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ORIGINAL ARTICLE

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Serial monitoring of interleukin-1β, soluble interleukin-2 receptor and lipopolysaccharide binding protein levels after death

A comparative evaluation of potential postmortem markers of sepsis

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Abstract We prospectively monitored the postmortem course of interleukin-1β (IL-1β), soluble interleukin-2 receptor (sIL-2R) and lipopolysaccharide binding protein (LBP) in septic and non-septic fatalities to evaluate their potential as biochemical postmortem markers of sepsis. Serum concentrations were determined by chemiluminescent immunometric assays. In both the sepsis group and the control group a postmortem increase of IL-1β levels with the progression of time after death was observed, in both groups mainly starting from the reference concentration of healthy individuals (5 pg/ml) and with no significant differences at later time points postmortem. SIL-2R (reference limit 1,000 U/ml) was highly elevated in all individuals included in the sepsis group at all time points postmortem with statistically significant differences between the sepsis and control groups ($p<0.01$). An excessive postmortem decrease of sIL-2R serum levels associated with progression of time after death was observed in all cases included in the sepsis group in contrast to just 1 out of 16 control cases. LBP (reference limit <10 g/ml) was elevated in all sepsis cases whereas in the control group LBP levels were below 10 μg/ml in 88%. The postmortem time course of LBP serum concentrations showed a continuous increase in both the sepsis and control groups. We conclude that sIL-2R and LBP seem to represent appropriate diagnostic tools for the postmortem diagnosis of sepsis in forensic autopsy practice. sIL-2R serum levels above 1,000 U/ml and LBP serum levels above 10 μg/ml in peripheral venous blood obtained in the early postmortem interval can be regarded as diagnostic hints for an underlying septic condition in a deceased person.

Keywords Interleukin-1β · Soluble interleukin-2 receptor · Lipopolysaccharide binding protein · Sepsis · Postmortem

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Introduction

Sepsis is a constellation of clinical signs and symptoms resulting from a generalised activation and expression of the host's inflammatory response [1, 2]. In clinical practice sepsis is currently diagnosed by cardinal signs such as tachypnoea, fever or hypothermia, tachycardia, and leukocytosis or leukopenia that are neither specific nor sensitive for sepsis [3, 4]. While diagnosing a septic condition may represent a problem even in the living patient, the postmortem diagnosis of sepsis is far more difficult since the major limitation to a precise postmortem diagnosis of sepsis is the often non-specificity of macroscopic and routine histological findings encountered in such fatalities. In addition, special problems may arise in medico-legal autopsy cases that occurred outside hospital where data on the medical history and clinical course or the symptoms prior to death are frequently not available at the time of autopsy.

It has become evident recently that endogenous mediators such as interleukin-1β (IL-1β), soluble interleukin-2 receptor (sIL-2R) and lipopolysaccharide binding protein (LBP) play a central role in the host's systemic inflammatory response and are part of a complex cascade

of pathways involved in the pathogenesis and course of sepsis [5, 6, 7, 8, 9, 10]. Recent clinical research has correlated the excessive release of these inflammatory proteins with the severity and outcome of sepsis [11, 12, 13, 14]. However, the specific role of these endogenous mediators in sepsis remains largely undefined. Several studies support the concept of a combination of several markers for the diagnosis and monitoring of sepsis in the living patient [15, 16, 17, 18, 19, 20].

As a step towards the further identification of potential biochemical postmortem markers of sepsis, we performed serial postmortem measurements of IL-1β, sIL-2R and LBP serum levels in femoral venous blood samples obtained during the early postmortem interval from sepsis-associated fatalities and non-septic control individuals to (1) assess if these markers can contribute to the postmortem diagnosis of sepsis, and (2) enlighten knowledge on the postmortem behaviour of these cytokines.

Materials and methods

Study groups

Two study groups were formed. In both groups, the time of death was well defined by clinical means (study group 1) as well as witness reports and police investigations (study group 2).

