Cognitive decline after sepsis

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The modern era of sepsis management is characterised by a growing number of patients who survive in the short term and are discharged from hospital. Increasing evidence suggests that these survivors exhibit long-term neurological sequelae, particularly substantial declines in cognitive function. The exact prevalence and outcomes of these neuropsychological sequelae are unclear. The mechanisms by which sepsis induces cognitive dysfunction probably include vascular injuries and neuroinflammation that are mediated by systemic metabolism disorders and overwhelming inflammation, a disrupted blood–brain barrier, oxidative stress, and severe microglial activation, particularly within the limbic system. Interventions targeting the blood–brain barrier, glial activation, and oxidative stress have shown promise in prevention of cognitive dysfunction in various experimental models of sepsis. The next step should be to translate these favourable effects into positive clinical results.

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Background

Sepsis—when an infection is complicated with systemic inflammation-induced organ dysfunction or tissue hypoperfusion—is a major challenge for physicians worldwide because of the uncontrollable increase in its annual incidence, major gaps in understanding of its pathophysiology, repeated failures in the development of specific treatments, and long-term and substantial sequelae after its survival. Irrespective of a country's growth, income, products, and geographical location, and irrespective of the definition used, sepsis affects roughly 100 people per 100 000.[1] Men and non-white people, and those with chronic comorbidities, are more at risk of development of sepsis.[1] Roughly one in five patients die within 1 month of sepsis,[2] twice as many as patients without infection in intensive-care units (ICUs).[3] Sepsis continues to kill patients beyond ICU and hospital discharge, with mortality rates up to about 40% 1 year after hospital discharge,[3,4] and 80% after 5 years.[4] Sepsis can result in neurological complications that include ICU-acquired paresis[5,6] and cognitive impairment,[4,7] with subsequent functional disabilities and poor quality of life.[4] Neurological sequelae might contribute to the excess long-term mortality that occurs after sepsis. Because of the increasing incidence of sepsis, the high prevalence of cognitive complications might translate into a substantial increase in the proportion of people with disabilities, and might therefore place an unprecedented burden on health-care systems worldwide. The growing evidence that sepsis can lead to chronic cognitive impairment is likely to generate new hypotheses for the pathophysiology that underlies Alzheimer's disease and neurodegenerative diseases in general. In this Review, we discuss mechanisms of sepsis-induced chronic brain dysfunction, the main clinical presentations and outcomes, and interventions.

Mechanisms

Overview

The CNS plays a major part in maintenance of homoeostasis during stress, mainly via the autonomic nervous system and hypothalamic–pituitary–adrenal axis. Inappropriate brain responses might favour cardiovascular instability, metabolic disorders, and a sustained pro-inflammatory state, which, in turn, might irreversibly damage the brain (figure 1). Moreover, several ICU interventions might directly and indirectly exacerbate brain injuries.

Cerebrovascular damage

Abrupt variations in systemic blood pressure are frequent during the initial phase of sepsis and include cardiovascular collapse alternating with brisk rises in blood pressure, which might be exacerbated by infusion of exogenous catecholamines. This chaotic cardiovascular state favours onset of ischaemic or haemorrhagic lesions to the brain. In post-mortem studies, septic shock has been associated with a high prevalence of ischaemic neurons and haemorrhage, particularly in areas that are susceptible to hypotension and hypoxia, such as Ammon's horn of the hippocampus.[8,9] These lesions are also related to sepsis-associated disseminated intravascular coagulopathy.[9,10] Similarly, findings from imaging studies of selected groups of patients with sepsis and abnormal neurological examinations have shown multiple cerebral infarcts in as many as one in three patients.[10,11] In a large cohort of patients with catecholamine-treated sepsis, 2% had strokes and 1% had CNS bleeding during hospital stay and up to 90 days after discharge.[12] Findings from a study[13] based on electronic health records from more than 3 million hospitalised adults in California showed that

