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Bacterial meningitis pathophysiology and treatment

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ABSTRACT

The bacterial meningitis is a medical emergency that is requires prompt diagnosis and treatments. However The most common and aggressive pathogens of meningitis are Streptococcus pneumonia and Neisseria meningitides. Antibiotic resistance is an impending problem. Moreover the Clinical and experimental research has advanced of understanding of the mechanisms that cause brain damage, squeal, and neuropsychological deficits. However With the current treatment procedure and summary of the current pathophysiological concept of acute bacterial meningitis.

KEYWORDS: Dexamethasone, bacterial meningitis, meningoencephalitis, pneumococci, meningococci

INTRODUCTION:

Despite modern antibiotics and improved critical care, bacterial meningitis (BM) remains an unresolved clinical problem. Even though the fact that are highly effective antibiotics kill bacteria productively, mortality rates can reach 34% [van de Beek et al. 2006]. Long-term sequelae affect up to 50% of survivors [1997; Bohr et al. 1984Weisfelt et al. 2006; de Gans and van de Beek, 2002; Schuchat et al.]. This review focuses primarily on the most common and typical causes of community-acquired bacterial meningitis, such as meningococci and pneumococci.

However the Two seminal studies proposed using dexamethasone as an adjunctive treatment to antibiotics to improve the outcome of acute BM [de Gans and van de Beek, 2002; Odio et al., 1991]. In contrast to these clinical data collected in the United States or Western Europe, several studies conducted in resource-poor countries found no positive effect.

Other underlying diseases, particularly AIDS [Scarborough et al. 2007; Molyneux et al. 2002], tuberculosis [Nguyen et al. 2007], malnutrition, and the fact that patients in these studies presented to emergency rooms at more advanced stages of the disease [Scarborough and Thwaites, 2008], could explain this difference.

As a result, in addition to the scientific and medical challenges of unravelling the molecular basis of bacterial meningitis, developing new treatments, and meeting new upcoming challenges such as increasing resistance of

pathogens to currently used antibiotics; for example, pneumococci up to 35% According to [Richter et al. 2002; Doern et al. 2001; Whitney et al. It is critical to note that the proportion of resistant isolates is highly dependent on geographical and other factors.

Definition of bacterial meningitis

Bacterial meningitis is an inflammation of the meninges, specifically the arachnoid and pia mater, caused by the invasion of bacteria into the subarachnoid space, which has been known for over a century [Flexner, 1907]. Pathogens use specific features of the immune system in the CNS to replicate and cause inflammation [Simberkoff et al. 1980]. In addition to bacteria, viruses, fungi, and non-infectious causes such as systemic and neoplastic disease, certain drugs can cause meningeal inflammation. Typically, the inflammatory process affects not only the meninges surrounding the brain, but also the brain parenchyma (meningoencephalitis) [Swartz, 1984], the ventricles (ventriculitis), and spreads along the spinal cord.

In recent years, neuronal damage, particularly in hippocampal structures, has been identified as a potential cause of survivors' persistent neuropsychological deficits [Zysk et al. [Nau et al., 1999b; 1996]. Bacterial meningitis is a serious condition. medical emergency necessitating immediate diagnosis and treatment

Epidemiology

The epidemiology of bacterial meningitis has changed dramatically in the last 26 years. Haemophilus influenzae, a major cause of meningitis in the past, has now vanished in developed countries, serving as a remarkable example of a successful vaccination campaign. Pneumococci are now the leading cause of bacterial meningitis in both children and adults in the United States and Europe. The disease's incidence ranges from 1.1 to 3 in the United States [Schuchat et al. 1997; Wenger et al. 1990] and Western Europe [Berg et al. 1996] to 12 in 100 000 in Africa [O'Dempsey et al. 1996].Individuals younger than 5 years and older than 60 years have the highest risk of disease. Some risk factors are known, such as a previous splenectomy, malnutrition, or sickle cell disease [Kastenbauer and Pfister, 2003; Fraser et al. 1973]. In areas where conjugate pneumococcal vaccines are used, there has been a significant decrease in invasive pneumococcal disease, including meningitis [Hsu et al. 2009; Whitney et al. 2003]. The increasing prevalence of pneumococci resistant to beta-lactam antibiotics is an emerging issue [Stanek and Mufson, 1999]. Prolonged persistence of pneumococci in the cerebrospinal fluid (CSF) may result in increased mortality and apparent neurological damage in survivors [Fiore et al. 2000; McCullers et al. 2000].These effects of living bacteria compel us to learn more about the effects of bacterial toxins and released cell wall and surface components on neuronal damage.