1. Sepsis group: 8 patients (5 males, 3 females, age range 14–77 years, mean age 53 years) from the intensive care unit of the Department of Anesthesiology, University Hospital Eppendorf, Hamburg, Germany, with the diagnosis of sepsis in vivo according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [3]. All patients included in this study group had a well documented medical history, including a precise anamnesis, microbiological investigations in vivo and the presence of detailed clinical and laboratory data (e.g., on circulatory and hematological parameters). Repeated blood cultures in vivo were positive for bacterial pathogens in all patients; the outcome of microbiology and individual patients' characteristics are shown in Table 1. The clinical cause of death was multiple organ failure due to sepsis in all cases and no other cause of death was revealed by autopsy and histology.
2. Control group: 16 selected autopsy cases (14 males, 2 females, age range 33–77, mean age 59.5 years, all fatalities occurred out of hospital) examined at the Institute of Legal Medicine, University Hospital Eppendorf, Hamburg, Germany, with no medical history of a septic condition prior to death and no other diseases found at autopsy except for the cause of death that was, where appropriate, verified by histology: myocardial infarction n=6, acute right cardiac failure due to chronic obstructive pulmonary disease n=5, acute alcohol intoxication (range of blood alcohol levels 325–480 mg/dl) n=4, and gastrointestinal bleeding (esophageal variceal hemorrhage) n=1. In each case a blood sample from the femoral vein obtained at autopsy was analysed for alcohol concentration using gas chromatography with mass spectrometry and an alcohol dehydrogenase-specific assay.

Table 1 Individual clinical and biological characteristics of the patients included in the sepsis group

Patient no.	Gender	Age	ICU days	Microbiology	Cause of sepsis
1	f	77	15	*Klebsiella pneumoniae*	Peritonitis (perforation of small bowel)
2	m	67	21	*Enterobacter cloacae*	Peritonitis (perforation of small bowel)
3	m	43	6	*Klebsiella oxytoca*	Peritonitis (abdominal gun shot wounds)
4	m	57	3	*Enterococcus spec., Corynebacterium spec.*	Peritonitis (perforation of small bowel)
5	m	14	4	*Staphylococcus aureus*	Burn injuries
6	f	58	11	*Escherichia coli, Enterococcus spec.*	Peritonitis (perforation of small bowel)
7	m	47	28	*Coagulase negative Staphylococci*	Liver failure following liver transplantation
8	f	64	18	*Streptococcus pneumoniae*	Oesophagogastrectomy

ICU Intensive care unit.

Toxicological analysis for drugs was performed on specimens from cardiac blood, urine and liver tissue using a full complement of analytical methods such as high pressure liquid chromatography and gas chromatography with mass spectrometry. Toxicological analyses for drugs other than alcohol were negative in all cases.

Serum samples

Postmortem blood samples were collected by aspiration with a sterile needle and syringe from the femoral vein (from the same site) at defined time points (between 1 and 48 h postmortem) from the individuals included in both study groups: at least 5 postmortem blood samples were obtained from each subject. In addition, one antemortem venous blood sample from the patients included in the sepsis group was analysed which was collected from the patients shortly before death within the scope of the clinical routine taking of blood on the intensive care unit (time span of antemortem blood sampling within 1 and 3 h prior to death). After centrifugation, the serum was immediately frozen at −80°C.

Determination of IL-1β, sIL-2R and LBP

Serum levels of IL-1β, sIL-2R and LBP were measured using chemiluminescent immunometric assays (Immulite IL-1β, Immulite IL-2R, Immulite LBP, Diagnostics Products Corporation, Los Angeles, CA) on an Immulite automated analyzer (Diagnostics Products Corporation, Los Angeles, CA). The lower detection limits of the assays are as follows: IL-1β 5 pg/ml, sIL-2R 5 U/ml, LBP 0.2 μg/ml.

