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Septic Encephalopathy

An Essay

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By

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Mitwally EL-Nabarawy

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List of Abbreviations

Abbr.	Full term
AAA	Aromatic amino acids
AESD	Acute encephalopathy with biphasic seizures and late reduced diffusion
AMPARs	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors
APC	Activated protein C
ARAS	Ascending reticular activating system
ATICE	Assessment to intensive care environment
ATP	Adenosine triphosphate
BBB	Blood brain barrier
C	Complement
CAM	Confusion assessment method
CAM-ICU	Confusion assessment method for the intensive care unit
CD14	Cluster of differentiation 14
CIM	Critical illness myopathy
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CVOs	Circumventricular organs
DIC	Disseminated intravascular coagulopathy
EEG	Electroencephalography

FLAIR	Fluid-attenuated inversion recovery
FOUR	Full outline of unresponsiveness
GABA	Gamma amino butyric acid
GCS	Glasgow coma scale
ICAM-1	Intercellular adhesion molecule 1
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LBP	LPS-binding protein
LPS	Lipopolysaccharide
LT	Leukotriene
MCP1	Monocyte chemo-attractant protein 1
MODS	Multi organ dysfunction syndrome
MRI	Magnetic resonance imaging
NCSE	Nonconvulsive status epilepticus
NMDARs	N-methyl D-aspartate receptors
NO	Nitric oxide
NSE	Neuron specific enolase
PAI-1	Plasminogen activator inhibitor 1
PEDs	Periodic epileptiform discharges
PRE	Posterior reversible encephalopathy
PROWESS-SHOCK	Prospective recombinant human activated protein C worldwide evaluation in severe sepsis and septic shock

RASS	Richmond agitation sedation Scale
ROS	Reactive oxygen species
SAE	Sepsis associated encephalopathy
SD	Standard deviation
SE	Septic encephalopathy
SEPs	Sensory evoked potentials
SIRS	Systemic inflammatory immune response
SOFA score	Sequential organ failure assessment score
TCD	Transcranial Doppler
TGF-β	Transforming growth factor β
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule

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INTRODUCTION

Sepsis is defined as the excessive inflammatory reaction of an organism to an infection. It is not a disease in itself, but rather is a systemic inflammatory response due to infection, burn, trauma, or other factors. Sepsis and its complications are the most frequent cause of high mortality in the intensive care unit (ICU) ***(Vandijck et al., 2006)***.

Detected sepsis cases make up to 75 % of all illnesses treated in the ICU, additionally, despite considerable progress in diagnosis and treatment, a high degree of mortality is still noted, and the morbidity rate has been increasing annually from about 1.5 % to as much as 8 % ***(Frontera, 2012).***

The high mortality rate persists among patients treated for sepsis, even 1 month to 1 year after they leave the ICU, this indicates that further examination of the effects of medical treatment for sepsis is necessary, especially considering that long-lasting disturbances in organ function may appear; both physically as, for example, dyspnea and mentally, as fatigue or depression ***(Woltmann et al, 1998).***

Because the nervous system is susceptible to many different factors, it is not surprising that the intensive inflammatory response of sepsis affects brain function. Liver or renal dysfunction accompanying sepsis may result in encephalopathy; however, sepsis may result in encephalopathy even in the absence of systemic organ failure**,** sepsis is typically regarded as being caused by infectious factors such as bacteria, viruses, or fungi. However, encephalopathy may also occur with metabolic disorders, exposure to toxins or radiation injury, disturbances in blood flow, and other factors. Among the many complications of sepsis, septic encephalopathy (SE) is considered the most frequent, and it is estimated that 9–17 % of patients with diagnosed sepsis exhibit symptoms of encephalopathy ***(Dobbs, 2011).***

SE has been described as a reversible syndrome; studies indicate long-lasting cognitive and depressive disturbances in patients after the sepsis resolves ***(Baugh et al., 2012).***

Recovery from these cognitive and mental symptoms of SE, as determined by the Glasgow Coma Scale, suggests that nervous system dysfunction is often slow. The mortality of SE remains high and correlates with the intensity of sepsis and its early diagnosis and proper treatment ***(Huberlant et al., 2009)***.

