Bacterial meningitis and neurological complications in adults

Parunyou Julayanont MD, Doungporn Ruthirago MD, John C. DeToledo MD

ABSTRACT

Bacterial meningitis is a leading cause of death from infectious disease worldwide. The neurological complications secondary to bacterial meningitis contribute to the high mortality rate and to disability among the survivors. Cerebrovascular complications, including infarction and hemorrhage, are common. Inflammation and increased pressure in the subarachnoid space result in cranial neuropathy. Seizures occur in either the acute or delayed phase after the infection and require early detection and treatment. Spreading of infection to other intracranial structures, including the subdural space, brain parenchyma, and ventricles, increases morbidity and mortality in survivors. Infection can also spread to the spinal canal causing spinal cord abscess, epidural abscess, polyradiculitis, and spinal cord infarction secondary to vasculitis of the spinal artery. Hypothalamic-pituitary dysfunction is also an uncommon complication after bacterial meningitis. Damage to cerebral structures contributes to cognitive and neuropsychiatric problems. Being aware of these complications leads to early detection and treatment and improves mortality and outcomes in patients with bacterial meningitis.

Key words: meningitis; meningitis, bacterial; central nervous system bacterial infection; nervous system diseases

INTRODUCTION

Bacterial meningitis is a leading cause of death from infectious disease worldwide. Despite the availability of increasingly effective antibiotics and intensive neurological care, the overall mortality remains high, with 17-34% of the survivors having unfavorable outcomes.[1,2,3] Neurological complications associated with bacterial meningitis are major contributing factors to this high disability and mortality among survivors. Being aware of these potential complications leads to early detection and treatment and may improve recovery and outcomes.

Corresponding author: Parunyou Julayanont, MD
Contact Information: p.julayanont@ttuhsc.edu
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In this article, we present a case of bacterial meningitis complicated by an unusual number of neurological complications that occurred in spite of a timely diagnosis, adequate treatment, and intensive neurological monitoring. We also review various neurological complications of bacterial meningitis in adults with emphasis on the incidence, clinical characteristics, pathophysiology, and treatment.

CASE

A 45-year-old man with rheumatoid arthritis and chronic hepatitis C infection presented with a two day history of low grade fever and confusion and required intubation. He had been recently treated for sinusitis

with five days of amoxicillin-clavulanate. Head computed tomography (CT) without contrast on admission showed the subarachnoid hemorrhage (SAH) in the fronto-parieto-temporal convexities and Sylvian fissures bilaterally. He also had opacification of the maxillary and sphenoid sinuses. Computed tomography angiography showed no aneurysm or any other explanation for the subarachnoid hemorrhage. A lumbar puncture showed yellowish cerebrospinal fluid (CSF) with 4,352 WBCs (neutrophils 87%, lymphocytes 2%, and monocytes 11%) and 1,707 RBCs with positive xanthochromia. The opening pressure was 58 cmH_2O, protein was 442 mg/dL, and glucose was 3 mg/dL. Cerebral spinal fluid gram stain and culture, *S. pneumoniae, H. influenzae, N. meningitides antigen panel, cryptococcal* antigen, beta D-glucan, fungal and mycobacterial cultures, and herpes simplex virus-1,2 DNA were all negative. The patient was empirically started on high dose ceftriaxone and vancomycin. Pus cultured from the left maxillary and ethmoid sinuses showed skin flora. Magnetic resonance imaging (MRI) of the head with gadolinium showed scattered leptomeningeal enhancement with residual SAH. His level of consciousness markedly improved, and he was extubated after seven days of antibiotics.

One week after extubation, the patient had an acute change in mental status. A repeat MRI showed hydrocephalus, obstruction of the cerebral aqueduct, and intraventricular empyema of the occipital horns of the lateral ventricles. It also showed a subdural empyema in the posterior fossa. He underwent posterior craniotomy with right occipital ventriculostomy. Intraoperatively, large amounts of pus were drained from the posterior fossa. No organisms grew from this culture. He had an MRI of the whole spine performed due to persistent leukocytosis and back pain. The MRI showed an epidural abscess extending from T9 to the thecal sac. Three milliliters of pus was aspirated from the epidural space between L1 and L2 level. No organism was found in the epidural pus.

A follow up head MRI showed new areas of ischemic infarction at right medial pons, left capsulothalamic area, right-sided splenium of corpus callosum, and mesial temporal areas bilaterally. A magnetic resonance angiogram of the head and neck showed diffuse irregularity of the intracranial arteries consistent with a diffuse intracranial vasculitis.

Over the next six weeks his condition improved significantly, and he was discharged to an inpatient rehabilitation facility with a modified Rankin Scale of 4. He could not remember events during his hospitalization. Three months later, he had some recovery with a modified Rankin Scale of 3 and a Barthel index of 55/100.

