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Adrenocorticotropic Hormone and Cortisol Levels in Relation to Inflammatory Response and Disease Severity in Children with Meningococcal Disease

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This prospective observational study investigated the relationship of the hypothalamic-pituitary-adrenal axis to inflammatory markers and to disease severity in children with meningococcal disease. In total, 32 children were studied: 10 with distinct meningococcal meningitis (MM), 10 with MM and septic shock, and 12 with fulminant meningococcal septicemia (FMS). Levels of adrenocorticotropic hormone (ACTH) and interleukin (IL)−6, IL-8, and IL-10 were lowest in the MM group and dramatically elevated in the FMS group. Cortisol and C-reactive protein levels were highest in the MM group and relatively low in the FMS group. Levels of ACTH and inflammatory markers decreased within the first 24 h of admission, but cortisol levels did not fluctuate. Cortisol was significantly inversely correlated with IL-6, IL-8, and IL-10 ($P \leq .04$). These results suggest that the adrenal reserve in children is insufficient to handle the extreme conditions and stress associated with severe meningococcal disease.

Invasive meningococcal disease in children is characterized by high morbidity and mortality, despite administration of early antibiotic treatment and improved supportive therapy [1]. During meningococcal disease, *Neisseria meningitidis* endotoxemia is followed by a cascade of proinflammatory mediators in blood, such as tumor necrosis factor (TNF)−α [2], interleukin (IL)−1 [3], IL-6 [4], and IL-8 [5]. Disease severity correlates with the levels of several of these proinflammatory cytokines [6, 7]. Concomitant with the proinflammatory response, an anti-inflammatory response (e.g., production of IL-10 [8]) is initiated. In addition, a plethora of other inflammatory mediators related to complement, coagulation, fibrinolysis granulocyte, and endothelial cell activation have been identified in patients who have meningococcal disease [1].

The balance between proinflammatory and anti-inflammatory responses strongly influences disease severity and outcome of meningococcal disease. The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the regulation of the anti-inflammatory response [9]. An inadequate HPA axis response during meningococcal disease may lead to a (relatively) inadequate response of adrenocorticotropic hormone (ACTH) and cortisol

and hence to a more severe course of disease. In some patients with meningococcal disease, an inadequate HPA axis response may be caused by adrenal hemorrhages, diagnosed postmortem as so-called Waterhouse Friderichsen syndrome [1]. In studies of cortisol in patients with meningococcal disease, results have been conflicting. Both higher and lower levels of cortisol have been found in patients with more severe disease, compared with levels in patients with mild disease, but no relationship between disease severity and cortisol levels was seen in other studies [10–14]. To further assess the relationship of plasma levels of ACTH, cortisol, and inflammatory mediators to each other and to disease severity in children with meningococcal disease, we undertook a prospective observational cohort study.

Patients and Methods

Patients. From August 1998 through April 2000, parents of children admitted to the pediatric intensive care unit (PICU) of Emma Children's Hospital in Amsterdam with the clinical diagnosis of meningococcal disease were asked to enroll their children in the study. Clinical diagnosis of meningococcal disease was defined according to Meningococcal Disease Survival Group criteria [15]. Cultures of blood, cerebrospinal fluid (CSF), if lumbar puncture was not contraindicated, and biopsy specimens from a purpural skin lesion were done to confirm the clinical diagnosis. Pediatric risk of mortality (PRISM) scores were calculated by using the most abnormal value of each variable recorded within the first 4 h after admission [16].

All patients were treated according to the management protocol for meningococcal disease of our PICU. Ceftriaxone (100 mg/kg once daily) is given as empiric antimicrobial treatment, but treatment is switched to penicillin as soon as bacteriologic confirmation and results of susceptibility testing are available.

