Assessment of Adrenal Function in the Initial Phase of Meningococcal Disease

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Assessment of Adrenal Function in the Initial Phase of Meningococcal Disease

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ABSTRACT. *Objective.* **To determine the status of the hypothalamic-pituitary-adrenal axis in children who had meningococcal disease and were admitted to 2 regional pediatric intensive care units.**

Methods. **Sixty-five children (34 boys; median age: 2.5 years; range: 0.2–15 years) had cortisol and adrenocorticotropic hormone (ACTH) levels measured on admission, then at 8 AM and 8 PM during the next 48 hours. At 48 hours, a low-dose short Synacthen test (LDST) (500 ng of 1–24 corticotropin/m^2) was performed in 42 patients (19 boys). Normal ranges for 8 AM cortisol and ACTH levels in unstressed children were 140 to 500 nmol/L and 2 to 11.3 pmol/L, respectively. Adrenal insufficiency (AI) was defined as a peak cortisol <500 nmol/L on the LDST or an 8 AM cortisol value <140 nmol/L.**

Results. **Five (7.7%) of the 65 children died, including 1 with primary AI. Cortisol levels were elevated on admission (median: 1122 mmol/L; range: 65–2110 nmol/L) with 81% of values more than the 8 AM normal range. The median ACTH level on admission was within the 8 AM normal range, but 40% of values were more than the 8 AM normal range. However, 7% and 8% of cortisol and ACTH values, respectively, were less than the normal range. Both cortisol and ACTH levels fell thereafter and showed no diurnal variation during the 48-hour profile. Six (14%) of the 42 failed the LDST. These patients had significantly lower mean 8 AM cortisol values than those with a normal peak value on the LDST. Five additional patients who did not have the LDST had 8 AM cortisol values <140 nmol/L. In the diagnosis of AI, the sensitivity of the 8 AM mean cortisol value at a cutoff of 400 nmol/L, judged against the LDST, was 83%; the specificity was 81%.**

Conclusions. **During the initial phase of meningococcal disease, raised cortisol and ACTH levels indicate an appropriate stress response within the hypothalamic-pituitary-adrenal axis. However, a substantial subpopulation (11 [16.9%] of 65) has evidence of adrenal dysfunction during this period. Morning cortisol values in the initial phase of meningococcal disease could be used as a potential early index of AI.** *Pediatrics* **2002;110:563–569; *adrenal insufficiency, septic shock, meningococcal septicemia, low-dose ACTH test.***

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ABBREVIATIONS. AI, adrenal insufficiency; ACTH, adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal (axis); LDST, low-dose short Synacthen test; PICU, pediatric intensive care unit; GMSPS, Glasgow Meningococcal Septicemic Prognostic Score; TNF, tumor necrosis factor; IL, interleukin; SD, standard deviation.

Meningococcal disease remains a leading cause of death in childhood and is the third most common cause of death in children outside infancy (after accidents and malignancy).[1] In the United Kingdom, there were 2661 notifications of meningococcal disease in 1998, with 210 deaths (mortality 7.8%) (personal communication, Public Health Laboratory Service Communicable Disease Surveillance Centre, United Kingdom). Both the incidence and the significance of any associated adrenal insufficiency (AI) contributing to increased morbidity and mortality in meningococcal disease remain unclear. Cortisol levels are generally elevated in septic shock[2,3]; however, low cortisol levels have been demonstrated in meningococcal disease,[2,4–8] suggesting AI. This was associated with bilateral adrenal hemorrhage.[2,4,6] AI has also been demonstrated in septic shock in both adults[9–14] and children.[15] In septic shock, the incidence of absolute AI, as defined by cortisol levels below 150 nmol/L, is <1%,[3,12,16] but relative AI, as assessed by a suboptimal response to the short Synacthen test, is more common, ranging between 24% and 66%, depending on the interpretation of the short Synacthen test.[9,12,16] However, it can be difficult to interpret both cortisol values and the response to the short Synacthen test in stressed patients with septic shock. This point is highlighted well by 2 recent studies that assessed the incidence of AI in septic shock in children. In one study, in which AI was defined as a post-Synacthen cortisol increment of <200 nmol/L, the incidence of AI was 52%.[15] In the second study, admission cortisol and adrenocorticotropic hormone (ACTH) levels were measured in children with meningococcal disease. The authors concluded that AI was probably uncommon.[17] Therefore, both the incidence and the methodology for the early detection of AI in meningococcal disease remain undefined. Corticosteroids have been used in the treatment of meningococcal disease, both to improve the audiologic and neurologic outcome in meningococcal meningitis[18] and to improve survival and outcome in meningococcal septic shock. Both indications for corticosteroid use have been the subject of much debate, however. High-dose cortico-

