Blood Levels of Cytokines in Brain-Dead Patients: Relationship With Circulating Hormones and Acute-Phase Reactants

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We hypothesized that increased levels of blood cytokines occur in brain-dead patients, and that these cytokines are responsible for some of the endocrine and/or acute-phase reactant abnormalities found in these patients. We measured blood levels of cytokines, hormones, and acute-phase reactants in 18 brain-dead potential organ donors at the moment of establishing the legal diagnosis of brain death and compared them with levels found in a control group. Although interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels were within the normal range, interleukin-6 (IL-6) levels were clearly above the normal range in all patients (median, 1,444 pg/mL; range, 75 to 11,780). In the brain-dead group, total thyroxine (tT_4), free T_4 (fT_4), triiodothyronine (T_3), thyrotropin (TSH), dehydroepiandrosterone sulfate (DHEA-S), testosterone, albumin, Zn, and osteocalcin levels were decreased, T_3 resin uptake index (T_3 RUI), corticotropin (ACTH), cortisol, 11-deoxycortisol (11-DOC), 17-hydroxyprogesterone (17-OHPr), aldosterone, luteinizing hormone, and follicle-stimulating hormone levels were normal, and reverse T_3 (rT_3), renin, and C-reactive protein (CRP) levels were increased. Multiple regression analysis demonstrated significant interrelations between IL-6 and T_4, T_3, testosterone, and CRP. We also studied the evolution of some of these parameters in four patients with severe head injury who finally developed brain death. IL-6 levels on admission to the intensive care unit (ICU) were above the normal limits, as in other patients with cranial trauma, but when the patients developed brain death, there was a pronounced increase in IL-6 levels. We conclude that brain death is accompanied by high levels of IL-6. IL-6 may be partially responsible for the hormonal and acute-phase reactant abnormalities found in these patients.

DIFFERENT SITUATIONS associated with tissue damage, such as bacterial infections,[1-3] burns,[4] pancreatitis,[5] head injury,[6,7] and major surgery,[8-11] have been reported to increase blood levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and interferon gamma. These cytokines are important mediators of both metabolic and immunologic responses.[12] IL-1, IL-6, and TNF activate the hypothalamic-pituitary-adrenal axis.[12,13] Although one important effect of these cytokines is to increase the release of hypothalamic corticotropin-releasing factor, they can also directly stimulate the corticotropes to release corticotropin (ACTH) and the adrenal glands to release glucocorticoids.[13,14] IL-1, IL-6, and TNF have been implicated in the pathogenesis of the sick euthyroid syndrome[15-17] and inflammation-induced hypogonadism.[12] These cytokines are also partially responsible for the acute-phase response.[18]

Brain death is characterized by extensive cortical necrosis.[19] In these necrotic areas, cell lysis and/or inflammation may stimulate monocytes and macrophages to release various immune cytokines.[12] Cytokines can also be produced within the head by neurons, microglial cells, pituitary cells, and endothelial and smooth muscle cells of brain blood vessels.[12]

Brain-dead organ donors have various endocrine and metabolic derangements.[19,20] Some of these abnormalities, such as diabetes insipidus, are due to hypothalamic-neurohypophyseal damage.[21-23] Other hypothalamic-pituitary dysfunctions may also occur.[22,24] The euthyroid low-triiodothyronine (T_3)–low-thyroxine (T_4) sick syndrome is a common occurrence.[21,23,25] The pathogenesis of these abnormalities is not well understood.

We hypothesized that increased circulating blood levels of cytokines occur in brain-dead subjects as a marker of brain necrosis, and that these cytokines are responsible, at least partially, for some of the hormonal and/or acute-phase reactant abnormalities found in these patients. The study was performed in two phases. First, we undertook a cross-sectional study (1) to assess circulating levels of cytokines at the moment of establishing the legal diagnosis of brain death, and (2) to correlate levels of these cytokines with simultaneous levels of blood hormones and acute-phase reactants. Second, we studied the time course of some of these parameters in patients with severe head injury, comparing those who finally developed brain death with those who did not.

