Septic Encephalopathy

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The Hospital where I work

A Section of our ICU

Septic Encephalopathy
vs
Sepsis Associated Encephalopathy

- Septic Encephalopathy is very interesting and ignored clinical condition
- Seldom in my 20 yrs carrier as Intensivist and Emergency Physician , a standalone diagnosis of Septic encephalopathy has been made even when it exists so much .
- It has got a very significant incidence
- It should be suspected in patients of sepsis who are not on sedatives otherwise show signs of mental dysfunction without lateralizing signs or structural changes in MRI .
- Therefore , it may be more prudent to use a nomenclature of Sepsis Associated encephalopathy which would mean a patient of sepsis is also suffering from brain dysfunction which is usually a part of Multiorgan Failure

Septic encephalopathy Manifestations

They may be very soft initially and deserve strong suspicion

This is diffuse disturbance in cerebral function

The principal neurological findings relate to altered mental status

Mild cases - confusion , inappropriate behavior ,Inattention and writing errors

severe Cases - delirium, agitation or coma.

J Clin Neurophysiol 1992; 9: 145-52.

Septic Encephalopathy-Manifestations

- Paratonic rigidity or Gegenhalten, a resistance to passive movement of limbs that is velocity-dependent (Most Common)
- The resistance felt during movements at normal rate disappears when the limb is moved slowly.
- Asterixis,
- Multifocal Myoclonus,
- Infrequently seizures and tremor
- Cranial nerve functions are almost invariably spared.
- Localizing signs like hemipareisis or gaze disturbances should indicate other pathology

EEG - may be sensitive tool but seldom done

- EEG serves as the most sensitive test for SAE.
- It may show mild, diffuse, reversible slowing .
- The severity of the EEG abnormality is usually parallel to the mental status impairment.
- As the encephalopathy worsens, mild slowing in the theta (>4 to <8Hz) range is followed by diffuse delta (<4Hz) waves,
- Then generalized Triphasic waves
- Finally by suppression or a generalized burst-suppression (alternating diffuse reductions in voltage with burst of higher voltage waves) pattern.
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- The relationships of EEG classifications to severity of encephalopathy and mortality have been very well illustrated .

Clin Invest Med 1990; 13: 297-304.

Mechanism of S.E.- Uncertain

- It is likely multi-factorial, given the variety of pathological findings.
- The early, fully reversible cases are not associated with structural change and are probably metabolic in nature.
- Other mechanisms, in addition to the metabolic disturbances, operate in more advanced cases.

Etiology and Pathophysiology

- Free radicals
- damage RBC and limit O2 delivery to brain
- Inflammatory mediators
- impair mitochondrial function and O2 extraction by the brain
- destroy BBB
- peri-microvessel edema
- disruption of astrocyte end feet
- aromatic molecules enter brain parenchyma and disturb NT

Ultimately, extensive neuronal injury

Y. Mateveli

8. Treatment – Related Causes

- Electrolytes like calcium, magnesium and phosphate over and above Sodium may lead to such manifestations and osmotic disorders may accompany disorders of water homeostasis,
- Enteral or parenteral feeding, renal impairment and errors in fluid replacement.
- Some volume expanders may produce hemorrhagic complications and hypocalcemia.
- Encephalopathies related to cardiopulmonary by-pass procedures and organ transplantations are well-documented.

Ann Emerg Med 1988; 17: 135-44.

1. Microvascular Disorder

- Reduced cerebral blood flow
- Increased cerebro-vascular resistance .
- Micro-thromboses
- Micro-infarctions may also occur.

These phenomenon may be related to production of cytokines [e.g., tumor necrosis factor-α (TNF-α), interferon-γ (IFNγ) and interleukins (IL)]

Lancet 1991; 732-6.

2. Amino Acids and Neurotransmitter imbalance

- S E suspect humans and animal models- both show an increased ratio of aromatic to branched chain amino acids in the plasma.
- This correlates with decreased norepinephrine, dopamine and serotonin concentrations in the brains of septic rats.
- Altered GABA Levels and GABA receptors activity in the brain,
- the levels of benzodiazepine-like substances (with inhibitory or sedating properties) and quinolinic acid that are elevated in hepatic dysfunction.

