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Acute Stress Response in Children with Meningococcal Sepsis: Important Differences in the Growth Hormone/Insulin-Like Growth Factor I Axis between Nonsurvivors and Survivors

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Septic shock is the most severe clinical manifestation of meningococcal disease and is predominantly seen in children under 5 yr of age. Very limited research has been performed to elucidate the alterations of the GH/IGF-I axis in critically ill children. We evaluated the GH/IGF-I axis and the levels of IGF-binding proteins (IGFBPs), IGFBP-3 protease, glucose, insulin, and cytokines in 27 children with severe septic shock due to meningococcal sepsis during the first 3 d after admission. The median age was 22 months (range, 4–185 months). Eight patients died. Nonsurvivors had extremely high GH levels that were significant different compared with mean GH levels in survivors during a 6-h GH profile (131 *vs.* 7 mU/liter; $P < 0.01$). Significant differences were found between nonsurvivors and survivors for the levels of total IGF-I (2.6 *vs.* 5.6 nmol/liter), free IGF-I (0.003 *vs.* 0.012 nmol/liter), IGFBP-1 (44.3 *vs.* 8.9 nmol/liter), IGFBP-3 protease activity (61 *vs.* 32%), IL-6 (1200 *vs.* 50 ng/ml), and TNFα (34 *vs.* 5.3 pg/ml; $P < 0.01$). The pediatric risk of mortality score correlated significantly with levels of IGFBP-1, IGFBP-3 protease activity, IL-6, and TNFα ($r = +0.45$ to $+0.69$) and with levels of total IGF-I and free IGF-I ($r = -0.44$ and -0.55, respectively). Follow-up after 48 h in survivors showed an increased number of GH peaks, increased free IGF-I and IGFBP-3 levels, and lower IGFBP-1 levels compared with admission values. GH levels and IGFBP-1 levels were extremely elevated in nonsurvivors, whereas total and free IGF-I levels were markedly decreased and were accompanied by high levels of the cytokines IL-6 and TNFα. These values were different from those for the survivors. Based on these findings and literature data a hypothetical model was constructed summarizing our current knowledge and understanding of the various mechanisms. (*J Clin Endocrinol Metab* 87: 3118–3124, 2002)

MENINGOCOCCAL SEPTIC SHOCK is the most severe clinical manifestation of meningococcal disease and is predominantly seen in children under 5 yr of age. This form of meningococcal disease is characterized by a rapid onset of disease, fever, purpura, and ultimately shock (1). Despite improved supportive care, the mortality of meningococcal septic shock has not diminished during the last few decades and still ranges between 20–50%. Critical illness leads to a spectrum of neuroendocrine and metabolic changes. Alterations in the GH/IGF-I axis have been reported in studies of critically ill adult patients, and it has been postulated that these alterations are due to the development of GH resistance (2–4). GH trials were initiated to improve the recovery of these critically ill adult patients (5, 6). However, these trials have been cancelled, because an increased mortality was observed in the treated patients (6). Only very limited research has been performed to elucidate the alterations of the GH/IGF-I axis in critically ill children. Recently, we reported differences between survivors and nonsurvivors regarding the adrenal and thyroid axis in children with meningococcal sepsis (7). Understanding the insufficient pituitary-adrenal axis in nonsurvivors might be essential to develop new diagnostics or even therapies to improve clinical outcome for these children (7). The present study evaluated the 6-h serum GH profile and serum or plasma levels of total IGF-I, free IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-3, IGFBP-3 protease, insulin, and glucose and related them to serum cytokine levels of IL-6 and TNFα during the first 48 h of admission in the pediatric intensive care unit (PICU) in children with septic shock due to meningococcal sepsis.

Abbreviations: ALS, Acid-labile subunit; IGFBP, IGF-binding protein; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality.

