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## Meningoencephalitis caused by *Streptococcus pneumoniae*: a diagnostic and therapeutic challenge

# Diagnosis with diffusion-weighted MRI leading to treatment with corticosteroids

**Abstract** Streptococcus pneumoniae is a common cause of bacterial meningitis but only rarely causes other infections such as brain abscess, encephalitis, encephalomyelitis or meningoencephalitis. We report on three adult patients with meningoencephalitis caused by S. pneumoniae. In all three, CT and MRI revealed widespread brain lesions, suggesting extensive parenchymal injury. Diffusion-weighted MRI showed lesions with restricted diffusion, reflecting local areas of ischaemia with cytotoxic oedema secondary to an immunologically mediated necrotising vasculitis and thrombosis. High levels of markers of neuronal, glial and myelin damage were found in the cerebrospinal fluid. According to the literature, brain parenchyma lesions in adults with pneumococcal meningoencephalitis are often associated with death or severe neurological deficit. Our patients were treated with pulse doses of glucocorticoids: this resulted in dramatic clinical improvement and an excellent final neurological recovery.

**Keywords** Meningoencephalitis · Meningitis · Encephalitis · *Streptococcus pneumoniae* · Glucocorticoids · MRI

#### Introduction

*Streptococcus pneumoniae* (*S. pneumoniae*) is a common cause of pneumonia, sinusitis and acute otitis media. Moreover, *S. pneumoniae* is a common cause of bacterial meningitis in both children and adults [1]. Extension of

pneumococcal infection into the parenchyma of the central nervous system, especially in adults, has only rarely been reported [1].

We report on three adult patients with meningoencephalitis caused by *S. pneumoniae*, who exhibited diffuse parenchymal lesions documented by CT and MRI. We discuss the improvement after treatment with pulse doses of glucocorticoids.

### **Case reports**

Patient 1

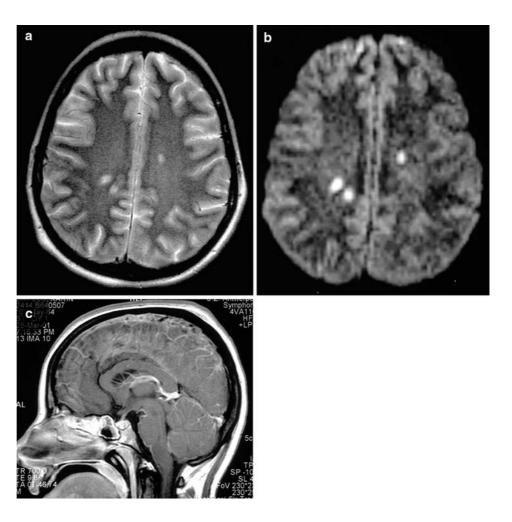
A 36-year-old woman was referred with sudden blurring of vision, confusion and dystonia. Her previous medical history included Graves' thyroiditis and a molar-pregnancy.

On her admission, a clinical examination revealed a Glasgow coma scale score of 7/15, nuchal rigidity and fever up to 40°C. The results of a fundoscopic examination were normal.

A contrast-enhanced brain CT scan was normal. A complete blood cell count revealed  $28.4 \times 10^9$ /l white blood cells (reference value  $4.4-10.0 \times 10^9$ /l) and biochemical analysis was compatible with rhabdomyolysis. Lumbar puncture showed 26 white blood cells per cubic millimetre (90% polymorphonuclear leucocytes), a total protein content of 903 mg/dl (reference value 15–45 mg/dl) and a glycorrhachia of 10 mg/dl (reference value 40–70 mg/dl). Gram staining revealed abundant gram-positive cocci in pairs. Endocarditis was excluded.

Owing to her excessive exhaustion, sedation and intubation were necessary. Intravenous ceftriaxone, 2 g twice a day, was administered. Two days after admission, her cerebrospinal fluid yielded a pure growth of S. pneumoniae. Seventy-two hours following admission, sudden bilateral mydriasis, with evolution to anisocoria, was noted. At that time an unenhanced brain CT scan showed several slightly hypodense lesions in the cerebral parenchyma of both hemispheres. Brain MRI revealed several patchy areas of increased signal intensity on T2weighted and turbo-fluid-attenuated inversion recovery (turbo-FLAIR) images, in both white and grey matter (Fig. 1a). The lesions were of high signal intensity on diffusion-weighted trace images (Fig. 1b) and of low signal intensity on apparent diffusion coefficient (ADC) maps (not shown). Pre-contrast T1-weighted images were normal. After intravenous injection of Gd-DTPA