With Haemophilus declining, Neisseria meningitides has emerged as the leading meningitis pathogen in developing countries, but it remains a major health concern in the United States and Europe. Meningococci frequently cause systemic disease, including fulminant gram-negative sepsis and disseminated intravascular coagulopathy, in addition to classical meningitis. According to WHO, at least 400 000 newly symptomatic infections occur each year, resulting in at least 50 000 deaths [Stephens et al. 2007]. In sub-Saharan meningitis belt has the highest incidence, with cyclic epidemics occurring at least once every decade.

Pathogenesis

Bacterial invasion

The current expectation is that high-grade bacteremia precedes meningitis and that bacteria spread from the bloodstream to the central nervous system (CNS).Alternatively, direct accesses to the CNS through Dural defects or local infection are potential entrance routes. However the clinical setting, such as defects should be identified by MRI or CCT scans. The physical site of bacterial invasion from the bloodstream remains unidentified. The Experimental evidence suggested that the picachoroid a, may be a site of invasion [Daum et al. 1978]. Meningococcal are found in the plica choroidea, as well as in the meninges [Pron et al. 1997] and pneumococci infiltrate the leptomeningeal blood vessels [Zwijnenburg et al. 2001; Rodriguez et al. 1991] in meningitis. These data suggest that several highly vascularized sites are potential entry locations. In order to cross the bloodbrain or the bloodCSF barrier and to overcome sophisticated structures such as tight junctions, meningeal pathogens must carry effective molecular tools

Streptococcal proteins, such as CbpA, interact with glycoconjugate receptors of phosphorylcholine and platelet activating factor (PAF) on eukaryotic cells, promoting endocytosis and blood-brain barrier crossing [Radin et al. 2005; Orihuela et al. 2004; Ring et al. 1998; Condell et al. 1995]. PilC1 adhesin from meningococci interacts with CD46 and connects to vitronectin and integrins [Unkmeir et al. 2002; Kallstrom et al. 1997].

Bacteria that cause meningitis in newborns, most notably group B streptococcal (GBS) and E. coli, have adhesive proteins that allow them to invade the CNS [Maisey et al. 2007; Prasadarao et al. 1997]. A thorough understanding of how bacteria activate and invade cells may enable us to prevent disease progression by blocking these interactions.

Performance reaction

Inflammatory activation of endothelial cells appears to be a requirement for bacterial invasion, but it also results in adhesion regulation.

Neurological Disorders: Therapeutic Advances ICAM-1 is made up of two (6) molecules [Freyer et al. 1999].

As a result, these molecules facilitate the multistep process of leukocyte invasion. Meningitis is distinguished by the presence of leukocytes, particularly granulocytes, in the CSF.

Early inflammatory response and bacterial invasion appear to occur concurrently, and activated leukocyte products such as MMPs [Kieseier et al. 1999] and NO [Koedel et al. 1995] and others contribute to early bloodbrain and bloodCSF barrier damage. Bacteria that enter the subarachnoidal space replicate, undergo autolysis, and cause additional inflammation.

Endothelial cells, perivascular macrophages, and mast cells, as previously mentioned, appear to be involved [Polfliet et al. 2001; Weber et al. 1997]. Meningitis is caused by heat-killed bacteria and pathogen-associated molecular patterns (PAMP) of meningitis pathogens such as lipoprotein (LP), lipoteichoic acid (LTA), peptidoglycan (PG), and lipopolysaccharide (LPS) [Hoffmann et al. 2007a; Ivey et al. 2005; Tuomanen et al.