Key messages

- More than half of sepsis survivors have long-term cognitive impairment
- Cerebrovascular damage, metabolic disorders, and brain inflammation are hallmarks of sepsis and precede cognitive impairment
- Brain changes during sepsis mainly include disruption of the blood–brain barrier, microglial activation, and altered neurotransmission; these lesions can be diffuse and often target the limbic system, specifically the hippocampus
- Appropriate management of the acute phase of sepsis—eg, following the Surviving Sepsis Campaign guidelines, can prevent cognitive impairment
- No specific treatment is available; future treatment might target the blood–brain barrier, microglial cell activation, or neurotransmission

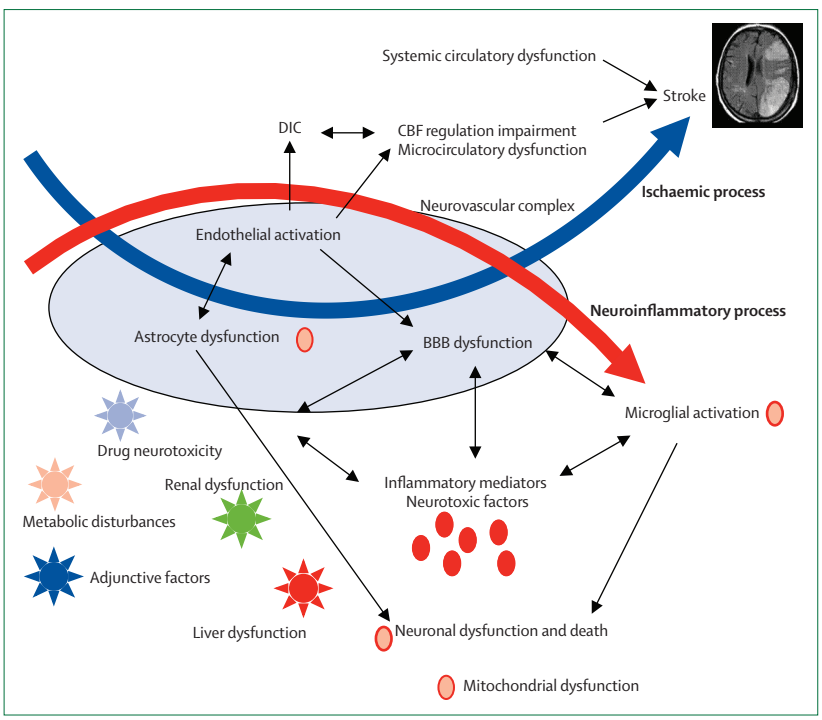

Figure 1: **Main mechanisms of sepsis-associated brain dysfunction**
Sepsis-associated brain dysfunction mainly results from ischaemic and neuroinflammatory processes. The ischaemic process includes macrocirculatory impairment, microcirculatory dysfunction, and DIC, which are the effects of endothelial activation. The neuroinflammatory process is related to dysfunction of the neurovascular complex, which encompasses the endothelium, BBB, and astrocytes, and allows for the passage of inflammatory mediators and neurotoxic factors. The resulting microglial activation amplifies the neuroinflammatory process. Ischaemic and neuroinflammatory (particularly microglial activation and astrocyte dysfunction) processes result in neuronal death or dysfunction (characterised by impairments in neurotransmission). Metabolic disturbances, hypoxaemia, liver and renal failure, and drug toxicities contribute to brain dysfunction. BBB=blood–brain barrier. CBF=cerebral blood flow. DIC=disseminated intravascular coagulopathy.