Fig. 1 Patient 1. MRI examinations of the brain, obtained on the 3rd day after admission. a Turbo-spin echo T2-weighted image (3800/96) shows three lesions of increased signal intensity in the white matter of the centrum semiovale, bilaterally. **b** A diffusion-weighted sequence (with b value of 1,000 s/mm<sup>2</sup>) shows markedly restricted diffusion, as evidenced by the high signal intensity of the lesions. c Sagittal contrast-enhanced T1weighted image (700/9.8) reveals marked cerebellar and leptomeningeal enhancement, as observed along the anterior surface of the pons. There were no intraparenchymal areas of enhancement



(at a dose of 0.1 mmol/kg body weight), diffuse leptomeningeal enhancement was seen (Fig. 1c). On the basis of these findings, the diagnosis of meningoencephalitis was made.

On examination by non-contrast CT 4 days later, the lesions had become more hypodense and sharply defined. After intravenous contrast injection, no enhancement was observed in or around the parenchymal lesions; however, there was marked leptomeningeal enhancement within the cortical sulci (data not shown).

Post-hoc analysis of a second cerebrospinal fluid (CSF) sample on day 3 after admission showed extremely high levels of markers of neuronal damage [neuron-specific enolase (NSE), glial damage (S-100) and glial filament protein, (GFAP)] [2] and demyelination [myelin basic protein (MBP)] (Table 1).

No evidence was found for other (viral) causes of encephalitis (culture of CSF remained negative for herpes, enterovirus and cytomegalovirus, and polymerase chain reaction (PCR) test results for herpes simplex and *Mycoplasma pneumoniae* in CSF were negative). A 5-day course of pulse therapy of 0.4 g/kg per day gammaglobulins (Sandoglobulin, Novartis Pharma, Brussels, Belgium) was initiated on day 5 after admission. No clinical improvement was noted. Because of the persistent nature of her neurological course and the unusual nature, the patient was subsequently (on day 10) treated with pulse doses of 30 mg/kg per day methylprednisolone (Solumedrol, Upjohn Company, Kalamazoo, USA) for 3 days; the glucocorticoid dose was tapered over 4 weeks.

Extubation was achieved on day 11 after admission, and a Glasgow coma scale (GCS) score of 8/15 was noted. The patient was discharged 18 days after admission to a step down unit with a GCS score of 9/15. A gradual but slow improvement of her neurological function was observed in the following weeks. The patient regained complete consciousness (GCS score 15/15) on day 28 after admission.

Three weeks after the patient's admission a new MRI examination showed a mild decrease in the size and number of the intraparenchymal lesions. After contrast injection however, several patchy areas of enhancement were seen in both cerebral hemispheres, indicating breakdown of the blood-brain barrier.

Right-sided homonymous hemianopsia and right-sided perceptive hearing loss had disappeared 6 months after admission. Brain MRI confirmed a further resolution of the lesions in the cortical and subcortical areas of the right frontal, right temporal and left occipital lobes 6 weeks after the initial presentation. The lesions in the centrum semiovale showed little change (data not shown).

#### Patient 2

A 56-year-old man presented with hyperventilation, lowgrade fever and rapid neurological deterioration. Clinical examination revealed a temperature of  $37.5^{\circ}$ C, a Glasgow coma scale score of 10/15, and nuchal rigidity.

A full blood count revealed  $18.3 \times 10^9$ /l white blood cells and a C-reactive protein level of 16.2 mg/dl (reference value < 0.5 mg/ml). A lumbar puncture was performed: the white blood count was elevated, with 70 cells/mm<sup>3</sup> (100% polymorphonuclear leucocytes), a total protein content of 770 mg/dl (reference value 10– 50 mg/dl) and a glycorrhachia of < 10 mg/dl. Gram staining revealed gram-positive diplococci. Neither serology nor PCR and viral culture showed evidence of a viral aetiology of the presumed meningitis.

Treatment consisted of intravenous ceftriaxone, 2 g twice a day, and ampicillin, 1 g four times daily. Penicillin-sensitive *S. pneumoniae* were subsequently cultured from the cerebrospinal fluid.