Discussion

Cerebrovascular complications

Ischemic and hemorrhagic strokes are common complications of bacterial meningitis. These complications are reported in 14-37% of patients and are associated with poor neurological outcomes and increased mortality.[4,5,6,7,8] Cerebrovascular complications can occur at the onset of the infection, during hospitalization, or weeks after successful treatment.[4,7,9]

Arterial infarction

Arterial infarction (Figure 1) occurs in 8-25% of bacterial meningitis cases and accounts for 70-85% of all cerebrovascular events.[4,5,6,7,10] Even though ischemic events tend to occur early in the course of disease (1-2 weeks), ischemic stroke or vasculopathy may develop months after successful treatment or recovery.[9,11,12] In 1,032 meningitis episodes, delayed cerebral thrombosis defined as initial recovery with sudden deterioration after the first week of admission caused by cerebral infarction occurred in 11 patients (1.1%).[13] The outcome of patients with delayed cerebral thrombosis is very poor.[13,14]

A reduced level of consciousness at admission, the presence of seizures, low CSF white cell counts, and high ESR are predictors of infarction or cerebral arterial narrowing.[5,7,15] The posterior circulation is less commonly affected than anterior circulation, and strokes in this region are better tolerated clinically than in the anterior circulation.[16,17] The middle cerebral artery is the most commonly affected artery in bacterial men-

ingitis-induced cerebral infarction.[4]

Cerebral angiography typically shows vascular changes in various segments of the arteries. Small vessel involvement may result in loss of arterial autoregulation demonstrated angiographically by focal abnormal parenchymal blush associated with hyperperfusion.[6] In a series of 35 patients, transient intracranial stenosis of the middle and anterior cerebral arteries was detected by transcranial Doppler sonograms (TCD) in 50 % of patients within day 3-5 of onset of the disease.[17] Some studies have demonstrated an association between the arterial narrowing detected by the bedside TCD and increased risk of stroke.[8,18]

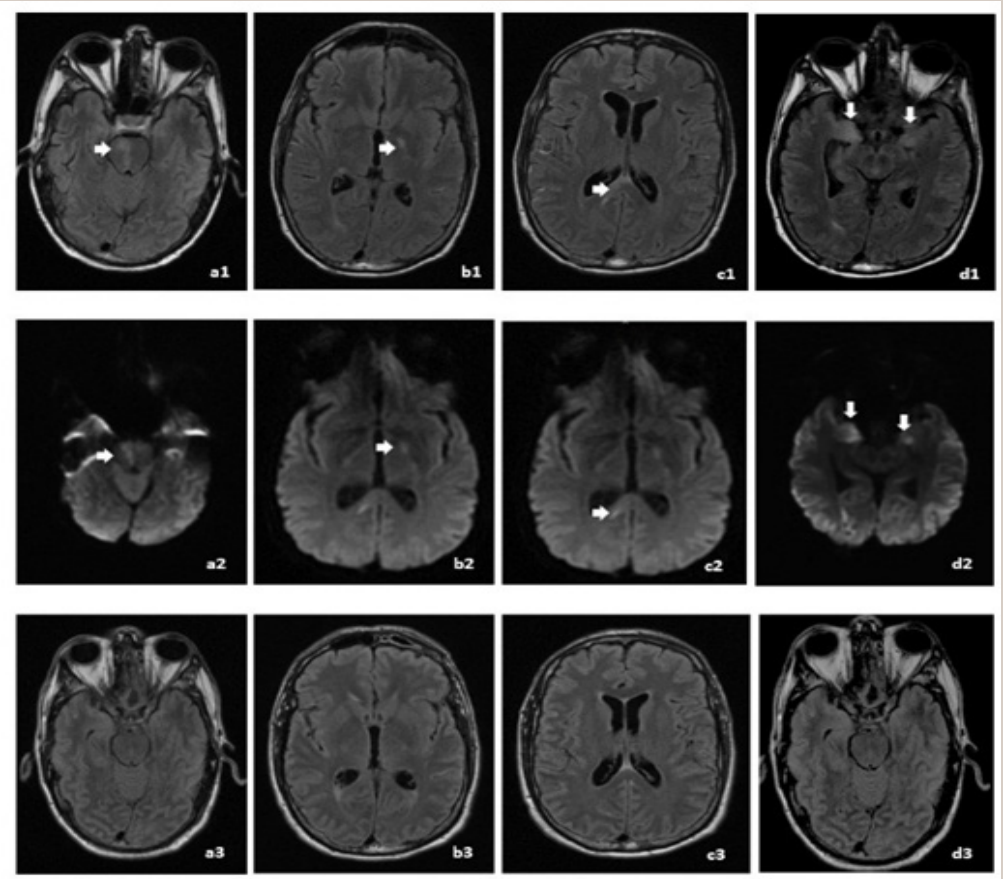

Figure 1. New infarction at the right medial pons (a1, a2), the left capsulothalamic area (b1, b2), the right-sided splenium of corpus callosum (c1, c2) and the bilateral mesial temporal areas (d1, d2) shown by FLAIR (top row) and DWI (middle row) (day 30 after admission); The MRI on the day of admission showed no infarction at these areas (a3,b3,c3,d3; bottom row)