1985]. Immune pattern recognition molecules such as CD14 and LBP act as sensors to detect PAMPs [Beutler, 2003].

TLR2 recognises pneumococcal PG and LP [Weber et al. 2003; Aliprantis et al. 1999], whereas TLR4 recognizes LPS and, interestingly, the pneumococcal toxin pneumolysin [Malley et al. 2003]. The intracellular adapter protein MyD88 transmits TLR signals.Downstream to a slew of inflammatory signalling cascades such as NFkB and MAP kinases, resulting in a rapid inflammatory response in meningitis [Lehnardt et al. 2006].

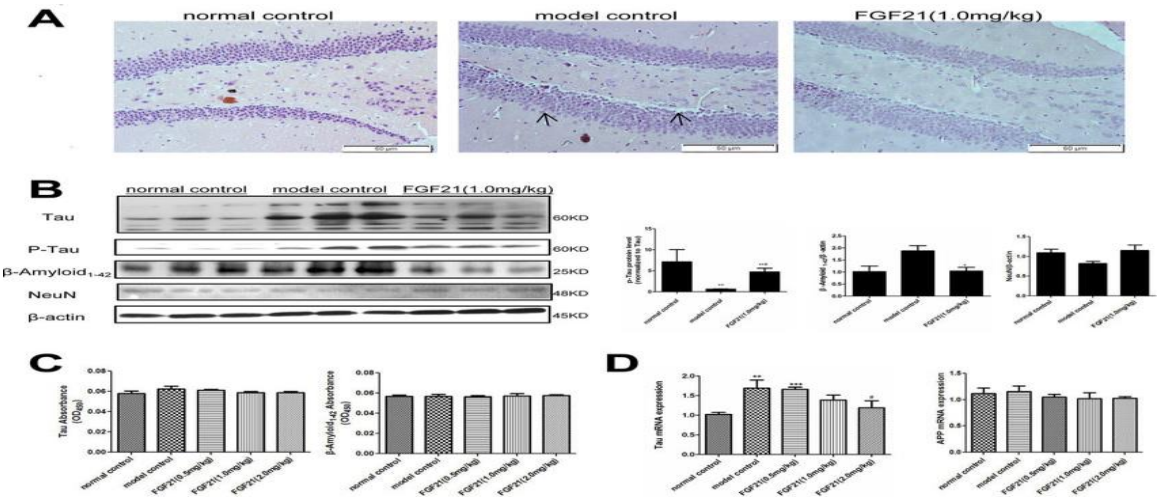
compartments that could deliver soluble bacterial and inflammatory toxic mediators [Rennels et al. 1985] Meningitis causes neuronal damage that is clearly multifactorial, involving bacterial toxins, cytotoxic products of immune competent cells, and indirect pathology caused by intracranial complications (Figure 1). In the case of S. pneumoniae, the pathogen associated with the highest frequency of neuronal damage, two major toxins, H2O2 and pneumolysin, a pore-forming cytolysin, have been identified. Neuronal damage was reduced by 52% in experimental meningitis caused by toxin-deficient pneumococcal mutants compared to wild-type bacteria [Braun et al. 2002]. The demonstration of direct bacterial toxicity emphasises the critical importance of rapidly eliminating living bacteria and their metabolism with antibiotics. Toxic activity may be significantly prolonged in insufficiently treated patients or resistant bacteria, causing neuronal damage.functions. These toxins appear to be the cause of Neurons and microglia are programmed to die. by causing immediate mitochondrial damage