Analysis of data

A linear regression model was used to calculate IL-1β, sIL-2R and LBP serum levels in the sepsis group and control group at the time of death. *P*-values were calculated for the sepsis and control group using the Wilcoxon Mann-Whitney U-test. To evaluate the statistical significance of the calculated IL-1β, sIL-2R and LBP postmortem serum levels in the sepsis group and to compare them with their authentic equivalents (as determined antemortem in the living patients), the Wilcoxon matched-pairs-signed-rank Test was used.

Results

Serum IL-1β concentrations

In the sepsis group, antemortem IL-1β levels were elevated above the reference limit of healthy individuals (5 pg/ml) in 4 out of the 8 cases (50%). The highest antemortem IL-1β serum level was measured in a case of burn injury (3,660 pg/ml, patient no. 5, 1.4 h antemortem) whereas in the remaining 3 cases the antemortem IL-1β serum concentrations ranged between 5.5 and 11 pg/ml (reference limit 5 pg/ml). In the samples obtained postmortem, IL-1β serum levels ranged between 5 and 13,685.7 pg/ml. Postmortem IL-1β levels exceeded 5 pg/ml in 7 out of the 8 cases (87.5%). In all of these 7 cases a continuous elevation of the IL-1β serum concentration was observed with an increase of the postmortem interval. The highest postmortem IL-1β serum level (13,685.7 pg/ml) was also measured in the case of burn injury (patient no. 5, 48 h postmortem). In the remaining 6 cases, IL-1β serum concentrations ranged between 5.2 (patient no. 1, 6 h postmortem) and 229.1 pg/ml (patient no. 2, 48 h

Table 2 Serum IL-1β, sIL-2R and LBP concentrations (values expressed as mean ±SD and median) and *p*-values at different time points after death of the sepsis group and control group

Serum marker	Hours postmortem	Sepsis group (S) (*n*=8)		Control group (C) (*n*=16)		*P*-value
		Mean	Median	Mean	Median	
IL-1β (pg/ml)	0	1391.3±3915.3	5.5	4.4±2.3	4.0	<0.01
	6	1429.4±4019.6	7.5	5.6±3.0	4.5	<0.02
	12	1469.1±4126.5	10.5	7.3±4.5	5.1	<0.05
	24	1553.1±4348.4	15.7	13.0±10.7	8.5	>0.1
	36	1646.5±4580.4	21.6	25.0±26.4	14.4	>0.1
	48	1756.1±4820.8	29.2	51.2±65.1	23.7	>0.1
sIL-2R (U/ml)	0	5627.1±3180.0	4520.6	623.6±197.1	652.0	<0.01
	6	5421.4±3151.8	4318.2	629.1±184.6	664.8	<0.01
	12	5226.8±3122.9	4125.4	638.3±179.5	620.3	<0.01
	24	4866.8±3063.0	3747.3	661.6±189.0	664.9	<0.01
	36	4541.7±2999.7	3442.4	691.1±190.5	726.9	<0.01
	48	4246.9±2932.8	3147.7	726.1±203.6	773.1	<0.01
LBP (μg/ml)	0	37.6 ±29.1	24.4	8.1±2.2	7.6	<0.01
	6	36.0±27.7	23.6	7.7±2.0	7.3	<0.01
	12	34.6±26.4	22.8	7.4±1.8	6.9	<0.01
	24	31.8±23.9	21.3	6.9±1.6	6.6	<0.01
	36	29.3±21.7	20.1	6.4±1.5	6.3	<0.01
	48	27.0±19.7	18.8	5.9±1.4	6.1	<0.01

postmortem). In the control group, IL-1β serum levels were between 5 and 231.3 pg/ml. In 11 out of the 16 non-septic control subjects, a continuous increase of IL-1β serum concentrations above the reference limit of healthy individuals (5 pg/ml) was also found with increasing length of the postmortem interval. In the remaining 5 cases, IL-1β serum concentrations did not exceed the reference limit (5 pg/ml) at any time point after death. When comparing IL-1β serum concentrations determined in sepsis group and control group at the calculated time of death (t=0), IL-1β serum concentrations were significantly higher in the sepsis group (p<0.01). IL-1β serum concentrations were still higher in the sepsis group 6 h after death, (p<0.02) but with an increase of the length of the postmortem interval more significant differences between the sepsis and control groups were not noticeable (p>0.1) (Table 2).