Patients were divided in 3 subgroups, according to disease severity, as described elsewhere [17]. One group included children with distinct meningococcal meningitis (MM; $>100 \times 10^6$ leukocytes/L of CSF) without persistent meningococcal septic shock (MS). MS was defined as initial systolic blood pressure <100 mm Hg in patients $\geqslant 12$ years old or <70 mm Hg in patients <12 years old who do not react adequately on volume loading and need continuous fluid and vasopressive drugs. The second group included children with MM and MS (MM/MS). Children in the third group had fulminant meningococcal septicemia (FMS), which included MS, defined above, and $<100 \times 10^6$ leukocytes/L of CSF (or absence of nuchal rigidity, if lumbar puncture was contraindicated or not done).

Sample collection. In addition to routine blood sampling, blood was drawn as soon as possible after admission and at 8 and 16 h after admission, for cytokine assays, and at 12 h after admission, for cortisol and ACTH assays. Because corticosteroids are routinely used in the treatment of meningococcal disease in our PICU, only cortisol levels measured in samples drawn before the first administration of systemic corticosteroids were considered in the analysis.

Assays. C-reactive protein (CRP) plasma levels were determined by use of a CRP ELISA with a detection limit of 0.1 mg/L [18]. IL-6, IL-8, and TNF-α plasma concentrations were analyzed by commercial ELISA, using detection limits of 3.0, 15.0, and 5.0 pg/mL, respectively (Central Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam). IL-10 plasma concentrations were measured as described by van der Pouw Kraan et al. [19]. Cortisol levels (detection limit, 50 nM) were measured with a luminescence EIA analyzer (Immulite I; Diagnostic Products). ACTH levels were determined by a commercial immunoluminometric assay (Nichols Institute) with a detection limit of 1 ng/L.

Statistical analysis. Statistical analysis was performed with SPSS for Windows, version 9.0. For normally distributed data, we used Student's t test to compare group means; otherwise, the Mann-Whitney U test was used. Proportions were compared by χ^2 test. $P < .05$, by 2-sided analysis, was considered statistically significant. The correlation between ACTH, cortisol, and cytokine or cell-activation marker levels was tested by regression analysis.

Results

During the study period, 40 patients with meningococcal disease were admitted to the PICU, and the parents of 32 of those patients gave permission for study participation. No differences from the baseline characteristics of children who were not included were seen (data not shown). *N. meningitidis* was isolated from 25 children (78%): 20 isolates were of serogroup B, and 5 were of serogroup C. Ten patients had MM, 10 had MM/MS, and 12 had FMS. Three patients died (1 in each group).

Baseline characteristics of the patients are shown in table 1. Nearly all were admitted to our PICU from area hospitals at which they received the first dose of antibiotics. The average time between admission to these hospitals and transfer to our PICU was 2 h, with no difference among the 3 severity groups. No significant differences were seen among the severity groups in the interval from admission to the time at which the first samples were obtained (MM group, 4.1 h; MM/MS group, 6.7 h; FMS group, 5.6 h). No patients in the MM group needed mechanical ventilation on the day of admission; 6 patients (60%) in the MM/MS group ($P < .01$) and 11 patients (92%) in the FMS group ($P < .01$) required such treatment. In addition, PRISM scores were significantly different among the 3 groups and were lowest in the MM group and highest in the FMS group. White blood cell counts, neutrophil counts, and platelet counts also dif-

Table 1. Baseline characteristics of subjects included in a study of children with meningococcal disease.

