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Tumor Necrosis Factor-α, Interleukin-1β, and Interleukin-6 Plasma Levels in Neonatal Sepsis

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ABSTRACT. Tumor necrosis factor-α, IL-1β, and IL-6 are thought to be involved in the pathogenesis of sepsis with gram-negative bacteria. We studied these cytokines during neonatal sepsis with mainly gram-positive bacteria. Ten newborns with clinical sepsis and 22 healthy controls were enrolled in the study. TNFα plasma levels proved to be increased in the newborns with sepsis up to 560 ± 234 pg/mL (ng/L) *versus* 36 ± 4 pg/mL (ng/L) in the control group ($p < 0.005$), whereas IL-6 plasma levels in newborns with sepsis were 79.700 ± 37.500 pg/mL (ng/L) *versus* 55 ± 28 pg/mL (ng/L) in the control group ($p < 0.01$). The IL-1β plasma levels were only slightly elevated in the group newborns with sepsis [up to 18 ± 5 pg/mL (ng/L) *versus* 7 ± 1 pg/mL (ng/L) in the control group ($p < 0.01$)]. After the start of therapy with antibiotics, both TNFα and IL-6 plasma levels decreased concomitantly with the improvement of the clinical situation within 2 d. These data confirm the abundant presence of TNFα and IL-6 during neonatal sepsis, whereas IL-1β appeared to be present in small amounts only. Nevertheless, the IL-1β but not the TNFα plasma level appeared to correlate inversely with the decrease in diastolic tension as standardized according to birth weight ($R = 0.66$, $p = 0.04$). TNFα, IL-1β, and IL-6 were not correlated with any febrile response in the group with sepsis. Inasmuch as only moderate temperature increases were seen in these patients, we hypothesize that a low IL-1β plasma level may explain the lack of a febrile response during neonatal sepsis. (*Pediatr Res* 33: 380–383, 1993)

Abbreviations

TNFα, tumor necrosis factor α

TNFα, IL-1β, and IL-6 are considered to be important mediators of the systemic host response to infection (1–6). These cytokines are produced mainly by activated monocytes and macrophages (7–9). During gram-negative sepsis in both children and adults, TNFα, IL-1β, and IL-6 serum levels are elevated (10–14).

The precise physiologic and, possibly, pathophysiologic role of systematically present cytokines is still unclear. High levels of cytokines might cause direct damage (2, 3, 15). For instance, injection of high amounts of recombinant human IL-1 can induce severe hypotension and fever in animals and humans (16–19). Similar effects have been observed when TNFα is given (6, 20–23). It is suggested in the literature that IL-1β potentiates the effects of TNFα several-fold (24, 25).

Neonatal sepsis is a disease with a high morbidity and mortality and is mainly caused by gram-positive bacteria (26). Because these microbial species are infrequently associated with infections in adults, their occurrence may be explained by the immature immune system in newborns (27). Cell wall fragments and toxins from gram-positive organisms can induce TNFα and IL-1β production (28–30). In agreement with this, a recent study indicates that TNFα serum levels are high in newborns with systemic infections and shock (31).

The aim of the present study is to seek a correlation between the plasma levels of TNFα, IL-1β, and IL-6 and the clinical phenomena observed during neonatal sepsis.

MATERIALS AND METHODS

EDTA blood (EDTA, 1.5 mg/mL blood) specimens were obtained by venipuncture or from an arterial catheter and immediately transported on ice to the laboratory. Plasma was separated from the blood within 30 min. Aliquots were stored at −80°C until assayed. The plasma TNFα, IL-1β, and IL-6 levels were measured using enzyme-linked immuoassays from Medgenix according to the manufacturer's procedure (EASIA-assay, Medgenix, Brussels, Belgium). Because of the smaller volume of the blood specimens that can be taken from neonates, we used an adapted method with smaller sample volumes (100 μL for TNFα and IL-1β measurements and 50 μL for the IL-6 measurement). The control, interassay, and intraassay values obtained with this procedure were within the same range as with the original method. The detection limit for TNFα was 25 pg/mL (ng/L); for IL-1β, 4 pg/mL (ng/L); and for IL-6, 6 pg/mL (ng/L). In the septic group, the first blood sample was taken before the start of antibiotic treatment, and the following samples were taken every 8 to 12 h over 2 to 3 d. In the control group, one sample was taken.

Informed consent was obtained from the parents of each newborn before the start of the study. The study was approved by the hospital ethics committee.

Statistical analysis. Differences between groups were analyzed with t test. Differences were considered significant at $p < 0.05$. All data are expressed as mean ± SEM.