Materials and Methods

Study protocol

Children more than 1 month and less than 18 yr of age with septic shock and petechia/purpura requiring intensive care treatment were enrolled in this study. The group consisted of 27 children admitted or referred to the PICU of Sophia Children's Hospital between July 1997 and April 1999. Patients were eligible for inclusion when they met the following criteria: 1) presence of petechia/purpura; 2) presence of shock for less than 6 h defined as persistent hypotension (systolic blood pressure, <75 mm Hg for children between 3–12 months, <80 mm Hg for 1–5 yr, <85 mm Hg for 6–12 yr, <100 mm Hg for children older than 12 yr), or evidence of poor end-organ perfusion, defined as at least two of the following: 1) unexplained metabolic acidosis (pH <7.3 or base excess below −5 mmol/liter or plasma lactate levels >2.0 mmol/liter); 2) arterial hypoxia (PO_2 <75 mm Hg, PO_2/FiO_2 ratio, <250; transcutaneous oxygen saturation, <96%) in patients without overt cardiopulmonary disease; 3) acute renal failure (diuresis, <0.5 ml/kg·h for at least

1 h despite acute volume loading or evidence of adequate intravascular volume without preexisting renal disease); or 4) sudden deterioration of the baseline mental status. The patients participated in a randomized, double-blinded, placebo-controlled, dose-finding study of protein C concentrate (human; Baxter-Immuno, Vienna, Austria). Protein C was administered after the first blood sampling on admission. As protein C does not influence the endocrine and metabolic assays or mortality, we did not account for it in the analysis of data during admission (8). The medical ethics committee of Erasmus University (Rotterdam, The Netherlands) approved the study protocol. Informed consent was obtained from the parents or legal representatives.

Clinical parameters

The pediatric risk of mortality (PRISM) score was calculated using the most abnormal values for 14 physiological variables during the first 6 h of admission. A higher score points to a higher risk of mortality (9).

Collection of blood

Arterial blood samples were collected within 2 h after admission (time zero) and at 24 and 48 h for determination of total IGF-I, IGFBP-3, IGFBP-1, IGFBP-3 protease, insulin, and glucose as well as routine laboratory variables. A 6-h GH profile was performed in 12 randomly selected patients. Blood samples for GH were taken every 30 min for 6 h, starting within 2 h after admission (time zero) and after 48 h.

Hormonal assays

GH. Serum GH determinations were performed in one laboratory (Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands). Serum GH was measured by immunoradiometric assay (CIS-Bio International, Gif-sur-Yvette, France; intra- and interassay coefficients of variation, 2.8% and 4.4%, respectively). The lower detection limit was 0.08 mU/liter. Results were expressed in milliunits per liter.

Analysis of GH secretion pattern in serum

The GH profiles were analyzed with the Pulsar program (10) adapted for Quick Basic by Rosberg and Albertsson-Wikland (PC-Pulsar, 1987). Peak selection criteria appropriate for our own assay conditions and dataset were established before the GH profiles were analyzed (11). With these settings the Pulsar program did not detect any peaks when 72 consecutive samples from each of 3 different plasma pools were assayed. From the Pulsar analysis, the following values were extracted: number of peaks, overall mean, maximal value, mean peak height, mean peak amplitude, mean peak length, and area under the curve above zero level. Based on Dutch consensus guidelines a normal 6-h GH profile in children above 1 yr was defined as a profile with a mean GH level of at least 5.6 mU/liter, with well defined GH peaks returning to baseline levels between GH pulses.

Total IGF-I, IGFBP-1, and IGFBP-3

Concentrations of total IGF-I, IGFBP-1, and IGFBP-3 in EDTA plasma were determined by specific RIAs (Utrecht Medical Center, Utrecht, The Netherlands). Technical details and data on stability and reproducibility after storage of plasma and serum samples have been described previously (12, 13). The levels of plasma total IGF-I, IGFBP-1, and IGFBP-3 were expressed as nanomoles per liter. Reference values for both total IGF-I and IGFBP-3 have been reported previously (12). Smoothed references constructed by the LMS method were used (14). To correct for age and gender, plasma IGF-I and IGFBP-3 levels were also expressed as SD scores using the respective LMS normative range data.

Free IGF-I

Dissociable free serum IGF-I was measured with a commercially available noncompetitive two-site immunoradiometric assay (Diagnostics Systems Laboratories, Inc., Webster, TX). Intra- and interassay coefficients of variation were 10.3% and 10.7%, respectively. The detection limit was 0.003 nmol IGF-I/liter. The concentration of free IGF-I was expressed as nanomoles per liter.