Variable	Children with MM ($n = 10$)	Children with MM/MS ($n = 10$)	Children with FMS ($n = 12$)
Clinical characteristics			
Male sex, no. (%)	5 (50)	7 (70)	7 (58)
Age on admission, years	6.0 ± 1.5	3.9 ± 1.0	5.2 ± 1.2
Duration of fever before admission, days	1.2 ± 0.1	1.2 ± 0.1	1.0 ± 0.0
Received mechanical ventilation, no. (%)	0	6 (60)[a]	11 (92)[a]
PRISM score, median (interquartile range)	6 (3–8)	11.5 (9–8)[a]	22 (18–27)[a,b]
Laboratory characteristics			
White blood cells, $\times 10^9$/L	13.9 ± 1.5	11.9 ± 1.9	7.3 ± 1.4[a]
Neutrophils, $\times 10^9$/L	11.7 ± 1.8	7.9 ± 1.8	5.4 ± 1.5[a]
Platelets, median $\times 10^9$/L (interquartile range)	155 (140–167)	105 (74–146)	50 (42–93)[a]
Creatinine, mg/dL	0.33 ± 0.06	0.57 ± 0.10[a]	0.89 ± 0.12[a]
Blood urea nitrogen, mg/dL	13.3 ± 1.9	18.6 ± 2.8	23.6 ± 1.4[a]
Alanine aminotransferase, IU/L	12.9 ± 2.4	20.5 ± 5.0	19.8 ± 6.5
Aspartate aminotransferase, IU/L	25.8 ± 4.0	43.7 ± 15.7	34.5 ± 6.0
Lactate, mM	2.1 ± 0.3	2.7 ± 0.5	5.1 ± 0.6[a,b]

NOTE. Data are mean ± SEM, unless otherwise noted. FMS, fulminant meningococcal septicemia; MM, distinct meningococcal meningitis; MM/MS, MM and septic shock; PRISM, pediatric risk of mortality.

[a] $P < .05$, versus MM group.

[b] $P < .05$, versus MM/MS group.

Table 2. Plasma levels of adrenocorticotropic hormone (ACTH), cortisol, cytokines, and C-reactive protein (CRP), on admission, in children with meningococcal disease.

Mediator	Children with MM ($n = 10$)		Children with MM/MS ($n = 10$)		Children with FMS ($n = 12$)	
	Test results, mean ± SEM	No. of children tested	Test results, mean ± SEM	No. of children tested	Test results, mean ± SEM	No. of children tested
ACTH, ng/L	110 ± 76	7	210 ± 84	4	387 ± 94[a]	10
Cortisol, nM	1269 ± 143	7	1026 ± 42	5	624 ± 83[b,c]	10
Ratio of ACTH to cortisol, per patient[d]	0.07 ± 0.04	7	0.22 ± 0.1	4	1.1 ± 0.48[b]	10
Interleukin-6, pg/mL	468 ± 292	9	40,331 ± 321,226	10	114,167 ± 41,133[a,e]	12
Interleukin-8, pg/mL	62 ± 32	9	5263 ± 4763[a]	10	30,838 ± 21,224[b,e]	12
Interleukin-10, pg/mL	27 ± 9	7	2845 ± 1433[a]	8	5988 ± 1636[b]	9
TNF-α, pg/mL	5 ± 0	7	5 ± 0	8	8 ± 2	9
CRP, mg/L	245 ± 23	9	179 ± 45	10	126 ± 31[b]	11

NOTE. FMS, fulminant meningococcal septicemia; MM, distinct meningococcal meningitis; MM/MS, MM and septic shock; TNF, tumor necrosis factor.

[a] $P < .05$, versus MM group.
[b] $P < .01$, versus MM group.
[c] $P < .01$, versus MM/MS group.
[d] Comparison done using the Mann-Whitney U test.
[e] $P < .05$, versus MM/MS group.

fered by group and were highest in the MM group and lowest in the FMS group. Creatinine and blood urea nitrogen levels were lowest in the MM group and highest in the FMS group (MM group vs. FMS group, $P < .05$). No differences among the groups were seen in liver function, as expressed by aspartate aminotransferase and alanine aminotransferase levels. Lactate levels were significantly lower in the MM and MM/MS groups than in the FMS group.

Levels of ACTH, cortisol, cytokines, and CRP in samples taken on the day of admission are shown in table 2. ACTH levels were lowest in the MM group and highest in the FMS group ($P < .05$). In contrast, cortisol levels were highest in the MM group and lowest in the FMS group (MM group vs. FMS group and MM/MS group vs. FMS group, $P < .01$). The mean of the individual ratios of ACTH to cortisol was highest in the MM group and lowest in the FMS group. Cytokine and CRP levels also differed by severity group. With the exception of TNF-α, levels of all cytokines were lowest in the MM group and highest in the FMS group (all differences between MM and FMS groups

were statistically significant). CRP levels were highest in the MM group and lowest in the FMS group ($P < .01$).