The inflammatory process in the subarachnoid space may have a primary role in causing vasculitis, vasospasm, and localized or diffuse thrombosis of the vessels (Figure 2).[7,19,20] Three phases of meningitis-induced cerebral angiopathy are recognized. The initial phase is the presence of vasospasm triggered by the surrounding purulent material in the subarachnoid space and Virchow Robin spaces. This is followed by myonecrosis of the vessel wall that subsequently results in vasodilatation. In the final phase, subendothelial edema and proliferation of smooth muscle eventually cause vascular stenosis.[19] The activation of coagulation and attenuation of fibrinolysis in the CSF may also contribute to the cerebral infarction.[21] Post-infectious processes may trigger autoimmunity to the cerebral vessels and cause late onset vasculopathy.

The role of antithrombotic or thrombolysis in the treatment of arterial ischemia associated with bacterial meningitis is unclear. Delayed vasculopathy is rare, and there are no systematic studies on how to best

treat this complication. Immunosuppressive therapy was reportedly beneficial in one case.[22] Clinical worsening has been reported during tapering corticosteroids in some cases.[9,22]

Venous infarction

Venous infarction involves thrombosis of either dural venous sinuses, deep veins, or cortical veins.[8,12] The incidence of venous infarction is far less than arterial infarction. In 87 pneumococcal meningitis patients, venous infarction occurred in 10% of cases.[12] The cortical vein was the most commonly affected vessel accounting for 46% of the venous infarctions followed by dural venous sinuses (36%) and the deep cerebral venous system, including internal jugular veins (18%).[12]

Due to the rarity of venous thrombosis in bacterial meningitis, prospective trials on the role of anticoagulants in this condition have not been performed. Based on limited information, heparin should be started cautiously after the patient develops clinical symptoms associated with venous infarction

Hemorrhagic stroke

Intracranial hemorrhage (ICH) is less common than ischemic stroke and occurs in 2-9 % of all bacterial meningitis patients, approximately 14-28% of all stroke events.[4,10,23] However, in a series of patients with S. aureus meningitis, ICH developed in 38% of cases and was highly associated with infective endocarditis (IE).[23] There are several types of ICH in bacterial meningitis, including intraparenchymal hemorrhage and microbleeds from arterial bleeding, hemorrhagic transformation of arterial or venous infarcts, subarachnoid hemorrhage (Figure 3), and abscess formation with subsequent hemorrhagic transformation.[10,23,24] In *S. aureus* meningitis, hemorrhagic transformation after cerebral infarction by septic embolism may occur.[23,25] Subarachnoid hemorrhage caused by

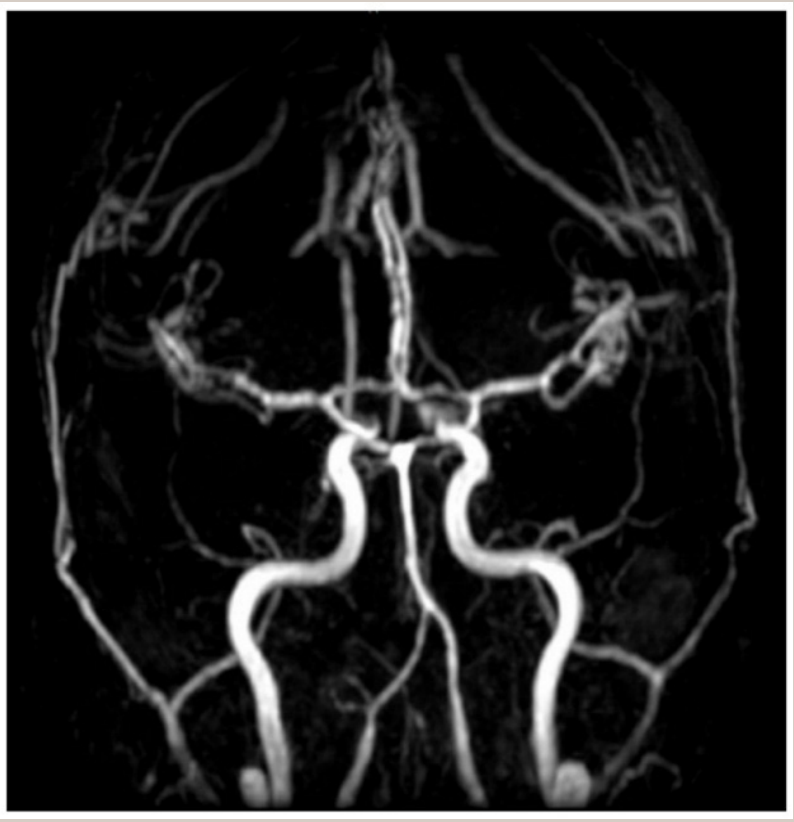

Figure 2. MRA head showed diffuse irregularity of the intracranial arteries compatible with vasculitis/ vasospasm (day 14 after admission)

