent incidence of bronchopulmonary dyplasia between the treated infants compared with controls.[11] When attempting to define relative adrenal insufficiency by examining cortisol values from this large cohort, low cortisol values at 24–48 h of life or 7–10 days of life did not predict inotropic support. Similarly, cortisol values at these two time points were not associated with bronchopulmonary dysplasia. Confounding our understanding of relative adrenal insufficiency is the difficulty of differentiating two groups of infants: those infants with inappropriately low cortisol values who may be suffering adverse effects owing to the deficient levels of the hormone, and those with developmentally appropriate low cortisol values related to prematurity and ongoing development of the hypothalamic–pituitary–adrenal axis, whose symptoms are attributable to other etiologies such as hypovolemia or sepsis.

Do we need a definition for relative adrenal insufficiency in this population of very low birth weight infants? One could argue that our treatment decisions may occur independently of having more definitive criteria for relative adrenal insufficiency. Hydrocortisone therapy is an effective adjunct treatment for pressor-resistant hypotension, and steroid therapy is well known to cause an increase in blood pressure.[12–14] But hydrocortisone therapy is not without risks. Hydrocortisone therapy has been shown to be associated with gastrointestinal perforations, particularly in infants with high cortisol concentrations.[11,15] There is an additional concern of drug interaction, with indomethacin use in conjunction with hydrocortisone treatment being an additional risk factor for gastrointestinal perforation.[11] Thus, hydrocortisone treatment in infants who do not have relative adrenal insufficiency, especially those with high cortisol concentrations, should be considered only with great caution.

Studies have suggested an association of bronchopulmonary dysplasia and relative adrenal insufficiency.[16,17] Despite this, prophylaxis of all extremely low birth weight infants did not result in a decrease in bronchopulmonary dysplasia. It remains unclear

whether having a better definition for relative adrenal insufficiency would allow targeting of treatment to a high-risk group. Bronchopulmonary dysplasia is an end result of multiple factors promoting inflammation in a vulnerable population,[18] and thus it is unclear if hydrocortisone treatment alone, beginning at what age and for what duration, is sufficient to impact the evolution of this chronic disease.

Therapies given to preterm infants should always be scrutinized for impact on long-term outcomes. To date, hydrocortisone therapy has not been associated with adverse neurodevelopmental outcomes.[19–21] There is also no evidence that relative adrenal insufficiency alone is associated with adverse long term-outcomes.[22] It likely that there is a subset of preterm infants with a more developmentally appropriate form of relative adrenal insufficiency, who may not require intervention or therapy that cannot be distinguished from those infants in whom relative adrenal insufficiency is a contributor to ongoing pathology. The later is the group who may benefit from appropriate treatment with hydrocortisone. Abnormal cortisol values alone, both basal and post ACTH stimulation, are not sufficient indication for requiring hydrocortisone therapy in the absence of symptoms. Further investigation is needed to continue to guide our understanding and treatment of relative adrenal insufficiency in very low birth weight infants.

Conflict of interest

The author declares no conflict of interest.

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