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# Amino acid imbalance early in septic encephalopathy

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**Abstract** *Objective*: To evaluate plasma amino acid concentrations and markers of inflammation in the early stage and the course of septic encephalopathy. *Design*: Prospective, case series of patients with well-defined septic encephalopathy. *Setting*: Surgical department and intensive care unit of a university hospital. *Patients*: Seventeen patients with sepsis according to the ACCP/SCCM consensus conference criteria and encephalopathy based on neuropsychological tests, compared to a control group undergoing uncomplicated thoracic surgery. *Interventions*: None. *Measurements and results*: SOFA score, blood samples for plasma amino acids, procalcitonin and interleukin-6. Sepsis was determined to be the cause of encephalopathy in 14 of the 17 patients. Six patients developed septic shock, four died within the study period of 28 days. Within 12 h of the onset of septic encephalopathy, mean values of PCT and IL-6 were elevated ($p<0.001$) and the amino acids unbalanced (the ratio of branched-chain to aromatic amino acids was decreased, $p<0.001$). During the course of sepsis the decreased amino acid ratio was significantly, but moderately, correlated with elevated PCT and IL-6 levels. On study days when PCT was higher than 2 ng/ml, the amino acid ratio was significantly lower. In no patient was severe liver dysfunction seen. *Conclusions*: Metabolic disturbances with changes in amino acid levels can occur early in septic patients, without serious liver abnormalities. The present data suggest a possible role of amino acids in the pathogenesis of septic encephalopathy.

**Keywords** Septic encephalopathy · Plasma amino acid concentrations: branched-chain and aromatic · Procalcitonin levels · Interleukin-6 levels

## Introduction

Septic encephalopathy is a diffuse cerebral dysfunction occurring in septic illness without evidence of specific intracranial infection. Clinical features include acute alterations in mental status, changes of consciousness and disturbed orientation. Septic encephalopathy is believed to occur early in the sepsis process, although this has yet to be demonstrated experimentally. Also, the mechanisms causing septic encephalopathy have not yet been clarified. The incidence of septic encephalopathy is reported to be between 23% and 71%, due in part to the variety of definitions used for sepsis and neurological disorders [1, 2, 3, 4, 5, 6, 7, 8, 9]. As the pathogenesis remains unknown, no specific therapy is yet available. The mortality of septic patients with encephalopathy is increased compared to that of septic patients with normal mental status. However, if a patient's septic conditions improve, the neurological symptoms are potentially reversible.

Several hypotheses for the pathogenesis of septic encephalopathy have been discussed in the literature: metabolic derangements, a disturbed blood-brain barrier, direct bacterial invasion of the central nervous system (CNS), endotoxin effects on the brain or altered cerebral micro- and macro-circulation [2, 6, 10, 11, 12, 13]. A characteristic finding in septic patients in general is elevated plasma levels of aromatic amino acids together with unchanged or decreased levels of branched-chain amino acids. Such metabolic alterations may be of importance in the pathogenesis of septic encephalopathy, since aromatic amino acids are precursors of neurotransmitters. Altered plasma levels of aromatic amino acids may influence their uptake into the CNS and the neurotransmitter synthesis thereafter [1, 4, 10, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. This hypothesis is based on several animal experiments and two clinical studies, where imbalances between branched-chain and aromatic amino acids were described. But since most of the patients examined were already in a coma [15] or in septic shock [14], it is not clear whether the amino acids patterns were changed at the beginning of septic encephalopathy.

We therefore prospectively investigated patients in the early stages of well-defined sepsis and acute neurological impairment. The balance between branched-chain (BCAA) and aromatic (AAA) amino acids was determined and correlated with procalcitonin (PCT) and interleukin-6 (IL-6) as biochemical markers of inflammation. To our knowledge, this is the first study to investigate these parameters within 12 h of the diagnosis of sepsis and encephalopathy, and then to follow the patients through the course of sepsis up to 28 days.