IGFBP-3-protease

Serum IGFBP-3-protease, which degrades IGFBP-3, was determined as described by Lamson *et al.* (15) and modified by Koedam *et al.* (16). In brief, the substrate indicator, *i.e.* nonglycosylated ^{125}I-labeled IGFBP-3 recombinantly derived from *Escherichia coli*, was incubated at 37 C in the presence of the serum being tested. Subsequently, proteolysis was visualized by SDS-PAGE and autoradiography. The amount of proteolysis was expressed as percentage of the intensity on the autoradiogram, which was associated with degradation products of IGFBP-3, relative to the total intensity.

Insulin and glucose levels

Insulin was measured in serum with an immunoradiometric assay. Upper and lower detection limits were 400 and 5 mU/liter, respectively. Glucose measurements were determined on routine clinical chemistry analyzers (Dimension ES, DuPont Medical Products, Wilmington, DE). Based on reference values hypoglycemia was defined as a serum glucose level below 2.6 mmol/liter, and hyperglycemia as a serum glucose concentration above 11 mmol/liter.

IL-6 and TNFα levels

IL-6 and TNFα levels were measured in serum with commercial assays (CLB, Amsterdam, The Netherlands). The detection limit (lowest positive standard) for IL-6 was 10×10^{-3} ng/ml, and that for TNFα was 5 pg/ml.

Statistics

Statistical analysis was performed with a statistical analysis software program (SPSS 9.0 for WINDOWS 95, SPSS, Inc., Chicago, IL). The Mann-Whitney test was used for comparison of clinical and laboratory tests between nonsurvivors and survivors. Wilcoxon's signed-rank test was used for comparison between different laboratory tests at various time points. Spearman's correlation coefficient was used to evaluate the relationship between parameters. Two-tailed $P \leq 0.05$ was considered statistically significant.

Results

Twenty-seven children admitted to the PICU fulfilled the inclusion criteria and were included in the study (17 boys and 10 girls). The median age was 22 months (range, 4–185 months). Blood cultures revealed *Neisseria meningitidis* in all 27 patients. Concomitant therapy during the study period included antibiotics, plasma (fresh-frozen plasma; mean dosage, 100 ml/kg BW) and inotropic agents for all patients. Eighteen patients required additional mechanical ventilatory support and sedation with benzodiazepines. Upon admission the median PRISM score of the nonsurvivors was significantly higher than that of the survivors (31 *vs.* 18, respectively; Table 1). Eight children (36%) died after a median stay on the PICU for 10 h (range, 2–40). There was a significant difference in age between nonsurvivors and survivors (9.5 *vs.* 27 months; $P < 0.05$). The various parameters of the GH/IGF-I axis are summarized in Table 1.

Analysis of GH secretion patterns

A 6-h GH profile analysis was performed in 12 patients within 2 h after admission during the day or at night (Table 2). Three of these children died during the course of their disease. On admission all 12 children showed spontaneous GH secretion, although the individual mean GH levels

TABLE 1. Differences between survivors and nonsurvivors on admission and during admission in survivors

	Nonsurvivors (n = 8)		Survivors (n = 19)							
	t = 0		t = 0	t = 12 h		t = 24 h		t = 48 h		
Age (months)	9.5	(6–23)^{a,S}	27	(18–81)						
PRISM score	31	(29–34)^{b,S}	18	(14–23)						
Total IGF-I nmol/liter	2.6	(1.01–4.93)^{a,S}	5.6	(3.7–10.8)	10.5	(7.3–14.4)^{b,d}	9.9	(5.5–14.2)^{b,d}	7.4	(3.8–10.1)
SD score	−3.5	(−5.3 to −2.0)	−2.4	(−3.1 to −1.0)	−0.4	(−1.7–0.38)^{b,d}	−0.2	(−2.1–1.1)^{a,d}	−2.2	(−2.8 to −1.0)
Free IGF-I nmol/liter	0.003	(0.003–0.003)^{a,S}	0.012	(0.003–0.024)	0.025	(0.016–0.039)^{b,d}	0.048	(0.036–0.11)^{b,d}	0.038	(0.025–0.1)^{b,d}
IGFBP-1 nmol/liter	44.3	(11.7–56.8)^{b,S}	8.9	(3.4–17.0)	10.6	(5.8–16.7)^{b,d}	6.0	(2.4–12.7)	1.4	(0.8–5.3)^{b,d}
IGF-I/IGFBP-1 ratio	0.069	(0.026–0.28)^{b,S}	0.55	(0.17–2.91)	0.99	(0.44–1.69)	1.53	(0.78–3.15)	3.9	(1.01–6.27)^{b,d}
IGFBP-3 nmol/liter	21	(11–44)	20	(13–28)	32	(21–44)^{b,d}	33	(22–49)^{b,d}	35	(22–49)^{b,d}
SD score	−4.7	(−7.6 to −0.83)	−5.5	(−6.1 to −3.2)	−2.0	(−4.8 to −1.3)^{b,d}	−2.4	(−3.4 to −1.6)^{b,d}	−2.2	(−4.2 to −1.7)^{b,d}
IGFBP-3 protease %	61	(42–80)^{a,S}	32	(25–38)	33	(25–39)			35	(32–51)^{a,d}