Serum sIL-2R concentrations

Postmortem serum sIL-2R concentrations were elevated above the clinical reference limit of healthy individuals (<1,000 U/ml) in all patients included in the sepsis group over the entire observation period (Fig. 1). In the antemortem blood samples, sIL-2R values ranged between 2,514 U/ml (patient no. 2) and 12,462 U/ml (patient no. 1); all values measured were above the reference limit of 1,000 U/ml. Postmortem concentrations ranged between 1,274.6 U/ml (patient no. 2, 48 h postmortem) and 10,809.7 U/ml (patient no. 1, 6 h postmortem). With progression of the postmortem period, a sharp decrease of sIL-2R serum levels was observed. In the control group, sIL-2R serum levels ranged between 230 U/ml and 1,008.3 U/ml. In one case where the patient had died from an acute alcohol intoxication, the measured sIL-2R levels (1,008.3 U/ml) slightly exceeded the reference limit of living individuals. A notable increase of serum levels was noticed in 1 out of the 16 control cases (cause of death in this case was myocardial insufficiency). In the remaining 15 cases, a sharp decrease of the postmortem serum levels was observed with time. The postmortem IL-2R concentrations in the sepsis group were significantly higher over the whole study period when compared with the control group (p<0.01). In addition, sIL-2R serum levels as calculated for the time of death were significantly higher in the sepsis group than in the control group (p<0.01) (Table 2).

Serum LBP concentrations

In the sepsis group, postmortem serum LBP values were significantly higher than in the control group over the entire investigation period (p<0.01) ranging from 99.1 µg/ml (patient no. 1, 6 h postmortem) to 15.2 µg/ml (patient no. 4, 48 h postmortem) (Fig. 2). In the control group values ranged from 13.1 µg/ml (6 h postmortem) to 3.8 µg/ml (48 h postmortem) (data not shown). A sharp decrease of LBP values was found in both study groups