SUBJECTS AND METHODS

Cross-Sectional Study

Blood samples were obtained from 18 brain-dead patients at the moment of diagnosis of legal brain death. According to Spanish law, the onset of brain death is defined by the irreversible cessation of all brain functions as detected by standard clinical tests and an isoelectric electroencephalogram.[26] This study was approved by our institution's Review Board. Relatives of the patients gave informed consent for blood samples to be taken for analysis. The study group consisted of 11 men and seven women ranging in age from 18 to 67 years (mean ± SD, 46.1 ± 18.8). All were healthy and were not undergoing medical treatment before the situation that resulted in brain death. Except for three, all were organ donors for transplantation. Causes of brain death included head injury (n = 7), intracranial hemorrhage (n = 7), hypoxic brain damage (n = 3), and cerebellar infarction (n = 1). The injury was limited to the head in all traumatic patients. The time from

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admission to the intensive care unit (ICU) to declaration of brain death ranged from 1 to 10 days (mean ± SD, 3.6 ± 3). Treatment with corticosteroids and occurrence of infectious diseases during hospitalization were exclusion criteria, since both could interfere with the results. Eleven patients received vasoactive drugs to produce an adequate hemodynamic situation: eight received dopamine at doses ranging from 5 to 15 μg/kg/min, two epinephrine, and one nitroprusside. Although six patients had been treated with thiopental at doses ranging from 3 to 7 g/d, this drug was witheld for the diagnosis of brain death, and thiopental levels were undetectable at the time of diagnosis. Five patients developed diabetes insipidus and were treated with vasopressin. As a control group, we used 18 healthy subjects matched for age and sex.

Blood concentrations of the following substances were measured: total T_4 (tT_4), free T_4 (fT_4), total T_3, T_3 resin uptake index (T_3RUI), thyrotropin (TSH) (all via radioimmunoassay [RIA] kits, Amersham, Buckinghamshire, England), reverse T_3 (rT_3) (RIA kit, Serono Biodata, Montecelio, Italy), ACTH (IRMA kit, Nichols Institute, San Juan Capistrano, CA), cortisol, 11-deoxycortisol (11-DOC), 17-hydroxyprogesterone (17OHPr) (all via RIA kits, ICN Biomedicals, Costa Mesa, CA), renin (RIA kit, Incstar, Sorin, France), aldosterone, testosterone, dehydroepiandrosterone sulfate (DHEA-S) (all via RIA kits, Diagnostic Products, Los Angeles, CA), follicle-stimulating hormone, luteinizing hormone (both via RIA kits, Serono Diagnostics, Coinsigna, Switzerland), IL-1β, IL-6 (both via IRMA kits, Medgenix, Fleurus, Belgium), TNF-α (ELISA kit, T-Cell Sciences, Cambridge, MA), albumin (Hitachi autoanalyzer, Mannheim, Germany), C-reactive protein (CRP) (nephelometry), zinc (atomic absorption spectrophotometry), and osteocalcin (RIA kit, Nichols Institute). Levels of gonadotropins and androgens were measured only in men. All these assays were previously validated in our laboratory.[27-30] Intraassay and interassay coefficients of variation were less than 7% and 15%, respectively, in all assays.

Longitudinal Study

We prospectively studied the evolution of some of these parameters in four patients (three men and one woman aged 37, 40, 44, and 56 years, respectively) with severe head injury who finally developed brain death. Blood samples were taken (1) upon arrival to the ICU, (2) the first morning at the ICU (9 AM), (3) the second morning at the ICU (9 AM), (4) the third morning at the ICU (9 AM), and (5) upon diagnosis of brain death (at 6, 7, 9, and 10 days at the ICU). These data were compared with data obtained at the same time points from another four patients with severe head injury, matched for age and sex, who did not develop brain death.

Statistical Methods

Results are expressed as the median and range, since the distribution was nonparametric. Comparisons between groups in the cross-sectional study were made with the Mann-Whitney *U* test. The relationship of cytokine levels with hormones and acute-phase reactants was analyzed by stepwise multiple regression, after logarithmic transformation of the variables, and Spearman rank correlation. The longitudinal study comparisons were made with the Mann-Whitney *U* test (between groups) and Kruskal-Wallis test (within groups). STATA software (Computing Resource Center, Santa Monica, CA) was used for statistical calculations. *P* values less than .05 were considered significant.

RESULTS

Cross-Sectional Study

Results of the different determinations in brain-dead and control groups are listed in Table 1. There were no differences in IL-1β and TNF-α levels between the two groups. In the brain-dead group, six of 18 patients had IL-1β levels below the sensitivity of the assay and 12 had detectable levels within the normal range. In the brain-dead group, nine of 11 patients had TNF-α levels below the sensitivity of the assay and two had detectable levels within the normal range. IL-6 levels were extremely high in the brain-dead group, with all determinations clearly above the normal range. There were no differences in IL-6 levels between patients with and without head trauma.