 Table 1
 Analysis of cerebrospinal fluid samples obtained in patients 1 and 3

Parameter	Units	Patient 1 (day 3)	Patient 3 (day 4)	Reference value <sup>a</sup>
Total protein	mg/dl	299	154	15-45
Glucose	mg/dl	55	89	40-70
Lactate	mmol/l	12.4	5.8	< 2.8
White blood cells	Number/mm <sup>3</sup>	134	44	< 2
NSE <sup>b</sup>	μg/l	51.8	6.4	P95 < 14.1
S-100 <sup>c</sup>	μg/l	22.6	2.9	P95 < 3.3
GFA-p <sup>d</sup>	μg/1	46.8	_	P95 < 1.5
MBP <sup>e<sup>T</sup></sup>	$\mu g/l$	7.5	2.2	P95 < 0.6

<sup>a</sup>Reference values for NSE, S-100, GFA-P and NBP reflect measurement of these proteins in more than 70 reference samples of so called "normal" cerebrospinal fluid with cell numbers and protein, lactate and glucose levels within the reference values and no oligoclonal IgG detectable

<sup>b</sup>Immunoluminescence (Byk Sangtec, Dietzenbach, Germany)

<sup>c</sup>As measured by immunoluminescence (Byk Sangter)

<sup>d</sup>ELISA according to Herrmann et al. [2]

<sup>e</sup>ELISA, D & L (Webster, Tex., USA)

Forty-eight hours after the patient's admission MRI was performed, as neither consciousness nor confusion had improved. Three areas of increased signal intensity on T2-weighed and turbo-FLAIR images were observed (Fig. 2a), with restricted diffusion on a diffusionweighted sequence. No breakdown of the blood-brain barrier was seen. Pyogenic ventriculitis was diagnosed, as the lateral ventricle was filled with irregular debris with signal intensity and restricted diffusion suggesting pus rather than intraventricular haemorrhage (Fig. 2b, c). Trans-oesophageal echocardiography, as well as multiple negative blood cultures, excluded endocarditis. Spinal cord MRI showed no abnormalities.

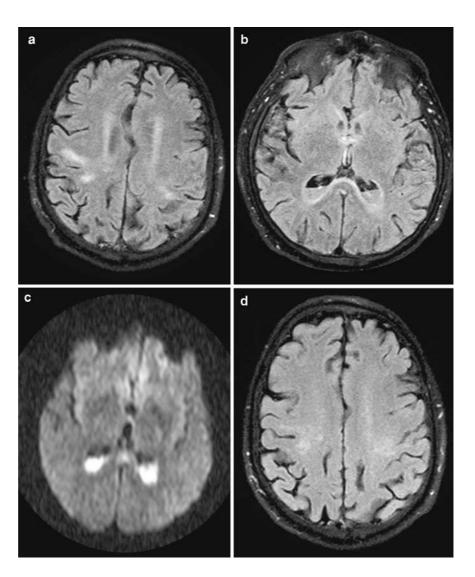
Because of the widespread lesions and the persistent nature of the neurological compromise, an intraventricular catheter was placed to measure the intracranial pressure, and pulse doses of 1 g methylprednisolone were given for 3 days. Methylprednisolone treatment was continued (first intravenously, afterwards orally) and tapered over a period of 3 weeks. The patient improved markedly and gradually achieved full consciousness (GCS score 15/15) on the 3rd day after initiation of glucocorticoid treatment.

Two and a half weeks after the patient's admission, a new MRI examination showed that the intraventricular sediment had disappeared; however, within the brain parenchyma, non-specific white matter lesions were seen, consistent with post-ischaemic damage (Fig. 2d). The patient was discharged on day 24 after admission and had recovered completely.

#### Patient 3

A 67-year-old man with a history of chronic atrial fibrillation was admitted to a community hospital with sudden loss of consciousness (GCS score 10/15), nuchal

Fig. 2 Patient 2. MRI examination of the brain, obtained on day 2 after admission, with axial turbo-FLAIR and diffusion-weighted images. Axial slices at the level of the centrum semiovale and the lateral ventricles are shown. a Turbo-FLAIR image through the centrum semiovale shows focal areas of increased signal intensity in the subcortical white matter. b, c The lateral ventricle is filled with irregular debris on turbo-FLAIR image (**b**), and diffusion-weighted image (c) indicates pyogenic ventriculitis. **d** A follow-up MRI examination 25 days after admission shows non-specific white matter lesions, compatible with post-ischaemic damage



rigidity and vomiting. Meningitis was clinically suspected, based on the presence of inflammatory markers. No lumbar puncture was performed because the patient was taking oral anticoagulants. Treatment with ceftriaxone, amoxy-clavulinic acid and dexamethasone (10 mg every 6 h for 4 days) was initiated. The antibiotic therapy was continued, as a positive antigen for *S. pneumoniae* had been found in a urine sample.