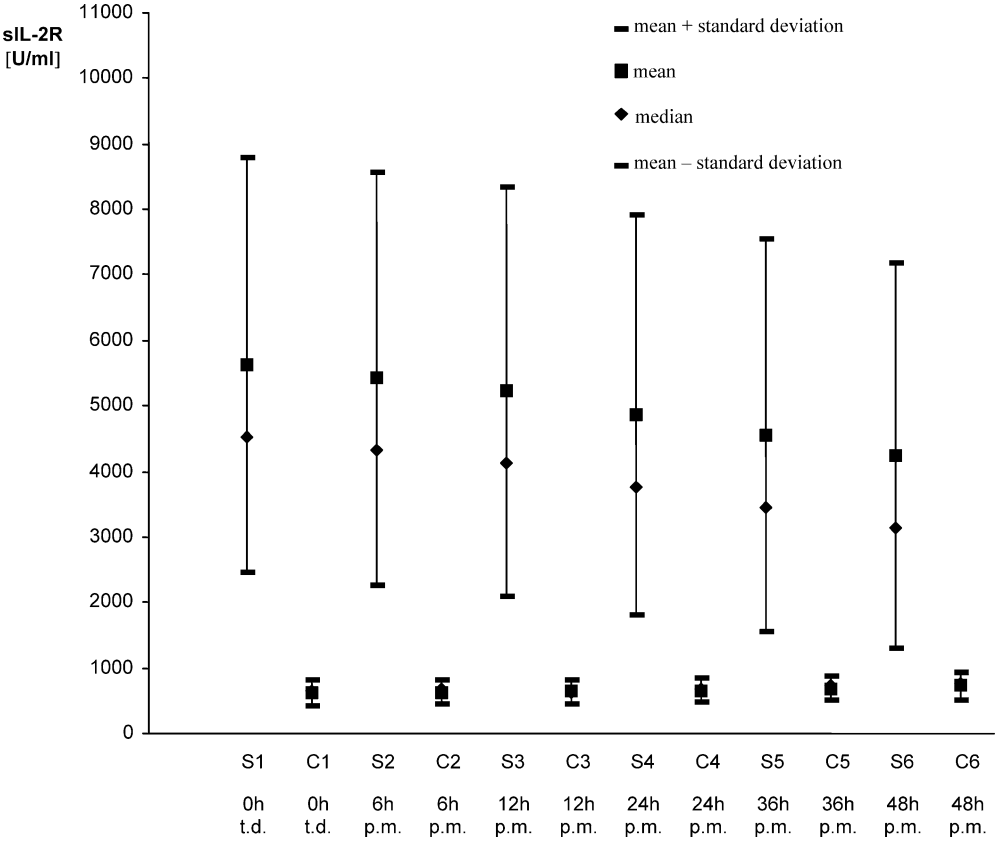

Fig. 1 Serum sIL-2R concentrations in the sepsis group (S) and control group (C) at different time points postmortem and at the calculated time of death (*t. d.* time of death, *p.m.* postmortem)

(Table 2). Up to 48 h postmortem, each LBP value determined in the sepsis group exceeded the reference limit of healthy individuals (10 μg/ml) whereas in the control group the LBP levels were below this value in 14 out of the 16 cases. The remaining 2 cases showed slight elevations with a maximum of 13.1 μg/ml (6 h postmortem), the patients died of acute alcohol intoxication and myocardial insufficiency, respectively. Postmortem serum LBP values as calculated for the time of death were significantly higher in the sepsis than in the control group ($p<0.01$) (Table 2). The antemortem LBP levels ranged from 16.8 μg/ml (patient no. 4) to 117 μg/ml (patient no. 1) (Table 3).

Comparison of antemortem IL-1β, sIL-2R and LBP concentrations and calculated concentration at the time of death in the sepsis group

In determining the offset, IL-1β, sIL-2R and LBP values were calculated for the time of death ($t=0$) and the results were compared with the real antemortem IL-1β, sIL-2R and LBP values determined in the sepsis group (Table 3). The antemortem IL-1β levels measured in the serum samples collected shortly before death correlated well with IL-1β levels calculated for $t=0$ in all patients in the sepsis group by using regression analysis on the IL-β logarithms. With exception of the patient who died of burn injuries (patient no. 5), the antemortem IL-1β levels in the remaining 7 cases ranged between 5 and 11 pg/ml with a mean value of 6.1 pg/ml and ranged from 5 to 14.3 pg/ml at the time of death with a mean value of 7.1 pg/ml (reference limit 5 pg/ml). In the case of fatal burn injuries, an antemortem IL-1β serum level of 3,660 pg/ml (patient no. 5, 1.4 h antemortem) and a high IL-1β serum level calculated for $t=0$ (11,081.1 pg/ml, patient no. 5) were observed (Table 3).

There was a good correlation between sIL-2R values calculated for the time of death and the values measured antemortem (Table 3). The antemortem values for sIL-2R ranged from 2,514 U/ml (patient no. 2) to 12,462 U/ml (patient no. 1) with a mean of 6,713.1 U/ml and all values were above the reference limit.

The best correlation was found for LBP with a range from 16.8 μg/ml (patient no. 4) to 117 μg/ml (patient no. 1) and a mean value of 41.6 μg/ml (Table 3).

Discussion

It the present study we assessed the diagnostic value of serial postmortem measurements of three inflammatory cytokines for the postmortem diagnosis of sepsis. The objective was to evaluate whether contemporary clinical concepts regarding the understanding of the role of inflammatory mediators in the pathophysiology of sepsis and recent clinical research data on the subject of different biochemical parameters can be adopted for the forensic elucidation of death due to sepsis.