ruptured inflammatory arteritis or aneurysms is a rare complication of bacterial meningitis.[10,23]

Vestibulocochlear neuropathy

The vestibulocochlear nerve is the cranial nerve most affected by bacterial meningitis. Hearing loss complicates 22-54 % of adult patients with pneumococcal meningitis; 23-47 % have moderate to severe hearing loss.[10,26,27] In meningitis caused by *Streptococcal suis*, hearing loss occurs in half of patients.[28] Hearing loss can also be caused by meningitis from *Neisseria meningitides, Haemophilus influenza, Streptococcus equi, and Streptococcus bovis*.[29,30]

Bacterial dissemination from the subarachnoid space to perilymphatic space of the cochlea leads to inflammation and damage of the blood-labyrinth barrier, ganglion, and hair cells which subsequently cause suppurative inflammation and ossification of cochlear and semicircular canals.[31,32] Use of corticosteroids can reduce hearing loss in adults with suspected or proven community-acquired bacterial meningitis.[33]

After profound hearing loss is established, cochlear implantation can improve hearing thresholds. The timing of implantation after meningitis is controversial. Early implantation can avoid dealing with labyrinthitis ossificans (LO) and improves hearing performances. In cases managed conservatively, periodic MRI may detect early signs of LO, and that would be an indication for implantation.[34,35]

Altered mental status (AMS) and increased intracranial pressure (ICP)

The spectrum of mental status changes seen in these cases ranges from irritability to coma. AMS occurs in approximately 80% of cases with bacterial meningitis. Increased ICP in bacterial meningitis is caused by several factors that raise intracerebral fluid volume, causing cerebral edema. These factors

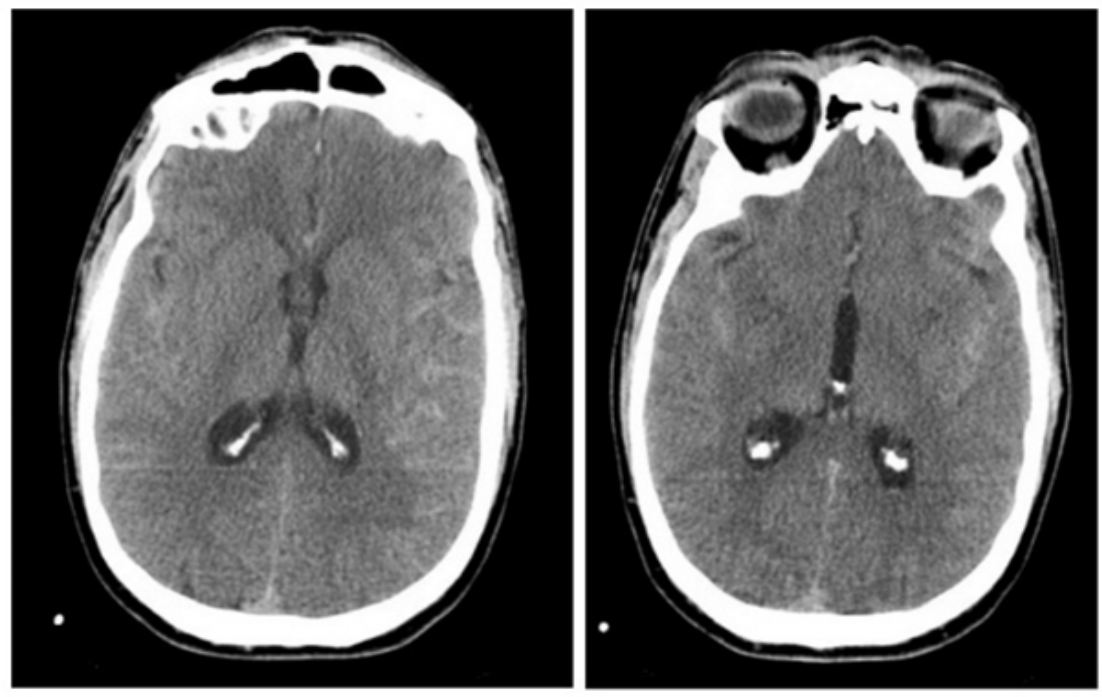

Figure 3. Diffuse subarachnoid hemorrhage in the bilateral posterior frontal temporal convexities extending minimally into the parietal lobes (on the day of admission)

include cytotoxic factors released by bacteria and neutrophils, vasogenic edema from increased blood-brain barrier permeability, and poor CSF reabsorption caused by arachnoiditis.

