

Transient Adrenocortical Insufficiency of Prematurity

There have been several reports of very low birthweight (VLBW) infants who experience systemic hypotension that is unresponsive to volume expansion and inotropic agents, but very responsive to corticosteroids. Ng et al have performed a prospective study of the pituitary adrenal axis in 137 VLBW infants, of whom 78 had refractive hypotension (group 2) and 59 remained normotensive (group 1). Human corticotropin releasing hormone (hCRH) (1mcg/kg IV bolus) was administered between 08:00 h and 10:00 h on days 7 and 14 of life. Serial samples for ACTH and cortisol were obtained at baseline, 15, 30, and 60 minutes after injection. Inclusion criteria were gestational age <32 weeks, birthweight <1500 grams, no postnatal systemic or inhaled corticosteroids, and an indwelling arterial line. Exclusion criteria were persistent hypoglycemia, systemic infection, necrotizing enterocolitis, or major surgery.

Results from groups 1 and 2 combined, showed that basal and peak cortisol and change in cortisol over the first 30 minutes after hCRH injection correlated significantly with the lowest recorded BP during the first 14 days of life and the BP measured at the initiation of the study on day 7. In contrast, ACTH levels on days 7 and 14 and cortisol on day 14 did not correlate with the lowest BP. Serum cortisol levels (after hCRH) on day 7 correlated negatively with the total dose of inotropic agents, while plasma ACTH levels were positively correlated.

The ACTH response to hCRH was significantly greater on both days 7 and 14 in group 2 infants, but cortisol responses were greater in group 1 than group 2 on day 7. Day 14 cortisol responses were similar in both groups. The authors state that this study demonstrates adrenal hyporesponsiveness in group 2 infants at day 7. Those

were the infants with significant hypotension requiring inotropic agents. By day 14, the transient nature of this endocrine dysfunction was evident as there were no significant differences between the two groups of infants. The authors term this dysfunction, transient adrenocortical insufficiency of prematurity or TAP.

Ng PC, Lee CH, Lam CWK, et al. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F119-F126.

Editor's Comment: *This is an interesting, well-conducted prospective study of a problem that is relatively common in many NICUs. Neonatologists have been using small doses of hydrocortisone in premature babies with hypotension refractory to inotropic agents for some time. However, the definition of the defect responding to this non-replacement, non-stress level of hydrocortisone administration has not been clarified. Ng et al have provided a clear demonstration that these infants have a transient adrenal, not pituitary immaturity, which requires hydrocortisone administration. They note that a previously reported trial of hydrocortisone versus dopamine for the routine treatment of hypotension failed to confirm its benefit. This is not surprising, given the distinct differences in the 2 groups of infants studied. A short course of hydrocortisone in premature infants with hypotension refractory to inotropic agents seems a reasonable therapeutic maneuver. Data now show that these corticosteroids do not need to be given for prolonged periods.*

William L. Clarke, MD

Long-term Mortality in the U.S. of Pituitary-derived Growth Hormone Recipients

Mills and colleagues from the NIH, FDA, and CDC presented long-term mortality data on patients who received pituitary-derived growth hormone (pGH) from the National Hormone and Pituitary Program (NHPP) during the years 1963–1985. Data through December 1996 were obtained for 6107 of the 6272 children who received pGH. Information regarding the reason for pGH treatment and the specific cause of death was obtained. Death certificates were reviewed in all but 3 instances. Causes of GH deficiency were categorized as idiopathic, organic (including tumor-related or non-tumor related—eg septo-optic dysplasia, histiocytosis, trauma, etc.), or other (including unknown causes, neurosecretory defect, Turner syndrome, etc.). Subjects were classified as having isolated GH deficiency, multiple hormone deficiencies, unspecified deficiency (insufficient information to classify), or not applicable (non-GH deficient). Subjects with adrenal insufficiency and/or a history of hypoglycemia were identified.