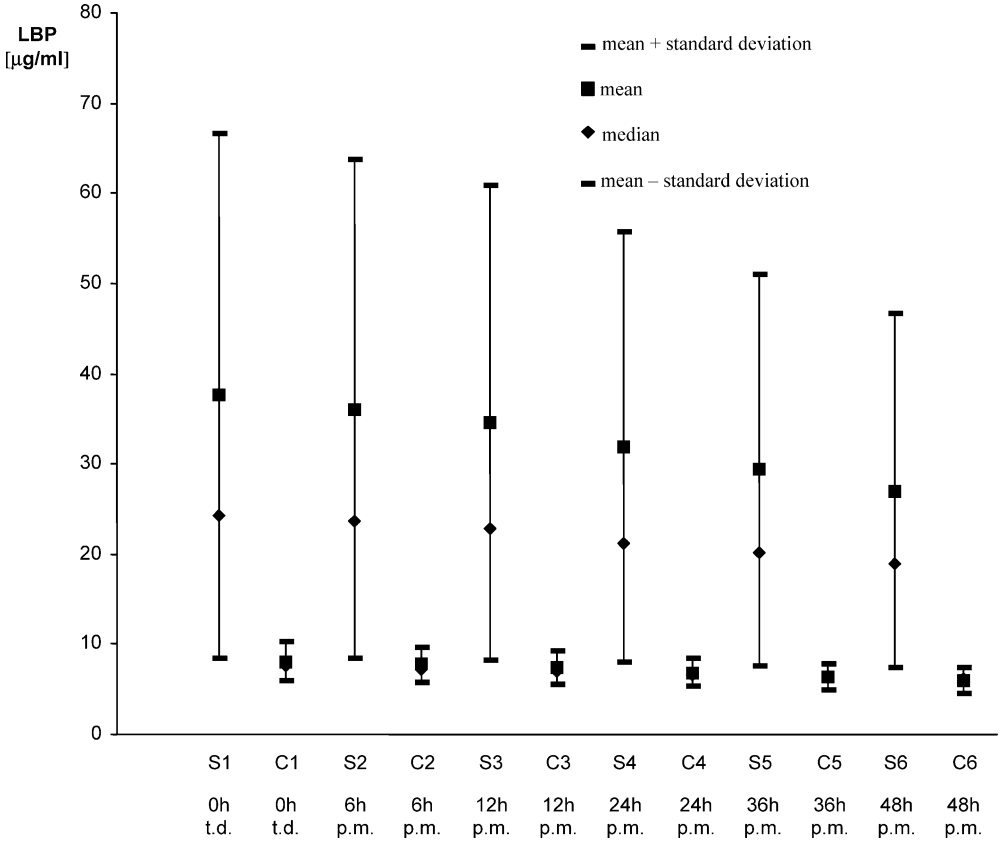

Fig. 2 Serum LBP concentrations in the sepsis group (S) and control group (C) at different time points postmortem and at the calculated time of death (*t.d.* time of death, *p.m.* postmortem)

Table 3 Individual antemortem IL-1β, sIL-2R and LBP serum concentrations of the subjects included in the sepsis group and calculated concentrations for the time of death (t=0)

Serum marker	Time	Patient no.							
		1	2	3	4	5	6	7	9
IL-1β (pg/ml)	a.m.	5.5	6.5	5.0	5.0	3660.0	5.0	11.0	5.0
	t=0	5.2	5.0	5.6	5.0	11081.1	5.4	14.3	9.1
sIL-2R (U/ml)	a.m.	12462.0	2514.0	8943.0	2782.0	8952.0	5327.0	7129.0	5596.0
	t=0	11125.6	2401.9	8937.4	2756.5	7266.3	3733.1	5308.2	3487.7
LBP (μg/ml)	a.m.	117.0	22.8	41.4	16.8	53.2	25.2	30.1	26.6
	t=0	103.4	21.9	34.9	16.2	53.7	22.1	21.6	26.6