steroids have not been shown to reduce mortality in septic shock.[19–22] Recently, there has been renewed interest in the treatment of septic shock with physiologic stress doses of corticosteroids for relative AI in both adults[9,10,23–25] and children.[15] The aim of this study, therefore, was to assess the status of the hypothalamic-pituitary-adrenal (HPA) axis, using both cortisol profiles and the low-dose short Synacthen test (LDST), and also to define a normal stressed cortisol value in all patients in the initial phase of meningococcal disease.

METHODS

Children with meningococcal disease were enrolled consecutively between February 1997 and April 1998 at the Manchester Children's Hospitals pediatric intensive care units (PICUs) and between March 1997 and November 1997 at the Royal Liverpool Children's Hospital PICU. All patients who were admitted with meningococcal disease were eligible for recruitment. However, some patients were not recruited as a result of clinical circumstance or of parental wish not to participate. The local research ethics committees of both hospitals had approved the study, and informed consent was obtained.

Meningococcal disease was defined as the presence of infection by *Neisseria meningitidis* as confirmed by blood culture, throat swab, serology, or polymerase chain reaction. Each child was assessed on admission using the Glasgow Meningococcal Septicemic Prognostic Score (GMSPS).[26] The GMSPS can be performed rapidly and is designed to predict outcome in meningococcal septicemia.[27,28] Assessment of disease severity was further defined by the amount of resuscitative fluids given within the first 48 hours of admission, the duration of inotropic support, the amount of positive pressure ventilation, and PICU stay in days. In each category, patients were assigned to 1 of 3 groups (Table 1). The levels of intervention that defined the most severe group were set to include approximately 10% of the cases.

Sixty-five children (34 boys; median age: 2.5 years; range: 0.2–15 years) had cortisol and ACTH levels measured on admission, then at 8 AM and 8 PM during the next 48 hours. At 48 hours, an LDST (500 ng of 1–24 corticotropin/m^2; CIBA Laboratories, Horsham, United Kingdom) was performed in 42 children (19 boys, 1 death). Blood samples were taken at 0, 10, 15, 20, 25, 30, and 45 minutes; kept on ice with serum separated immediately; and stored at −70°C for later measurement of cortisol. Results thus were not available to the clinicians during the acute phase of the meningococcal disease.

Serum cortisol was measured using the Immuno 1 automated analyzer (Bayer Diagnostics, Newbury, Berks, United Kingdom). All samples from individual patients were analyzed sequentially in the same batch to minimize analytical variability. The assay consistently reveals a between-batch coefficient of variation of 6.5%, 6.3%, and 4.9% at mean cortisol levels of 77, 480, and 1440 nmol/L, respectively. Serum ACTH was assayed using an immunoradiometric kit supplied by Nichols Institute Diagnostics (Newport, Essex, United Kingdom). Each sample was analyzed in duplicate. The between-batch coefficient of variation was 6% at a mean ACTH concentration of 10 pmol/L and 5% at a mean of 92 pmol/L. The laboratory subscribes to the UK National External Quality Assessment Scheme for both serum cortisol and ACTH. Measured against the all laboratory trimmed mean value, the serum cortisol assay manifests a 6-month running mean bias of −7.2%, whereas that of the ACTH assay is 9.9%. The normal ranges, as defined by our laboratory, in unstressed children for morning cortisol and ACTH values were 140 to 500 nmol/L and 2 to 11.3 pmol/L, respectively.