Measurements made on the day of admission demonstrate a short cytokine half-life (table 3). Mean levels of IL-6, IL-8, and IL-10 were highest shortly after admission (i.e., within the first 8 h) and decreased in the second or third 8-h period after admission, whereas CRP levels were low in the first 8 h but significantly higher thereafter. These trends were most pronounced in the FMS group (figure 1). In contrast, levels of TNF-α were very low (they were only slightly higher than the detection limit and remained at that level for the first 24 h after admission; data not shown). ACTH levels showed a decreasing pattern; they were high on admission but declined rapidly within 24 h after admission. In contrast to ACTH levels, cortisol levels did not show large fluctuations within this time period.

Table 4 shows the results of regression analysis for relevant correlations between ACTH, cortisol, and cytokines. A significant correlation was seen between ACTH and IL-6 and IL-8 but not between ACTH and IL-10. The correlation between cortisol

Table 3. Plasma levels of adrenocorticotropic hormone (ACTH), cortisol, cytokines, and C-reactive protein (CRP), in the first 24 h after admission, in children with meningococcal disease.

Mediator	Group I (testing at 8 h)		Group II (testing at 16 h)		Group III (testing at 24 h)	
	Test results, mean ± SEM	No. of children tested	Test results, mean ± SEM	No. of children tested	Test results, mean ± SEM	No. of children tested
ACTH, ng/L	288 ± 62	19	14 ± 2[a]	6	19 ± 13[a]	3
Cortisol, nM	910 ± 91	20	1028 ± 57	6	770 ± 151	3
Interleukin-6, pg/mL	57,532 ± 17,662	25	9687 ± 5606[b]	23	6151 ± 4272[a]	17
Interleukin-8, pg/mL	14,973 ± 10,353	25	3167 ± 2384	23	1634 ± 1388	18
Interleukin-10, pg/mL	3286 ± 936	19	645 ± 227[a]	18	137 ± 97[a]	13
CRP, mg/L	153 ± 21	24	227 ± 18[b]	22	255 ± 20[a]	17

[a] $P < .01$, versus group I.
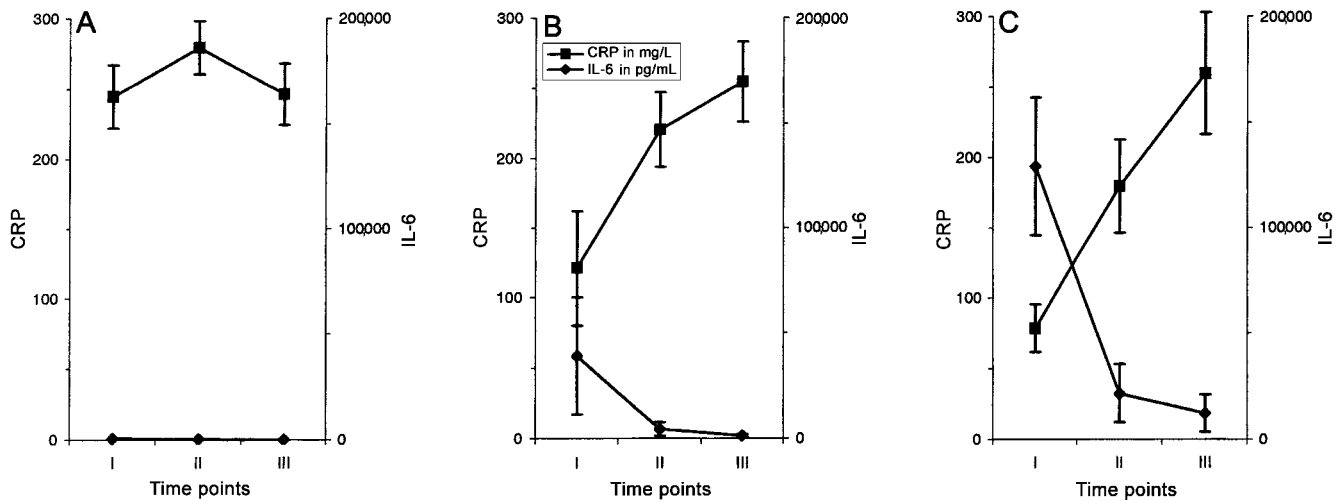[b] $P < .05$, versus group I.