## Materials and methods

### Study group

The study was performed at the Department of Surgery and Department of Anaesthesiology and Intensive Care Medicine at a university hospital. Full approval of the ethics committee and informed consent from the patient or their relatives was obtained prior to enrolment. Surgical and ICU patients were screened twice daily for the timing of the onset of sepsis and neurological criteria. The onset of sepsis had to be within the previous 12 h, using the sepsis definitions according to the ACCP/SCCM Consensus Conference [25]. For inclusion, patients also needed to have shown acute alterations in mental status (e.g., disorientation, confusion, altered consciousness) within 12 h. Approximately 40 beds were screened regularly over a 2year period.

Septic patients were only regarded as eligible if symptoms of encephalopathy had existed for no longer than 12 h. Patients with primary cerebral disease, encephalopathy with known different pathogenesis (e.g. hepatic encephalopathy), inherited coagulopathy, age under 18 years or pregnancy were not enrolled. Most patients screened with sepsis did not meet these strict inclusion criteria. Encephalopathy was then confirmed by three neuropsychological tests: the Benton test was used for orientation in time, the Mental Control test involves the alphabet, counting backwards and summing integers and the Syndrom Kurztest (SKT) is a longer test battery with nine performance sub-tests, including language fluency, recall, recognition and attention/concentration tasks of various levels of difficulty. The SKT is standardised for four age groups and three intelligence levels, and is internationally validated. We used two parallel forms for repeated testing [26].

Seventeen patients were prospectively entered into the study. Three patients were excluded because their cerebral symptoms were later determined to have other possible causes. Two patients developed delirium tremens in connection with alcohol withdrawal, while thalamus infarction caused exclusion of the third patient. Septic encephalopathy remained the diagnosis in 14 patients, 7 male and 7 female. The mean age was 60 years. In ten patients, the sepsis occurred postoperatively. The other four patients suffered from trauma, empyema or pancreatitis. The severity of organ dysfunction was assessed for each study day using a SOFA score ("Sequential Organ Failure Assessment") [27].

### Control group

A control group of 20 subjects who experienced significant levels of stress but without signs of sepsis or infection was derived from patients undergoing thoracic surgery at the same hospital (7 female, 13 male, mean age 62). Carcinoma and metastasis was the reason for surgery in 19 patients, while one patient was operated for emphysema. Amino acids, PCT and IL-6 were measured immediately preoperatively and postoperatively and then at 2, 6, 12, 24, 48 and 72 h postoperatively.

### Assays

Clinical and biochemical tests were performed on a daily basis during the first 4 days, then approximately weekly for up to 28 days. Amino acid concentrations in plasma were measured with an amino acid analyser "LC 3000" from Biotronik-Eppendorf (Germany) using ion exchange chromatography with post-column derivation. An external standard (Benson) was used for calibration. The group of branched-chain amino acids was comprised of valine, leucine and isoleucine (BCAA). The aromatic amino acids included phenylalanine and tyrosine (AAA). The ratio of BCAA:AAA was calculated for each sample. Procalcitonin was determined with an immunoluminometric assay, LUMItest PCT, from B.R.A.H.M.S. Diagnostica (Berlin, Germany). The detection limit was 0.3 ng/ml. IL-6 levels were measured by an enzyme immunoassay, Interleukin-6-EASIA, from Medgenics Diagnostics (MEDGENIX) with a limit of detection at 3 pg/ml.

### Statistical analysis

Group data are expressed as means ± SD. To examine differences between patient groups, the Mann-Whitney U-test was used. Spearman's rank-correlation coefficient was calculated to assess the association between markers of inflammation and the ratio of BCAA:AAA.

## Results

Table 1 shows organ dysfunction as assessed at the onset of the study, as well as over the entire course of sepsis (days 2–28). In no case was the liver function severely affected when assessed by the SOFA score. During the first study day, three patients needed ventilation therapy be-