Patients in the brain-dead group had decreased levels of tT_4, fT_4, T_3, and TSH and increased levels of rT_3. They also showed a trend for an increased T_3RUI, which did not reach significance. No differences in ACTH, cortisol, 11-DOC, and 17-OHPr levels were observed between the groups. DHEA-S levels were decreased in male brain-dead patients. Renin was increased in brain-dead patients, whereas aldosterone showed a nonsignificant trend for decreased levels. Testosterone levels were decreased in male brain-dead patients, whereas gonadotropins were within the normal range. CRP levels were increased in the brain-dead group, and albumin, Zn, and osteocalcin were decreased.

Multiple regression analysis of hormonal parameters, acute-phase reactants, and cytokines detected significant interrelations between IL-6 and tT_4 (Spearman correlation coefficient $r_s = -.46$, $n = 15$, $P < .05$), IL-6 and T_3 ($r_s = -.61$, $n = 16$, $P < .01$), IL-6 and testosterone ($r_s = -.65$, $n = 8$, $P < .05$), and IL-6 and CRP ($r_s = .46$, $n = 14$, $P < .05$).

Longitudinal Study

Results of determinations at the different times in the two groups are listed in Table 2. On admission to the ICU, both groups showed normal levels of tT_4, fT_4, T_3, and Zn, whereas cortisol and IL-6 levels were above the normal range. In those patients who developed brain death, tT_4, fT_4, T_3, and Zn decreased progressively and reached their lowest levels at brain death. A similar pattern was found in the other group for the fourth sample (the third morning at the ICU), but in the last sample, these parameters improved. Cortisol levels were highest on admission to the ICU in both groups, but a statistically significant decrease was observed only in the brain-dead group. Upon diagnosis of brain death, cortisol levels tended to be lower in brain-dead than in non–brain-dead patients, but the difference was not significant (probably due to the small number of patients). Within the period of study, IL-6 levels were above the normal range in both groups, but at brain death a dramatic increase was observed.

DISCUSSION

Transplantation of organs in their optimal metabolic state requires better knowledge of the hormonal and metabolic situation of brain-dead subjects, since some kind of intervention on the metabolism of the donor could improve clinical transplantation results.

Previous studies have assessed endocrine function in

Table 1. Cytokines, Hormones, and Acute-Phase Reactants in Brain-Dead Patients and Control Subjects

Parameter	Control Group				Brain-Dead Group		
	No. of Subjects	Median	Range	*P*	No. of Subjects	Median	Range
IL-1 (pg/mL)	18	<5	<5-18	NS	18	9.5	<5-26
TNF (pg/mL)	10	<10	<10-22	NS	11	<10	<10-25
IL-6 (pg/mL)	18	<5	<5-17	<.0001	16	1,444	75-11,780
tT_4 (μg/dL)	18	8	4.9-11.2	<.0001	17	4.7	2.8-8.6
fT_4 (ng/dL)	18	1.2	0.75-1.94	.01	18	0.86	0.44-1.28
T_3RUI	18	1	0.85-1.13	NS	17	1.020	0.77-1.16
T_3 (ng/mL)	18	107	86-171	<.0001	18	22	<20-107
rT_3 (ng/mL)	18	0.25	0.1-0.37	.001	14	0.43	0.08-1.01
TSH (mIU/mL)	18	2.3	0.7-5.3	<.0001	17	0.28	<0.1-1.6
ACTH (pg/mL)	18	19	9.3-50	NS	18	11.7	4.2-116
Cortisol (μg/dL)	18	16.2	5.1-28	NS	15	15.4	3.2-38
11-DOC (ng/mL)	18	3	2.1-7.5	NS	18	3	0.7-35.5
17-OHPr (ng/mL)	11	1.5	0.3-2.8	NS	12	0.95	0.09-2.5
DHEA-S (ng/mL)	10	1,832	895-3,840	.019	10	1,310	190-1,920
Renin (ng/mL/h)	18	3	1.4-6.5	<.0001	18	16	0.3-42
Aldosterone (pg/mL)	18	227	33-449	NS	16	64	20-414
LH (mIU/mL)	11	4.1	1-15	NS	10	4.1	0.8-21.8
FSH (mIU/mL)	11	2.8	1.7-5.8	NS	10	3.6	1-10.2
Testosterone (ng/mL)	11	5.4	3.9-9.9	.003	10	1.1	0.2-6.6
Albumin (g/dL)	18	4.6	3.6-5.2	<.0001	16	3	2-5
CRP (mg/dL)	18	<0.14	<0.14-4.2	.002	15	10.4	0.3-46.7
Zn (μg/dL)	18	88.5	35-133	.0001	16	46.5	3-82
Osteocalcin (ng/mL)	13	5.1	2.6-8.1	.0001	10	1.2	0.3-2.9

