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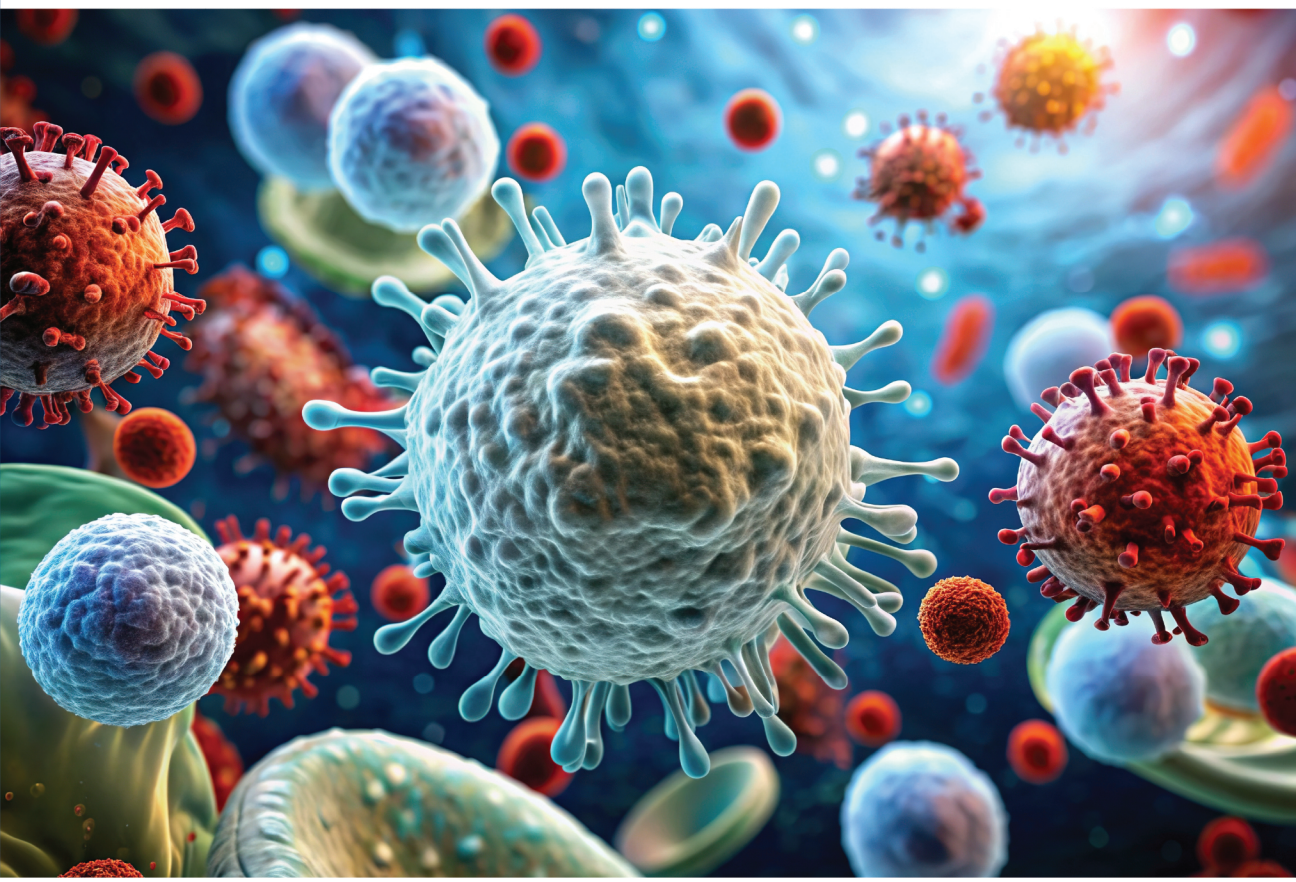

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CHAPTER

Septic Encephalopathy

Kapil Gangadhar Zirpe, Shrirang Nagorao Bamne

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INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to an infection.[1]

The body's over-reaction/unexpected response causes damage to its own tissues and organs.

Sepsis-related brain dysfunction is neglected entity in critically ill patients because there are no defined clinical parameters or biomarkers to assess and confirm cerebral dysfunction occurring as a result of sepsis.

Septic encephalopathy characterized by diffuse dysfunction of brain involving cognitive dysfunction, delirium, and coma. Systemic inflammation caused by sepsis, causing cerebral dysfunction gives spectrum of myriad manifestation.