Values are expressed as median (interquartile range), ^{a} $P < 0.05$ and ^{b} $P < 0.01$.
^{d} Significantly different compared with t = 0.
^{S} Significantly different between nonsurvivors and survivors.

varied considerably but regardless of the time of the day. Nonsurvivors had higher median values of mean GH levels than children who survived (131 *vs.* 7 mU/liter; $P < 0.01$; Table 2). Upon admission nonsurvivors had extremely high GH levels, whereas most survivors had normal or low GH levels with a very limited number of small GH peaks (Fig. 1). The median values of mean GH levels and the area under the curve above zero level in survivors did not change significantly between 0 and 48 h after admission, but there was a significant difference in the number of GH peaks (two *vs.* three; $P < 0.05$; Fig. 1 and Table 2).

Total and free IGF-I levels

On admission all patients had significantly lower serum total IGF-I levels compared with healthy peers or when levels were adjusted for gender and age and expressed as the SD score (Table 1 and Fig. 2). Mean total IGF-I SDS levels were lower in the nonsurvivors compared with the survivors, but this difference did not reach statistical significance. Nonsurvivors had significantly lower free IGF-I levels on admission compared with survivors (Table 1 and Fig. 2). In five nonsurvivors and one survivor free IGF-I was not detectable. A significant negative correlation was found between the PRISM score and the levels of total IGF-I and free IGF-I (Table 3).

During admission the survivors showed a significant increase in serum total IGF-I levels at 12 and 24 h, followed by a significant decrease from 24 to 48 h, whereas a significant increase was found in free IGF-I levels at 12, 24, and 48 h (Fig. 2).

IGFBP-1 levels

On admission the nonsurvivors had extremely high median serum IGFBP-1 levels (44.3 nmol/liter), significantly higher than those of survivors (8.9 nmol/liter; Table 1 and Fig. 2). For comparison, normal serum IGFBP-1 levels for nonfasted healthy subjects usually range between 1.0–2.3 nmol/liter. IGFBP-1 levels showed a significant correlation with the PRISM score ($r = +0.45$; $P < 0.01$; Table 3). In survivors the plasma levels of IGFBP-1 decreased significantly between 0 and 48 h. IGFBP-1 levels did not correlate with insulin levels on admission in all patients or at 24 and 48 h in those who survived. In contrast, on admission a significant inverse relationship was found between serum IGFBP-1 and glucose levels ($r = -0.45$; $P < 0.05$). This correlation was not found at 24 and 48 h in those who survived.

IGFBP-3 levels

On admission both nonsurvivors and survivors had significantly lower median serum IGFBP-3 levels, expressed as the SD score, than their healthy peers. There was no significant difference in median serum IGFBP-3 SD score between nonsurvivors and survivors (Table 1 and Fig. 2). A significant increase in median IGFBP-3 SD score was found during the course of the disease in those who survived.