11% of patients who developed stroke during their hospital stay had sepsis, resulting in a sepsis-associated adjusted odds ratio of new onset of stroke of 6·0 (95% CI 5·38–6·69). The risk of sepsis-associated stroke was almost four times greater in patients with new onset of atrial fibrillation than in those without or with pre-existing atrial fibrillation. In another study, 5·3% of survivors of sepsis who had new onset of atrial fibrillation during the acute phase had ischaemic stroke within the 5 years after hospital discharge.[14] However, the exact prevalence of these events in patients with sepsis is probably underestimated. In addition to systemic haemodynamic instability, new onset of arrhythmia-related cardiac embolism[13,15] and endothelial activation related to impaired cerebral blood flow and microcirculation[16] might also contribute to stroke in sepsis.[9,10] This cerebrovascular damage might result in long-term neurological sequelae, particularly decline in cognitive function.[17] For example, in patients who have undergone operations for cardiac valve replacement or repair, cognitive impairment noted 6 weeks after the operation is most likely to be preceded by non-overt brain infarcts, as detected by diffusion-weighted MRI.[18] The subtle brain haemorrhages in patients who have died from septic shock[8,9] might mimic the cerebral microbleed syndrome that has been associated with progressive declines in cognitive function.[19]

Metabolic disorders

Deregulated metabolism is the hallmark of sepsis and includes hypoxia, hyperglycaemia, hyperuraemia, increased levels of several aminoacids, and hyperammonia.[20] The degree of deregulated metabolism might parallel that of brain dysfunction in sepsis.[21] In patients with acute respiratory distress syndrome, low initial arterial oxygen tension is associated with a risk of subsequent decline in cognitive function.[22] Guanidino compounds, such as creatinine, guanidine, guanidinosuccinic acid, and methylguanidine, might at least partly account for the uraemic neurotoxic effects.[23] Specifically, guanidine compounds might activate *N*-methyl-D-aspartate receptors and inhibit γ-aminobutyric-acid receptors. In rodents, high concentrations of these metabolites have been measured in plasma after endotoxaemia[24] and in the brain after caecal ligature and puncture-induced sepsis.[25] These compounds might trigger astrocyte and microglial apoptosis,[26] which might play a part in cognitive impairment and dementia.[27] Accumulation of glucose in brain tissue during sepsis might also contribute to cell apoptosis[28] and activate oxidative stress and matrix metalloproteinase 9,[29] and might subsequently induce chronic changes in the function and integrity of the blood–brain barrier. In a retrospective analysis[30] of 74 survivors of acute respiratory distress syndrome, cognitive impairment 1 year after hospital discharge was significantly associated with the degree of stress-induced hyperglycaemia noted during patients' ICU stays. In survivors of surgical ICUs, both hypoglycaemia and hyperglycaemia are associated with striking and persistent declines in cognitive function.[31]

Brain inflammation

Inflammation of the CNS is a common complication of sepsis.[32] Inflammatory mediators, including invading pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), activate important brain areas, particularly those within the limbic system, hypothalamic–pituitary axis, and brainstem, to allow counteracting neuroendocrine responses to be mounted.[32] These areas are protected behind the blood–brain barrier, and inflammatory mediators are trafficked to the brain via several routes. One route is the so-called autonomic immune-modulatory reflex, in which terminal nerve endings of afferent autonomic nervous fibre-expressing PAMP and DAMP receptors sense the threat within the site of the infection.[33] This afferent pathway connects to several brainstem nuclei, particularly the nuclear tractus solitarius and locus coeruleus, has neuronal projections to the parvoventricular and supraoptic nuclear cells within the hypothalamus, and has non-anatomical connections to the limbic system, particularly the amygdala and

hippocampus. Efferent autonomic fibres peripherally modulate most of the components of the inflammasome (a multiprotein complex, the composition of which depends on the cause of innate immunity activation)—eg, vagus nerve stimulation prevents cytokine-induced and endotoxin-induced systemic inflammation.[34] Another route involves circulating inflammatory mediators entering the brain through areas that physiologically lack a blood–brain barrier, mainly the circumventricular organs, and possibly actively crossing the blood–brain barrier via specific carriers.[35,36] These mediators then diffuse into deep regions of the brain and are recognised by PAMP and DAMP receptors expressed by neurons and glial cells in different parts of the limbic, noradrenergic and vasopressinergic, and hypothalamic–pituitary systems. Potentiation of cytokine concentrations in the blood and between the blood and brain might be an important regulator of cytokine transport across the blood–brain barrier.[37] This organised trafficking of inflammatory mediators into the brain should allow for appropriate brain signalling to control peripheral local and systemic inflammation, while preventing neuronal damage.