The management of increased ICP includes appropriate fluid management, osmotic therapy, hypertonic saline, hyperventilation with the $PaCO_2$ 25-35 mmHg, head elevation, and CSF drainage. In a double-blind, randomized controlled trial, oral glycerol therapy used to decrease intracranial pressure increased mortality and neurological disability in adult patients with bacterial meningitis (83%).[36] A retrospective study suggested that lumbar drainage of CSF targeting ICP of < 10 mmHg in severe bacterial meningitis was safe and contributed to lower mortality and morbidity.[37] At this point, these various measures to decrease ICP are best used based on clinical indication rather than as a routine treatment.

Hydrocephalus

Hydrocephalus occurs in 3-21% of patients.[38,39,40] This condition is associated with higher mortality and poorer neurological outcomes.[38,39] Because the infection affects primarily the meninges, communicating hydrocephalus due to blockade of CSF absorption by leptomeningeal inflammation is more common. Obstructive hydrocephalus due to aqueduct obstruction is less common and can result from infected debris or complicated intraventricular pus as found in this case (Figure 4). Mild to moderate hydrocephalus can be conservatively managed with close monitoring; severe hydrocephalus causing increased intracranial pressure must be treated with neurosurgical intervention.

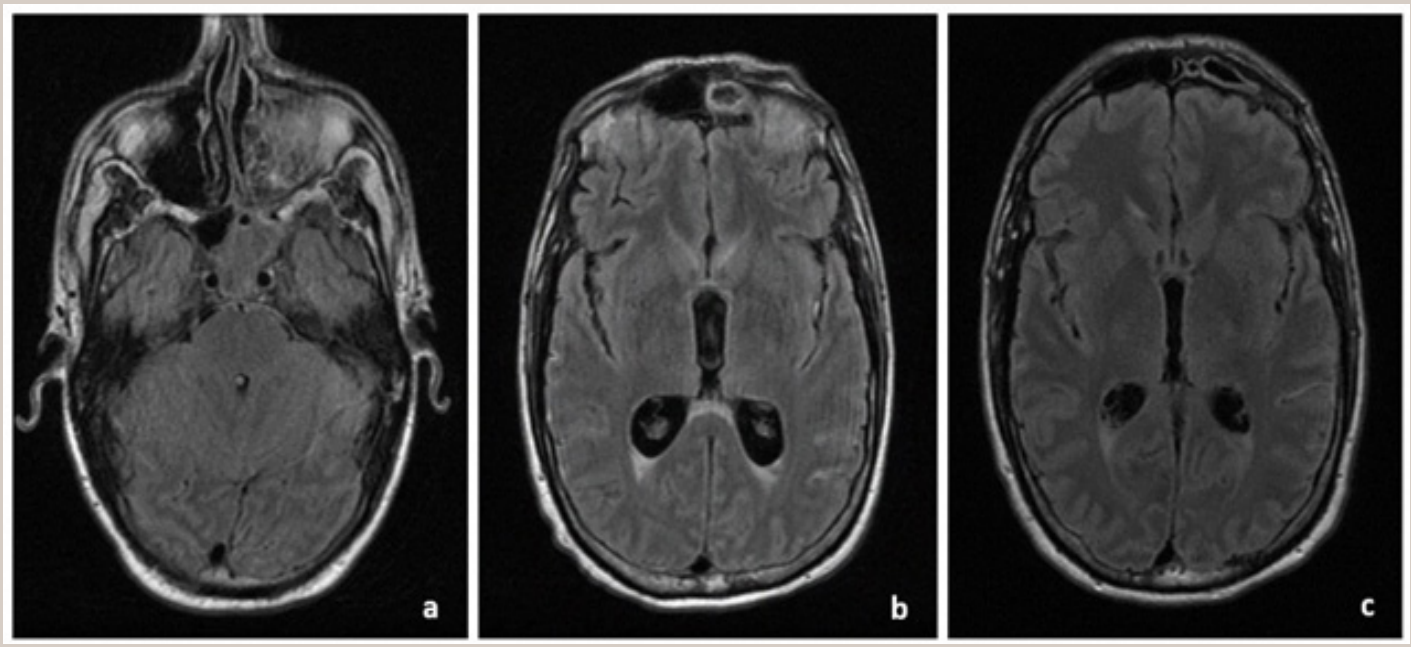

Figure 4. Increase in size of the third and lateral ventricles with normal size of the fourth ventricle (a,b; day 14 after admission) comparing with the MRI on day 2 after admission (c) suggesting obstructive hydrocephalus at the level of cerebral aqueduct.

