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Practical Pearl

Persisting Vasculitis After Pneumococcal Meningitis

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Abstract

Introduction: Bacterial meningitis is associated with a high mortality and a high incidence of neurological sequelae. Parainfectious vasculitis leading to ischemic brain damage is a known complication of bacterial meningitis but its treatment is uncertain.

Methods and Results: We report the case of a 53-year-old man with pneumococcal meningitis who developed numerous ischemic lesions in the brainstem and basal ganglia caused by parainfectious vasculitis. Clinical and radiological improvement was observed after delayed corticosteroid initiation. Symptomatic vasculitis relapsed after steroid withdrawal and stabilized after reintroduction of the immunosuppressive therapy. Although the cerebrospinal fluid (CSF) contained high levels of MMP-9 at the time of symptomatic vasculitis, a significant decrease of the enzyme accompanied the introduction of corticotherapy and the regression of vasculitic symptoms. No relation between the level of MMP-9 and the white blood cell count in CSF could be found.

Conclusion: Parainfectious vasculitis may respond to late corticosteroid treatment. MMP-9 level in CSF may be a marker of vasculitic complication in bacterial meningitis.

Key Words: Matrix metalloproteinases; vasculitis; pneumococcal meningitis; corticosteroids.

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Introduction

The mortality rate among patients with bacterial meningitis and the frequency of neurological sequelae among those who survive are high, despite major progress in intensive care and effective antimicrobial chemotherapy *(1,2)*. Case fatality rates and risk of sequelae following meningitis are reported to be higher for *Streptococcus pneumoniae* than *Neisseria meningitidis* or *Hemophilus influenzae (3,4)*. Furthermore, following the introduction of *Hemophilus* type b vaccine, *S. pneumoniae* has become the most common cause of the disease *(5)*. The ability of *S. pneumoniae* to alter the host inflammatory response *(6)* accounts for the high level of neurological (74.7%) and systemic complications (37.9%) observed *(7)*. Neurological complications include seizure (27.6%), diffuse brain swelling (28.7%), hydrocephalus (16.1%) hearing loss (19.7%), and ischemic or hemorrhagic brain damage (21.8%) *(7)*. In a recent retrospective study, Kastenbauer et al. showed that 67% of ischemic injuries were caused by identified arteritis *(7)*. This dramatic complication is related to a complex proinflammatory cascade initiated by the release of bacterial wall components, pneumolysin, cell surface proteins and free radicals *(6)*. Following pneumococcal autolysis a rapid increase of proinflammatory cytokines (interleukin [IL]-1β, tumor necrosis factor [TNF]-α, IL-6) and chemokines (IL-8, macrophage inflammatory protein [MIP] 1-2) is observed in cerebrospinal fluid

(CSF) and leads to the blood–brain barrier (BBB) disruption *(8)*. Over the past few years, experimental studies provided some evidence for a central role of matrix metalloproteinases (MMPs) in bacterial meningitis *(6,9–14)*. MMPs are zinc-dependent endopeptidases that can degrade all components of the extracellular matrix. MMPs are expressed as zymogens by brain-resident cells *(15–17)* and leukocytes *(18)*. The extracellular processing of the zymogen generates the active form of the enzyme. In experimental meningitis, MMPs contribute to BBB disruption, neuronal injury, and leukocyte recruitment across the endothelium into the CSF *(14,19–21)*. Despite our increasing understanding of the pathophysiological cascades involved in bacterial meningitis, to date only dexamethasone has demonstrated its clinical efficacy as adjunctive therapy *(3,22,23)*. Dexamethasone decreases the rate of hearing loss and mortality *(3,23)*. However, the actual impact of corticosteroids on delayed vascular complications and secondary ischemic brain injury is unknown.

We report a case of cerebral vasculitis following acute pneumococcal meningitis responding to delayed corticosteroid treatment, later associated with cyclophosphamid. Serial CSF examinations showed a time relationship between MMP-9 levels and the vasculitic process, but no relation with CSF cellularity.