AIM OF THE ESSAY

The aim of the essay is to provide a concise overview about septic encephalopathy; possible causes in ICU, pathophysiology, its differential diagnosis and complications.

Furthermore to discuss risk factors, early diagnosis, acute management, prognostic criteria and its preventive measures.

Definition & Pathophysiology

There are many different terms that define sepsis, its clinical manifestations and its complications. (Table 1)

Table (1): Consensus definitions of a spectrum of clinical entities that results in organ failure ***(Ringer et al., 2011).***

Systemic Inflammatory Response Syndrome (SIRS): An inflammatory response to a wide variety of clinical insults manifested by two or more of the following symptoms: - temperature >38°C or <36°C - heart rate >90/min - respiratory rate >20/min or $PaCO_2$ <32 mmHg - WBC count >12 Gpt/l or <4 Gpt/l, or >10 % immature (band) forms.
Sepsis: SIRS caused by infection
Severe Sepsis: Sepsis with at least one organ dysfunction or hypoperfusion
Septic Shock: Severe sepsis associated with hypotension that is resistant to adequate fluid resuscitation
Bacteremia: The presence of viable bacteria in the blood stream
Multiple Organ Dysfunction Syndrome (MODS): Impairment of two or more organ systems in an acutely ill patient where homeostasis cannot be maintained without therapeutic intervention

Sepsis is characterized by the inflammatory reaction of the whole body and simultaneous activation of congenital anti-inflammatory mechanisms, and a balance among these processes is of the critical significance, it is then defined as

the Systemic Inflammatory Response Syndrome (SIRS) caused by the infection ***(Green et al., 2004).***

Despite the considerable progress in the diagnosing and treatment, there is a still high rate of mortality in sepsis which is the most frequent cause of death among patients of intensive care units, and additionally the morbidity increases from 1.5% to 8% annually. Moreover, the overall mortality reaches from 30% to 50% of cases ***(Riedemann et al., 2003).***

The SIRS occurs when at least two of the following appear:

- Hyper- or hypothermia – if the body temperature is above 38°C or below 36°C
- Tachycardia – the pulse rate over 90 per minute
- Tachypnea – frequency of breaths above 20 per minute, or the value $PaCO_2$ below 32 mm Hg
- Leukocytosis – number of white blood cells above 12 000 per mm^3, or leukopenia – number of white blood cells below 4000 per mm^3 ***(Kunze, 2002).***

After the recognition of SIRS, it is necessary to define the causative pathogen, the most frequent factor causing sepsis is the infection (75-85%) caused by both Gram-negative and Gram-positive bacteria. The infection mainly

spreads out through lungs, kidneys and urinary tract and also abdominal organs ***(Astiz and Rackow, 1998).***

It is interesting that in almost 2/3 of cases of the severe sepsis, the identification of the pathogen responsible for the infection failed. Therefore, the statement of the bacteria in the blood is not necessary to diagnose SIRS but if it occurred in the blood, it is so called bacteremia. Sepsis can be also caused by viruses as well as fungi ***(Hoesel et al., 2006).***

Often the primary reason of the sepsis can be trauma, surgical treatment or burns, and also tumor diseases and pneumonia; persons with the compromised immunity and elderly people are most exposed. The course of the sepsis is complicated and concerns the cellular as well as tissue level. In the early phase, both the cellular and humoral response of the immune system undergoes hyperactivation ***(Kunze, 2002).***

It manifests mainly by enhanced production and release of pro-inflammatory mediators such as TNF-α and interleukins: IL-1, IL-6, and IL-8 by endothelial cells, neutrophils, macrophages and lymphocytes, simultaneously soluble elements of the immune system are activated ***(Hoesel et al., 2006).***