**Table 1** Organ dysfunction in the early stage (day 1) and entire course (days 2–28) of septic encephalopathy (*SE*)

| Dysfunction | Parameter | Day 1 Number of patients | Entire course Number of patients |
|---|---|---|---|
| Respiratory | Ventilation | 3 | 9 |
| Renal | | | |
| 1 SOFA point | creatinine 110–170[a] | 2 | 0 |
| 2 SOFA points | creatinine 171–299[a] | 2 | 1 |
| 3 SOFA points | creatinine 300–440[a] | 3 | 3 |
| 4 SOFA points | creatinine >440[a] | 0 | 1 |
| Liver | | | |
| 1 SOFA point | Bilirubin 20–32[b] | 5 | 0 |
| 2 SOFA points | Bilirubin 33–101[b] | 1 | 4 |
| Thrombocytes | | | |
| 1 SOFA point | $<150\times10^3/mm^3$ | 2 | 0 |
| 2 SOFA points | $<100\times10^3/mm^3$ | 1 | 1 |
| 3 SOFA points | $<50\times10^3/mm^3$ | 1 | 1 |
| Septic shock | | 0 | 6 |

[a] Creatinine in µmol/l
[b] Bilirubin in µmol/l

**Table 2** Individual liver function tests in the early stage (day 1) and entire course (days 2 –28) of septic encephalopathy (*ALAT* alanine transaminase, *γGT* gamma glutamyl transpeptidase, *ND* not done)

| Patient | Day 1 | | | Entire course | | |
|---|---|---|---|---|---|---|
| | Bilirubin[a] | ALAT[b] | γGT[c] | Bilirubin[a] | ALAT[b] | γGT[c] |
| 1 | 29.7 | 10.8 | 15 | 18.4 | 19.2 | 26.4 |
| 2 | 18.7 | 3.6 | 42 | 83.2 | 44.4 | 209.4 |
| 3 | 27.9 | 6.6 | 15.6 | 19 | 23.4 | 21.6 |
| 4 | 13.8 | ND | ND | 18.6 | 52.8 | 28.2 |
| 5 | 30.6 | 52.8 | 28.2 | 63.9 | 71.4 | 46.2 |
| 6 | 14.3 | ND | ND | 14.3 | 48 | 57.6 |
| 7 | 16.4 | ND | ND | 12.6 | 21 | 66.6 |
| 8 | 25 | 7.2 | 3.6 | 95.2 | 69 | 155.4 |
| 9 | 13.2 | 20.4 | 17.4 | 15.2 | 49.8 | 20.4 |
| 10 | 90.6 | 10.2 | 10.2 | 85.8 | 10.2 | 10.2 |
| 11 | 11.4 | 15.6 | 19.8 | 16.9 | 45.6 | 121.2 |
| 12 | 30.3 | 21.6 | 26.4 | 17.5 | 52.8 | 46.8 |
| 13 | 8.1 | 12 | 16.8 | 6.5 | 9.6 | 12 |
| 14 | 15.3 | 159 | 39 | 18.3 | 115.2 | 93.6 |

[a] Bilirubin (maximum) in µmol/l
[b] Alanine transaminase (maximum) in U/l
[c] Gamma glutamyl transpeptidase (maximum) in U/l

cause of clinical deterioration. Over the course of the study, nine patients needed ventilation and six developed septic shock (treatment with catecholamines was necessary despite adequate volume therapy). Table 2 shows bilirubin values and liver function tests as obtained in routine clinical management. The group mean values for the PCT and IL-6 markers of inflammation are shown in Table 3. The values for both variables were significantly greater on the first study day for the sepsis patients compared to the mean of all study days for the control patients.

**Table 3** Amino acid markers of inflammation in the early stage (day 1) of septic encephalopathy (*SE*) compared to control patients

| Marker | | Patients with SE (*n*=14) First study day | Control patients (*n*=20) All study days |
|---|---|---|---|
| Amino acids ratio (BCAA:AAA) | Mean | 2.24[a] | 3.22[a] |
| | Standard deviation | 0.58 | 1.09 |
| | Minimum | 0.99 | 1.16 |
| | Maximum | 2.89 | 6.82 |
| | Samples | 14 | 137 |
| PCT (ng/ml) | Mean | 16.74[a] | 0.25[a] |
| | Standard deviation | 39.75 | 0.18 |
| | Minimum | 0.46 | 0 |
| | Maximum | 149.3 | 0.70 |
| | Samples | 14 | 145 |
| IL-6 (pg/ml) | Mean | 809.57[a] | 73.85[a] |
| | Standard deviation | 831.77 | 116.30 |
| | Minimum | 116 | 0 |
| | Maximum | 2654 | 714 |
| | Samples | 14 | 89 |