AI was defined as a peak cortisol value on the LDST of <500 nmol/L or an 8 AM cortisol value of <140 nmol/L. When steroid therapy had been given at the discretion of the supervising clinician, the patient was excluded from the study.

To test the utility of an 8 AM cortisol in predicting response to the LDST, we assessed sensitivity and specificity over the range of cortisol values. An 8 AM cortisol value of 400 nmol/L gave the highest values of sensitivity and specificity. Sensitivity was defined as the number of children with cortisol values below the cutoff as a percentage of those who failed the Synacthen test; specificity was defined as the number of children with cortisol values above the cutoff as a percentage of those who passed the Synacthen test.

Statistical analysis was performed using SPSS Version 7.5.1 statistical software (SPSS, Inc, Chicago, IL). Mean differences were calculated using the independent samples *t* test and relationships between variables assessed by Pearson or Spearman's correlation. ACTH values were log transformed for analysis. $P < .05$ was considered significant.

RESULTS

During the study period, a total of 86 cases of meningococcal disease were admitted to the PICUs at Manchester and Liverpool (Fig 1). ACTH and cortisol profiles were obtained in 68 children. Three children were excluded from the study because hydrocortisone therapy had been commenced. One of these children died of overwhelming septicemia. A total of 65 children were therefore enrolled into the study (34 boys; median age: 2.5 years; range: 0.2–15 years). Five (7.7%) of the 65 children died. During the study period, there were a total of 8 deaths out of the 86 cases of meningococcal disease (mortality: 9.3%). Three of the 5 deaths in the study cohort were attrib-

TABLE 1. Disease Severity Assessment*

Group Definition	8 AM Mean Cortisol	Admission ACTH	Peak Cortisol on LDST
Colloid (mL/kg) in first 48 h			
<150	21	13	13
≥150 <250	25	18	22
≥250	6 (11%)	3 (9%)	6 (15%)
Duration of inotropes (h)			
<48	15	8	8
≥48 <150	30	22	27
≥150	4 (8%)	0	4 (10%)
Duration of ventilation (h)			
<50	11	9	4
≥50 <180	36	25	32
≥180	4 (8%)	0	4 (10%)
PICU stay (h)			
<100	19	13	10
≥100 <200	27	21	25
≥200	5 (10%)	0	5 (12.5%)

* Values indicate the number of patients in each subset. Values in brackets represent the percentage of the group in the most severe category.

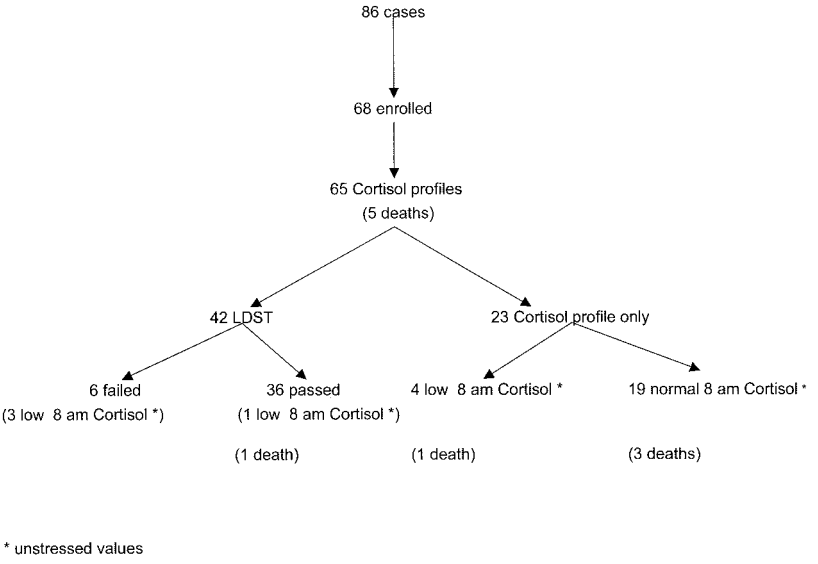

Fig 1. Flow chart for the children enrolled into this study, showing investigations performed and highlighting groups in which deaths occurred.