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone.

brain-dead patients[20-25,30] or the blood cytokine profile in head trauma,[6,7] but our study is the first to link cytokines, hormones, and acute-phase reactants in brain-dead patients.

We have demonstrated that IL-6 levels are markedly increased in brain-dead patients, whereas circulating levels of IL-1β and TNF-α are not. The origin of circulating IL-6 in these patients might be the brain, since other causes of increased levels of IL-6 were excluded (infections, tissue damage in other parts of the body, etc.), and there were no differences between patients with and without head trauma. In this respect, Fassbender et al[31] have shown a significant increase in plasma IL-6 but not IL-1 or TNF within the first hours after an acute stroke. The increase in this cytokine was significantly correlated with the extent of the brain lesion and was also significantly associated with poor functional and neurologic outcome. Another possible mechanism is that a humoral factor released from the

Table 2. Time Course of IL-6, Hormones, and Zinc in Two Groups of Patients With Severe Head Injury

Parameter	ICU Stay										Kruskal-Wallis Probability
	On Admission		1st Morning		2nd Morning		3rd Morning		At Brain Death		
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	
Brain-dead (n = 4)											
tT_4 (μg/dL)	9.6	8.1-11.2	9.8	8.5-12.9	6.8	6-10.4	6.1	5-6.4	3.6	2.8-4.5*	.005
fT_4 (ng/dL)	1.39	1.13-1.55	1.61	0.93-1.62	1.12	0.84-1.13	0.95	0.84-0.98	0.88	0.44-1.14*	.04
T_3 (ng/mL)	135	56-149	44	33-62	34	29-40	21	21-35	<20	<20-21†	.003
Cortisol (μg/dL)	55	50.9-58	65	33.8-85	39	33.7-68	47.2	30-60	14	9.2-27.5†	.024
IL-6 (pg/mL)	39	15-126	131	78-207	82	69-249	119	41-159	2,221	1,897-2,731*	.015
Zn (μg/dL)	101	31-113	57	34-94	50	38-72	65	65-79	36	26-82†	.023
									Same Day at ICU		
Non–brain-dead (n = 4)											
tT_4 (μg/dL)	8	7.1-8.8	5.7	5.4-6.3	4.9	4.6-7	4.8	3.8-5.5	6.8	1.8-7.9	.02
fT_4 (ng/dL)	1.49	1.11-1.55	1.19	1.14-1.45	1.07	1.06-1.35	0.95	0.89-0.95	1.48	1.25-1.55	.006
T_3 (ng/mL)	98	47-134	38	27-70	27	<20-53	25	<20-45	40	<20-50	NS
Cortisol (μg/dL)	47.2	18.9-55	20.2	12.8-29	18.2	16.6-27.2	24.8	11.4-26	20.4	14.6-25.7	NS
IL-6 (pg/mL)	84	41-215	56	52-149	66	56-81	106	50-148	43	18-154	NS
Zn (μg/dL)	65	52-133	62	34-142	65	45-75	84	52-123	80	54-114	NS

*P = .02 *v* non–brain-dead group.

†P = NS *v* non–brain-dead group.

necrotic tissue could trigger a systemic production of IL-6, as recently reported in rats with inflammation induced by burns.[32] Catecholamines at supraphysiologic doses can induce increased levels of IL-6.[33] Regrettably, we did not measure catecholamine levels in our patients, but other investigators have shown that catecholamine levels decrease after brain death[34,35]; therefore, catecholamines are probably not involved in the increase in IL-6 in our patients, although this possibility remains to be investigated. IL-6 levels on admission to the ICU do not identify those patients who will finally develop brain death. The pronounced increase in IL-6 levels occurs after brain death.