The excessive or sustained systemic inflammation that has been noted during sepsis might disrupt the blood–brain barrier and subsequently flood the brain with pro-inflammatory molecules. This breakdown of the barrier has been invariably shown in small[25,38] and large[39,40] animals with sepsis, and has been strongly suggested in patients.[11,41,42] Metabolic disorders[43] and various inflammatory mediators[37] contribute to blood–brain barrier leakage by both facilitating active transport and disrupting tight junctions. The complement system, particularly C5a anaphylatoxin—the receptor for which is strongly expressed by astrocytes and, to a lesser extent, by endothelial cells in response to inflammation—probably plays a major part in blood–brain barrier leakage associated with sepsis.[44] Matrix metalloproteinase 8 can cleave collagen in the extracellular matrix of the choroid plexus, resulting in increased permeability of the barrier.[45] Likewise, in a rat model of sepsis, matrix metalloproteinase 2 and 9 contributed to altered blood–brain barrier permeability, and their specific blockade protected the animals from brain inflammation and cognitive impairment.[46]

Together with C3 anaphylatoxin, C5a (ie, the alternative complement pathway) contributes to regulation of microglial activation during endotoxaemia.[47] Sepsis is associated with sustained and major astrocyte and microglial cell activation.[8,9,28,48] Survivors of sepsis are now thought to possibly have persistently high circulating concentrations of pro-inflammatory mediators after hospital discharge.[49] Conceivably, these survivors might also have persistent so-called neuroinflammation, which increasingly seems to precede neurodegenerative disorders, such as Alzheimer's, Parkinson's,[50] and Huntington's diseases.[51] Investigators of a large cohort study[52] of patients aged 45–69 years who were followed up for 10 years showed the association between increased circulating pro-inflammatory mediators—ie, interleukin 6 and C-reactive protein—and a decline in cognitive function. Both vasogenic and cytotoxic oedema predominantly affect the limbic system, specifically the hippocampus and amygdala.[8,25] Inducible nitric oxide synthase 2 is overexpressed in these areas and favours cell apoptosis and oxidative stress.[8,9] Moreover, mice deficient in the inducible nitric oxide synthase 2 gene seem to be protected from endotoxin-induced neuroinflammation, synaptic changes, and cognitive impairment.[48] Similarly, animals with genetic or pharmacological restrictions of NADPH oxidase type 2 are protected from oxidative stress—specifically, at the level of the hippocampus—and do not develop cognitive sequelae after faecal peritonitis.[53] In addition to peroxynitrite formation, oxidative stress might change mitochondrial function.[54]

Ultimately, the processes discussed previously can lead to neuronal death or dysfunction. Sepsis is associated with substantial changes in several pathways that regulate neuronal function, including the