IGFBP-3 protease activity

On admission the median serum IGFBP-3 protease activity was significantly (~2-fold) higher in nonsurvivors than in

TABLE 2. Characteristics of individual children who underwent a 6-h serum GH-profile

On admission						GH profile					
						On admission			On day 3		
Sex	Age (month)	Time GH profile	Outcome	PRISM score	IL-6 (ng/ml)	Mean GH (mU/liter)	Peak no.	AUC_0 (mU/liter)	Mean GH (mU/liter)	Peak no.	AUC_0 (mU/liter)
M	21	17.30	Survivor	18		5.0	2	56	14.4	3	167
F	52	1.30	Survivor	20	313	4.5	0	48	10.7	3	152
M	18	17.50	Survivor	27		7.4	3	74	28.5	2	313
F	185	20.00	Survivor	14	0.2	14.7	2	119			
F	27	19.45	Survivor	14	41	2.7	2	31	16.2	4	203
F	32	16.00	Survivor	10	31	18.8	1	219			
F	15	6.00	Survivor	18	81	3.3	1	36	42.5	3	502
M	4	2.30	Survivor	12	8	39.2	2	485	32.2	3	359
M	23	12.20	Survivor	20	64	17.7	0	207	18.1	1	215
M	24	12.10	Non-surv	37	2934	153	0	1847			
M	10	19.15	Non-surv	32	1959	131	0	1549			
M	5.5	20.00	Non-surv	34	1185	131	0	1555			

M, Male; F, female; Non-surv, nonsurvivor; Peak no., number of GH peaks during 6-h profile; AUC_0, area under the curve of GH above zero level.

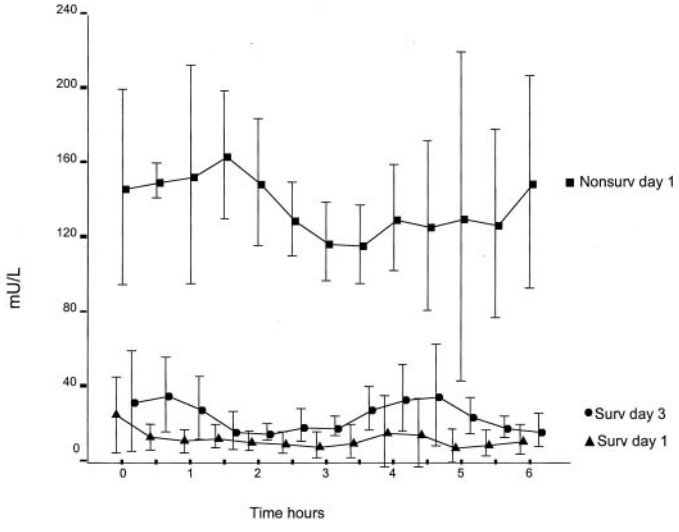

FIG. 1. Differences in mean ± 2 SE GH levels between nonsurvivors and survivors on admission and survivors on d 3.

survivors (61% *vs.* 32%, respectively; Table 1). IGFBP-3 protease activity correlated significantly with the PRISM score ($r = 0.60$; $P < 0.05$; Table 3). The median serum IGFBP-3 protease activity of survivors did not change significantly between 12 and 48 h, whereas a significant increase was observed between 0 and 48 h ($P < 0.05$).

Insulin and glucose levels

On admission nonsurvivors had significantly lower median serum insulin and glucose levels than survivors [insulin, 5 *vs.* 13 mU/liter ($P < 0.01$); glucose, 3.9 *vs.* 6.3 mmol/liter ($P < 0.05$)]. At that time two patients (both nonsurvivors) suffered from hypoglycemia (2.4 and 1.6 mmol glucose/liter), whereas two other children (both survivors) exhibited supranormal glucose levels (11.6 and 14.3 mmol glucose/liter). On admission the PRISM score did not correlate with insulin and glucose levels. At 48 h the median serum insulin levels of the survivors had increased significantly (from 13 to 19 mU/liter), whereas the median levels of glucose had not changed (from 6.2 to 6.0 mmol/liter).

IL-6 and TNFα levels

On admission nonsurvivors had significantly higher median serum levels of IL-6 and TNFα than survivors [IL-6, 1200 *vs.* 50 ng/ml ($P < 0.01$); TNFα, 34.0 *vs.* 5.3 pg/ml ($P < 0.01$)]. These levels correlated significantly with the PRISM score, IGFBP-1 and IGFBP-3 protease ($r = 0.56–0.69$), and the levels of total IGF-I and free IGF-I ($r = -0.40$ to -0.55; Table 3).