utable to meningitis with raised intracranial pressure; 2 were the result of overwhelming septicemia. One of these children had evidence of primary AI (adrenal gland failure) with a raised ACTH of 71.7 pmol/L and a low cortisol of 56 nmol/L. The LDST (500 ng/m^2 1–24 corticotropin) was performed in 42 children at 48 hours (19 boys, 1 death).

Cortisol and ACTH Profiles

Cortisol levels were elevated on admission (median: 1122 nmol/L; range: 65–2110 nmol/L) with 81% of cortisol values greater than the 8 AM normal range. The median ACTH level on admission (median: 8.7 pmol/L; range: 0.7–174.5 pmol/L) was within the 8 AM normal range, but 40% of values were greater than the 8 AM normal range. However, 7% and 8% of cortisol and ACTH values, respectively, were less than the 8 AM normal range. Both cortisol and ACTH levels fell thereafter and showed no diurnal variation during the 48-hour profile. Fifty-four percent and 6% of 8 AM cortisol and ACTH values remained greater than the 8 AM normal range, whereas 7% and 36% of values were less than the 8 AM normal range (Figs 2 and 3). Eight of the 65 children (12.3%) had 1 or more

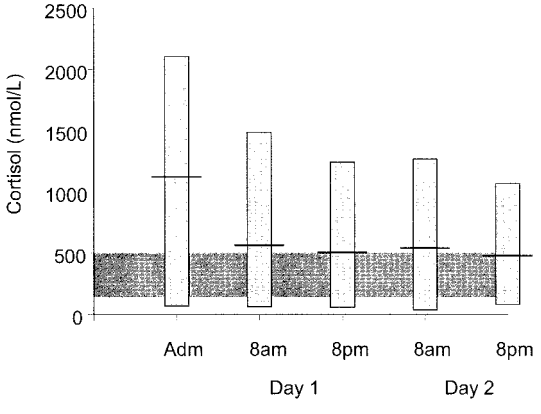

Fig 2. Cortisol profile in the initial phase of meningococcal disease. The median and the range at each time point are shown. The shaded box represents the normal range for cortisol in unstressed children (140–500 nmol/L).

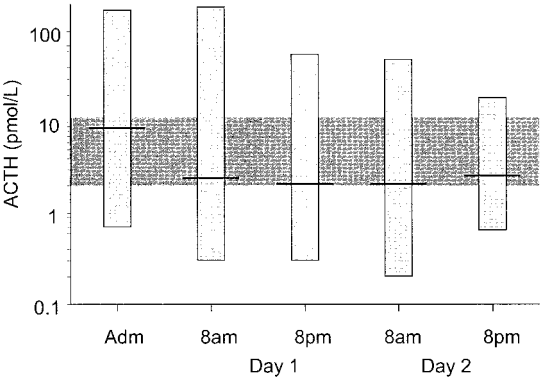

Fig 3. ACTH profile in the initial phase of meningococcal disease. The median and the range are shown. The shaded box represents the normal range for ACTH in unstressed children (2–11.3 pmol/L).