Figure 1. Interleukin (IL)–6 and C-reactive protein (CRP) levels, in the first 24 h after admission, in children with meningococcal disease. *A,* Distinct meningococcal meningitis. *B,* Meningococcal meningitis with septic shock. *C,* Fulminant meningococcal septicemia. I, First 8 h after admission; II, second 8 h after admission; III, third 8 h after admission.

and IL-6, IL-8, and IL-10 was statistically significant; however, no significant correlation between cortisol and ACTH was demonstrated.

Discussion

In this study, levels of ACTH were higher and levels of cortisol were lower, on admission, in patients with FMS than in patients with MM with or without MS. In addition, plasma levels of IL-6, IL-8, and IL-10 were higher but CRP levels were lower, on admission, in patients with FMS than in the other patient subgroups, confirming earlier reports that a strong relationship exists between proinflammatory and anti-inflammatory cytokines, CRP, and disease severity in patients with meningococcal disease [2–4, 6–8, 14]. We used the clinical research definition proposed by Brandtzaeg [17] to make our study comparable with other studies. The results of our analysis did not change when other severity scoring systems were used (e.g., the Glasgow Meningococcal Septicemia Prognostic Score; data not shown). A significant correlation was found between ACTH and IL-6 and IL-8 and between cortisol and IL-6, IL-8, and IL-10.

In other studies, comparison of levels of ACTH and cortisol in patients with meningococcal disease yielded conflicting results [11–14]. In the 1960s, Migeon et al. [12] reported lower levels of cortisol in a small number of patients with meningococcal disease who were "moribund" on admission than in patients who met the criteria for "severe" or "moderate" disease. However, the definition of these criteria was not precise, and the laboratory methods then in use were not as accurate as current techniques. In addition, others who used the same severity criteria reported contrary [11] or nonconfirmatory [13] findings.

More recently, Riordan et al. [14] found higher levels of ACTH and lower levels of cortisol in patients with meningococ-

cal disease who died (10 patients) than in patients who recovered from the disease (86 patients), a result that is in accordance with our finding of lower cortisol levels in patients with more severe disease. However, 9 of the 10 patients in their study cohort who died were in the FMS group, and yet mean levels of cortisol in that group were higher than in the less severely affected MM group. In contrast to our results, the authors could not demonstrate any correlation between cortisol and IL-6, TNF-α, or ACTH. However, it is not clear whether all cortisol and ACTH results were from samples taken before any steroid treatment was started. In addition, sample time was not mentioned in their study, which is very important in light of the short half-life of cytokines.

Another preliminary study confirms our findings. When patients with meningococcal sepsis without signs of shock, patients with MS who survived, and patients with MS who did not survive were grouped, the largest increase in ACTH levels in association with an insufficient increase in cortisol levels on admission was observed in patients whose conditions were most severe, that is, those who did not survive. However, the mortality rate was high (26%). Moreover, data on the preclinical disease period were not available (J. A. Hazelzet, personal communication). In our

Table 4. Regression coefficients for relevant correlations between adrenocorticotropic hormone (ACTH), cortisol, and cytokines.

Mediator	ACTH		Cortisol	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Interleukin-6	248 (58–439)	.014	−174 (−325 to −25)	.026
Interleukin-8	133 (47–220)	.005	−100 (−167 to −33)	.005
Interleukin-10	11 (−2 to 23)	.09	−9 (−16 to −1)	.036
Cortisol	−0.3 (−0.7 to 0.1)	.1	—	—

NOTE. CI, confidence interval.

study, the mortality rate was much lower (10%), and ACTH and cortisol levels in the patients in our study who did not survive did not differ in comparison with those in surviving patients in the same category or in the cohort.