Discussion

Our study is the first to describe changes in the GH/IGF-I axis in children with acute, life-threatening meningococcal sepsis, showing differences between nonsurvivors and survivors. All children had septic shock, with significantly lower serum levels of total and free IGF-I and higher serum IGFBP-3 protease activity and serum IGFBP-1 levels compared with healthy children. However, nonsurvivors, had extremely high mean serum GH levels during a 6-h profile and, compared with survivors, had significantly lower total and free IGF-I levels, higher IGFBP-3 protease activity, and IGFBP-1 levels. Our study showed that extremely high mean plasma GH levels were highly associated with lethal outcome. In contrast, studies in critically ill adults revealed normal or high plasma GH levels regardless of patient outcome (17–24).

In this study survivors had normal or low GH profiles compared with healthy children. In contrast, nonsurviving children had extremely elevated mean plasma GH levels, with extreme baseline GH levels above 88–120 mU/liter, without low trough values between GH peaks. Their mean plasma GH levels were significantly higher than those of survivors and were 25 times higher than those reported in critically ill adults (17). One of the explanations for the extremely elevated plasma GH levels in nonsurviving children might be an increased GH secretion in response to the endotoxin and cytokine load (25). Furthermore, the low serum IGF-I levels might have intensified GH production by a lack of feedback inhibition of pituitary GH secretion. The lost relationship between GH secretion and plasma IGF-I, which is a characteristic feature of critical illness in adults (26), is thus also seen in this study.

