Cystic Encephalomalacia following Vasculopathy and Vasospasm of Proximal Intracranial Arteries Due to Pneumococcal Meningitis in an Infant

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Abstract

Despite the availability of modern antibiotics, pneumococcal meningitis in both children and adults remains a severe disease—one known to frequently cause grave complications and residual disability. Although the appearance of arterial vasospasms in bacterial meningitis systematically has been investigated and reported on for adult patients, such research is lacking when it comes to infants. We report on a 4-week-old infant who, 6 days after onset of pneumococcal meningitis, suffered severe neurological deterioration with treatment-resistant seizures and coma. Generalized cortical and subcortical edema developed in conjunction with diminished cerebral blood flow, as depicted in magnetic resonance angiography and serial Doppler-sonographic examinations. The ischemia resulted in extensive cystic encephalomalacia. We propose that the degree of variation in cerebral blood flow in the acute phase was the result of an extensive arterial vasculopathy involving vasospasms. Awareness of this complication and prospective serial Doppler-sonographic examinations may improve our understanding of the connection between brain edema and vasculopathy. At present, however, no effective treatment appears available.

Keywords
- vasospasm
- infarct
- vasculopathy
- Streptococcus pneumoniae
- infant
- meningitis
- brain edema

Introduction

Despite progress in anti-infective therapy and intensive care, the prognosis of young infants with pneumococcal meningitis is still uncertain. A third of pediatric patients are reported to survive with neurological deficits,1 whereas most adult patients die or remain severely handicapped. We present the case of an infant with diffuse brain edema and intracranial arterial vasospasms arising 1 week after onset of meningitis and resulting in diffuse multicystic encephalomalacia. Although arterial vasospasm is a known complication of subarachnoid hemorrhage and bacterial meningitis in adults,2 this complication has rarely been reported in infantile meningitis.

Case Report

The 4-week-old female infant presented to our hospital with muscular hypotonia and diarrhea. At admission, a left-sided
peripheral facial palsy was noted. Blood samples showed a normal white blood count and C-reactive protein (CRP) of 52 mg/L (normal < 5 mg/L). Cerebrospinal fluid (CSF) showed normal cell count and magnetic resonance imaging (MRI) of the brain was normal. Blood cultures did not show any bacteria. On the second day in hospital, CRP value had dropped to 26 mg/L, the infant was in a good general condition, a viral infection was assumed, and antibiotic therapy was withheld.

On the evening of the third day, body temperature rose to > 39°C, and during the night the infant developed opisthotonus and a tense fontanel. Septic workup the following morning revealed a rise of CRP to 151 mg/L, 1,000 polymorphonuclear cells/µL in CSF, as well as evidence of gram-positive cocci. By that time, the blood cultures of the second day had turned positive showing *Streptococcus pneumoniae*. Clinically, the patient now showed anisocoria with a fixed pupil on the left side, gaze deviation to the left, and tonic posturing of the left arm. Antibiotic treatment with vancomycin and tobramycin was started and switched to penicillin G upon report of the repeated culture results. Supportive treatment with dexamethasone (i.e., 0.6 mg/kg/day) was initiated.

Despite this treatment, the neurological condition of the child deteriorated further. Starting on day 5, the amplitude-integrated electroencephalography showed increasing epileptic activity, followed by clinically apparent seizures. Treatment with phenobarbital and levetiracetam was started, but had to be expanded to thiopental due to ongoing seizure activity. Transfontanelle ultrasound of the brain on day 5 showed a slight distension of the lateral as well as third and fourth ventricles and signs of venticulitis and meningitis. Doppler examination of the cerebral arteries at this time showed normal systolic peak flow velocities (SPVF) in the anterior cerebral artery (ACA) of maximum 52 cm/s (normal value for age: 58 ± 15 cm/s) and a resistance index (RI) of 0.7 (normal value: 0.65–0.81). The CRP value rose further to a maximum of 258 mg/L on day 8, then falling to 34 mg/L on day 10.