[a] Mann-Whitney U-test $p<0.001$

The group mean of the amino acid ratio (BCAA:AAA) in the early stage of septic encephalopathy is shown in Table 3 and it is significantly lower than the control value. The mean value for this BCAA:AAA ratio did not change appreciably for the sepsis patients over the course of the study – it was 2.27±0.67 for 77 observations over all study days combined. The amino acid ratio (BCAA:AAA) was correlated with the markers of inflammation using the Spearman rank-order coefficient. A lower BCAA:AAA ratio was significantly, but not strongly, associated with higher levels of both PCT ($r$=–0.412, $p<0.01$) and IL-6 ($r$=–0.312, $p<0.01$).

The relationship between the amino acid ratio and PCT was further explored retrospectively. We calculated cut-off points for PCT (2.0 ng/ml, based on the literature) and for the amino acid ratio (2.0, based on our empirical observations). On study days when PCT levels in the septic patients measured higher than 2 ng/ml, a significantly lower BCAA:AAA ratio was observed (2.04 versus 2.50, $p<0.01$). On study days when the BCAA:AAA ratio was lower than 2, the PCT levels were significantly higher ( 37.45 versus 4.99, $p<0.001$).

Table 4 shows results from day 1 for the neuropsychological tests. We attempted to perform all three tests, but in four patients the septic encephalopathy was too severe at the time of testing to quantify the neurological disor-

**Table 4** Neuropsychological tests (results in points) in the early stage (day 1) of septic encephalopathy (*SE*) (*severe SE* disorder too severe to calculate points)

| Patient | Benton<br>Normal: 0–2<br>Severe: > 13 | Mental control<br>Normal: 6<br>Severe: 0–1 | SKT<br>Normal: 0–4<br>Severe: 19–27 |
|---|---|---|---|
| 1 | 95 | Severe SE | Severe SE |
| 2 | Severe SE | Severe SE | Severe SE |
| 3 | 48 | 0 | Severe SE |
| 4 | 0 | 4 | 11 |
| 5 | 2 | 4 | 11 |
| 6 | Severe SE | Severe SE | Severe SE |
| 7 | 14 | 2 | 12 |
| 8 | Severe SE | Severe SE | Severe SE |
| 9 | 5 | 4 | 6 |
| 10 | 2 | 4 | 5 |
| 11 | 12 | 5 | 17 |
| 12 | 2 | 0 | 5 |
| 13 | 0 | 4 | 12 |
| 14 | Severe SE | Severe SE | Severe SE |

der. We were able to perform the neuropsychological tests repeatedly in the five patients who did not have to be ventilated during sepsis. In the course of the study, four of these patients achieved normal results in all tests. The fifth patient had normal results except for mild disturbances within the SKT at the end of the study period, and this was an improvement over the severe disturbances in all tests that this patient had exhibited on the first day. Consequently, the septic encephalopathy was regarded as reversible in these five patients. The BCAA:AAA ratio was higher at the end of the study period when compared to the early stage in three of these five subjects and unchanged in the other two. The severity of septic encephalopathy did not correlate with changes in amino acids.

## Discussion

These data demonstrate, for the first time, that amino acid metabolism is indeed disturbed even in the early stages of well-defined septic encephalopathy. The ACCP/SCCM sepsis criteria were used, encephalopathy was confirmed by the battery of psychological tests and all patients began the study within 12 h of the onset of symptoms of sepsis and encephalopathy. For the most representative control values we combined all available samples from our control subjects, since a larger variety of metabolic conditions was covered: preoperative fasting period, intra-operative and postoperative stress and body temperature changes.