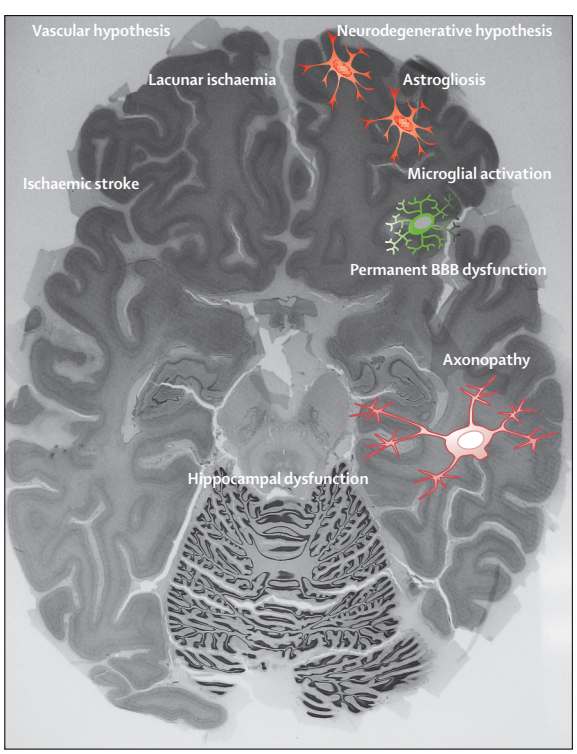

Figure 2: **Two hypotheses of the mechanism of long-term cognitive decline after sepsis**
The vascular hypothesis states that multiple lacunar or cortical strokes might have roles in long-term cognitive decline. The neurodegenerative hypothesis implicates microglial activation and axonopathy, with persistent BBB dysfunction and microglial activation producing neurotoxic mediators that lead to chronic impairment of neurotransmission. These two mechanisms are not mutually exclusive. The hippocampus and frontal cortex seem to be the most frequently affected regions. BBB=blood–brain barrier.

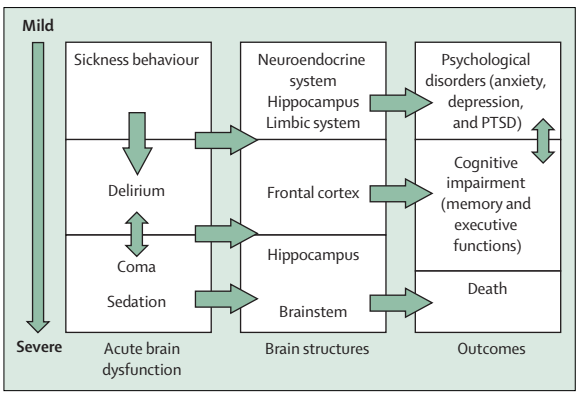

Figure 3: **Relations between acute brain dysfunction, brain structures, and outcomes**
Sickness behaviour includes the neuroendocrine, hippocampal, and limbic systems, and is associated with occurrence of psychological disorders. Delirium mainly includes the frontal cortex and hippocampus, and is associated with occurrence of long-term impairments in executive functions and memory. Coma includes the structures that are implicated in awareness and consciousness, notably the brainstem. PTSD=post-traumatic stress disorder.

β-adrenergic,[55] γ-aminobutyric-acid receptor,[56] and cholinergic[57] systems. In rats, cognitive impairment is associated with reduced cholinergic innervation.[57] In critically ill patients, delirium might partly result from an imbalance between dopaminergic and cholinergic neurotransmission,[58] and might be ameliorated by treatment with γ-aminobutyric-acid agonists, such as benzodiazepines.[59] Several risk factors for delirium occur during sepsis, including increases in neurotoxic aminoacids, failure in liver and kidney functions, electrolytic disturbances, and administration of antibiotics (eg, β-lactams). Finally, cognitive impairment might be preceded by axonopathy. Brain MRI might allow characterisation of vascular and inflammation injuries that might trigger postsepsis development of neurodegenerative disorders (figure 2).[41]

Clinical presentation

The clinical manifestations of cognitive impairment can be noted in the initial phase of sepsis, at recovery from the initial phase, and long term after hospital discharge. The acute phase of sepsis is characterised by so-called sickness behaviour, which is an evolutionarily acquired syndrome that increases withdrawn behaviour and allows the host to focus on fighting the infection. This syndrome typically includes withdrawal from social activities, anxiety, anorexia and bodyweight loss, hypersomnia or sleepiness, psychomotor retardation, fatigue, inabilities to calculate and concentrate, and deregulated body temperature.[60] These clinical manifestations accord with the predominance of neuroinflammation within the hypothalamic–pituitary axis, which controls body temperature, eating, drinking, and energy metabolism, and within the hippocampus (implicated in conversion of short-term to long-term memories) and amygdala (implicated in behaviour related to reward and fear, and in social function; figure 3). In patients in ICUs, this syndrome is typically masked by use of sedation and mechanical ventilation during early management of sepsis. During the acute phase, changes in brain function can be evidenced by impaired consciousness, delirium and, rarely, seizures or abnormal motor movements. In a prospective cohort study[11] of 222 patients with septic shock, comprehensive investigations identified 71 patients with abnormal neurological examinations, which included delirium (49%), coma (46%), focal deficit (18%), and seizure (10%). In sedated patients with sepsis, assessment of brainstem reflexes can help to characterise brain injuries. Specifically, patients with sepsis and abolished oculocephalic responses are at a very high risk of developing altered mental statuses (figure 4).[61] Electrophysiological studies have shown a broad range of abnormalities related to slow waves, theta waves, triphasic waves or burst suppression, periodic epileptiform discharges, and electrographic seizures, which are associated with the degree of severity of the illness.[62,63] In a prospective observational study of septic shock,[11] malignant electroencephalogram activities were associated with ischaemic lesions and diffuse leukoencephalopathy on brain MRI. Radiological manifestations noted in the acute phase of sepsis precede altered cognitive function 6 months after ICU discharge.[10,11]