Acute brain function alteration, so called sepsis-associated encephalopathy (SAE) occurs before the alteration/dysfunction of other organ functions in sepsis.[2,3]

Retrospective analysis of a prospective multicenter database shows incidence of septic encephalopathy in sepsis of 53%.[4] Acute renal failure and metabolic factors are the modifiable factors contributing for septic encephalopathy. Septic encephalopathy is associated with longer intensive care unit (ICU) stay, increased mortality, persistent cognitive impairment, and physical functional limitations.[5]

The mechanisms by which sepsis induces cognitive dysfunction is probably by overwhelming inflammation, systemic metabolic disorder associated with vascular injuries which cause neuroinflammation, oxidative stress, and severe microglial activation, particularly within the limbic system.[6] Studies and long-term follow-up of patients who survived from septic shock and had septic encephalopathy during their stay in ICU, developed early dementia later in life.[7]

Excessive production of inflammatory cytokines, such as tumor necrosis factor (TNF)-α and high mobility group box-1 protein (HMGB1), results in neuroinflammation and progressive loss of brain cells, as noted with antagonism of HMGB1 and TNF-alpha receptors.[8,9]

Neurological symptoms in SAE vary from mild impairment in consciousness to coma, generalized to focal seizures.[10] Nonconvulsive seizures remains underdiagnosed in SAE. electroencephalography (EEG) helps in delineating the nonconvulsive seizures. Future risk of seizures in survivors is increased in those had evidence of seizure related to SAE. The delay in diagnosis or treatment of nonconvulsive status epilepticus (NCSE) in SAE patients associates with an increase in morbidity and mortality.[3,11]

Electroencephalography helps in differentiating with myoclonic jerks associated with electrographic discharges

from nonepileptic myoclonus that are notably present in toxic or metabolic encephalopathy.[12,13]

The typical stepwise approach of seizures management begins with benzodiazepines and follows with anticonvulsants up to anesthetic drugs such as propofol or thiopental, which are able to induce burst suppression and interrupt the pathological electrical circuits, even in nonconvulsive state.

Sepsis-associated encephalopathy can present not only as spectrum of alteration in sensorium but as seizure episode.[6,10] 15–20% of SAE presents with incidences of seizure (convulsive or nonconvulsive) during the course or may be as first manifestation of SAE.[3,11] Due to lack of widespread use of EEG in intensive care unit, cases of subclinical seizure, which constitute major part of SAE seizures remains underdiagnosed. As it remains underdiagnosed, leads to increased morbidity and mortality. So it explains why SAE is associated with increased morbidity and mortality, increased incidences of seizure, later in life of sepsis survivors. Though underlying multiorgan involvement or dysfunction is also contributing to this statistics of disability and mortality. So it should come in routine practice for early evaluation of altered sensorium of sepsis patient with EEG and other investigation methods to have data, to have ongoing knowledge about pathophysiological/imaging/waveform changes in such group of patient, not just labeling as septic encephalopathy, but to have more information, how can clinician intervene early in such group of patient to have better outcomes.

Hyperventilation can be an early feature and paratonic rigidity might be the only neurological finding, besides delirium, in early SAE; advanced disease is associated with critical illness polyneuropathy in 70% of cases.

Most common clinical manifestation of SAE is altered level of consciousness which varies from mildly reduced awareness to unresponsiveness to verbal command, tactile stimulation, even to painful stimulation.

Sepsis-associated encephalopathy precedes other organ dysfunction, so gives alert signal to bystander to take patient to hospital, so timely interventions at hospital (via fluid resuscitation, antimicrobial, antifungal, and anti-inflammatory medicines) can retard further proceeding of organ dysfunction.

The evaluation of cognitive dysfunction is made difficult by the absence of any specific investigations or biomarkers and the common use of sedation in critically ill patients. SAE thus remains diagnosis of exclusion which can only be made after ruling out other causes of altered mentation in a febrile, critically ill patient by appropriate investigations.