Clinical features and diagnosis

Clinical characteristics Early symptoms of bacterial meningitis include fever, malaise, and headache; later, meningismus (neck stiffness), photophobia, phonophobia, and vomiting develop as signs of meningeal irritation [van de Beek et al. 2004]. Headache and meningismus are symptoms of inflammatory activation of the trigeminal sensory nerve fibres in the meninges, which can be experimentally blocked by 5-HT1B/D/F receptor agonists (triptans) [Hoffmann et al. 2002]. However, the role of triptans in headache control in patients with bacterial meningitis is unknown [Lampl et al. 2000].Meningismus may be absent very early in the disease, in patients who are deeply comatose, in children, and in immunocompromised patients, such as those with liver cirrhosis [Cabellos et al. 2008]. It is critical to remember that the classic triad of fever, neck stiffness, and altered mental state occurs in less than half of adults with proven bacterial meningitis [Heckenberg et al. 2008; van de Beek et al. 2004]. Around 34% of patients develop focal neurological signs such as epileptic seizures or limb paresis, and up to 70% have impaired consciousness or 15% are in coma [van de Beek et al. 2004]. An examination of the integument may reveal pete chiae, a sign of meningococcal infection, or Osler's nodes, a sign of bacterial endocarditis. Meningitis occurs in approximately 6% of patients with bacterial endocarditis, and is frequently the first symptom [Angstwurm et al. 2004; Jones et al. 1969]. S. aureus, which is uncommon in bacterial meningitis, and pneumococci are the most common pathogens in this con text. Pneumococcal meningitis, endocarditis, and pneumonia can all be diagnosed at the same time (Austrian's syndrome) [Dalal and Ahmad, 2008].Meningococcal disease can manifest as a fulminant gram-negative sepsis with significant cardiovascular insufficiency and diffuse intravascular coagulation, posing a risk of ischemic tissue damage. Notably, a petechial skin rash is not limited to meningococcal disease but can also be found in septicemia caused by streptococci or S. agalactiae.

Laboratory tests

The presence of bacteria in the CSF via Gram staining (Figure 2) or a positive bacterial culture is essential for the diagnosis of bacterial meningitis. CSF detection rates can reach 95 percent, while blood cultures yield only about 55 percent positive results. CSF microscopy diagnostic yield can be improved by centrifu gating a larger sample and gaining experience. If microscopic and cultural identification of the pathogen fail, polymerase chain reaction (PCR) may be used, but it is not yet a routine test. PCR is useful for strain identification, particularly in meningococcal disease [Fox et al. 2007].Although latex agglutination-based rapid tests for major meningitis pathogens are available, their poor sensitivity and specificity make them unsuitable for routine clinical use at this time [Hayden and Frenkel, 2000].



CT A cranial CT scan can detect intracranial complications such as brain edoema, hydrocephalus, and infarcts. Furthermore, bone window imaging detects parameningeal lesions such as sinusitis, mastoiditis, and odontogenic abscess. Local infections are common in pneumococcal meningitis and may necessitate surgical treatment.The use of a cranial CT before lumbar puncture is still debated, with the main concern being the risk of cerebral herniation due to increased intracranial pressure. Patients with focal neurological deficits or seizures, as well as those with altered consciousness, should have a cranial CT before lumbar puncture. If the technique is not available, treatment must begin on clinical suspicion and without a CSF examination. CT abnormalities are found in less than 3% of patients without focal signs or seizures and with a normal level of consciousness [Joffe, 2007; Hasbun et al. 2001];CSF can be drawn here without first undergoing CT scanning. A normal CT scan, however, does not rule out intracranial hypertension or the possibility of herniation [Oliver et al. 2003].