Information about the cognitive function of patients who have survived sepsis remains scarce. Studies of survivors of acute respiratory distress syndrome, including many patients with sepsis, have reported changes in cognitive functions in 25–45% of patients 1 year after hospital discharge.[64,65] Findings from a single-centre study[66] nested within the ABC trial,[67] which is a multicentre randomised trial assessing a protocol of sedation and mechanical ventilation weaning in a large ICU population, showed a prevalence of cognitive impairment of 79% at 3 months and 71% at 1 year after ICU discharge. In a large cohort study[4] using data derived from electronic health records, the risk of development of cognitive impairment according to the trajectories of patients in ICUs with and without sepsis was assessed. Compared with their cognitive state before sepsis, survivors of sepsis showed a three-times increase in the odds of development of moderate-to-severe cognitive impairment. This negative effect on patients' trajectories was not reported in patients admitted to hospital without sepsis. Similar effects have been seen in critically ill patients with pneumonia. Investigators of one study[68] showed that, on one hand, patients with cognitive impairment were at an increased risk of acquiring pneumonia, and on the other hand, patients with no past medical history of altered cognition with pneumonia were more likely to have abnormal mini-mental state scores. These findings are suggestive of an interaction between severe infection and cerebral function. The few available studies[4,7,68–70] that have assessed neuropsychological function have used variably comprehensive and advanced methods, which notably include the Teng

Modified Mini-Mental State (3MS),[71] scale-based interviews,[72] the Informant Questionnaire on Cognitive Decline in the Elderly,[73] the Repeatable Battery for the Assessment of Neuropsychological Status,[74] and the Trail Making Test Part B.[75] Nevertheless, findings from these studies have shown a consistent prevalence of cognitive impairment. Long-term neurological complications after sepsis are associated with brain injuries, which could be focal or diffuse, and with the brain structures that are damaged. The clinical manifestations often affect verbal fluency and memory and attention, whereas visual memory and visuospatial construction might be preserved.[69] Executive function might also be altered. The risk and degree of cognitive impairment are unrelated to age and comorbidities,[4,7] psychiatric complications, physical activities,[54] severity of illness,[7,68,69] or use of sedative or analgesic drugs.[7] The presence and duration of delirium during the initial phase of critical illness[7,70] and reduced brain volume as assessed by the ventricle to brain ratio measured by MRI[70] are strong predictors of impaired cognition 1 year after ICU discharge. Asymmetrical reductions in the volumes of the hippocampi have also been found to qualitatively and quantitatively correlate with cognitive function in sepsis survivors.[69] Data for ultimate outcomes of patients with sepsis-associated cognitive decline are scarce, and whether these patients eventually resume normal cognition is unknown. Cognitive impairment has been reported up to 5 years after hospital discharge.[4,76] The causal relation between sepsis and onset of dementia remains unproven. For example, the bidirectional association between pneumonia and cognitive impairment[62] might be due to undiagnosed underlying bulbar impairment, which is a common feature of neurodegenerative disorders.

