Pitfalls in the Diagnosis and Management of Invasive Pneumococcal Meningoencephalitis – What We Can Learn From a Case

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ABSTRACT: Invasive pneumococcal meningitis is a life-threatening infectious disease affecting the central nervous system. It continues to be the most common type of community-acquired acute bacterial meningitides. Despite advances in neuro-critical care, the case fatality rate remains high. Rapid diagnosis and initiation of antibiotic therapy precludes mortality and long-term neurological sequelae in survivors. However, not all cases are easily recognised, and unanticipated complications may impede optimal course and outcome. Here, we describe a case of invasive pneumococcal meningoencephalitis in a 65-year-old man with an unusual initial presentation and pitfalls in the course of the disease. We highlight the importance of early diagnosis and treatment as well as recognition and management of complications.

KEYWORDS: Infectious diseases, neurology, intensive care

Introduction

Acute bacterial meningitis is a potentially fatal infection in both community and hospital settings affecting the pia mater, the arachnoid, and the subarachnoid space.1 Streptococcus pneumoniae accounts for most cases of meningitides in adults.2 Immediate diagnosis and initiation of antibiotic treatment are key to favourable outcome.3

Case Report

A 65-year-old man in good health presented with altered level of consciousness, pre-clinically suspected having an acute stroke. A few days prior to admission, he had pain in his right ear. On presentation in the emergency room, he was comatose (Glasgow Coma Score [GCS]: 7) and febrile (ear temperature 39°C). Nuchal rigidity, Kernig’s and Brudzinski’s signs, and focal neurological deficits were absent. Laboratory analyses revealed a serum C-reactive protein level of >300 mg/L with normal white blood cell count and a marked metabolic acidosis (pH 7.2, lactate: 4.4 mmol/L). Cerebral computed tomography (cCT) showed liquid in the right mastoid cells (Figure 1A; black arrow), intracranial gas formation (Figure 1B and C; white arrows), and enlarged horns of the lateral ventricles suggesting hydrocephalus (Figure 1C). Lumbar puncture was performed immediately followed by empirical intravenous antimicrobial therapy with ceftriaxone (2 g), vancomycin (1 g), and acyclovir (800 mg) within 35 minutes after admission. Cerebrospinal fluid (CSF) analyses revealed 1800 leucocytes/μL (mainly poly-nuclear), a marked elevation of lactate (16.6 mmol/L) and protein (7300 mg/L) and low glucose level (<0.11 mmol/L), consistent with acute bacterial meningitis. Gram stain showed gram-positive diplococci (Figure 2; arrow) followed by a polymerase chain reaction detecting S pneumoniae, so anti-infectious treatment was changed to ceftriaxone (2 g twice daily) and dexamethasone (the latter for 4 days, starting 2 hours after antibiotics). As the clinical and neuro-radiological results pointed towards a per continuitatem infection from the mastoid cells, a mastoidectomy was performed.

Despite decreasing acute-phase proteins and leucocytes within three days and stabilised haemodynamic, respiratory, and metabolic situations, the patient remained deeply comatose (GCS: 4–5 with extension or flexion of the extremities following noxious stimuli) after complete weaning of sedation. On day 3, clinical observation revealed discrete intermittent clusters of myocloni of the left shoulder consistent with status epilepticus followed by a left-sided hemiplegia. Diffusion-weighted magnetic resonance imaging was performed excluding an underlying structural brain lesion. Anticonvulsive therapy was started with repetitive boli of midazolam. As status epilepticus persisted, levetiracetam was added (4 g daily). However, seizures were finally controlled with continuously administered intravenous midazolam. As status epilepticus persisted, lenitracetam was added (4 g daily).
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have any immediate effect on the patient’s neurological condition. Within the next week, the patient significantly improved and started to show signs of consciousness with eye opening and reaction to stimuli. Gag reflex and swallowing remained severely impaired, so tracheotomy and percutaneous endoscopic gastrostomy were performed. By the time the patient was transferred to a neurological rehabilitation, he had a GCS of 10, and the left-sided hemiparesis had resolved.

Discussion

Bacterial meningitis in adults in the Western world is most often caused by \textit{S pneumoniae}, whereas in children, infection with \textit{Neisseria meningitidis} is more common. Mortality was up to 30\% in early studies, but recent data suggest an improved survival rate of 95\%.\textsuperscript{4} Neurological sequelae in survivors are found in up to 50\% of the patients, with impaired hearing and neuropsychological deficits being the most common.\textsuperscript{5} The most important factor when treating patients suspected of having bacterial meningitis is time from admission to adequate antibiotic treatment, as any delay significantly worsens prognosis.\textsuperscript{3} Other independent predictors for unfavourable outcome are advanced age, low GCS, cranial nerve palsies, positive blood cultures and <1000 leucocytes/uL as well as a high protein concentration in CSF on admission.\textsuperscript{1,6} However, studies regarding the incidence and clinical impact of complications such as status epilepticus are lacking. As to the CT signs of hydrocephalus in patients with bacterial meningitis, a retrospective study reported this as a rare complication in adults.\textsuperscript{7}