Seizures

Seizures can complicate bacterial meningitis as a result of the inflammatory exudate, bacterial toxins, and changes within the cortex. Seizures are reported in 15-30 % of adult patients with bacterial meningitis.[41] Seizures occurring in the acute phase of the bacterial meningitis in adults are a poor prognostic factor and suggest a more severe and diffuse spread of the infection to the brain parenchyma.[41,42] These patients have a higher risk of recurrent seizures over the ensuing five years and have a higher risk of persistent neurologic deficits and death.[41,43]

Brain abscess and focal cerebritis

Brain abscess and focal cerebritis can be either the cause of or a complication of bacterial meningitis. Brain abscess is a more common complication of meningitis due to *S. aureus* and less often in meningitis from *S. pneumoniae, H. influenzae, and N. meningitidis*.[23]

Treatment requires broad spectrum antibiotics, such as third or fourth generation cephalosporins plus metronidazole, which also cover anaerobic bacteria, and neurosurgical consultation. If patients have a history of trauma or recent neurosurgical procedures, vancomycin should be added to an empirical regimen.

Subdural effusion/ empyema

Bacterial meningitis can result in collection of extra-axial fluid that may be sterile (subdural effusion) or infected (subdural empyema). Subdural empyema (Figure 5) is reported in 5% of patients with bacterial meningitis.[44] Patients can present with fever, new onset of seizure, or increased ICP. Differentiating subdural empyema from effusion requires clinical features and neuroimaging. Most cases of subdural empyema are unilateral, but they have potential to spread rapidly through the dural folds to the base of the brain

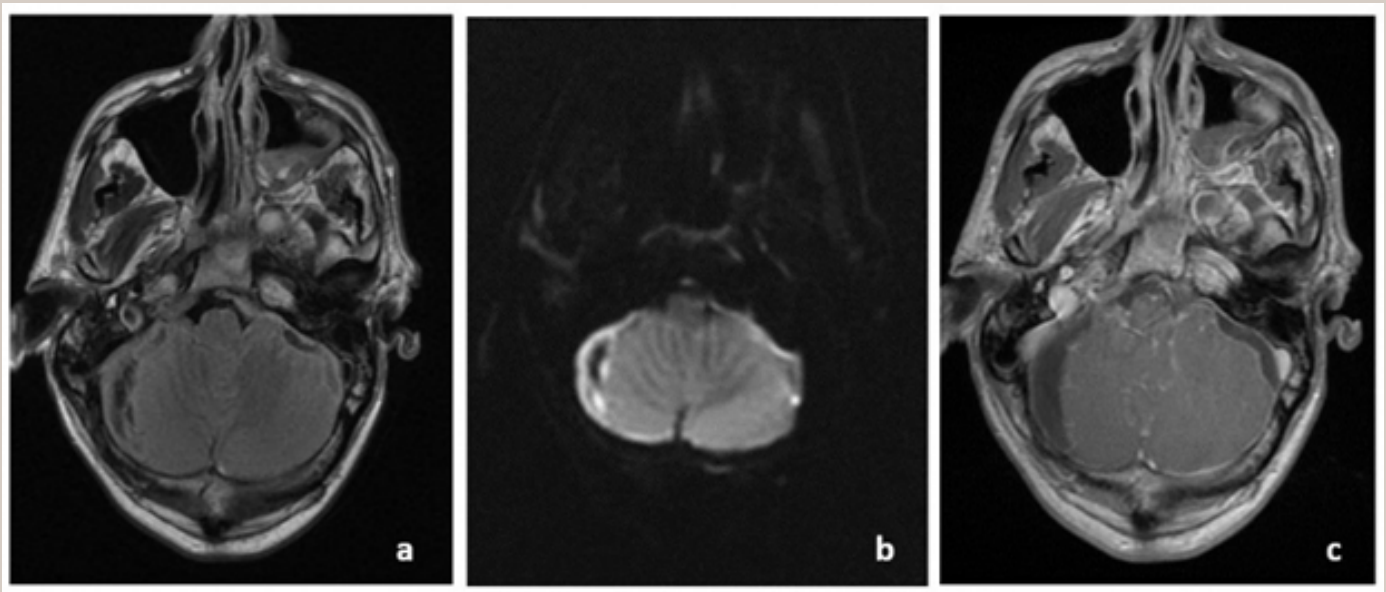

Figure 5. Subdural empyema at the posterior fossa on FLAIR (a), DWI (b) and T1 with gadolinium contrast (c) MRI (day 14 after admission)