On day 9, narrow lateral ventricles and abnormal low SPVF in ACA of 12 cm/s (RI 0.5) and the right middle cerebral artery (MCA) of 8 cm/s (normal value: 75 ± 15 cm/s) with a markedly reduced arterial pulsation were noted. On the same day, MRI and magnetic resonance angiography (MRA) of the brain showed marked edema of both cerebral hemispheres in cortex and peripheral white matter (Fig. 1A). On diffusion-weighted imaging, extended restriction of diffusion in both hemispheres was found (Fig. 1C, D). Time of flight angiography revealed markedly reduced flow in almost all intracranial arteries (Fig. 1B). No signs of sinus thrombosis, subdural empyema, or brain abscesses were detected.

Due to this deterioration, the infant was electively intubated and ventilated and thiopental anesthesia was resumed. After placement of an intraventricular intracranial pressure (ICP) probe, increased ICP was documented (i.e., 23 mm Hg—corresponding to 31 cm H₂O; normal value for infants 3.5–5.5 cm H₂O). Blood pressure was 85/50 mm Hg with a mean arterial pressure (MAP) of 64 mm Hg, resulting in a cerebral perfusion pressure (CPP) of 41 mm Hg (CPP = ICP – MAP). Dopamine and noradrenaline were started to maintain a high-normal blood pressure to keep the CPP around 40 mm Hg. Additionally, brain edema was treated with mannitol.

On day 11, SPVF in MCAs showed a distinct side difference (122 cm/s on the right and 41 cm/s on the left side). Suspecting vasospasm, treatment with nimodipine was started (continuous infusion of 5 µg/kg/h). Under this treatment, the transcranial Doppler ultrasound signal improved on the following days with SPVF in the MCA range of 40 to 73 cm/s on the right and 18 to 70 cm/s on the left side. However, on day 18, dramatic changes appeared again with flow velocities changing from normal to accelerated (SPVF 120 to 140 cm/s) to almost pulseless, “pseudo-venous” antegrade flow patterns (SPVF 4 cm/s in the right and 10 cm/s in the left MCA) and back (Fig. 2). Use of clonidine had no positive effect on intracerebral blood flow.

After stabilization of cerebral blood flow (CBF) in transcranial Doppler measurements, dopamine and nimodipine were weaned from day 28 and eventually stopped on days 31 and 33, respectively. Antiepileptic treatment could be weaned to monotherapy with levetiracetam. From day 18 onward, progressive formation of subcortical cysts was evident on cerebral sonography. A cranial MRI on day 31 showed extensive postischemic parenchymal loss in both hemispheres, some parts of the basal ganglia and mesencephalon fitting to the diffusion restrictions seen on day 9. Time of flight angiography now showed a normal flow in the intracranial arteries.

The child survived severely handicapped. The last cerebral MRI was performed at the age of 6 months. It showed supratentorial hydrocephalus with extensive parenchymal loss and CSF obstruction (Supplementary Fig. 1, supplementary material). Due to the severe overall disability, insertion of a ventriculoperitoneal shunt was withheld and after a short period with increased head growth, microcephaly developed. At the age of 1 year, the girl is severely hypotonic and shows no directed movements. She suffers from periods of severe restlessness and complex-focal seizures requiring anticonvulsive treatment and sedation. She continuously has an abnormally low body temperature around 35°C to 36°C, but does not require monitoring due to bradycardia or respiratory irregularities. She is blind without any visual contact. Brain stem audiometry showed no potentials. Treatment with physiotherapy is performed in a program of palliative care.

**Discussion**

Mortality from pneumococcal meningitis is high despite appropriate antibiotic therapy (i.e., 9% in children aged below 5 years), and survivors are often neurologically damaged (i.e., 35% of children aged below 5 years). Neurological injury in *S. pneumoniae* meningitis is mainly due to intracerebral complications like cerebral edema, cerebral vasculitis, infarctions, intracranial hemorrhage, cerebral necrosis, hydrocephalus, and sensorineural hearing loss.
Possible mechanisms of arterial alterations in bacterial meningitis include (1) inflammation of the vessel walls (i.e., vasculitis) resulting in thickening of the vessels intima that can lead to a complete obstruction of the lumen (2) vasospasm, probably due to a liberation of vasoconstrictive agents (3) purulent exudate in the subarachnoidal space giving rise to mechanic constriction of local vessels (4) obstruction of the arterial supply at the foramen magnum by