Patients. During a 6-mo period, 18 consecutive newborns with clinical suspicion of sepsis were evaluated. Two or more of the following clinical symptoms were considered to be indicative for sepsis (26, 32, 33). The symptoms used in the study were lethargy, apneic spells, poor peripheral circulation, and poor feeding. The 18 newborns underwent venipuncture for leukocyte count (1/L); leukocyte differentiation; measurement of C-reactive protein

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(μg/mL or mg/L). TNFα, IL-1β, and IL-6 (pg/mL or ng/L); and blood culture. All patients began taking antibiotics at the time of suspicion of sepsis.

Sepsis was defined as clinical suspicion and a positive blood culture, or as clinical suspicion and inflammatory phenomena within 72 h: leukopenia less than 5.10^9/L, a leukocytosis greater than 20.10^9/L with an increase of the total immature neutrophil percentage, and a C-reactive protein greater than 50 μg/mL (mg/L) were considered inflammatory phenomena. Sepsis was found in 10 of 18 patients; of those 10, eight had positive blood cultures. The other two sepsis patients (no. 8 and 10) had negative blood cultures, probably because their blood was obtained only after they started receiving antibiotic therapy. Their blood parameters (as defined above) indicated sepsis. In eight patients, sepsis was not indicated by blood culture or blood parameters; these patients were not included in the study. Antibiotics were discontinued in these patients after 3 d, and they recovered within a few days.

The control group included 22 healthy controls (11 females, 11 males; mean gestational age 36.5 ± 1 wk; mean birth weight 2867 ± 178 g; mean age 4 ± 1 d). Blood for cytokine measurements was obtained once when blood samples were taken for glucose, bilirubin, or Hb measurements.

In one individual in the control group, an IL-1β plasma level was not measured due to an inadequate volume of the plasma sample. One patient in the septic group was lost for followup due to transfer to another hospital. In this case, cytokine plasma levels were not available on the 2nd and 3rd d. In four patients in the septic group, the C-reactive protein level was not measured due to inadequate sample volume. Patient data of the 10 septic newborns (mean gestational age 33 ± 1 wk, mean birth weight 2005 ± 266 g) are shown in Table 1. The antibiotic regimen was ampicillin (150 mg/kg/d) and cefotaxime (100 mg/kg/d), when newborns became septic in the first days of life ($n = 5$). In the case of sepsis in newborns aged 7 d or more ($n = 4$), the initial antibiotic therapy was flucloxacillin (100 mg/kg/d) and cefotaxime (100 mg/kg/d). The rectal temperature was monitored every 3 h. Diastolic tension was monitored continuously with an arterial catheter ($n = 2$) or every 15 min with an automatic sphygmomanometric method (Dynamap, Criticon Inc.) ($n = 8$). When the clinical situation deteriorated during treatment with these antibiotics, therapy was changed to gentamicin (5 mg/kg/d) and imipenem (50 mg/kg/d). This was the case in the neonate with the *Enterobacter* sepsis only. None of the newborns died.

RESULTS

In all the newborns with sepsis, IL-6 plasma levels were elevated at the time of the first blood sample. Values of 79 700 ± 37 500 pg/mL (ng/L) *versus* 55 ± 28 pg/mL (ng/L) in the control group were found ($p < 0.01$) (Fig. 1). IL-1β plasma levels were detectable in nine out of the 10 newborns with sepsis. Values of 18 ± 5 pg/mL (ng/L) *versus* 7 ± 1 pg/mL (ng/L) in the control group were measured ($p < 0.01$) (Fig. 2). TNFα plasma levels were found to be elevated in eight of the 10 newborns with sepsis. Values were 560 ± 234 pg/mL (ng/L) in the septic group *versus* 36 ± 4 pg/mL (ng/L) in the control group ($p < 0.01$) (Fig. 3). In one patient with sepsis due to *Staphylococcus epidermidis*, the TNFα value increased slightly during the first 12 h of therapy [from 73 to 103 pg/mL (ng/L)]. With the improvement of the clinical situation after the start of therapy, TNFα, IL-1β, and IL-6 plasma levels decreased and normalized in all patients in nearly 2 d (Figs. 1, 2, and 3).

In the septic group, no correlation was found between the rectal temperature at the time of the first blood sample and the TNFα, IL-1β, or IL-6 plasma level in the first blood sample (Fig. 4).

Although low, the initial IL-1β level proved to be correlated with the difference between the mean diastolic blood pressure according to birth weight minus the measured diastolic blood pressure ($r = 0.66$, $p = 0.04$; 34) (Table 1). The elevation of the initial TNFα plasma levels did not correlate significantly with the difference in diastolic tension, nor did the IL-6 plasma levels.

DISCUSSION

In this report, we show that newborns with gram-positive sepsis have elevated TNFα and IL-6 plasma levels, whereas IL-1β is only slightly increased. The observed increases of TNFα and IL-6 plasma levels in this study extend the results obtained in children and adults during gram-negative sepsis (10–14). The increase of TNFα in this study extends the findings reported in a recent paper in which TNFα was measured only once in newborns suspected for sepsis (31).

