VIA MEDICA

REVIEWS

Molecular mechanisms of bacterial infections of the central nervous system

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Abstract

Central nervous system (CNS) infections may involve the meninges, brain and/or spinal cord. The most common etiologic agents are *Streptococcus pneumoniae*, group B *Streptococci*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Listeria monocytogenes*. CNS is characterized by specific structure and function. Despite a unique system of brain barriers and autonomous immune system, CNS is very susceptible to microorganisms which may invade directly, via the blood, or less frequently by reverse axonal transport. The complex process of bacteria and activated polymor-phonuclear leukocyte transfer to the subarachnoid space, which is devoid of natural immune defence mechanisms, initiates an inflammatory response that subsequently spreads to the brain tissue. Consequences of these changes include damage to the blood-brain barrier, development of vasogenic cerebral oedema, and intracranial pressure-volume disturbances leading to impaired CNS perfusion.

Anaesthesiology Intensive Therapy 2017, vol. 49, no 5, 387–392

Key words: neuroinfection; astrocyte; microglia; blood–brain barrier; brain, oedema

Anatomically, central nervous system (CNS) infections may be categorized into meningitis, encephalitis, and myelitis. Infections may involve one or more of these anatomical locations [1]. In terms of acuity and severity of the disease process, the most dangerous type of CNS infection is bacterial meningitis [2]. The incidence is 3-5 cases per 100,000 population per year, and mortality is up to 26% [3]. The most common etiologic agents are *Streptococcus pneumoniae, group B Streptococci, Neisseria meningitidis, Haemophilus influenzae*, and *Listeria monocytogenes* [4].

CNS is characterized by specific structure and function. Despite a unique system of brain barriers and autonomous immune system, CNS is very susceptible to microorganisms which may invade directly, via the blood, or less frequently by reverse axonal transport [5]. Meningitis is mostly initiated by nasopharyngeal bacteria with abundant surface adhesion proteins [6]. Their invasive capability depends on the presence of polymeric immunoglobulin receptor (pIgR) on the epithelial cell surface, responsible for transcellular antibody transfer [7]. It is believed that by binding to pIgR, bacterial choline-binding protein A (CbpA) forms a channel for bacterial translocation to the intravascular space [8]. In addition, bacterial hyaluronidase degrades hyaluronate and induces additional damage to the protective barriers [9]. It was found that intravascular pathogen survival depends on the presence of cell membrane polysaccharides imparting protection from phagocytosis [9]. As the intravascular space is separated from CNS by the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), severe bacteraemia is not the only prerequisite for the development of meningitis [10]. The morphological and functional substrate of BBB is the tight junction, formed by adjacent basal laminae of the endothelial cells of CNS microvasculature (Fig. 1) [11]. Its large electrical resistance, precluding perivascular flow, low pinocytic activity, and selective, fully controllable BBB transport system eliminate any possibility of uncontrolled protein, ion, and microorganism transfer to CNS [12–16]. BBCSF located at the choroid plexus, with a relatively large vascular surface, is the place of direct contact of the cerebrospinal fluid with the blood [17, 18]. For most pathogens causing meningitis, the exact place of penetration into the subarachnoid space (SAS) is not clearly known.
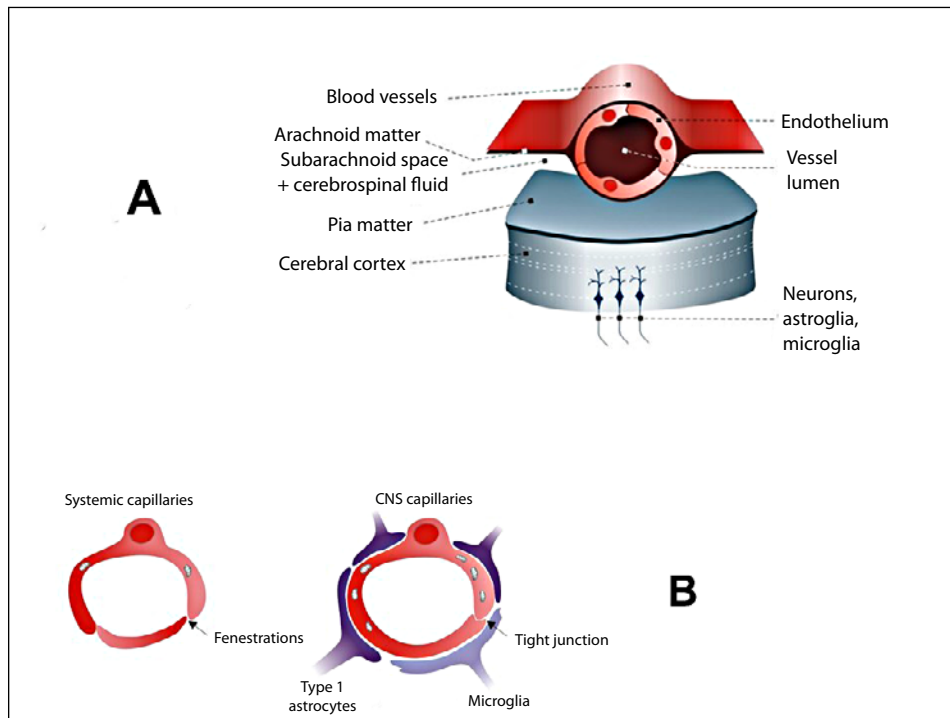
Figure 1. A — morphology of the subarachnoid space. Interrelations between blood vessels and cerebral tissue; **B** — comparison of central nervous system (CNS) and peripheral microcirculation structure