PATHOPHYSIOLOGY

The pathophysiology of SAE is complex and it may involve:

- Neurotransmitter dysfunction
- Inflammatory
- Ischemic lesions to the brain, microglial activation, and blood–brain barrier (BBB) dysfunction

Microglia, the mononuclear phagocytes of the brain. They form about 10% of the total cell population of the brain. However, they display multiple morphological phenotypes and, expectedly, multiple functional profiles depending on their environment.[14,15]

The word BBB is misnomer as there happens bidirectional exchange of molecules, nutrients, etc., without any restriction. In humans, circumventricular organs (CVOs) include following **(Fig. 1)**:[16,17]

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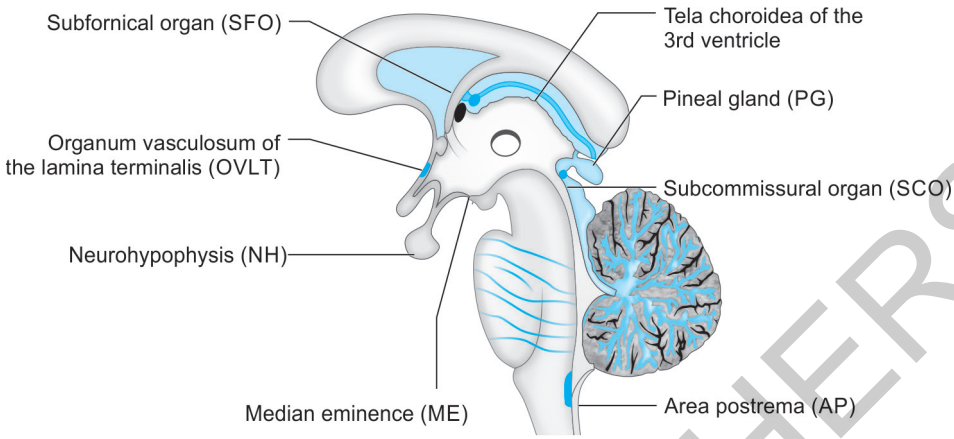

Fig. 1: Location of different circumventricular organs around the fourth and third ventricles.

- The median eminence
- Adjacent neurohypophysis
- Organum vasculosum
- Lamina terminalis
- Subfornical organ
- Area postrema

The CVOs are characterized by their small size, high permeability, and fenestrated capillaries. CVO is easy way for cytokines and other inflammatory mediators to get entry in brain other than increased permeability of BBB.[17,18] In response to systemic inflammation with increasing degrees and duration of systemic inflammation, the vascular BBB becomes more permeable to solutes, undergoes an increase in lymphocyte trafficking, and is infiltrated by innate immune cells; endothelial cell damage may occasionally occur.

Brain is first organ to get affected by systemic inflammation of sepsis.[19] Thus altered sensorium is window provided by nature which can be picked up easily, so to recognize and act early to hamper further progression of sepsis.

We know that its immune dysregulation in the form of extreme immune response to infection ,which has triggered chain of immune response in sepsis, giving rise to manifestations of it, in the form of multiorgan dysfunction. Neural, humoral pathway of communication with brain, and central nervous system (CNS) response through efferent neuronal pathway, neurotransmitter to have anti-inflammatory response, is attempt of CNS as extinguisher for ongoing cascade of events of sepsis. It explains that brain not only just controls voluntary, unvoluntary action, but beyond that.

INVOLVEMENT OF BRAIN IN MANIPULATION OF PERIPHERAL INFLAMMATORY RESPONSE

Inflammatory signal reaches brain through humoral and neuronal pathway, through activation of afferent vagal nerve fibers through cytokines.[18] Brain processes this response and sends signals through neurotransmitter release. This efferent pathway for inflammatory response is constructed of:

- Brain cholinergic nuclei
- Efferent vagus nerve
- Peripheral α7 nicotinic acetylcholine receptors (α7nAchRs)

The efferent pathway has potential to regulate immune cell proliferation, differentiation, and cytokine release, thus

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mitigating inflammation.[20] This action of acetylcholine neurotransmitter have been studied for treatment of autoimmune conditions as rheumatic disease, chronic inflammatory neurodegenerative conditions, viz., Alzheimer disease, vascular dementia, and multiple sclerosis.[21-23] At the same time excess of acetylcholine as seen in chronic obstructive pulmonary diseases, atopic dermatitis responsible for disease, and progression.[24,25] So we come to know from this, that varied activity, response of acetyl choline depending upon cell, tissue, organ, and receptor.

Impaired functioning of the central nervous system (CNS), as seen in traumatic brain injury (TBI), can lead to immune paralysis due to disturbances in the hypothalamo-pituitary-adrenal (HPA) axis, as well as sympathetic and parasympathetic dysfunction. The vagus nerve presents with obvious overactivity. This is assessment for loss of brain cholinergic nuclei.[26,27]

Thus, the viability and functional homeostasis of the brain cholinergic system are essential for the integrity of cholinergic anti-inflammatory activity.