IL-1β plays a central role in the host's inflammatory response to sepsis and appears early in the course of infection. This proinflammatory cytokine is part of a complex cascade of mediators all participating in the pathogenesis of sepsis and septic shock. IL-1β is predominantly produced by monocytes/macrophages as an inactive 31 kDa precursor protein (pIL-1β) and is processed to its active 17.5 kDa form by the specific interleukin-1β converting enzyme (ICE). During infection, IL-1β is detectable within the circulation and serum concentrations may have prognostic significance on patient outcome [2, 7, 8]. The reference limit of IL-1β serum concentrations in living individuals is less than 5 pg/ml. In the present study we found a notable postmortem increase of IL-1β levels in both study groups. As a possible explanation for the excessive increase of IL-1β levels in the sepsis group and the lesser increase in the control group, we favour an excessive systemic cellular autolysis as being responsible, thus leading to a considerable release of IL-1β preformed and stored in monocytes, macrophages, lymphocytes and endothelial cells (those cells that release cytokines upon systemic inflammatory host activation) in a higher concentration in septic individuals than in non-septic controls. However, this hypothesis is in contrast to the assumption of Blackwell and co-workers who theorised that cytokines are not stored in the cytoplasm but are newly synthesised [2]. In the serum samples obtained antemortem from the sepsis-related fatalities, IL-1β levels were elevated above the detection limit in only four out of eight cases (50%). Therefore, IL-1β seems to be of no great value for the postmortem diagnosis of sepsis.

SIL-2R is a marker of lymphocyte activation, with a molecular weight between 40 and 45 kDa and is produced by T-cells and granulocytes [10]. The reference value of sIL-2R in healthy individuals is below 1,000 U/ml. Recently, several clinical studies have shown the diagnostic and prognostic benefits of sIL-2R determination in patients with sepsis and septic shock [9, 10, 17, 19, 20, 21, 22]. During sepsis and multiple organ failure, sIL-2R levels can rise above 27,120 U/ml whereas in healthy subjects the highest sIL-2R concentration reported so far is 654 U/ml [19]. The results of the present study show that serial postmortem measurements of serum sIL-2R concentrations can be considered as a valuable diagnostic tool to distinguish sepsis-associated fatalities from underlying non-septic causes of death postmortem. While postmortem sIL-2R levels were highly elevated above the reference limit of 1,000 U/ml in all individuals included in the sepsis group at all time points postmortem, in 15 out of 16 controls (94%) sIL-2R concentrations were below the reference limit. This observation is well in line with the clinical concept of a positive correlation between an increase in mortality rate in critically ill patients and sIL-2R levels above 1,000 U/ml [19, 20]. Using linear regression analysis sIL-2R levels calculated for the time of death correlated well with the antemortem sIL-2R levels measured in blood samples collected shortly before death (Table 3).

The acute phase protein LBP is a 60 kDa serum glycosylated protein, forming high-affinity complexes with bacterial endotoxins (lipopolysaccharide, LPS) and functioning as an opsonin, that is produced and secreted by hepatocytes [5, 6]. The reference limit of LBP in healthy individuals is less than 10 μg/ml. During the host's acute phase response to sepsis, the concentration of LBP can rise up to 50 μg/ml within 24 h [18]. In the samples obtained antemortem from the sepsis-related fatalities and over the entire postmortem period up to 48 h, LBP levels were elevated above 10 μg/ml. In contrast, in the control group the LBP levels were below 10 μg/ml in 14 (88%) out of the 16 cases. We found a notable postmortem decrease in LBP serum levels that correlated well with the progression of the time after death in all cases included in the sepsis group as well as a postmortem decrease in LBP levels to a lesser degree in the serum samples obtained from non-septic individuals. The decrease of LBP serum levels in both groups may be explained by (1) postmortem proteolysis of LBP with the onset of significant hemolysis (thus resulting in non-detection of LBP in serum) and (2) no relevant postmortem release of LBP from hepatocytes due to a considerable resistance of the hepatocytes to autolysis in the early postmortem interval. The authentic LBP levels (as determined antemortem in the living patients) and their postmortem equivalents that were calculated for the time of death using linear regression analysis showed a statistically significant correlation in all septic-related fatalities (Table 3).