Indirect evidence suggests that *Hemophilus influenzae* enters CSF through the choroid plexus [19], while Streptococcus pneumoniae penetrates via the meningeal vessels [20]. Recent studies indicate that bacterial transfer from the blood to SAS occurs within the endothelium and its ultrastructures [10]. Three mechanisms of pathogen BBB crossing have been identified. The first of these is possible with disrupted continuity of tight junctions and/or endothelial cells. The remaining two mechanism involve leukocyte-mediated transfer through BBB, either with or within the leukocyte, and active transcytosis [10]. The first mechanism is most commonly observed. Pathogen invasion and transmigration provokes activation of the platelet activating factor (PAF) receptor on the endothelial cell surface, which binds bacterial wall phosphorylcholine [21]. A vacuole formed by the endothelial cell, PAF receptor, and the bacterium allows pathogen translocation to SAS [22]. Pathogens present in CSF proliferate freely due to lack of natural defence mechanisms such as polymorphonuclear leukocytes (PMNL), the complement system, and immunoglobulins [23–25]. PMNL activated by the presence of bacteria migrate by a complex process from the intravascular space to SAS. During this process, a sequential activation of vascular endothelial cell and PMNL receptors and adhesion ligands occurs, leading to binding, activation, persistent adhesion, and migration [26]. The transfer process is initiated by P-, E- and L-selectins. Next, activated PMNL binds via the macrophage antigen 1 (Mac1)