Treatment

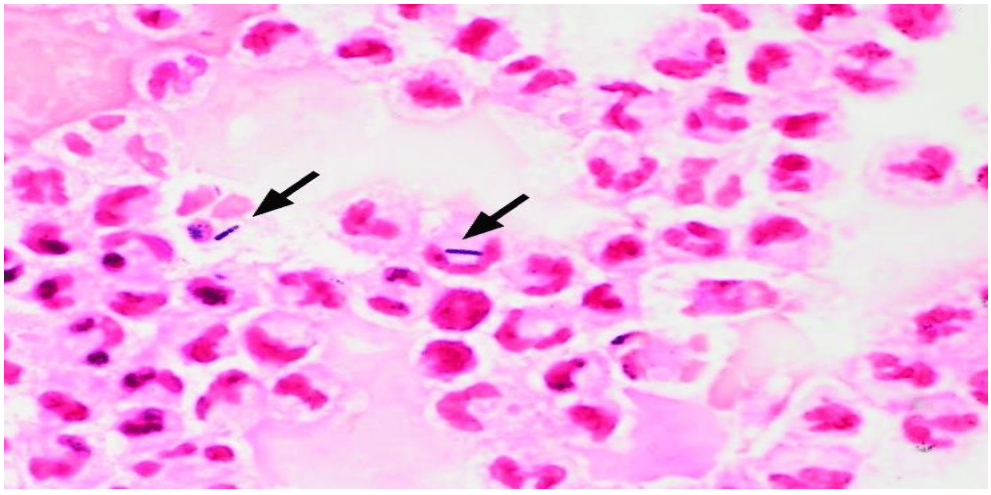
Antibiotics

Immediate antibiotic therapy is required and should not be delayed by diagnostic delays, such as waiting for a CT scan. In cases of suspected meningococcal disease, prehospital antibiotic treatment is recommended, but this is dependent on the local resistance situation and the medical environment [Sudarsanam et al. 2008]. A blood

culture should be obtained prior to treatment. Because microbiological identification of the pathogen is not always possible, the first choice of antibiotics is usually empirical. Regional antibiotic resistance rates, patient age, predisposing conditions, and resources are all factors to consider. (Table 1).

Microbiological identification and susceptibility testing of the causative agent are critical factors in antibiotic therapy success. Antibiotic chemotherapy should be adjusted in light of emerging resistances in order to provide highly active yet narrowly targeted coverage. However, for meningococci or pneumococci, penicillin G monotherapy should be used only after susceptibility has been established. Most pathogens require 10 14 days of treatment; a shorter course of 5 7 days is sufficient for uncomplicated meningococcal disease, while 3 4 weeks of treatment is recommended for L. monocytogenes and Enterobacteriacae. Treatment duration data are scarce and mostly based on expert opinion [Tunkel et al. 2004].Suspected or confirmed meningococcal meningitis necessitates patient isolation for the first 24 hours of treatment; chemoprophylaxis is advised for close contacts (Table 1). In patients who do not improve clinically after 48 hours of treatment, cerebral imaging and a repeat lumbar puncture should be considered to assess antibiotic failure.

Corticosteroids In experimental models of bacterial meningitis, corticosteroids reduce brain edoema, intracranial hypertension, and meningeal inflammation. Subsequent clinical studies have produced contradictory results regarding the potential benefits of steroid use in meningitis patients. Evidence currently available supports a lower incidence of severe hearing loss in children with H. influenzae meningitis [Odio et al. 1991; Lebel et al. 1988], but data on other paediatric pathogens is limited. A single double-blind RCT of 301 adult patients revealed lower mortality and a lower frequency of hearing loss and neuropsychiatric sequelae [de Gans and van de Beek, 2002]. Subgroup analysis revealed that dexamethasone's protective effects are limited to pneumococcal meningitis (death: 34% versus 14%; unfavourable outcome: 52% versus 26%) [van de Beek et al. 200] Expert opinion and several societal guidelines recommend routine dexamethasone treatment for children (0.15 mg/kg every 6 hours for 2 4 days) and adults with community acquired meningitis (10 mg every 6 hours for 4 days). If H. influenzae (children) and S. pneumoniae (adults and children) are ruled out as the underlying pathogens, this therapy should be discontinued. Notably, H. influenzae and S. pneumoniae infections in children are declining in those countries.