Therapeutic options

Non-specific interventions

Optimisation of initial management of patients with sepsis prevents brain injuries and subsequent declines in cognitive function. Appropriate implementation of the updated Surviving Sepsis campaign guidelines[77] is associated with important reductions in short-term and long-term mortalities.[78] Thus far, the potential benefits of implementing these guidelines on the risk of developing cognitive impairment have not been assessed. Findings from a single-centre case-control study[31] using electronic health record data suggested that appropriate control of blood glucose, especially prevention of hypoglycaemic episodes and rapid brisk variations in blood sugar concentrations, might reduce the risk of long-term cognitive impairment. In a single-centre randomised trial[79] of critically ill children who were followed up for about 4 years, no differences were noted in intelligence or cognitive functions between those who received strict glucose control and those who received typical care. However, children in the intervention group had significantly more episodes of hypoglycaemia than did those in the control group.[79] In an ancillary study[80] of a multicentre trial that was done in patients undergoing cardiac surgery, perioperative maintenance of normal blood glucose significantly reduced the short-term and long-term risks of impaired memory function. Additional trials are needed to support the association of cognitive function preservation with glucose control in patients with sepsis admitted to ICUs. Maintenance of glucose homoeostasis might prevent cognitive declines via reductions in oxidative stress and blood–brain barrier permeability.[28,29] Similarly, oxygen treatment might prevent neuronal and glial cell ischaemia and apoptosis, and favour recovery of blood–brain barrier integrity.[81]

The Surviving Sepsis campaign guidelines[77] recommend that patients should initially be resuscitated with an intravenous bolus of crystalloids. Hypo-osmotic fluids should perhaps also be avoided to prevent additional cerebral oedema.[82] In patients who were mechanically ventilated in ICUs, systematic implementation of a strategy that combines protocols of sedation interruption and mechanical ventilation weaning did not prevent cognitive impairment after 3 months or 1 year of follow-up.[66] These findings are in accordance with the absence of correlation between use of sedative and analgesic drugs and cognitive disorders 1 year after hospital discharge.[7]

Specific treatments

Although no specific treatment is available for routine practice, several interventions might prevent sepsis-related declines in cognitive function by attenuating the initial and extended neuroinflammation. First, some treatments might restore blood–brain barrier integrity.

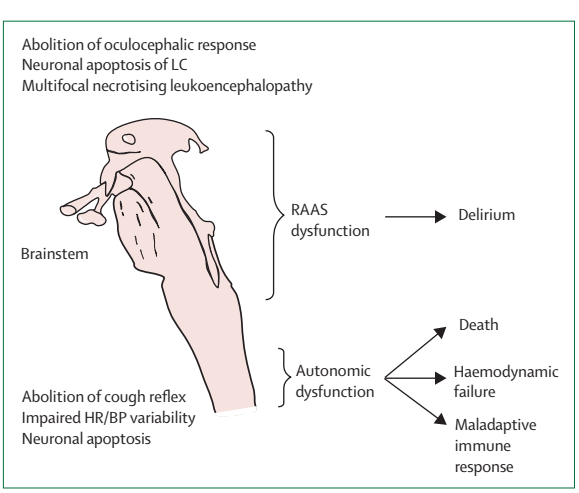

Figure 4: **Evidence for brainstem dysfunction in critically ill patients**
The brainstem dysfunction that is seen in patients who are comatose or sedated accounts for the mortality. PTSD=post-traumatic stress disorder. BP=blood pressure. HR=heart rate. LC=locus ceruleus. RAAS=renin–angiotensin–aldosterone system.

On one hand, β-blocking drugs might modulate barrier permeability and function via direct action on brain endothelial cells and inhibition of matrix metalloproteinase 9.[83] On the other hand, in pigs with cerebral oedema induced by faecal peritonitis, treatment with a β2-adrenergic receptor agonist significantly reduced breakdown of the blood–brain barrier via direct effects on intracellular concentrations of cyclic AMP and the indirect effect of reducing the cytokine burden.[40] Several drugs have been shown to improve blood–brain barrier integrity and function in various brain injuries, such as erythropoietin in cerebral malaria,[84] intravenous immunoglobulins in ischaemic stroke,[85] haemin (a haem oxygenase 1 inducer) in traumatic brain injury,[86] and hydrocortisone in cytokine-induced brain injury.[87,88] The effects of these treatments on sepsis-induced blood–brain barrier leakage and cognitive decline remain uncertain.