integrin to the intercellular adhesion molecule 1 (ICAM-1) at the vascular endothelial cell, which results in persistent adhesion and induces chemotactic gradient-mediated PMNL transfer to SAS [27, 28]. Peptidoglycan and lipoteichoic acid released from the bacterial wall activate the membrane CD14 (mCD14) receptor and the toll-like receptor 2 (TLR2) in peripheral blood-derived PMNL, which in turn stimulates translocation of the nuclear factor κB (NF-κB) from the cytoplasm to the nucleus [29]. NF-κB is the main activator of gene transcription responsible for production and release of inflammatory mediators, such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [30]. Of note, IL-1β and TNF-α play a key role in stimulating expression of adhesion molecules that mediate PMNL transfer from the blood vessels to SAS [31]. Morphological and functional changes in PMNL that occur intravascularly lead to endothelial cell proliferation, and bacteria and PMNL translocated to SAS, along with released proteins, form the inflammatory infiltrate [5]. These changes result in vascular obstruction and morphological evidence of inflammatory reaction within SAS, peaking at 48 hours (Fig. 2A). If destructive processes are halted, vessel recanalization, arachnoid fibrosis, and formation of adhesions occur within the next few days [5] (Fig. 3A). Impaired cerebral tissue perfusion due to vascular occlusion leads to impaired homeostasis of the CNS immune system, consisting mainly from microglial cells and astrocytes.
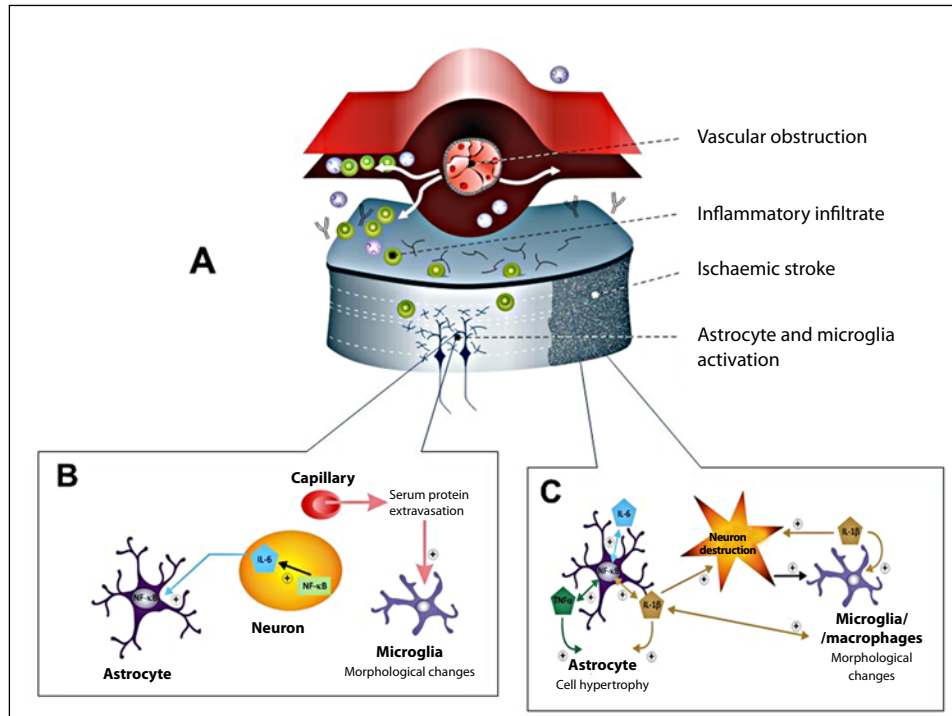
Figure 2. A — bacteria-activated polymorphonuclear leukocytes (PMNL) result in vascular obstruction and ischemic changes in the cerebral cortex. PMNL and bacteria translocated to the subarachnoid space (SAS) form inflammatory infiltrates; **B** — ischeamic changes activate neuronal NF-κB, and later astro- and microglia; **C** — astro- and microglial cells undergo morphological and functional changes, which result in TNF-α, IL1-β, and IL-6 synthesis and release
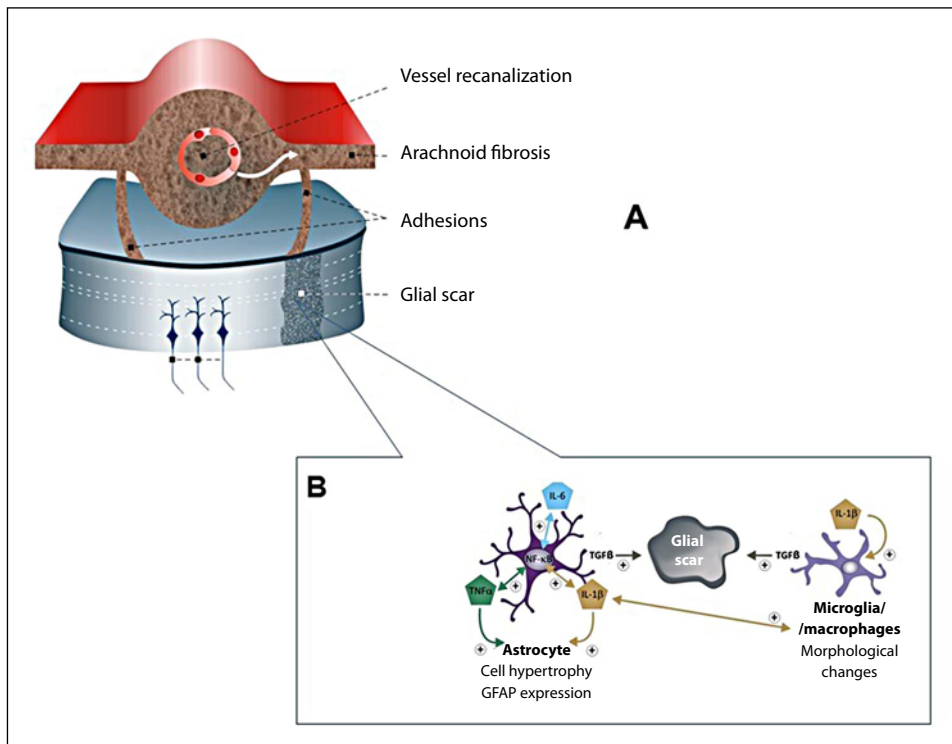