Some countries encourage immunization. The first steroid dose should be given 15-30 minutes before starting antibiotic treatment, or at the very least concurrently. Dexamethasone does not reverse existing brain edoema or intracranial hypertension in later stages of meningitis, so delaying treatment is not beneficial. In contrast, there is concern about aggravated neurotoxicity, which appears to have no clinical relevance [Weisfelt et al. 2006; Zysk et al. 1996] and may impair antibiotic pen etration into the CSF as a con sequence of dexamethasone treatment [Paris et al. 1994]. Current evidence does not support the routine use of corticosteroids in resource-constrained countries [Scarborough and Thwaites, 2008].

Other symptomatic therapy

Severe headache necessitates extensive analgesia, which frequently includes opioids. If seizures occur, antiepileptic treatment is indicated; prophylactic treatment is not advised.

Complications

Mortality from bacterial meningitis can reach 36% [van de Beek et al. 2006], with S. pneumoniae and L. meningitidis being the most common pathogens. Long-term neurological sequelae have been reported in up to 55% of survivors [Weisfelt et al. 2006; de Gans and van de Beek, 2002; Bohr et al. 1984; Schuchat et al. 1997]. This negative outcome is due to both intracranial and systemic complications. Complications are most likely in the first few days of therapy. The most common issues are sensorineural hearing loss and vestibular dysfunction. They are most common in H. influenzae and S. pneumo niae infections. As previously stated, adjunctive dexamethasone therapy reduces the incidence of these complications. Brain edoema, vascular changes, and hydrocephalus are the most dangerous intracranial complications, all of which contribute to increased intracranial pressure and parenchymal damage [Pfister et al. 1992]. Clinically, patients may experience a sustained or progressive change in their mental state or level of consciousness. If patients do not improve after 48 hours of antibiotic treatment or if new focal signs develop, CT imaging should be performed. In general, patients with meningitis should have their beds elevated (30 degrees).

Osmotherapy is one treatment option for brain edoema. Therapeutic hypothermia, which has been shown to to be effective in experimental models of bacterial meningitis [Angstwurm et al. 2000], has not been studied in patients, but lowering elevated body temperature appears to be beneficial.

Up to 20% of patients develop hydrocephalus, which usually manifests as malresorption due to increased CSF outflow resistance. Patients with hydrocephalus and impaired con sciousness should be closely monitored on subsequent CTs; they may eventually require external ventricular drainage (EVD). EVD has the added benefit of ICP monitoring. ICP, clinical improvement, and CT follow-up are used to determine the amount of drainage. Normalization of CSF protein and leukocyte counts usually makes EVD unnecessary; otherwise, a ventriculoperitoneal shunt should be placed. In comatose patients with generalised brain edoema, invasive ICP monitoring should be considered. Vascular complications include vasculitis, vaso spasm, and septic thrombosis of the dural sinuses and cortical veins [Haring et al. 1998, 1993; Pfister et al. 1992], which frequently result in large cerebral territory infarction. Such diagnostic considerations should be prompted by clinically new focal

neurological deficits in the course of meningitis. MR, CT, and MR or CT angiograms are all useful diagnostic tools. In the absence of controlled trials, the risks and benefits of anticoagulation in septic sinus thrombosis are unknown. Similarly, there are no evidence-based treatments for meningitis-associated vasculitis or vasospasm.In the case of suspected vasculitis, hemodilution and nimodipine may be administered similarly to subarachnoid haemorrhage, and dexamethasone has been suggested. Extracranial complications include sepsis, disseminated coagulopathy, multiorgan failure, arthritis, and electrolyte imbalance, all of which are typically caused by the syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

Neuropsychological deficits are common in bacterial meningitis survivors. Long-term cognitive impairment is most common in adults following pneumococcal meningitis, with a lower incidence following meningococcal meningitis [van de Beek et al. 2002]. Short-term and working memory, executive functions, and associative learning of verbal material were all affected in adults aged 1 to 11 years after bacterial meningitis [Schmidt et al. 2006], while other authors emphasise psychomotor slowing as a primary feature [Hoogman et al. 2007; Merkelbach et al. 2000].Children may experience persistent learning difficulties, impaired short-term memory, and behavioural deficits, resulting in poor academic performance [Grimwood et al. 2000].

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