Our results support the idea that the HPA axis plays an essential role in metabolism and the anti-inflammatory response: a relatively low level of cortisol is clearly associated with a more severe course of disease. The importance of induced endogenous glucocorticoids in protection against life-threatening effects of infection-elicited cytokine responses and the key role of IL-6 in the induction of this HPA response have been shown in several animal models [20–22]. The interaction between IL-6 and the HPA axis also plays an important role in the induction of the acute phase reaction (APR) during sepsis [22, 23]. One could speculate that an inadequate response from the HPA axis or from the interaction between IL-6 and the HPA axis (i.e., cortisol production) during sepsis may lead to an inadequate or less brisk APR [21], despite high IL-6 levels. This is supported by our findings of extremely high levels of IL-6 and yet the lowest levels of CRP in the patients who were most severely affected, in comparison with patients who had milder disease (figure 1). Less activity of combined IL-6 and cortisol-driven APR could, in turn, result in a reduced availability of anti-inflammatory proteins, such as acid glycoprotein and various protease inhibitors of inflammatory, coagulator, and complement cascade, at the onset of disease [22]. We did not detect any difference in pre-clinical disease periods among the severity groups (table 1). Therefore, an alternative explanation, that the low values and slow increase of CRP in the FMS group are related to earlier admission, seems less likely.

Our findings demonstrate that patients with more severe meningococcal disease have a relative adrenal insufficiency, with plasma cortisol levels that are, on average, 2-fold higher in the MM group than in the FMS group (table 3). On the basis of a postsynacten increment of <200 nM, Hatherill et al. [24] reported an incidence of adrenal insufficiency of 52% in a group of 33 children who had MS of variable cause. However, they found no clear relationship between baseline cortisol levels and the postsynacten increment. According to other studies, a cortisol level of <138 nM during severe stress is definite evidence of adrenal insufficiency [25]. By this definition, none of our children had an absolute adrenal insufficiency. This is likely true, but a state of functional inadequacy (that is, low adrenal glucocorticoid output when stress is at its extreme) may exist, as demonstrated by the levels of ACTH and cortisol and the mean of ratios for individual patients among severity groups within a cohort of patients with meningococcal disease (table 1).

These results are important in the context of the renewed interest in the use of corticosteroid therapy to treat sepsis. Although other studies investigating the efficacy of corticosteroids to treat sepsis have had conflicting results, 2 meta-analyses have shown that administration of corticosteroids provides no benefit to patients who have MS [26, 27]. However, recent reports have shown that more modest doses of glucocorticoids have a beneficial effect on several hemodynamic parameters [28, 29]. The potentially negative effects of administration of corticosteroids to patients with MS should be taken into account. In experimental models, not only a priming dose of lipopolysaccharide (LPS) but also pretreatment with corticosteroids, often for a prolonged period of time, causes a so-called generalized Shwartzman reaction of systemic vascular injury, disseminated intravascular coagulation, and organ failure on subsequent exposure to LPS [30]. However, the experimental setting differs greatly from the clinical setting of human meningococcemia, in which steroid treatment is started only after the first release of LPS and administration of antibiotics has already taken place. Only randomized trials with sufficient power can answer the question of whether the beneficial effect of corticosteroid administration to patients with meningococcemia outweighs the potential of negative side effects.

In conclusion, we found that cortisol levels on admission were inversely related to levels of most inflammatory cytokines and to disease severity in children with meningococcal disease. Our findings support the idea that cortisol has a role as an anti-inflammatory mediator in the proinflammatory and anti-inflammatory balance in patients who have meningococcal disease and a relatively insufficient adrenal function, judging by strongly elevated levels of ACTH on admission. These findings seem to justify further research into the efficacy of corticosteroid therapy for patients with meningococcal disease.

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