Figure 3. A — restoration of the subarachnoid space (SAS) with arachnoid fibrosis, formation of adhesions, and microvascular recanalization; **B** — glial scar forms in hypoperfused cortex; GFAP — glial fibrillary acidic protein
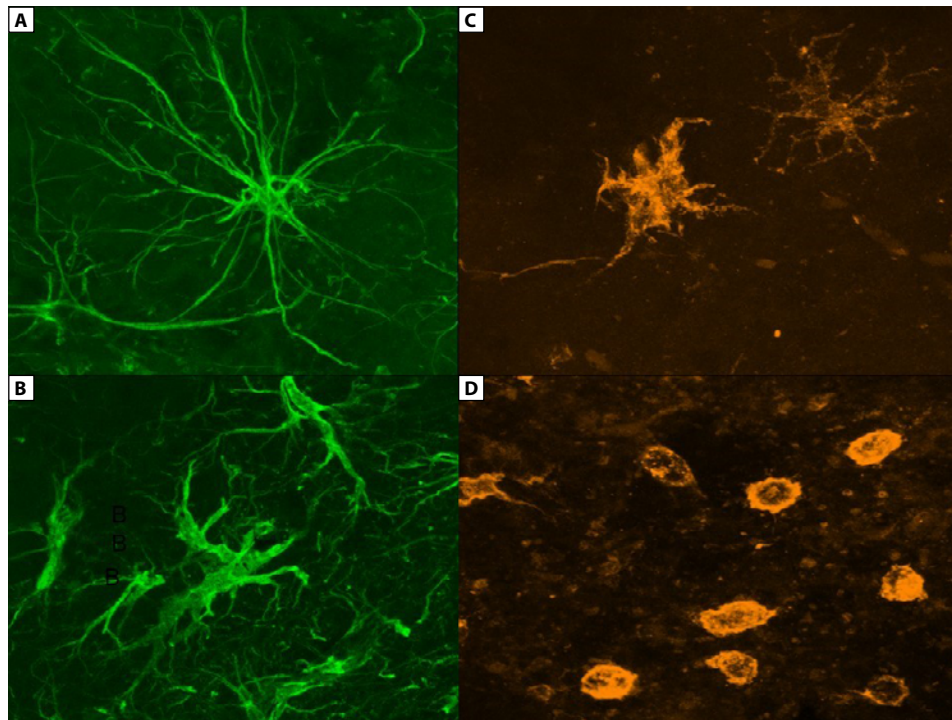
Figure 4. A — resting astrocyte; **B** — fully activated astrocyte; **C** — resting microglial cell; **D** — active microglial cell, an equivalent of a polymorphonuclear leukocyte (PMNL)