ISCHEMIC BRAIN INJURY

Reduction in brain perfusion has an immense gravity in the development of SAE, and this can directly contribute in the abnormal cellular metabolism and oxidative stress.[28]

Reduced cerebral perfusion in patients of sepsis was found in a study (small number of patients). Here cerebral blood flow (CBF) was significantly less despite maintaining normal MAP.[29] Later study done by Taccone et al. on experimental sheep with induced sepsis-peritonitis and studied cerebral microcirculations in craniotomized sheep, found that, over 18 hours duration, cerebral microcirculation/functional capillary density decreased as well decrease in perfused microvessels, with decreased brain oxygen partial pressure, despite having mean arterial blood pressure of 65–70 mm Hg[30] in same study it was found that at 18 hours of sepsis, some developed septic shock (MAP below 65 mm Hg), continued to have maintained similar microcirculation/capillary density, still continued to have same functioning microcirculation density, cerebral tissue oxygen partial pressure except increased lactate to pyruvate ratio, compared to animals with sepsis but maintained MAP between 65 and 70 mm Hg. Study published in 2022 by Taccone et al., on experimental sheep fecal peritonitis sepsis model, showed that despite reversal of hypotension using fluids, norepinephrine, there was no reversal in microcirculation (in terms of proportion of small perfused vessels, functional capacity density of microcirculation, and mean flow index). There was partial improvement in lactate to pyruvate ration, partial pressure of brain tissue oxygen, but they were below baseline and physiological levels. Glutamate (excitotoxic) brain levels remained increased despite maintaining MAP with fluid, norepinephrine in hypotensive sheep.

Conclusively CBF is found to be significantly lower in patients with sepsis compared to that of normal controls, which shows a tight association with brain metabolism impairment.[29,30]

Multiple factors are involved in the pathogenesis of disturbed cerebral perfusion and microcirculation:[31]

- Abnormal vasoconstriction,
- Vasopressors,
- Hypotension, and
- Inflammatory insults

Disseminated intravascular coagulation is one of the important pathological conditions contributing to development of septic encephalopathy.[32]

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Vicious cycle of neuroinflammation–ischemic injury in sepsis affecting normal CNS. Ischemic process accentuate further neuroinflammation by increasing inflammatory cell infiltration in these area of ischemia or relative ischemia.[33,34] Thereby immunological balance needed to maintain functionality of CNS in sepsis.

Disturbed Calcium Homeostasis

Increased intracellular calcium concentration alters cognitive function, memory.[35]

Mitochondrial Dysfunction

Sepsis-associated released cytokines, reactive oxygen free radicals, and nitric oxide are associated with a decrease in mitochondrial adenosine triphosphate (ATP) production. Mitochondrial is powerhouse of cell, deficient energy, adversely affecting cellular survival in studies of rat with sepsis, mitochondrial dysfunction promoting neuronal apoptosis by mechanism of involvement of activation of apoptosis gene family (*BAX* gene, which is causing release of cytochrome C).[36,37]

Complement Factor Involvement

In experimental SAE of mice complement cascade involvement was demonstrated in alteration of BBB, similarly inhibition of complement factor C5a shown decreased inflammatory response, decreased brain edema, decreased neuronal/astrocyte apoptosis, and restoration of BBB function as illustrated in **Flowchart 1**.[38,39]

EFFECT OF ANTIBIOTICS ON SEPSIS RELATED ENCEPHALOPATHY

Antimicrobial-related encephalopathy can present as anxiety, agitation, and insomnia headache, dizziness/vertigo, drowsiness, paresthesia, tremor, confusion, convulsions, hypoesthesia, visual and hearing disorders, somnolence, and aphasia.

Antimicrobials, antivirals, antifungals, and antimalarials can cause encephalopathy/neurotoxicity.

Reason for discussion of all these drugs under the heading of septic encephalopathy is that all these drugs being used in association with ongoing infection, sepsis, so there role in contribution for causing septic encephalopathy cannot be neglected.

Its development varies from day 1 up to day 10 of its exposure. Its effect can be precipitated underlying renal dysfunction and unadjusted dosages of antimicrobials. Usually resolution happens 2–7 days after discontinuation of known antimicrobials.