cortisol values less than the 8 AM normal range for unstressed children (<140 nmol/L). The time of the child's admission did not significantly affect the admission ACTH or cortisol value. There was no difference in the ACTH or cortisol profile between the genders. Children who were younger than 2 years had significantly higher mean 8 AM cortisol (720 ± 395 nmol/L) and ACTH values on day 1 (4.2 ± 3.3 pmol/L) than those who were older than 2 years (cortisol: 476 ± 239 nmol/L [P = .009]; ACTH: 2 ± 2.5 pmol/L [P = .01]). There were no significant differences in ACTH or cortisol values between children who died and those who survived. However, 1 child who died had evidence of primary AI as indicated above. Another 3 of the children who died also had borderline low 8 AM cortisol values between 158 to 214 nmol/L. In the whole group, there was a significant correlation between the mean 8 AM cortisol value and both the ACTH value on admission (r = 0.47; P = .004) and the mean 8 AM ACTH value (r = 0.37; P = .004; Fig 4). However, Fig 4 also shows that 15 children (36% of the group) had an ACTH level less than the normal range. These children had significantly lower cortisol values than those with normal ACTH values.

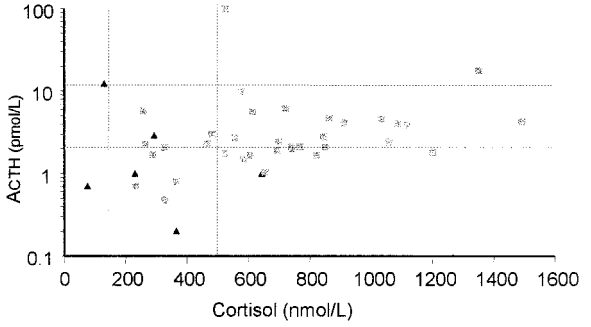

Fig 4. Mean 8 AM cortisol versus mean 8 AM ACTH. Dotted lines represent the normal ranges in unstressed children for cortisol and ACTH. Squares represent patients whose peak cortisol on the LDST was >500 nmol/L; triangles represent patients who failed the LDST (peak cortisol <500 nmol/L).

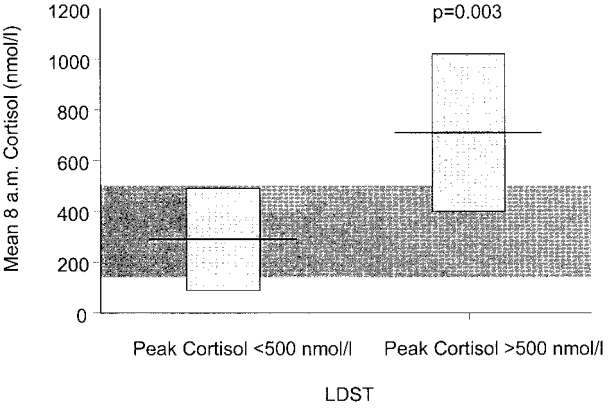

Fig 6. Mean 8 AM cortisol values versus peak cortisol response on the LDST. Horizontal bars and boxes represent mean ± 1 SD. The shaded box represents the normal range for cortisol in unstressed children (140–500 nmol/L).

LDST

Six patients (14%) failed the LDST (peak cortisol <500 nmol/L; Fig 5). There was no difference in the response to the LDST in relation to gender, age, or time of admission. The child who died had a normal peak cortisol value on the LDST. There was no correlation between the response to the LDST and the mean 8 AM log ACTH values. Children who had a peak cortisol value on the LDST of <500 nmol/L had significantly lower mean 8 AM cortisol values (290 ± 203 nmol/L) than those with a peak cortisol value >500 nmol/L (710 ± 313 nmol/L, $P = .003$; Fig 6).

The sensitivity of the 8 AM mean cortisol value using a cutoff of 400 nmol/L, judged against the peak value on the LDST of <500 nmol/L, as a index of AI was 83%, whereas the specificity was 81%. Of the 8 children who had 1 or more cortisol values <140 nmol/L, 4 had the LDST. Three had both a peak value of <500 nmol/L and an increment of <200 nmol/L, and the other an increment value of <200 nmol/L only. There were no deaths. Of the 4 who did not have the LDST, 1 died.

For defining a "normal stressed" cortisol value, patients who failed the LDST and/or had a cortisol value <140 nmol/L were excluded from analysis. In the remaining group ($n = 54$), the mean admission cortisol value was 1100 nmol/L (95% confidence interval: 950-1250 nmol/L) and the mean 8 AM cortisol value was 640 nmol/L (95% confidence interval: 550–730 nmol/L).