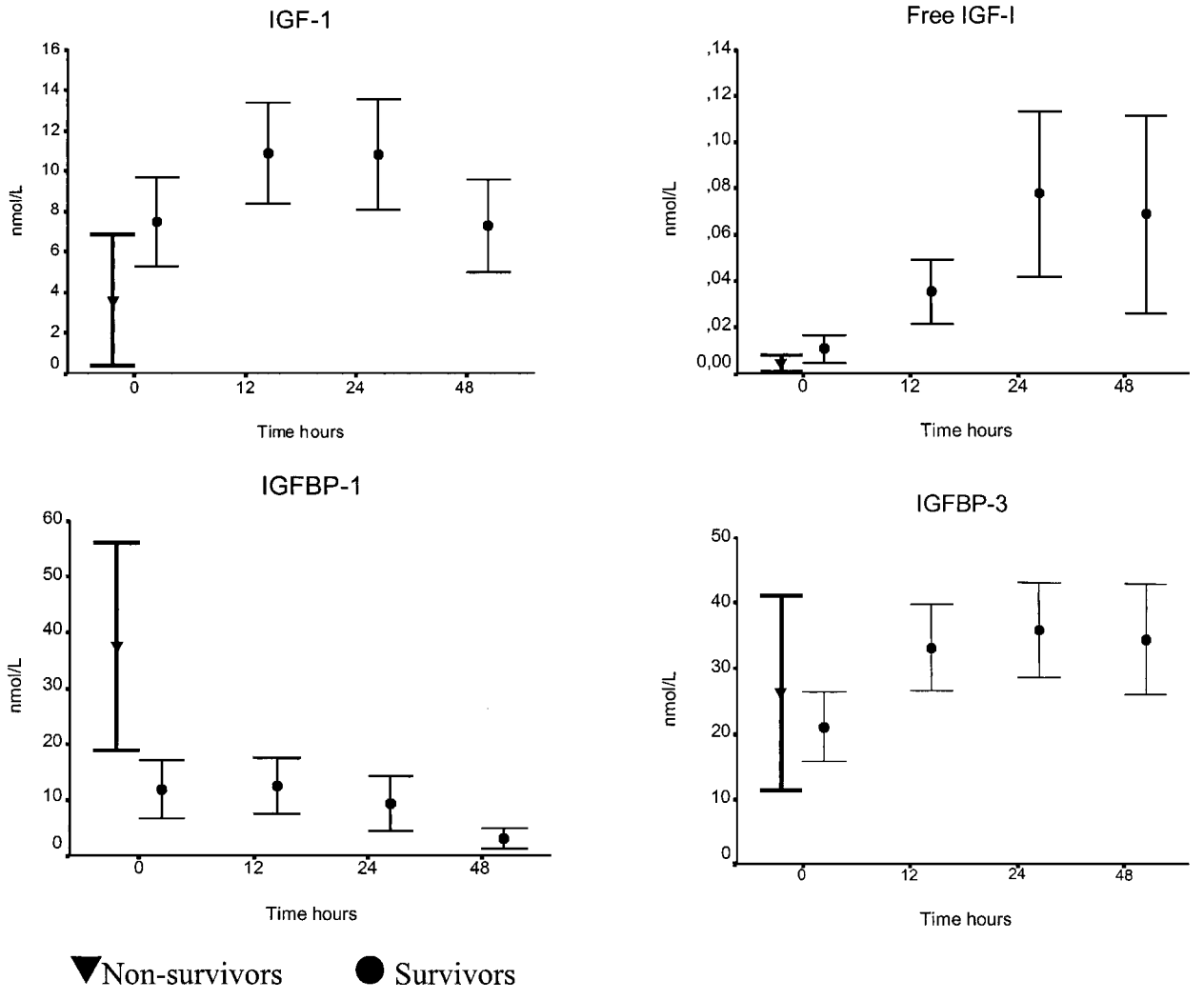

FIG. 2. Differences in levels of total IGF-I, free IGF-I, IGFBP-1, and IGFBP-3 between nonsurvivors and survivors upon admission and 12, 24, and 48 h after admission in survivors. *Error bars* represent the mean and 95% confidence intervals.

TABLE 3. Non linear correlation coefficients (Spearman) between different parameters on admission

	Total IGF-I	Free IGF-I	IGFBP-I	IGFBP-3	IGFBP-3 protease	IL-6	TNF-α
PRISM	−0.44[a]	−0.55[a]	0.45[a]	−0.19	0.60[a]	0.69[b]	0.64[b]
Total IGF-I		0.84[b]	−0.48[a]	0.54[b]	0.10	−0.40[a]	−0.45[a]
Free IGF-I			−0.50[a]	0.32	−0.29	−0.55[a]	−0.55[a]
IGFBP-I				0.06	0.19	0.60[b]	0.59[b]
IGFBP-3					0.44	0.02	−0.09
IGFBP-3 protease						0.66[a]	0.56[a]
IL-6							0.86[b]

[a] $P < 0.05$ (two-tailed).
[b] $P < 0.01$ (two-tailed).

All patients had significantly lower serum levels of total and free IGF-I and IGFBP-3 and higher IGFBP-3 protease activity compared with healthy children. Low serum IGFBP-3 levels and increased serum IGFBP-3 protease activity have also been demonstrated in critically ill adult patients (17, 27). Nonsurvivors, however, had significantly lower total and free IGF-I levels and higher IGFBP-3 protease activity than children who survived; however, IGFBP-3 levels were not different. Because nonsurvivors had extremely high GH levels one would have expected higher IGF-I and IGFBP-3 levels compared with the survivors. There are a few possible explanations for these differences. The production of IGF-I and IGFBP-3 in the liver might be severely reduced in nonsurvivors due to more severe perfusion disturbances, which were reflected in high levels of serum lactate as previously reported (7). It has also been shown that levels of cytokines, particularly TNFα, which was significantly higher in nonsurvivors, inhibit the hepatic production of IGF-I and IGFBP-3 (28). In this study there were also significant inverse relationships between the TNFα and IL-6 levels and the

serum levels of total and free IGF-I. Furthermore, cytokines might have inhibited GH receptor mRNA expression (29) and will lead to reduced GH receptor function (4). As a result, a reduction of hepatic production of IGFBP-3 and acid-labile subunit (ALS) will occur, and less IGFBP-3 and ALS will be available to form stable 150-kDa ternary complexes with IGF-I in the circulation (30). Less stable 50-kDa binary IGF-I/IGFBP-3 complexes will be formed. Consequently, influenced by IGFBP-3 protease, the rate of dissociation of IGF-I from IGFBP-3 is increased, and the distribution of serum IGFs among the pool of 150-kDa (ternary) and 40-kDa (binary) complexes is altered (31). The higher IGFBP-3 protease activity in nonsurvivors may serve as an attempt to increase the bioavailability of already diminished IGF-I. Nonsurvivors and survivors showed the same level of IGFBP-3, which can be explained by the assay used, which was not able to detect binary IGFBP-3 complexes. Thus, the total of ternary and binary IGFBP-3 complexes in survivors might have been higher than that in nonsurvivors.