Two days after the patient's admission, generalised tonic-clonic convulsions were observed, necessitating intubation and ventilation. A brain CT scan was normal. The patient was transferred 24 h later to the University Hospital because of a new episode of generalised convulsions.

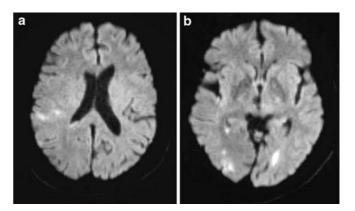
On day 4 after the onset of symptoms, brain MRI showed widespread lesions with restricted diffusion throughout the left and right hemisphere (Fig. 3). A lumbar puncture showed 20 white blood cells/mm<sup>3</sup> (60% lymphocytes, 40% polymorphonuclear leucocytes), a high total protein content and an elevated lactate level (Table 1). Gram staining revealed no bacteria, but PCR for *S. pneumoniae* was positive. Again, results of PCR and viral culture tests of the cerebrospinal fluid were negative.

The patient was treated by pulse doses of 1 g methylprednisolone, administered intravenously for 3 days. Methylprednisolone treatment was continued (first intravenously, afterwards orally) and tapered over a period of 4 weeks. The patient improved slowly but gradually. A tracheotomy was placed on day 15 after admission. A follow-up MRI on day 26 after admission showed no residual intraparenchymatous lesions. Full consciousness, as well as normal results after neurological examination, was achieved on day 28 after initiation of glucocorticoid treatment.

#### Discussion

Bacterial meningitis continues to be associated with high morbidity and mortality both in children and in adults. The morbidity (20-30%) and death (16 - 33%) associated with pneumococcal meningitis have changed little in the past 30 years [3]. In our three patients, extensive involvement of the brain parenchyma was observed, consistent with a diagnosis of meningoencephalitis.

Occlusive, necrotising vasculitis, arterial thrombosis and septic cortical thrombophlebitis may accompany bacterial meningitis and meningoencephalitis [4, 5]. Vasculitis, with thrombosis of arteries, veins, or sinuses, can produce focal neurological signs as a result of necrosis of cerebral tissue [6]. It is hypothesised that inflammation and thrombosis of both arteries and small cortical veins may be caused either by the accumulation of large numbers of inflammatory cells between the



**Fig. 3** Patient 3. MRI examination of the brain, obtained on day 4. Axial diffusion-weighted images show multiple lesions with markedly restricted diffusion predominantly involving the grey-white matter junction in the left and right hemisphere. Other lesions involved the frontal, parietal and occipital region (a, b)

endothelium and internal elastic lamina of small arteries and arterioles (to the point of obliteration of the lumen) or by direct invasion of blood vessel walls by organisms. Autopsy data obtained from patients with pneumococcal meningoencephalitis indicate that perivascular or nodular inflammatory muffs may appear in the white matter, accompanied by obliterating vasculitis, glial satellitosis, neuronophagy and foci of demyelination of varied and irregular size [7].

In a recent retrospective study of 87 adults with pneumococcal meningitis, arterial cerebrovascular complications were reported in as many as 21.8%. This included several cases of vasculitis suggested by arterial narrowing, vessel wall irregularities, focal dilatations and occlusions of distal branches of the middle cerebral artery on cerebral angiography [8].

Radiological follow-up and outcome of meningoencephalitis are poorly documented. In the early course of successfully treated (isolated) meningitis, a CT scan of the brain is usually normal. In children, CT may be useful in defining intracranial complications of bacterial meningitis. Cerebral infarcts or cerebritis have been described in children as complications of meningitis [9]. This suggests ischaemia, either due to bacterially induced vasculitis or venous infarction. Low-attenuation areas on CT scans may occasionally be observed in acute pneumococcal meningitis in adults [10]. We postulate that the intraparenchymal lesions documented on CT and diffusion-weighted MRI in our three patients reflect focal areas of ischaemia with cytotoxic oedema secondary to necrotising vasculitis and thrombosis [11]. ADC maps that show areas of restricted diffusion as low ADC had been obtained but were not archived. The predominant involvement of the deep white matter, with relative sparing of the cortical grey matter, suggests small vessel involvement. In one patient with meningococcal (not pneumococcal) meningoencephalitis, extensive symmetrical white matter abnormalities in the posterior temporal, temporo-occipital and parietal regions were described 24 years after documented meningococcal meningoencephalitis, indicating a meningitic vasculitis of the insular branches of the middle cerebral arteries [12]. MR angiography might be a useful tool in demonstrating narrowing of intracranial arteries; unfortunately, MR angiography was not obtained in our three patients.