These results extend the findings of two previous studies using patients in later stages of septic encephalopathy. Sprung et al. [14] showed an elevation in aromatic amino acids along with a decrease in branched-chain amino acids in 15 patients with septic encephalopathy who were already in septic shock. Treatment with dopamine had already been started (mean dose: 18.9±4.9 µg/kg per min). Fourteen patients were ventilated and all of them had elevated liver function tests. Mizock et al. [15] found high levels of phenylalanine in plasma and cerebrospinal fluid in 11 septic patients who were already in stupor and coma. Because these studies did not report amino acid levels earlier in sepsis, little can be concluded about their role in the pathogenesis of septic encephalopathy. We can now add that the derangement between the branched-chain and aromatic amino acids is observable early in the encephalopathy.

Aromatic amino acids are precursors of neurotransmitters. It has been hypothesised that elevated blood levels of aromatic amino acids could cause enhanced uptake into the CNS. Then neurotransmitter synthesis could be disturbed and/or false neurotransmitters generated [1, 4, 10, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]. Whether a decreased ratio of BCAA:AAA could result in such a disturbance of cerebral neurotransmitters is still speculative, although experimental studies suggest this is possible [10, 22, 23]. An association between amino acid and neurotransmitter metabolism has been found in a rat model of septic encephalopathy. Elevated transport of aromatic amino acids into the CNS has been demonstrated, as well as a reduction of aromatic amino acids in the brain following an infusion of branched-chain amino acids. These changes may be partly explained by competition for the amino acid transport system in the blood-brain barrier, which serves both branched-chain and aromatic amino acids.

While these present data suggest a possible role of amino acids in the early stage of septic encephalopathy, not all the data we were able to collect fell neatly into the expected directions. Within the septic group itself, the BCAA:AAA ratio was not related to the severity of cerebral symptoms even on the first day. In fact, very low BCAA:AAA values were observed in some patients with only mild neurological symptoms. Also, during the course of sepsis, the amino acid ratio did not rise in all patients in whom the septic encephalopathy reversed.

Beyond the encephalopathy issue, a change in amino acid levels with sepsis has been reported, typically increased aromatic and unchanged or decreased branched-chain amino acids [16, 18, 19]. A low BCAA:AAA ratio was reported by Vente [16] and others [28]. Furthermore, Sprung et al. [14] showed increased aromatic amino acids were positively correlated with both the APACHE II score and the mortality rate. Freund et al. [18] observed that patients who did not survive sepsis had higher levels of aromatic amino acids than did survivors, who had higher levels of branched-chain amino acids.

The amino acid alterations may be a result of septic catabolism, which includes insulin resistance, impaired glucose and lipid utilisation, muscle proteolysis and relative hepatic insufficiency [14, 18, 19, 20, 29, 30]. Muscle proteolysis releases amino acids into the circulation,

although branched-chain amino acids are degraded by muscle cells. The metabolism of aromatic amino acids depends on liver function. Not all septic patients who have shown amino acid alterations have had obvious liver dysfunction. For example, Vente et al. [16] found no relation between low BCAA:AAA ratio and bilirubin. In our study, six patients had elevated levels of bilirubin on the first study day, and during the study period no patient suffered severe liver dysfunction. Thus, we believe that the amino acid alterations in our patients resulted from the various metabolic effects of sepsis, without a major contribution from the liver.

To modify septic catabolism, parenteral nutrition regimes with higher amounts of BCAA are used. Effects on proteolysis, urea genesis, production of acute-phase proteins and plasma levels of other amino acids (the non-proteinogenous amino acid taurine included) have been reported [31, 32, 33, 34]. However, the influence of these on mortality remains controversial [32, 35].

In addition to the SOFA score, we analysed the biochemical markers of inflammation IL-6 and PCT, which were both elevated in patients with septic encephalopathy. The decreases in the BCAA:AAA ratio in the present study were associated with increases in PCT and IL-6. In particular, when using a PCT cut-off value of 2 ng/ml, which is near levels proposed in the literature for diagnosing sepsis [36, 37, 38], the BCAA:AAA ratio was indeed quite low (near 2.0), indicating severe underlying metabolic derangements. A BCAA:AAA ratio that low was observed within the control group only 9 times during 137 study days (in 6 of 20 patients), as compared to 30% of the samples of septic patients.

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