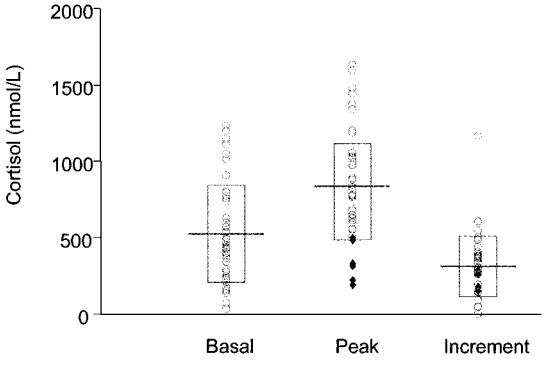

Fig 5. Results from the LDST (500 ng/m² 1–24 corticotropin). An inadequate response was defined as a peak cortisol value of <500 nmol/L (6 of 42 patients, as indicated by the diamonds). Horizontal bars and boxes represent mean ± 1 SD.

Assessment of Disease Severity

Children with a GMSPS of 9 or greater had a significantly higher mean 8 AM cortisol value (685 ± 330 nmol/L) compared with those with a GMSPS of <9, who had a mean 8 AM cortisol value of (388 ± 282 nmol/L; $P < .01$).

When patients were divided into groups defined by the level of intensive management (Table 1), the mean 8 AM cortisol values significantly increased between those with mild (group 1) versus moderate (group 2) requirements (Fig 7). Between those with moderate and extensive intensive care requirements (group 2 vs group 3), the mean 8 AM cortisol values decreased, although this was not significant (Fig 7). ACTH values on admission significantly increased between groups 1 and 2 for all of the 4 intensive management categories (colloid: ACTH 9 pmol/L for group 1 vs 37 pmol/L for group 2 [$P = .02$]; inotropic support: 10 pmol/L vs 32 pmol/L [$P = .03$]; duration of ventilation: 7 pmol/L vs 31 pmol/L [$P = .009$];

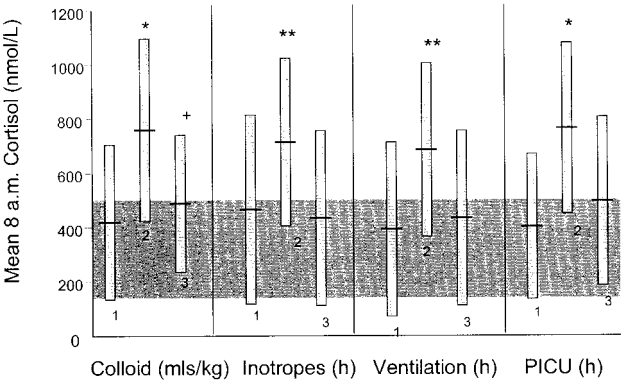

Fig 7. Mean 8 AM cortisol values versus the amount of colloid given in the first 48 hours, duration of inotropic support, ventilation, and PICU stay (see Table 1). Horizontal bars and boxes represent mean ± 1 SD. *$P = .001$ (group 1 vs group 2); **$P = .01$ (group 1 vs group 2); +$P = .07$ (group 2 vs group 3). The shaded box represents the normal range for cortisol in unstressed children (140–500 nmol/L).

duration of PICU stay: 8 pmol/L vs 34 pmol/L [P = .01]).

When peak cortisol values on the LDST versus intensity of management were assessed, a different pattern was seen with those requiring most care having lower peak cortisol values (Fig 8). There was no difference in peak cortisol between those with mild versus moderate requirements.