No published data are available so far concerning the time course, clearance and half-life of IL-1β, sIL-2R and LBP under various in vitro (ex vivo) conditions. In vivo, IL-1β has a half-life of a few minutes. After a transfusion of contaminated erythrocytes, peak IL-1β levels were detectable after 4 h and returned to normal values 19–28 h posttransfusion in survivors, whereas in the non-survivors these levels remained elevated for 22 h [2]. To date, no in

vivo data are available on the half-life of sIL-2R and LBP. Following surgical procedures in humans, LBP levels have been reported to increase after 3 h with a maximum after 12 h [23] and in animal experiments maximum LBP concentrations were described after 24 h [18].

Apart from sepsis, elevated levels of IL-1β, sIL2R and LBP have been demonstrated in a number of life-threatening conditions. SIL-2R is known to be elevated in viral infections, autoimmune diseases, several malignancies and organ graft reactions [9, 10, 21, 22]. LBP levels are usually enhanced after extensive surgical procedures like cardiopulmonary bypass operations [23]. Therefore, these conditions have to be excluded by knowledge of the previous medical history and autopsy findings when using IL-1β, sIL-2R and LBP as postmortem markers for sepsis.

Special constellations of death due to sepsis are frequently encountered in forensic autopsy practice, e.g., septic conditions following iatrogenic interventions or infected pressure sores [24, 25]. Since in a number of such cases information about the circumstances of death or data of the deceased's symptoms prior to death are often not available at the time of the autopsy, especially when fatalities occurred out of hospital, and in addition, gross pathology and histology is, apart from the detection of septicopyemic abscesses, usually unspecific in sepsis-associated fatalities [26], the postmortem diagnosis of fatal sepsis is occasionally more difficult in medico-legal casework than it is in clinical pathology.

A broad spectrum of inflammatory mediators such as acute phase proteins and cytokines are involved in the pathogenesis of sepsis and recent clinical research has extensively focused on the identification of different biochemical parameters for the diagnosis and monitoring of sepsis in vivo. The present prospective study gives an initial insight into the postmortem behaviour of IL-1β, sIL-2R and LBP in sepsis and non-septic individuals. In earlier studies prospectively investigating postmortem serum levels of different inflammatory mediators involved in the pathophysiology of sepsis, we were able to determine postmortem reference limits for procalcitonin (1 ng/ml), interleukin-6 (1,500 pg/ml) and C-reactive protein (10 mg/l) in postmortem femoral blood samples [27, 28]. Postmortem LBP serum levels that were monitored serially in the present study show a similar behaviour when compared to postmortem serum levels of C-reactive protein, as investigated earlier [27, 28]. Both are acute phase proteins secreted by hepatocytes showing a continuous increase in both septic fatalities and non-septic controls after death.

According to our results, sIL-2R and LBP seem to represent appropriate diagnostic tools for the postmortem diagnosis of sepsis in forensic autopsy practice: sIL-2R serum levels above 1,000 U/ml and LBP serum levels above 10 μg/ml in peripheral venous blood obtained in the early postmortem interval can be regarded as diagnostic hints for an underlying sepsis in a deceased. At least two postmortem measurements of sIL-2R and LBP should be performed at different time points postmortem with the objective to calculate the most probable level at the time of death by using linear regression analysis. For a more definite analysis, in order to prove an underlying sepsis at the time of death beyond any reasonable doubt, e.g., in sepsis-related fatalities following medical procedures or the infection of pressure sores, a combination of several biochemical postmortem markers of sepsis is recommended.

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