The thyroid parameters demonstrated the existence of a low-T_3–low-T_4 sick syndrome in these patients, as previously reported.[21,23,25,30] The etiology of this syndrome seems multifactorial. Recently, attention has been focused on the role of cytokines as inducers of this syndrome. Administration of IL-1 or TNF to animals or healthy volunteers induces alterations in circulating thyroid hormones that resemble those of the sick euthyroid syndrome.[15,16] However, Chopra et al[36] found no relationship between serum T_3 and serum TNF levels in patients with this syndrome. Boelen et al[17] found that the low-T_3 syndrome in nonthyroidal illness was inversely correlated with high serum IL-6 levels, although IL-6 accounted for only 28% of the variation of serum T_3. Hashimoto et al[37] found that serum IL-6 concentration was inversely correlated with T_3 level in children with acute respiratory infection. In our study, there was a significant correlation between IL-6 and both T_3 and T_4, confirming the findings of these investigators. This suggests that IL-6 may be partially responsible for these abnormalities, although, as Boelen et al[17] have suggested, the increased IL-6 and decreased T_3 levels might well be independent expressions of the acute-phase reaction, and a still-unknown component of this reaction might be responsible for the generation of the sick euthyroid syndrome. Furthermore, in brain-dead patients, hypothalamic-pituitary damage may be present,[22,24] aggravating the effects of IL-6 on thyroid metabolism.

In our patients, adrenal function at the moment of brain death was characterized by ACTH and cortisol levels within the normal range of unstressed individuals, as previously reported.[21,23,25] These levels were probably inappropriately decreased for a stressful situation. In other studies, cortisol and ACTH levels could be decreased because of glucocorticoid therapy, but none of our patients received this type of drug. Mastorakos et al[14] have recently reported that recombinant IL-6 is the most potent stimulus to ACTH and cortisol release, but despite the high endogenous levels of IL-6 in our patients, there was no evidence of activation of the hypothalamic-pituitary-adrenal axis upon diagnosis of brain death, probably due to hypoxic hypothalamic-pituitary damage and/or dysfunction. A similar abnormality has recently been reported in patients with African trypanosomiasis.[38] In these patients, there is evidence of adrenocortical insufficiency due to ACTH deficiency despite high levels of IL-6. The investigators suggested that the parasite could have caused direct hypothalamic-pituitary damage.

In our patients, we also found two abnormalities previously described in intensive-care patients, ie, an elevated plasma renin activity accompanied by inappropriately low plasma aldosterone[39] and low levels of adrenal and gonadal androgens in the presence of normal gonadotropins.[40] Blood levels of gonadotropins were inappropriately low in relation to testosterone concentrations. It has been reported that IL-1 inhibits steroidogenesis in the testes, whereas it blocks activation of the hypothalamic-pituitary axis.[12] The influence of IL-6 on this axis is unknown,[12] but the significant inverse correlation between IL-6 and testosterone in our patients suggests that this cytokine is also involved. As with the thyroid and adrenal parameters, some kind of hypothalamic-pituitary damage and/or dysfunction seems to be present, since gonadotropin levels were not increased. It is possible that massive brain infarction is manifested by both high IL-6 and low pituitary hormone levels, reflecting hypothalamic-pituitary damage. This is in contrast to other forms of inflammatory stress in which hypothalamic-pituitary-adrenal function is increased while gonadotropins are inappropriately decreased due to cytokine inhibition of luteinizing hormone–releasing hormone neurons.

The increased levels of CRP and low levels of Zn indicate the presence of an acute-phase reaction in brain-dead patients. The significant correlation of serum CRP with IL-6 levels suggests that this cytokine is an important mediator of this response, as generally accepted in other clinical situations.[5,18,41] We also found a decreased level of osteocalcin (a marker of osteoblastic function) in brain-dead patients. We had previously reported that stressful situations induce a decrease in circulating osteocalcin.[29] The correlation coefficient between IL-6 and osteocalcin did not reach statistical significance, but this could be due to the small number of patients studied.

In conclusion, IL-6 levels are increased significantly in brain-dead patients and are probably responsible, at least in part, for some of the hormonal changes. It remains to be seen if some type of anti–IL-6 strategy can normalize the metabolic situation of the different organs in brain-dead patients and therefore improve clinical transplantation results.

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