Second, interventions targeting microglial cell activation, notably within the hippocampus and other areas of the limbic system, or in the hypothalamic–pituitary axis, might favourably affect cognitive function. In endotoxin-challenged mice, pretreatment with an interleukin 1 receptor antagonist attenuates hippocampal gliosis and results in a subsequently substantial improvement in cognitive function, which is independent of the HMGB1 signalling pathway.[89] In mice with faecal peritonitis-induced sepsis and encephalopathy, treatment with apocynin—a selective NADPH oxidase type 2 antagonist—during the acute phase of sepsis downregulates oxidative stress and glial activation within the hippocampus and prevents secondary cognitive impairment.[53] Selective inhibition of the alternative complement pathway with monoclonal antibody 1379 monoclonal antifactor B antibody has been shown to significantly reduce post-traumatic neuroinflammation and subsequently improve cognitive function.[90] Treatment with a recombinant of anaphylatoxin C5a provides neuroprotection by ameliorating glutamate toxicity.[91] Minocycline can attenuate microglial activation within the hippocampus in a two-hit rat model of trauma and sepsis, but this effect does not translate into prevention of cognitive impairment.[92] Investigators of one experimental study[93] noted that, in rats with caecal ligature and puncture-induced sepsis, treatment with minocycline attenuated brain oxidative damage and improved long-term cognitive function. Histone deacetylases, which modify chromatin structure, interact with gene transcription. In both endotoxin challenge and faecal peritonitis models, inhibition of histone deacetylases induces marked suppression of hippocampal inflammation and neuronal apoptosis, with favourable effects on spatial learning and memory function.[94] Similar findings were noted in an experimental study[95] with valproic acid, which is a class I histone deacetylase inhibitor. Finally, in rats with caecal ligature and puncture-induced sepsis, rivastigmine treatment was associated with preserved memory acquisition.[96] However, this drug was possibly associated with increased mortality in critically ill patients with delirium.[97]

Search strategy and selection criteria

We identified references for this Review through searches of PubMed with no date or language restrictions, with the latest date of the search as July 31, 2014. We used the terms "sepsis", "encephalopathy", "delirium", "mental status", "cognition", "cognitive function", "dementia", "neurodegenerative disorders", "human studies", and "animal studies". We analysed the full texts of all articles deemed to be relevant to this Review on the basis of titles and abstracts. We also searched the reference lists of these articles for additional relevant publications.

Rehabilitation

Physical and occupational treatment might reduce the occurrence of delirium and severity of critical illness neuromyopathy.[98] Preliminary data show that cognitive treatment that targets memory and executive functions is feasible in the ICU. In a pilot trial,[99] 20 survivors of ICUs were randomly assigned to either both cognitive and physical rehabilitation programs, or to conventional follow-up. Patients from the experimental group showed improved executive functions compared with the control group. Continuing studies are assessing the long-term benefits of such therapies.[100]

Implications for practice and research

Arguably, the available evidence in the literature favours screening of sepsis survivors at times of ICU and hospital discharge with the 3MS test. Patients with abnormal 3MS test results should then be considered for more comprehensive analyses using, for example, the Repeatable Battery for the Assessment of Neuropsychological Status method, and might be referred to memory clinics for long-term follow-up. Thus far, therapeutic options are limited to optimisation of initial management of patients, notably by implementation of the Surviving Sepsis campaign guidelines.[77]

Future research needs to clarify the relation between sepsis and onset of dementia. Along with translational research, available commercialised interventions that might restore blood–brain barrier integrity, reduce oxidative stress, and alleviate microglial activation deserve investigation in sepsis trials. These treatments might include hydrocortisone, minocycline, erythropoietin, haemin, immunoglobulins, or recombinant C5a.

Contributors

Both authors conceived the structure of the Review. DA ran the literature search, and both authors selected relevant reports. DA drafted the report and TS provided revisions.

Declaration of interests

We declare no competing interests.

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