Lancet 1982; 1: 18-20
Intensive Care Med 2002; 28: 293-8

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•3. Brain Micro-abscesses

• The existence of brain microabscesses with retinal microabscesses, have been well reported

•Micro abscesses in Brain May have uncertain significance in view of them being so microscopic that they are undetectable even In high resolution MRI Scan 6

• A more recent paper found microabscesses to be one of the pathological conditions associated with central autonomic dysfunction in sepsis.

• Microabscesses could cause neuronal damage and dysfunction due to local release of cytokines and other inflammatory mediators

•*Neuropathol Appl Neurobiol 2002; 28: 159.*

4. Failure of Other Organs

- Hepatic or renal failure may, in themselves, cause an encephalopathy.
- S E often precedes multi-organ failure, this secondary mechanism would not explain the early encephalopathy of sepsis.
- However, it is felt that multi-organ failure likely plays a contributory role in producing brain dysfunction in advanced sepsis though the mechanism may be ill understood

5. Cytokine Action in the Brain

- Inflammation induced Activated Neutrophils and Monocytes produce interleukin-1 (IL-1α and IL-1β), IL-6 and TNF-α.
- Interleukin- 1 can affect brainstem, limbic and hypothalamic structures to produce “illness behavior” ,, depressed mood and cognitive impairment.
- Interleukin-1 also stimulates the production of prostaglandin E-2 which in turn produces fever and activation of the hypothalamic-pituitary adrenal axis to increase cortisol production.

Trends Neurosci 2002; 25: 154-9.

Cytokine Action in the Brain

- Interleukin- 1a may directly affect a number of brain nuclei in circum-ventricular organs that are not guarded by the blood-brain barrier and choroid plexus.
- Activation of these structures could alter limbic function in the Amygdala and hypothalamus, thereby causing depression and anorexia

Adv Exp Med Biol 1999; 461: 25-46.

6. Excitotoxicity and Oxidative Stress

- Antibiotics often fail to prevent neurologic complications of sepsis, in part because antibiotic induced destruction of bacteria releases endotoxins (LPS) which produces inflammation
- LPS increases cerebral levels of pro-inflammatory cytokines such as interferon γ .
- Together, LPS and cytokines act on brain astrocytes and up-regulate inducible Nitric oxide synthase (iNOS) i27,28
- Nitric oxide synthase enzymes use reduced NADPH, oxygen and arginine to produce NO and superoxide.29 which evoke oxidative responses

Intensive Care Med 2002; 28(8): 24-33.

7. Apoptosis

- Apoptosis is a form of programmed cell death that may be triggered by TNF-α stimulation.
- An alternative mechanism involves mitochondrial damage that triggers apoptosis.
- It is reasonable to suppose that the CNS cells and/or the brain's capillary endothelium are affected in a similar way by TNF-α or another cytokine.

Neuropath Appl Neurobiol 2002; 28: 159.

Diagnosis and DD

- Existence of encephalopathy and Sepsis has to be firmly established
- Other following causes of encephalopathy have to be excluded
- Meningitis , Brain abcess , Head injury , Tropical infections like Malaria , Dengue , Scrub Typhus , Typhoid Fever , TBM , HSV , Leptospirosis must be ruled out
- All Metabolic causes including Hepatic , Uremic , Electrolyte imbalance should also be ruled out as principle cause , however some degree of these failures may be associated in all such patients
- Extensive use of Drugs in ICU like Imepenem , Sedatives , analgesics may produce a syndrome like that of SAE

Diagnosis

- CT brain scans are normal.
- MRI scans are usually unremarkable, but occasional patients show various degrees of vasogenic edema .
- Cerebrospinal fluid analysis shows only a mild Protein elevation but not in all .