Penicillin antibiotic-related encephalopathy has been reported. Because of molecular similarities of beta-lactam ring with gamma-aminobutyric acid (GABA) thus competing and inhibiting GABA transmission. Also penicillin group of drug binds to benzodiazepine receptors, reducing number of receptors by downregulation, thus reduced inhibition of neuronal excitation alters and may increase neuronal excitation and encephalopathy. It seems that plasma drug level correlates with its encephalopathic effect. Similar is true for piperacillin-tazobactam. After stopping the antimicrobials or after hemodialysis, there was improvement in encephalopathy.[40-44]

Cephalosporin group of antibiotics, not exceptional in having neurotoxic effect. They are having more or less similar mechanism of action as medication-induced suppression of inhibitory postsynaptic responses, mainly regulated by neurotransmitter $GABA_A$.[45,46]

Cefazolin, ceftazidime, and cefepime having much greater BBB penetration

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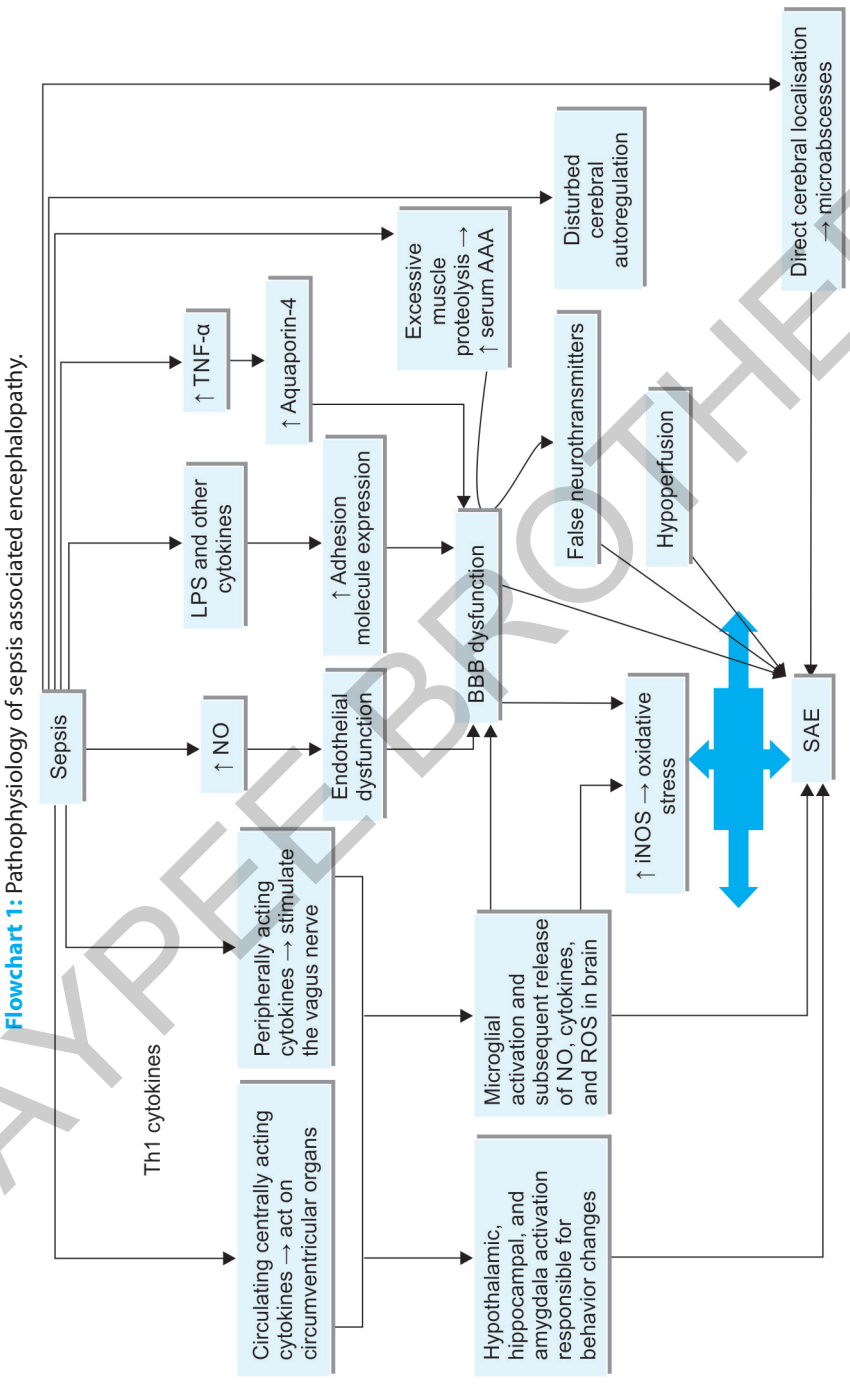
Flowchart 1: Pathophysiology of sepsis associated encephalopathy.