Observed mortality was compared to that expected in a similar US cohort. Relative risks were calculated and a proportional hazards model constructed.

There were 433 deaths from 1963–1996 compared to an expected number of 114. Thus the overall risk of death was nearly 4 times that of the general population (RR, 3.8; 95% CI, 3.4–4.2; $p < .0001$). Only subjects with idiopathic isolated GH deficiency had a death rate similar to that expected for the population at large. The highest risk categories included patients with either benign or malignant tumors, adrenal insufficiency, and hypoglycemia. Tumors, hypoglycemia, adrenal insufficiency, and multiple hormone deficiencies were demonstrated to be significant, independent risk factors by proportional hazards analysis. There were 26 deaths from Creutzfeldt-Jakob disease (CJD). Two deaths were from colorectal cancer; one of whom had familial polyposis and the other had received radiation for a CNS tumor. One subject died from Hodgkin's disease. Thus, the reported associations between GH therapy and colorectal

cancer or Hodgkin's disease were not observed.

Of interest is that 24.5% of the deaths were sudden and unexpected. Of those, multiple hormone deficiencies were present in at least 74%, a history of hypoglycemia was present in 31% and seizures had occurred in 52%. Deaths followed a clinical course suggestive of adrenal insufficiency in 56% of deaths. Sudden unexpected death was also associated with the presence of a medical problem other than isolated GH deficiency—craniopharyngioma (24%) or other intracranial tumors (14%). Hypoglycemia in children was associated with a 9 fold increase in risk. The death rate in those with adrenal insufficiency remained stable as children aged.

The authors emphasized 3 findings. First, hypoglycemia was an important risk factor for death, which decreased as the children aged and presumably could identify and treat their own symptoms. Second, tumors were an important cause of death, even though the risk of colorectal cancer, Hodgkin's disease and overall cancer deaths were not increased. Third, adrenal insufficiency was an unexpected high-risk factor leading to death even in adulthood. They stated that increased steroid doses for even supposedly trivial infections was important as 30 of these 35 subjects were found dead or comatose and most likely died of unrecognized or inadequately treated adrenal insufficiency.

Mills JL, Schonberger LB, Wysowski DK, et al. Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. *J Pediatr* 2004;144:430-436.

First Editor's Comment: *This report presents some alarming and some re-assuring information. That patients who had received pGH have a markedly increased relative risk of dying is alarming. That the cause of their deaths, in many instances could be prevented by appropriate glucocorticoid administration for rather trivial infections suggests that endocrinologists are not teaching*

or reminding patients of the importance of increasing their medications or seeking medical assistance at the first sign of infection. The reassuring news is that there does not appear to be an increased risk of colorectal cancer, Hodgkin's disease or other cancers in this cohort. Furthermore, there have been no new cases of CJD in subjects who began pGH treatment after 1977.

These data are interesting and compelling and deserve to be read by those who care for these children. At quick glance, it might appear that pGH administration was a dangerous treatment. On closer inspection, the facts are much friendlier. One can anticipate discussing these findings with parents of these patients.

William L. Clarke, MD

Second Editor's Comment: *This is an important paper which clearly documents higher mortality risks of hypopituitary patients and the surprisingly high number of unexpected sudden deaths. The concern with CJD is justified and requires continuous surveillance, but there isn't much we can do to prevent it in those who harbor the prion. However there is a lot we must do when treating hypopituitary patients to prevent unexpected fatalities. Adrenal insufficiency must be aggressively treated particularly in patients who vomit when ill. It is not clear why the patients in this report failed to do so, but it is clear that more emphasis is needed so patients receive appropriate steroid replacement during periods of stress. Familiarity breeds complacency—or so it seems. However, there were 20 sudden deaths in patients without adrenal insufficiency. The possibility that uncontrolled diabetes insipidus played a role should also be kept in mind, particularly when oral DDAVP therapy may not be effective, such as when a patient vomits.*

Fima Lifshitz, MD

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