The absence of ring enhancement, as observed in our patients, is a characteristic, but not pathognomonic, argument against a pyogenic brain [11]. It is important to note that all initial post-contrast images were obtained before the administration of glucocorticoids (which might close the blood-brain barrier and thus block enhancement). To our knowledge, only three reports on MRI findings in streptococcal meningitis or meningoencephalitis have been published [13–15]. Wanibuchi et al. [15] described marked contrast enhancement of the arachnoid membrane, without parenchymatous involvement or cerebral vessel abnormalities, on MR angiography. Diffusion-weighted MRI showed multiple widespread parenchymatous foci of increased signal intensity, consistent with multiple acute infarctions in the right middle and posterior cerebral arteries in this patient, with a CT scan suggestive of subarachnoid haemorrhage. Multiple small acute infarctions, similar to those observed in our first case, have been described in the watershed zone in the centrum semi-ovale in a misdiagnosed case of pneumococcal meningitis [14]. Hyperintense lesions along both the convexities and Sylvian fissure on diffusion-weighted imaging but with a normal T2-weighted sequence were observed in another adult patient with S. pneumoniae meningitis [13]. Death, bilateral amblyopia and severe neurological debilitation were encountered in those three patients, respectively [13–15].

To the best of our knowledge, this report is also the first to document such very high levels of markers of both neuronal and glial damage, as well as myelin breakdown products in cerebrospinal fluid in meningoencephalitis in general, and particularly due to *S. pneu-moniae* [16]. If we take into account the widespread parenchymatous involvement in our patients, it is not surprising that markers of damage to different cerebral cell types were present. Streptococcal cell wall components are bioactive and can induce cytokine production by activated endothelium, epithelium and leucocytes, chemotaxis for leucocytes, reduction of blood-brain barrier permeability and cytotoxicity to ciliated cells of the choroid plexus and neurons [17].

Treatment options for inflammatory central nervous system disorders include corticosteroids, intravenous immunoglobulins (IVIGs), plasmapheresis, or other immunomodulatory medications. Both IVIGs and corticosteroids exert various immunomodulatory actions [18, 19]. Glucocorticoids and IVIGs may cause suppression of the synthesis of cytokines or modulation of phagocytosis and have been used in a wide range of neurological diseases accompanied by vasculitis and/or demyelination [18, 19]. Although there are suggestions that corticosteroids may worsen infections, the use of a 4-day treatment with the corticosteroid dexamethasone in patients with pneumococcal meningitis has been found to reduce the risk of death significantly [20].

The efficacy, however, of IVIGs or glucocorticoids, alone or in combination, has mostly been proposed in isolated cases of cerebral parenchymal injury, as in cerebral vasculitis, encephalomyelitis or meningoencephalitis [21–24]. Although we need to acknowledge that some of the improvement may have been related to the natural course of the disease, the relatively abrupt reversal of the clinical progression and the good neurological outcome, in all three patients (with a predictable poor outcome related to the cerebrovascular lesions), makes it less probable. The therapeutic action may be due to an immune-modulating action on several pathophysiological phenomena that were encountered in our patients. These included cytotoxic oedema secondary to vasculitis and thrombosis, as suggested by the CT and MRI appearance, the marked inflammatory reaction, as suggested by high markers of neuronal and glial damage, and acute demyelination, as suggested by high MBP values in the two available CSF samples.

#### Conclusions

In conclusion, we have shown that adult patients with *S. pneumoniae* meningoencephalitis can present with widespread lesions in the brain parenchyma. We have highlighted the value of MRI, and especially diffusion-weighted imaging, in diagnosing these lesions. The use and success of glucocorticoids in our patients was based on the evidence that this parenchymal injury was apparently provoking myelin (as well as neuronal and glial) destruction. A short course of dexamethasone has recently been shown to be beneficial in patients with pneumococcal meningitis [20].

None of our patients had received corticosteroids as part of their early therapy prior to the first dose of antibiotics. Data on the benefit from later use of (highdose) corticosteroids, as in our three patients, do not exist. Larger prospective studies are needed to evaluate the therapy of high dose and prolonged course of corticosteroids in the modulation of the inflammatory parenchymal response as observed in streptococcal meningoencephalitis.

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