DISCUSSION

During the initial phase of meningococcal disease, in the whole group, raised cortisol and ACTH levels indicate an appropriate stress response within the HPA axis. However, a significant number of children (11 [16.9%] of 65) had evidence of early AI. This study has shown that a normal stress response in meningococcal disease is a cortisol value on admission >950 nmol/L and a mean 8 AM cortisol value >550 nmol/L. During the 48-hour cortisol profile, there was no diurnal variation. Both raised cortisol values[2,3] and loss of diurnal variation have previously been noted in severe sepsis.[29,30] The mechanism for this may be secondary to the surge of circulating inflammatory mediators in response to severe sepsis. Initially, the proinflammatory cytokines, tumor necrosis factor (TNF), interleukin (IL)-1, and interleukin-6 stimulate the HPA axis[31,32] by directly stimulating both the pituitary and the adrenal glands to produce ACTH and cortisol, respectively.[33] However, at high concentrations, TNF and IL-1 can block the corticotropin-releasing hormone stimulatory effect on the pituitary[32] and the ACTH-induced release of cortisol.[33] The increased cortisol values may also be secondary to a decrease in cortisol degradation. Cortisol is normally eliminated via the kidneys. In this study, children who had meningococcal disease complicated by acute renal failure had significantly higher mean 8 AM cortisol values. However, they also had significantly higher log ACTH values on admission, suggesting that the increased cortisol values were secondary to increased pituitary drive and not to decreased cortisol degradation. In addition, a reduction in corticosteroid-binding globulin may contribute to the increased levels of free cortisol.[34]

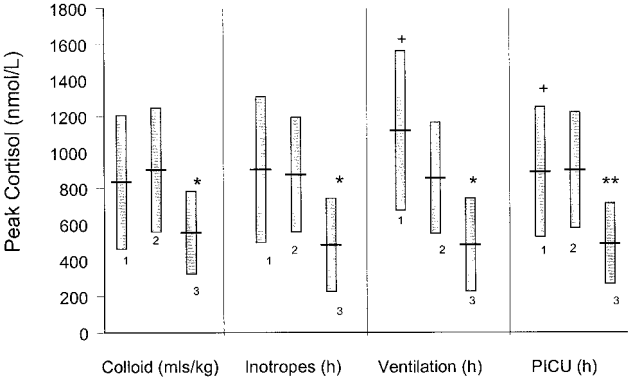

Fig 8. Peak cortisol values on the LDST versus the amount of colloid given in the first 48 hours, duration of inotropic support, ventilation, and PICU stay (see Table 1). Horizontal bars and boxes represent mean ± 1 SD. *P = .02 (group 2 vs group 3); **P = .01 (group 2 vs group 3); +P = .04 (group 1 vs group 3).

The LDST (500 ng/m^2 1–24 corticotropin) was used in preference to the standard-dose ACTH test as it has been found to be a more sensitive and physiologic assessment of adrenal function.[35,36] It was suggested recently that the LDST rather than the standard-dose Synacthen test should now be the standard assessment for AI.[37,38] A peak value of <500 nmol/L was used in preference to an increment value of <200 nmol/L to define AI. This was because children who had an increment value of <200 nmol/L had both high basal cortisol (median: 774 pmol/L; range: 532-1234 pmol/L) and peak cortisol (median: 819 pmol/L; range: 628-1373 pmol/L) values on the LDST, indicating adequate adrenal function. The relationship between a high basal cortisol and low increment value on the LDST has been described previously.[39]

Of the 5 children who died, 1 had evidence of primary AI with a raised ACTH and a low cortisol. Three of the children who died also had borderline low 8 AM "unstressed cortisol" values between 158 and 214 nmol/L and markedly low levels judged against "stressed" cortisol values, suggesting AI. Six children (14%) had a peak value on the LDST of <500 nmol/L, indicating AI. All of these children survived. One of this group in the acute phase of meningococcal disease had a marked improvement in hemodynamic parameters after commencing hydrocortisone therapy, allowing a reduction in inotropic support. This patient was not excluded from the study because the assessment of the HPA axis had been performed before commencing hydrocortisone therapy. The beneficial cardiac effects of hydrocortisone therapy have been demonstrated in adults with septic shock.[9,10,23–25]