(AAA: aromatic amino acids; BBB: blood–brain barrier; LPS: lipopolysaccharide; NO: nitric oxide; NOS: inducible nitric oxide synthase; ROS: reactive oxygen species; SAE: sepsis-associated encephalopathy; Th1: type 1 helper cells; TNF: tumor necrosis factor)

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capability as well $GABA_A$ receptor higher affinity, so proposed to be more neurotoxic.[47]

The GABA inhibitory effect of fluoroquinolones,[48] possibly some may have neuroexcitatory effect via N-methyl-D-aspartate receptors.[49]

Macrolides

Clarithromycin and azithromycin use have been associated to delirium, disorientation, and impaired concentration, time of symptom presentation near about similar to other antimicrobials as mentioned earlier and it will disappear after discontinuation of drug.

Its hydroxyl(14-OH) metabolite of clarithromycin, causing neuropsychiatric side effects, thus drug which are inducer of cyp3A4, increasing levels of 14-OH metabolite of clarithromycin.

Clarithromycin neurotoxicity has been not only attributed to inhibitory action on glutaminergic transmission but also direct neurotoxicity of the active metabolite 14-hydroxyclarithromycin, alterations of cortisol and prostaglandin metabolism, clarithromycin-induced allosteric modulation of $GABA_A$ and receptors with increased cellular excitability may be another reason for seizures.[50]

Nitroimidazole Antimicrobial

Metronidazole is an antimicrobial with anaerobic coverage. Time to onset of metronidazole-induced encephalopathy can be months after treatment start, with resolution within days to weeks. Mechanisms for metronidazole neurotoxicity may include modulation of GABA within the cerebellar and vestibular areas, and the generation of neurotoxic radials from reactions with catecholamine neurotransmitters.[51]

Antituberculosis Drug

Isoniazid-induced CNS toxicity presents as seizure, memory impairment, and coma. Though CNS side effect is not a common phenomenon with isoniazid. The mechanism of isoniazid-induced neurotoxicity is thought to be related to decreases in GABA concentrations, owing to the inhibition of pyridoxine metabolism, isoniazid metabolite, and hydrazine[52]

EVALUATION OF SEPSIS-ASSOCIATED ENCEPHALOPATHY

Varied signs and symptoms of SAE so for diagnosis, we cannot rely on Confusion Assessment Method for the ICU (CAM-ICU) score or the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV) criteria. Spectrum of sepsis-related encephalopathy is so wide and variable, we need to more vigilant clinically as well on investigatory parameters for its diagnosis.

Electroencephalography

Electroencephalography is used to assess electrical properties of brain. By assessing electrical waveform of brain, one can know about abnormal electrical activities and location of origin of abnormal electrical activity. This can help clinician in knowing cause for encephalopathies, viz., metabolic, septic, toxin related, and seizure.[53,54]

Young et al. described septic encephalopathy-related EEG pattern in 1992 as electrical activity of brain varies from most mild changes to extensive pattern of theta activity, delta rhythm, triphasic waves, and burst supressions.[55] Triphasic waves and burst suppression were present in severe disease. Predominant theta wave pattern can correlate with milder form of encephalopathy. Benefit of EEG in undermining subclinical

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convulsive pattern, by knowing and treating underlying undiagnosed seizure, can change outcome. Though EEG is not pathognomic in SAE, but studying pattern of waves, its origin, and distribution in cerebral regions in such encephalopathy, can help in formulating certain waveform and sequence pattern which may have prognostication value.

Brain Imaging

Any form of stress to brain and/or inflammation of brain depending upon its accountable volume, persistence of it, can result in acute and chronic changes in neurochemical systems and specific brain regions, which can result in long-term changes in brain "circuits", involved in the stress response. So this gets reflected on brain imaging as shown in Mendelian randomization study by John A William et al.[56] More than twenty thousand participants were involved in study and found association of interleukin-6 with gray matter volume and cortical thickness in different regions of brain as it affects microglia, astrocytes, and possibly neurons. This process was found to be related to development of neuropsychiatric illness.