New in this study are the profiles of TNFα, IL-1β, and IL-6 plasma levels during the first 61 h of sepsis, the correlation between the IL-1β plasma levels and the decrease in diastolic tension, and the obvious lack of a febrile response during sepsis in newborns with low IL-1β plasma levels.

Although *in vitro* studies observed a defective production of IL-6 and TNFα by umbilical cord blood monocytes in cell cultures, newborns can produce as much TNFα and IL-6 during sepsis with gram-positive bacteria as adults or children with sepsis (11–14, 35, 36). In our present *in vivo* study, the production of TNFα and IL-6 proved to be independent of the gestational age, even though *in vitro* studies observed dependence on the gestational age (37–39).

Animals and humans given an i.v. injection of recombinant human IL-1, lipopolysaccharide, or endotoxins developed decreased systemic arterial pressure (6, 17–19, 40, 41). Human

Table 1. *Clinical data of patient group**

Patient	GA (wk)	BW (g)	Sex	Age (d)	Temp (°C)	BP (mm Hg)	ΔBP	Blood culture	Leuko (×10⁹/L)	i%	CRP (μg/mL or mg/L)	TNFα (pg/mL or ng/L)	IL-1β (pg/mL or ng/L)	IL-6 (pg/mL or ng/L)
1	40.0	4850	F	2	37.9	39/26	19	GBS	4.9	8	387	327	38	89 700
2	35.0	1350	F	7	38.5	43/32	−4	*S. epid.*	10.7	16		180	10	523
3	29.0	1320	F	15	38.3	55/34	−6	*S. epid.*	10.6	8	11	103	10	148
4	32.0	1440	M	8	38.0	64/53	−24	*S. epid.*	17.5	1	11	45	8	31
5	32.5	1320	F	7	38.5	28/17	11	*Entbac.*	4.4	5	159	902	47	410 000
6	26.0	950	F	1	37.5	33/23	3	GBS	3.7	5	75	144	9	142 000
7	34.0	2320	M	1	37.7	47/28	5	GBS	2.0	4		30	13	66 300
8	31.0	1706	M	7	38.2	35/29	1		2.3	5	71	2200	32	55 500
9	37.0	2980	F	1	36.8	92/55	−19	GBS	2.7	21		25	6	30 400
10	34.0	1830	F	1	37.5	40/25	6		1.5	0		1640	4	2 300

* GA, gestational age; BW, birth weight; age, age at the moment of diagnosis; temp, temperature at the moment of diagnosis; BP, blood pressure at the moment of diagnosis; ΔBP, mean blood pressure according to birth weight minus measured blood pressure at the time of diagnosis; leuko, leukocyte count; i%, immature neutrophil percentage; CRP, peak values of C-reactive protein within 72 h (μg/mL or mg/L); GBS, group B streptococcus; *S. epid.*, *Staphylococcus epidermidis*; *Entbac*, *Enterobacter*. TNFα, IL-1B, and IL-6 are levels in plasma.

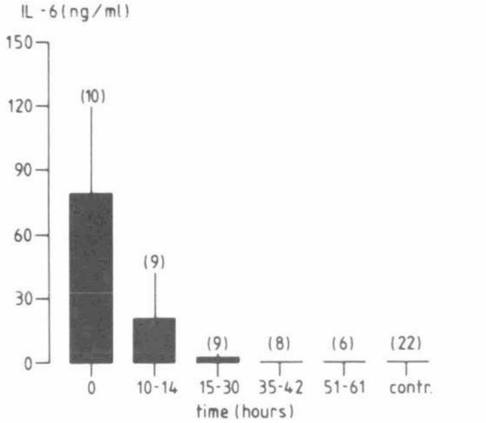

Fig. 1. IL-6 plasma concentrations during the first 61 h of treatment in 10 newborns with sepsis. IL-6 plasma levels as mean ± SEM, in ng/mL or μg/L (total number of neonates included in each group of hours is indicated above the column).

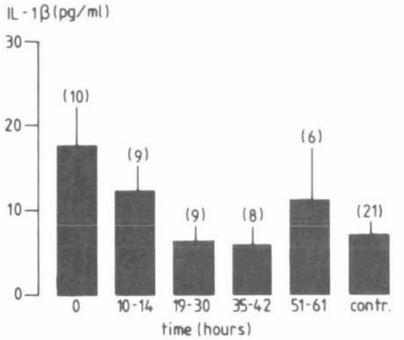

Fig. 2. IL-1β plasma concentrations during the first 61 h of treatment in 10 newborns with sepsis. IL-1β plasma levels as mean ± SEM, in pg/mL or ng/L (total number of neonates included in each group of hours is indicated above the column).