Fig. 1 Magnetic resonance imaging and magnetic resonance angiography on day 9. (A) The T2-weighted image shows an extended edema in the cortex and the peripheral white matter. (B) Time of flight angiography reveals intracranial flow only in the middle cerebral artery on the right (arrow). The flow in the internal carotid arteries on both sides is markedly reduced as well as in both anterior cerebral arteries and the left middle cerebral artery. In the proximal parts of the posterior cerebral arteries, a flow signal is present. The flow signal on the lateral parts of the image stems from extracranial arteries (dotted arrows). (C) The diffusion-weighted image shows a restricted diffusion with a reduction in the apparent diffusion coefficient (D), prominent in the territories of the middle cerebral artery on the left, in parts on the right, as well as in the territories of the posterior cerebral artery on both sides.

Fig. 2 Systolic peak flow velocities as determined by Doppler ultrasound measurements in the anterior cerebral artery (ACA) (until day 9) and both middle cerebral arteries (MCAs) (days 9–34) over the time course (note: from day 9 onward, measurements in the right and left MCA were done with greatest consistency; only these findings are depicted in this graph).
herniation of the cerebellar tonsils. In addition, more distal vascular complications have been observed, namely the elevation of the peripheral vascular resistance caused by increased ICP. Brain edema can be causal, as well as a segmental or general hyperperfusion occurring after reopening of closed vessels due to an impaired autoregulation of cerebral arteries.

In infants with bacterial meningitis, cerebral infarctions (arterial and venous) can be seen in up to 30%. In a study of 13 infants between 1 day of age and 32 months with bacterial meningitis, multiple infarcts were found on diffusion-weighted imaging performing MRI 2 to 5 days after presentation—most commonly in the frontal lobes. Diffuse brain involvement was seen in four children, all of whom died or had a very poor outcome.

In our case, despite response of the infection to antibiotic treatment and concomitant therapy with dexamethasone, the infant developed severe neurological complications. Starting 6 days after the onset of meningitis, we noticed an extensive brain edema associated with severely reduced blood flow in all major cerebral arteries. We have no explanation for the late onset of brain edema in our patient; usually edema occurs around the second to third day after onset of meningitis. ICP was elevated, but not to an extent that should have compromised CPP on the background of an almost normal mean arterial blood pressure. However, cerebral blood flow is not only dependent on CPP but also on the cerebrovascular resistance (CVR) (CBF = CPP/CVR). The latter might have been increased by surrounding edema and by diffuse arterial vasculopathy involving vasospasm. We believe that the intermittent extremely increased and rapidly changing SPVF in transcranial Doppler examinations of multiple cerebral arteries in our patient (Fig. 2) are indicative of vasospasms. However, for a doubtless documentation of vasospasms, CBF in the extracranial part of the internal carotid artery would have had to be measured at the same time to rule out general hyperemia (calculation of the Lindegaard ratio).

Transcranial Doppler ultrasound has been shown to be a useful and valid tool for the detection of vasospasm, mostly as consequence of subarachnoidal hemorrhage, but also in the course of bacterial meningitis in adults. In infants, vasospasm of intracranial arteries has only rarely been reported before. Bode and Harders described transient stenoses of main cerebral arteries by transcranial Doppler sonography in 11 children with different neurologic diseases, including children with bacterial meningitis. Iijima et al reported on a 36-day-old girl with late-onset group B streptococcal meningitis suffering from a stenosis of the suprarenal portion of the bilateral internal carotid arteries as well as of the bifurcation of the basilar artery shown by MRA on day 16 after onset of meningitis.

In adults, vasospasm due to subarachnoid hemorrhage is often treated with high-normal blood pressure, hypervolemia, and hyperperfusion (triple H therapy) in combination with intravenous or oral nimodipine. However, in our very young patient, the mentioned combined treatment was not able to prevent the extensive ischemic damage.

Our case illustrates that the inflammatory reaction in pneumococcal meningitis besides brain edema may lead to extensive arterial vasculopathy with vasospasm of intracranial arteries. Routinely CBF monitoring by means of transcranial Doppler ultrasound examinations should be performed during the acute phase of meningitis to detect any potential disturbance of intracranial circulation. However, a satisfactory treatment of intracerebral vasculopathy and vasospasm in this situation is currently not known.

Declaration of Conflicting Interests
The authors declare no conflict of interest.

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References