Hopkins et al. showed brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome.[57]

Suchyta et al. assessed brain imaging structural changes and neuropsychological outcome in 64 ICU patients. Many Patients were on mechanical ventilation. About 64% patients found to have abnormal brain imaging, whereas 48% survivor patients developed cognitive impairment, 6% developed psychiatric disorder.[58] Later similar results shown by Sutter et al., 479 consecutive ICU patients who underwent brain magnetic resonance imaging (MRI) over a 2-year period. Patients who were critically ill (including sepsis) having acute onset of neurological dysfunctions, viz., altered mentation, seizures, focal deficit, and underwent MRI brain imaging. Most prevalent lesions found to be white matter hyperintensities and MRI lesions were associated with unfavorable neurological outcomes.[59]

Posterior reversible encephalopathy can be one of neurological manifestation in sepsis, septic shock, patient presenting with altered sensorium, visual disturbance, and seizure.

In the prospective observational study by Orhun et al., concluded that posterior reversible encephalopathy syndrome (PRES) is highly prevalent in SAE, often encompasses unusual brain regions, and usually presents with generalized seizures. Patients with SAE and PRES do not appear to have distinguishing clinical and diagnostic workup features. However, generalized seizures may serve as warning signs for presence of PRES in patients with SAE.[60]

In PRES, MRI-T2 shows hyperintensities in affected regions and hypointensities in affected regions in T1 imagings.

Somatosensory Evoked Potential

Evoked potentials, when investigated in sepsis, show evidence of increased latencies and decreased amplitudes.[61]

Although there is no hallmark biomarker for SAE, elevated plasma levels of S100β or neuron-specific enolase (NSE) can get raised. Their exact significance; however, remains unclear.[62,63]

PREVENTION AND TREATMENT OF SEPSIS-ASSOCIATED ENCEPHALOPATHY

Diagnosis of SAE is many time diagnosis of exclusion, treating SAE is challenging as there

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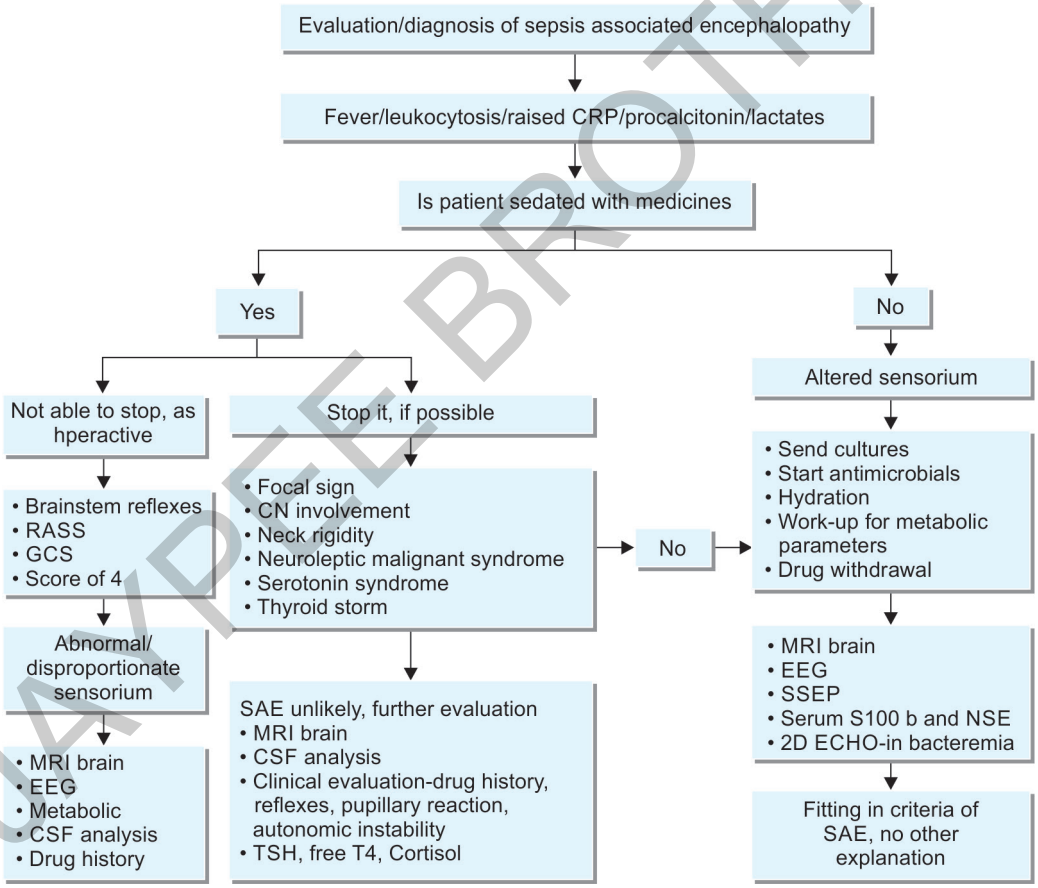
is no specific targeted therapy except treating underlying sepsis by antimicrobials, antiviral, and antifungals. None of the therapies that aim to treat the pathophysiological mechanisms of SAE have been proven effective in humans.