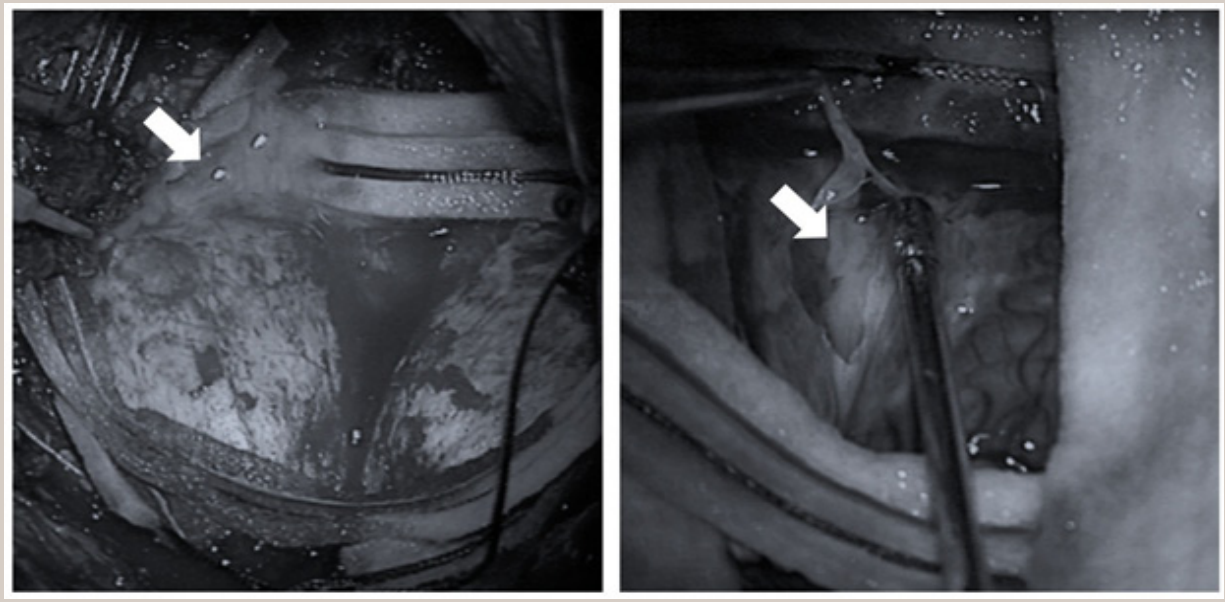

Figure 6. Posterior craniotomy for subdural empyema drainage and extraventricular drainage for hydrocephalus. Arrows indicate subdural pus.

and spinal canal. Small subdural effusions usually resolve spontaneously, while patients with subdural empyema tend to have persistent or recurrent fever or focal neurological deficits requiring surgical drainage (Figure 6).

Ventriculitis and pyogenic intraventricular empyema

Ventriculitis and intraventricular empyema were not considered a common complication of bacterial meningitis. With the advent of routine MRI, it has become apparent that signs of pyogenic ventriculitis are not uncommon. In one retrospective series, this complication was seen in 54.7% of acute bacterial meningitis.[44] Pyogenic intraventricular empyema shows restricted diffusion on the diffusion-weight imaging at the dependent parts of the ventricles (Figure 7). In ventriculitis, imaging may show irregular debris in ventricles, hydrocephalus, and ependymal contrast enhancement.[44,45] The role of intrathecal and intraventricular antibiotic is not well studied in bacterial meningitis in non-neurosurgical cases. Systemic antibiotic therapy is usually sufficient to treat the ventriculitis.[46]

Hypothalamic and other endocrine dysfunction

Hypothalamic-pituitary dysfunction is not a common complication of bacterial CNS infection. An analysis of the pituitary function of 19 patients with previous CNS infections, including meningitis, 10 to 56 months after acute infection, showed that 21% had isolated corticotropic insufficiency, and 11 % had borderline gonadotropic insufficiency. No patient had somatotropic or thyrotropic insufficiency, evidence of diabetes insipidus, or abnormal prolactin concentrations.[47] These cases suggest that screening for pituitary insufficiency may be justified in some patients with bacterial meningitis.[48] Diabetes insipidus is seen in bacterial meningitis caused by *S. pneumoniae and N. meningitides*.[49,50]