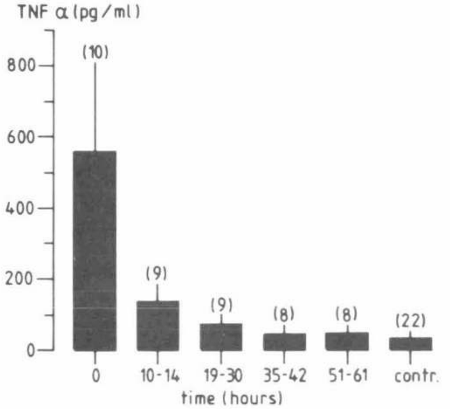

Fig. 3. TNFα plasma concentrations during the first 61 h of treatment in 10 newborns with sepsis. TNFα plasma levels as mean ± SEM, in pg/mL or ng/L (total number of neonates included in each group of hours is indicated above the column).

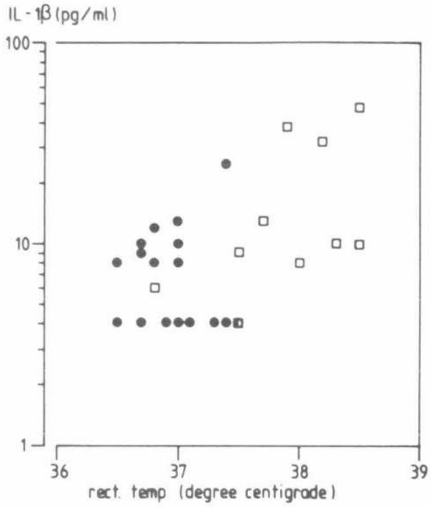

Fig. 4. IL-1β plasma concentrations *vs* the rectal temperature. IL-1β plasma level (pg/mL or ng/L) of each newborn in the patient group (□) and the control group (●) in the first blood sample plotted against the rectal temperature (°C) of every individual newborn at the time of the first blood sample ($R = 0.378$, $p = 0.28$).

recombinant TNF also induces decreased blood pressure in animals and humans, but in animal studies the decrease in mean blood pressure was delayed (21, 23). After bacterial challenge, TNFα induces an increase in IL-1 appearance that can be reduced with antibodies to TNFα (42). Hypotension due to lipopolysaccharide or endotoxins can be blocked with recombinant IL-1 receptor antagonist (17, 18, 40). This suggests that the hypotension in studies with TNF, endotoxins, or lipopolysaccharide is due to IL-1 induction. Although the IL-1β plasma levels are remarkably low in our study, IL-1β plasma levels measured *in vivo* during sepsis in newborns appear to be correlated with the decrease in diastolic tension according to birth weight. Before conclusions can be drawn, however, this needs further investigation.

IL-1β has been indicated as the most pyrogenic cytokine (16). Systemic IL-1β induces a sudden prostaglandin E_2 increase in the anterior hypothalamic center. This increase of hypothalamic prostaglandin E_2 raises the set-point temperature, which results in a febrile response (16).

In contrast to adults and children, newborns have little or no febrile response to infection or sepsis (32). There is no difference between the IL-1β secretion of stimulated cord blood monocytes from preterm and term newborns and the secretion of stimulated monocytes of adults (37). However, IL-1β production by stimulated cord blood monocytes was decreased in infants with infectious complications postpartum (38). In our study, the IL-1β plasma levels found in newborns during sepsis were remarkably low, especially when compared with findings during adult sepsis in which IL-1β plasma levels varied between 120 and 1500 pg/mL (ng/L) (11, 14, 43). During sepsis in newborns, the monocytes may be inable to secrete more IL-1β. Luger *et al.* (44) observed an association between fatal outcome of sepsis in adults and an inability of IL-1 production in monocytes of those patients. Apart from IL-1, some authors found a relation between IL-6 and fever, but IL-6 is thought to be less pyrogenic than IL-1β (45, 46). IL-6 release is induced by TNF and IL-1; therefore, the levels of IL-6 also may often correlate with the amount of fever. Although a moderate febrile response was seen in some newborns with sepsis, we found no correlation between the temperature degree and the IL-1β or IL-6 plasma levels.

In conclusion, during neonatal sepsis with mainly gram-positive bacteria, TNFα, IL-1β, and IL-6 plasma levels were increased 15-fold, 2-fold, and 1.500-fold, respectively.

IL-1β plasma levels in neonatal sepsis correlate with the decrease in diastolic blood pressure according to birth weight. Although there is a slight difference between the IL-1β plasma levels in the groups, there is no correlation between the temperature degree and the IL-1β plasma level. Also, the IL-6 plasma level is not correlated with the temperature degree. Therefore, we hypothesize that a low IL-1β plasma level may explain the lack of a febrile response and that the increase of IL-6 plasma levels and fever are not directly related.

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