Need to evaluate and treat underlying metabolic/electrolyte/glucose abnormalities, follow the evaluation as mentioned in **Flowchart 2**.

Benzodiazepines, viz., lorazepam and midazolam may help in controlling delirium of sepsis, but repeated dosages may cause clouding of consciousness, which we are not desiring. Neuroleptics are another choice.

Dexmedetomidine, an alpha-2 agonist, has been associated with less delirium than continuous lorazepam and midazolam in critically ill patients (the MENDS trial).[64] In this trial, about 37% patients were

Flowchart 2: Evaluation/diagnosis of sepsis associated with encephalopathy.



(CN: cranial nerve; CRP: C-reactive protein; CSF: cerebrospinal fluid; ECHO: echocardiogram; EEG: electroencephalography; GCS: Glasgow Coma Scale; NSE: neuron-specific enolase; RASS: Richmond Agitation Sedation Scale; SAE: sepsis-associated encephalopathy; SSEP: somatosensory evoked potential; TSH: thyroid-stimulating hormone)

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having sepsis and acute respiratory distress syndrome (ARDS). Pandharipande et al.[64] have shown that delirium and coma-free days were 7 versus 3 days (up to study day 12) in dexmedetomidine versus lorazepam group.

Meta-analysis of 19 randomized controlled trials (RCTs) have shown that dexmedetomidine in sepsis patients could significantly reduce mortality compared with benzodiazepines. Dexmedetomidine can significantly decrease inflammatory response in patients with sepsis compared with other sedatives.[65] Systemic administration of dexmedetomidine attenuated these septic effects. The neuroprotective effects of dexmedetomidine may be mediated by α2A adrenoceptors in astrocytes.[66] Yoanna Skrobik et al. performed double blind placebo controlled, randomized trial in critically ill ICU patients (around 90% were mechanically ventilated patients, averagely 40% were having sepsis), using low dose dexmedetomidine infusion overnight from 9.30 PM to 6.15 AM with or without ongoing other sedatives, particularly opioids were unaltered, while other sedatives were halved. They targeted Richmond Agitation Sedation Scale (RASS) of –1. This low dose infusion of dexmedetomidine was continued (overnight) and followed till ICU discharge. They started injection dexmedetomidine infusion at rate of 0.2 μg/kg/h and slowly every 15 minutes interval increased by 0.1 μg/kg/h rate if RASS score was 0 or above, to achieve RASS of –1. If RASS was more than target, then infusion rate was decreased in similar manner. The average maximum infusion rate was 0.51 ± 0.22 mg/kg/h. It was found that 80% of patients were delirium free versus 54% in placebo group. This is the first pharmacologic intervention study shown to prevent delirium in critically ill adults with dexmedetomidine low dose infusion.[67]

Steroids have also been shown to reduce posttraumatic stress syndrome.[68] Steroid-related psychosis is well known entity, but its dose dependent related adverse event. That can happen shortly after administration of high dose of steroid.[69]

Steroids may help in halting progression or prevention of septic encephalopathy as its anti-inflammatory and inflammatory cascade involved in development of septic encephalopathy. Theoretically it may not be wrong that beneficial effect of steroid on hemodynamic and improved endogenous catecholamine responsiveness can further might help in SAE. As we know in severe sepsis and septic shock, we use low dose steroid therapy, so this dose expectedly not have psychotic effect. So beneficial effect of low dose steroid in septic shock in retarding progression, development of SAE may be outweighed compared to its psychosis-related adverse effect.

CONCLUSION

Evolving septic encephalopathy-associated pathophysiology and improvement in evaluation of electrical and structural changes in brain will help in development of target molecules for prevention, early diagnosis, and treatment of SAE. Dexmedetomidine is novel molecule for prevention and treatment of septic encephalopathy, only drawback is hypotension with its use, which can be further exacerbated in sepsis patients because of ongoing sepsis-related vasodilation and/or septic cardiomyopathy, so traditional way of treating delirium, in addition to the treatment of underlying sepsis, is the option by the time it takes over.

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