Normally, circulating IGFBP-1 is mainly regulated by insulin through inhibition of gene transcription in the liver, constituting a major determinant of free IGF-I availability (32, 33). In this study no correlation was found between IGFBP-1 and insulin, which indicates that other factors might be involved. During unfavorable metabolic conditions the hepatocyte appears to alter the production of IGF regulatory proteins by increasing cAMP production, which stimulates IGFBP-1 and suppresses IGF-I and ALS production (34, 35). In addition, in critically ill patients circulating IGFBP-1 undergoes posttranslational modification and exists primarily in a highly phosphorylated form (36). Phosphorylated IGFBP-1 has a significantly higher affinity for circulating free IGF-I and thus will bind more free IGF-I, thereby limiting the hypoglycemic potential of free IGF-I in a setting of low substrate availability and increased energy requirements (37, 38). As a consequence of the increased binding of circulating free IGF-I to IGFBP-1, there is reduced IGF-I availability, which will lead to limited IGF-I-induced glucose uptake to the tissues (30). Thus, in nonsurvivors the elevated levels of phosphorylated IGFBP-1 might have bound all of the severely reduced circulating free IGF-I. In addition, in nonsurvivors, the observed low levels of glucose and insulin (7) decreased the availability of glucose for the cell and may have contributed to the alteration in cell metabolism inevitably leading to cell death. Furthermore, our study demonstrated highly significant positive relationships on admission between serum TNFα and IL-6 levels and serum IGFBP-1 levels; all levels were highest in children who died. It has previously been shown that both TNFα and IL-6 can directly stimulate IGFBP-1 production by HepG2 human hepatoma cells (39). Increased IGFBP-1 levels have also been associated with increased mortality risks in acutely ill adult patients (40). Thus, very high serum IGFBP-1 levels might serve as a predictor for lethal outcome in children with meningococcal septic shock. We postulate that in nonsurvivors there was an ultimate attempt to regulate the metabolism, but the physiological reserves of the IGF-I/IGFBP system were totally consumed, resulting in insufficient free IGF-I availability for the tissues.

An important question remains of whether the extremely elevated plasma GH levels in the nonsurvivors have deleterious effects. In various studies it is suggested that administration of GH leading to high plasma GH levels might potentiate the deleterious effects of bacterial endotoxin, thereby contributing to septic shock (6, 41). GH and many cytokines belong to the same receptor family and share a number of common postreceptor signaling pathways (42). For that reason the extremely high levels of cytokines and GH observed in our nonsurvivors might have induced either overactivity or dysregulation of the receptors or depletion of messengers necessary for the effective transduction of signals via the receptors or via postreceptor signaling pathways. This might have interfered with the necessary adaptive immunological, metabolic, and hormonal responses, contributing to the cascade of adverse events leading to death.

During the first 48 h after admission survivors demonstrated an increase in the number and amplitude of GH peaks, mean GH, free IGF-I, and IGFBP-3 levels and a decrease in IGFBP-1 levels. These changes may represent a mechanism to recover from sepsis and may point to restoration of anabolic function.

In conclusion, our study shows that nonsurviving children with meningococcal sepsis had extremely high levels of cytokines, mean GH, and IGFBP-1, very different from levels in those who survived. Our results indicate that meningococcal sepsis induced complex pathophysiological mechanisms, many of which are not yet known and which are probably interlinked. Surviving children showed adaptive responses aiming at increasing host defense and metabolic substrates for survival, whereas nonsurvivors showed exaggerated responses. It is not yet known why children respond in either way.

Based on the extreme levels of TNFα and IL-6 observed in nonsurvivors, one might conclude that these levels depend on the magnitude of the endotoxin load, but they might also depend on the individual capacity to respond with effective adaptive mechanisms. In that respect, genetic predisposition and/or age-related maturation of the various systems might play a role. The remarkable alterations in the GH/IGF-I axis in the nonsurvivors raised the question of whether these hormonal abnormalities influenced the outcome of the disease or proved to be an effect, rather than a cause, of the pathology.

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