Diagnostic accuracy of meningeal signs

The sensitivity of the classic triad of fever, nuchal rigidity, and altered mental status in adults presenting with community-acquired acute bacterial meningitis is low, and absence of specific clinical signs is not unusual. Hence, missing signs of meningeal irritation, as in our patient, must never lead to premature exclusion of the diagnosis.\textsuperscript{1} In a large prospective cohort, the combination of neck stiffness, fever, and loss of consciousness was present in only 41\% of the patients,\textsuperscript{8} and in a prospective study of 297 adults with suspected meningitis and the presence of meningeal signs before lumbar puncture, Kernig’s sign (sensitivity, 5\%; likelihood ratio for positive results [LR(+)], 0.97), Brudzinski’s sign (sensitivity, 5\%; LR(+), 0.97), and nuchal rigidity (sensitivity, 30\%; LR(+), 0.94) did not accurately discriminate between patients with meningitis and those without.\textsuperscript{9} Nuchal rigidity was present in 30\%, and Kernig’s or Brudzinski’s signs were found in only 5\% of the patients with meningitis as confirmed by CSF analyses.\textsuperscript{9} Although this study suggests that the classic meningeal signs do not reliably identify patients with meningitis, the underlying pathophysiological mechanism for absent meningeal signs is unknown. However, there are 3 important aspects that may provide at least some explanation: (1) the diagnostic signs may be incorrectly evaluated,
(2) the diagnostic signs may be associated with poor inter-observer reliability, or (3) the meningeal signs may simply be poor diagnostic tools. Future studies that standardise examination and interpretation of these diagnostic signs and evaluate inter-observer reliability will further clarify the findings of this initial study. Hence, clinical decisions regarding diagnostic testing and the need for lumbar puncture should not rely on the presence or absence of these meningeal signs only. Because better bedside tests are lacking, immediate neuroimaging and lumbar puncture are recommended in patients with suspected meningitis.

**Antibiotic treatment**

Because pneumococci resistant to penicillin are becoming more and more frequent, initial therapy should consist of a broad-spectrum cephalosporin combined with vancomycin, which can later be switched to a classical penicillin if no resistances are detected. In addition, concomitant administration of dexamethasone before or with antibiotics is able to reduce mortality by 6% in pneumococcal meningitis.10 Even though in our patient the strains isolated from blood and liquor cultures were penicillin susceptible, we continued treatment with ceftriaxone because of its lower epileptogenic potential compared to penicillin.

However, according to our recent systematic review regarding seizures as adverse events of antibiotic drugs, evidence for epileptic adverse events of both penicillins and cephalosporins is weak.11 The choice of antibiotic treatment has become increasingly challenging with rising prevalence of multi-resistant bacteria over the last decades resulting in limited treatment options. Hence, the selection of an antibiotic compound should be driven by the bioavailability of the drug in the affected organ system and the susceptibility profile of suspected or identified pathogens. Both the impact of antibiotic-related seizures and the increasingly limited treatment options lead to a delicate balance between the risk of insufficient antibiotic treatment and sequelae from seizures or status epilepticus.

According to an observational cross-sectional study regarding the occurrence and prognostic relevance of seizures in adults with community-acquired bacterial meningitis, seizures occur significantly more often in patients with pneumococcal meningitis than in meningococcal infection and are associated with increased mortality.12

**Seizures and status epilepticus**

Subtle or nonkonvulsive status epilepticus (NCSE) is a challenge to detect because clinical clues may be absent or very discrete (such as twitching of oral or ocular muscles, nystagmus, and eye deviation), requiring an EEG for diagnosis.13 Therefore, the incidence and prevalence of seizures in infectious meningoencephalitides is probably still widely underestimated. In an intensive care unit (ICU) population with various neurological disorders, and unexplained altered level of consciousness, NCSE, or subtle status epilepticus was diagnosed by EEG in up to 80%,14 and the implementation of continuous video EEG monitoring in a general ICU significantly increased the detection rate of NCSE compared with 2 historic controls.15 Although subtle and NCSE are seen in many different ICU populations including patients with hypoxic-ischemic, traumatic, or haemorrhagic brain injuries,16,17 studies of the diagnostic yield of continuous video EEG monitoring in patients with infectious meningitides are lacking. However, the incidence of NCSE in this context is likely to be high and missed diagnosis frequent.

To what degree the left-sided hemiparesis represented a postictal phenomenon remains unclear. However, in the light of the preceding results from clinical examination, laboratory and neuro-radiological investigations, and the subsequent complete recovery from hemiparesis, other causes including structural brain lesions seem very unlikely.

In conclusion, rapid diagnosis and treatment are key to reduce neurological sequelae and mortality in pneumococcal meningoencephalitis. However, because highly reliable clinical signs and symptoms have not been recognised yet, this remains challenging. As several complications, such as hydrocephalus and status epilepticus, may cause secondary brain damage, heightened awareness, prompt recognition, and immediate treatment of such complications are crucial for optimal outcome.

**Author Contributions**

PSG and RS acquired and interpreted the clinical data, planned the work, wrote and revised the manuscript. Both authors approved the final submitted version.

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