Eight children (12.3%) had a cortisol value <140 nmol/L, indicating AI. This degree of AI has been previously noted to be rare in septic shock (<1%).[3,12,16]

There was a significant correlation between the mean 8 AM cortisol and ACTH values, indicating integrity of the HPA axis in the group as a whole. Previous studies in adult septic shock have revealed no such relationship.[40,41] However, 4 of the 6 children who failed the LDST and an additional 11 from the rest of the group (36% of the total) had mean 8 AM ACTH values <2 pmol/L, possibly indicating secondary AI (ie, hypothalamic-pituitary dysfunction; Fig 4). This group had significantly lower cortisol values than patients with ACTH values within the 8 AM normal range, reinforcing the evidence for secondary AI. This study has therefore shown that both primary and secondary AI occurs in the acute phase of meningococcal disease, the causes of which, however, remain unclear. Primary AI has been noted with adrenal hemorrhage[2,4,6,42] or may be related to adrenal ischemia.[16,43,44] Secondary AI may be related to the proinflammatory cytokines. IL-6 is a potent stimulus for ACTH release[45] but has been shown to be reduced in adults with septic shock and AI.[9] IL-6 also inhibits the secretion of TNF and IL-1,[33] which actively stimulate the HPA axis. Therefore, a deficient IL-6 response to sepsis may result in AI. Brainstem ischemia has also been associated with low

ACTH values and therefore may be another causative factor.[46]

When examining adrenal function compared with general markers of disease severity (volume of colloid infused, time on inotropes, time ventilated, and duration of intensive care support), it is found that mean cortisol initially rises as the level of intervention increases. However, in those 10% with the highest levels of support, mean cortisol tends to fall. For the peak cortisol response to Synacthen, levels do not change in those with low or moderate levels of support but fall in those receiving the highest level of intervention. These data suggest that the adrenal axis is not functioning optimally in those with the most severe meningococcal disease.

If this subgroup of patients with AI could be readily identified, it would be expected that this group might benefit from replacement hydrocortisone. Low-dose hydrocortisone has been shown to reverse shock[22] and improve survival.[9,22,23] This study has shown that a peak cortisol on the LDST of <500 nmol/L can be used as a test for AI. However, this study has also shown that a mean 8 AM cortisol of <400 nmol/L, judged against the peak value on the LDST of <500 nmol/L, as an index of AI has a sensitivity of 83% and a specificity of 81%. Therefore, morning cortisol values could be used as an assessment of adrenal dysfunction in the acute phase of meningococcal disease. We propose that a multicenter intervention study to identify children with a low "stressed" cortisol level within the first 48 hours of admission and suitably powered to evaluate morbidity and mortality should be undertaken.

During the initial phase of meningococcal disease, raised cortisol and ACTH levels indicate an appropriate stress response within the HPA axis. However, a significant subpopulation has clear evidence of adrenal dysfunction. This can be either primary adrenal or secondary pituitary dysfunction. In addition, a substantial number of children seem to have a mild secondary AI. We suggest that morning cortisol values could be used as a potential early index of significant AI. The next step will be to design an intervention study using hydrocortisone to achieve normal stress cortisol levels in these children, with sufficient power to detect differences in mortality and/or morbidity.

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ESCHEWING SHAME

"In the 1960s the results of a large randomized controlled study of tolbutamide (demonstrated that this drug) was associated with an increase in mortality in patients who developed myocardial infarction . . . the response was doubt, outrage, even legal proceedings against the investigators; the controversy went on for years. Why?

An important clue surfaced at the annual meeting of the American Diabetes Association soon after the study was published. During the discussion a practitioner stood up and said he simply could not, and would not, accept the findings, because admitting to his patients that he had been using an unsafe treatment would shame him in their eyes. Other examples of such reactions to improvement efforts are not hard to find. Indeed, it is arguable that shame is the universal dark side of improvement."

Davidoff F. Shame: the elephant in the room. *BMJ.* 2002;324:623–624

Submitted by Student

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