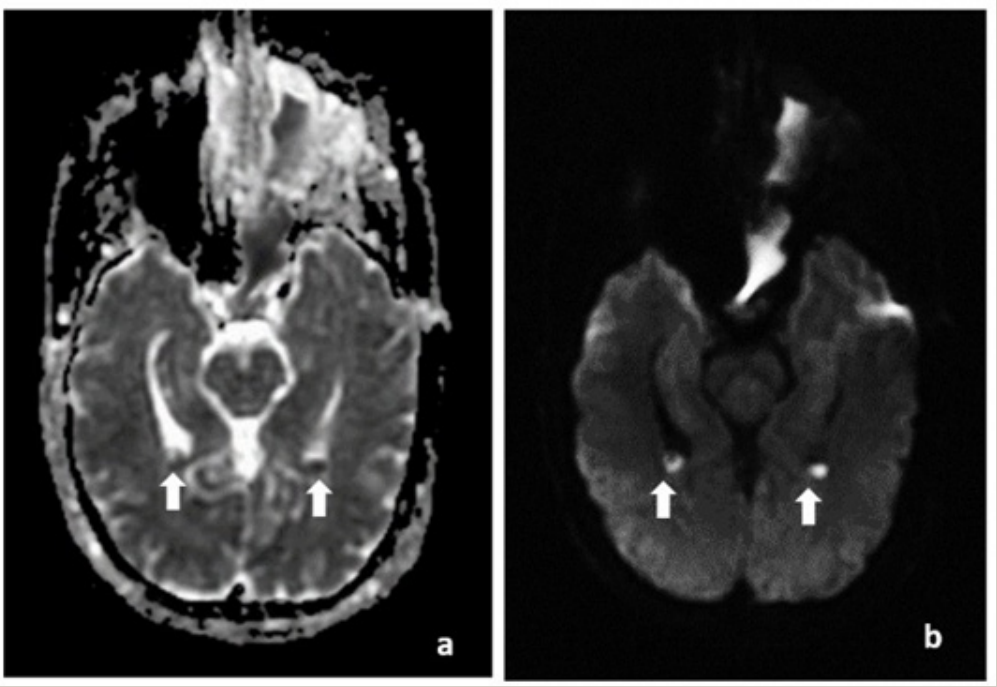

Figure 7.

Intraventricular material in the occipital horn of lateral ventricles with hypointensity in ADC (a) and restricted diffusion in DWI (b) MRI suspecting intraventricular empyema (day 14 after admission)

Myelopathy and radiculopathy

Myelopathy is also a rare complication of bacterial meningitis. The majority of the cases occur in children, and the presenting symptoms are quadriparesis, paraplegia, bowel and bladder dysfunction, and a sensory level loss.[51] In cases with cervicomedullary involvement, respiratory arrest can happen abruptly or following lumbar puncture. Subarachnoid infection can cause vasculitis or vasospasm of the arteries of the spinal cord resulting in spinal cord infarction. Brain edema with herniation can cause compressive vasculopathy by compressing the spinal artery around the foramen magnum and cause infarction of the craniocervical cord. Hypotension during the septic shock can also contribute to spinal vasculopathy.

Compressive myelopathy directly causes spinal cord damage. Tonsillar herniation secondary to increased ICP may compress the brainstem at the cervicomedullary junction resulting in compressive myelopathy.[52,53] Spinal epidural abscess is a rare complication of bacterial meningitis that can compress the spinal cord. The diagnosis of epidural abscess requires radiological confirmation with MRI with gadolinium or CT myelogram. Early detection and drainage can prevent permanent damage.[54]

Myelitis is another serious form of myelopathy caused by bacterial meningitis. *Meningococcal, Neisserial and Streptococcal* meningitis have been reported to cause myelitis in adults.[55,56] Inflammation in the subarachnoid space can spread from the intracranial space to the spinal canal and cause polyradiculitis. Patients can have asymmetrically flaccid weakness of proximal and distal muscle groups of the extremities with alteration of sensation and decreased deep tendon reflexes.

Cognitive and neuropsychiatric outcomes

Cognitive and neuropsychiatric impairments following bacterial meningitis can be the result of direct damage to cerebral structures by the infection

or can be secondary to complications from the infection. The degree of cognitive impairment ranges from relatively mild to severe and occurs in up to 32% of surviving adults.[57] Functions that are more commonly affected included psychomotor and cognitive processing, visuospatial skills, concentration, and memory. Treatment with dexamethasone during the acute infection did not seem to help long term cognitive function after bacterial meningitis.[57,58] Other common and often very incapacitating long term consequences of bacterial meningitis are depression and reduced quality of sleep.[59,60,61]

Conclusions

Bacterial meningitis is a central nervous system infection which causes high mortality rates in adults. The direct infection at the leptomeninges can cause indirect complications to other nervous system structures, such as cerebral and spinal vessels, ventricles, cranial nerves, brain parenchyma, spinal cord, spinal nerve roots, hypothalamus, and pituitary. The onset of these complications can occur from disease presentation to several months after the treatment. Awareness of these complications should lead to the early detection and appropriate treatment which can improve the recovery outcomes.

Author Affiliations: Parunyou Julayanont and Doungporn Ruthirago are residents in the Department of Neurology at Texas Tech University Health Sciences Center in Lubbock, TX. John C. DeToledo is the chairman of Neurology at TTUHSC in Lubbock.
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