Activation of astro- and microglia is a sensitive marker of CNS changes. Factors affecting their activation may include water and electrolyte imbalances due to ischemia, exposure to blood serum components, damage to BBB, reduced production of some proteins, and altered neuronal transcription activity [32]. Due to neuronal damage, translocation and activation of NF-κB occurs in the astrocytes within several hours, leading to gene transcription and production and release of inflammatory mediators including TNF-α (Fig. 2B), IL-1β, and IL-6 [33] (Fig. 2C).

By similar mechanisms, morphological and metabolic changes occur in the microglia. These cells become larger, their processes retract, and enzymatic pathways leading to TNF-α, IL-1β, IL-6, and nitric oxide synthesis become activated [34] (Fig. 4C, D).

Within several days after the insult, neuronal damage, BBB discontinuation, and PMNL infiltration ensue (Fig. 2B). Astrocytes become fully activated and able to migrate and proliferate [35] (Fig. 4B). The purpose of activation of these mechanisms is to restore tissue structural integrity. Gene expression changes occur, leading to synthesis of antioxidative proteins along with TNF-α, IL-6, and IL-1β [35]. During these pathological processes, extensive tissue damage, the presence of neuronal and/or axonal debris, and consequences of disrupted BBB continuity lead to full activation of microglial cells (Fig. 4D). They achieve a capability for migration, proliferation, and phagocytosis, along with IL-1β synthesis and release [36].

Formation of the glial tissue, also known as glial scar, is a repair response of mostly the astroglia but also microglia (Figure 3B). Main contributors to glial scar formation include vimentin-rich, hypertrophic processes of activated astrocytes (Fig. 4B), macrophages, and the extracellular matrix [37]. Astrocytes show high nuclear NF-κB content and TNF-α, IL-6, and IL-1β expression [37, 38]. In addition, reactive astrocytes in the glial scar modulate their activity and stimulate expression of transforming growth factor β (TGF-β) [38, 39]. TGF-β enhances the forming scar by stimulating synthesis of collagen fibres, fibronectin, tenascin, thrombospondin, and proteolytic protein inhibitors [40] (Fig. 3B). Macrophages are a major component of the forming glial scar. They derive from both microglial cells (Fig. 4C) and PMNL and are characterized by high IL-1β and TGF-β content which decreases with time [40]. A gradual reduction of the number of microglial cells in the scar occurs due to apoptosis [41].

Intensive research of the recent years led to the discovery of metalloproteinases (MMPs) which are a family of more than 20 tissue proteases [44]. Inactive forms of MMPs are produced and released by activated astro- and microglial cells, along with cerebral vessel endothelial cells [44]. Endogenous tissue MMP inhibitors (TIMPs) are responsible for maintaining an adequate balance of MMP activity [44]. PNML, astrocytes and microglial cells activated by the infectious process release TNF-α, IL-6, and IL-1β, which leads to activation of MMPs and inhibition of TIMPs. Active forms of

MMP-2 and MMP-9 induce damage to the structural proteins of the tight junctions - the morphological and functional BBB substrate [44]. Consequences of these pathological processes at the molecular level include loss of BBB with transfer of water and osmotically active components from the intravascular space to the interstitium, which results in vasogenic cerebral oedema [44]. The volume of translocated water determines both the extent of the damage and the level of intracapillary hydrostatic pressure [45]. The absolute increase in intracranial water volume, which disturbs pressure-volume relationships, leads to a reduction in cerebral perfusion pressure with imminent structural damage.

ACKNOWLEDGEMENTS

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