Crit Care Med 1992; 20: 724-6
J Neurol Sci 1985; 12: 303-7.
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Diagnosis - Biochemistry

- Serum urea, Creatinine, Bilirubin and alkaline Phosphatase seem to have direct prognostic significance
- However The degree of renal impairment is rarely sufficient to account for the brain dysfunction.
- Hepatic failure is, however, usually difficult to assess clinically or to quantify biochemically.
- Encephalopathic septic patients have greater elevation of aromatic amino acids and lower concentrations of branched chain amino acids .
- This is similar to the unbalanced ratio found in hepatic failure.

Crit Care Med 1991; 19: 753-7.

Differential Diagnosis

Exclude ----------

* Meningitis
* Brain abcess
* Head Injury
* Other Specific Infective Encephalopathies
* Metabolic Encephalopathies

MANAGEMENT

- First one must establish the diagnosis.
- Sepsis associated encephalopathy is a diagnosis by exclusion:
- There should be no clinical or laboratory evidence of direct central nervous system infection (e.g., meningitis, macroscopic intracranial abscess or empyema), head trauma, fat embolism,
- .
- It is especially important to perform a lumbar puncture on obtunded patients with systemic inflammatory response syndrome, to rule out meningitis.
- Seizures (uncommon) should be treated with standard anti-epileptic medications such as phenytoin.

Management

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•Prompt, specific treatment of the septic illness (appropriate antimicrobial therapy, drainage of abscesses, etc.) with prevention of multi-organ failure will save lives, as mortality is directly related to the severity of sepsis and the number of failed organs

• With the administration of a mixture of amino acids with high concentrations of branched-chain amino acids, Freund and colleagues successfully reversed SAE in five patients.

•This short-term improvement is gratifying, but such treatment may not be helpful for advanced cases with multi-organ failure.

*Anesth Analg 1982; 61:*903-11.

Antibiotics and Septic Encephalopathy

- Antibiotics may fail for several reasons.
- First, the bacteria may be resistant.
- Second, the antibiotics may act too slowly, leaving sufficient time for severe inflammatory injury to develop.
- Third, the killing of bacteria may release inflammatory agents such as LPS.

Prognostic Factors

In Bacteremic patients, mortality is directly related to the severity of the EEG abnormality:

0% with normal, 19% with theta, 36 with delta, 50% with triphasic waves and 67% with suppression or burst-suppression.2

Clin Invest Med 1990; 13: 297-304.

Prognosis - Severity of septic encephalopathy (graded by GCS) correlated with mortality

Table 2.—Septic Encephalopathy and Mortality

Altered mental status, No. (%)		
No	6/23 (26)	$P=.6$
Yes	9/27 (33)	
Clinical grade of encephalopathy, No. (%)		
0	7/26 (27)	$P=.5$
1-2	5/18 (28)	
3-4	3/6 (50)	
Glasgow Coma Score, No. (%)		
15	3/19 (16)	$P<.05$
13-14	3/15 (20)	
9-12	4/8 (50)	
3-8	5/8 (63)	

JAMA. 1996 Feb 14;275(6):470-3
(prospective study in 50 sepsis patients)

Prognosis -Bactermia Role in SE

Table 3.—Septic Encephalopathy and Presence of Bacteremia

Altered mental status, No. (%)		
No	3/23 (13)	$P<.001$
Yes	16/27 (59)	
Clinical grade of encephalopathy, No. (%)		
0	4/26 (15)	$P<.001$
1-2	14/18 (78)	
3-4	1/6 (17)	
Glasgow Coma Score, No. (%)		
15	4/19 (21)	$P=.09$
13-14	9/15 (60)	
9-12	2/8 (25)	
3-8	4/8 (50)	

JAMA. 1996 Feb 14;275(6):470-3 (prospective study in 50 sepsis patients)

Innovative Therapies in S E

Drugs or agents, e.g., activated protein C, that affect or counteract the pro-coagulant state in sepsis may be directly or indirectly beneficial to brain function in sepsis.

However, the potential benefits of this therapy on SAE directly will be difficult to separate from systemic effects

THANK YOU

CRITICAL CARE & TRAUMA HOSPITAL

जीवन सेवा