Case Report

A 53-year-old healthy African male presented with a 2-day history of fever and back pain. He was admitted to a local hospital for confusion and stupor. A lumbar puncture showed purulent CSF with Gram-positive cocci. Therapy with ciprofloxacin, ceftriaxone and co-trimoxazole was initiated. The following day, the patient developed a left-side hemiplegia,

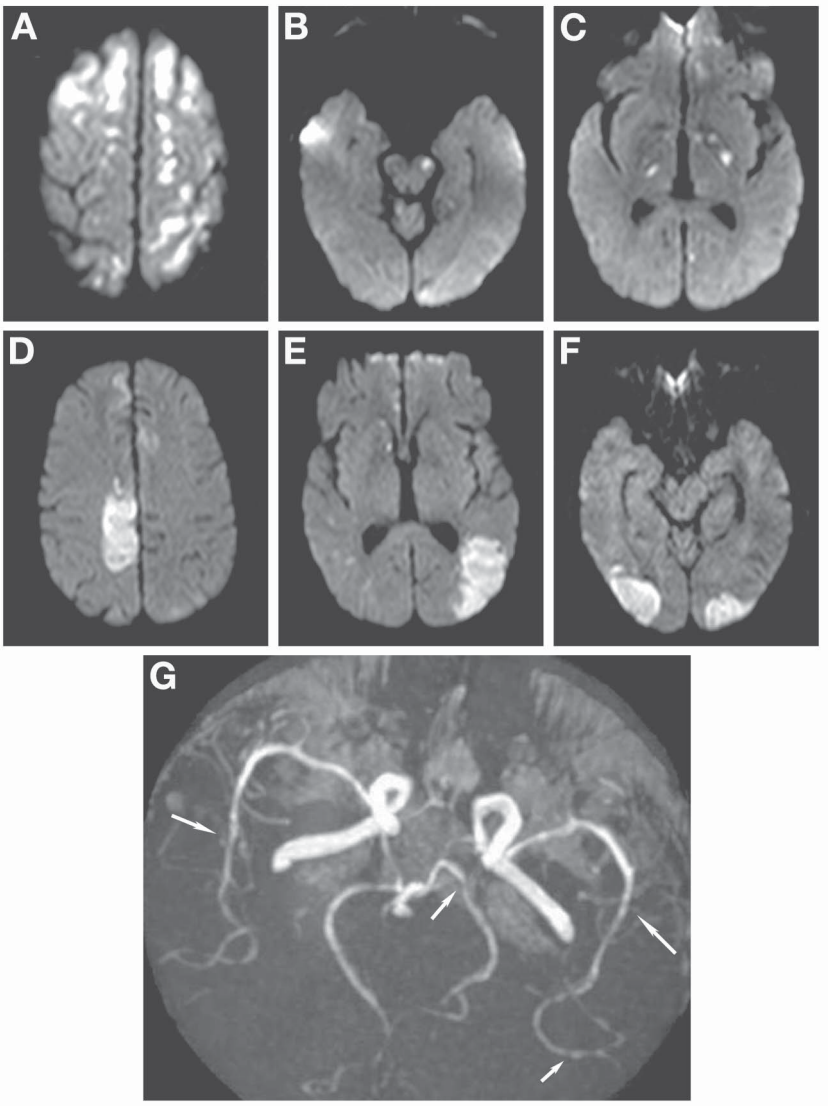

Fig. 1. Axial diffusion-weighted MRI shows multiple lesions in the superior part of the frontal and parietal lobes **(A)** in the midbrain **(B)** and in the basal ganglion areas **(C)**. After reduction of prednisone, repeated MRI revealed new right fronto-parasagital lesions **(D)**, left temporo-occipital **(E)**, and occipital areas **(F)**. Angio-MRI revealed vessel-wall irregularities (arrows), focal dilatation, and narrowing, mostly in the middle and posterior cerebral arteries **(G)**.

was unresponsive and only capable of eye pursuit. Brain computed tomography (CT) showed bifrontal hypodensities. Six days after admission to the local hospital, the patient was transferred to our ICU. A second brain CT scan performed on admission confirmed bifrontal lesions and new hypodensities in the right posterior arm of the internal capsula. The lumbar puncture showed a white blood cell count of 300/mm^3 with 84% neutrophils, 14% lymphocytes, 2% monocytes, 3.9 mmol/L glucose, 2.53 g/L proteins, but cultures remained sterile and a polymerase chain reaction confirmed the pneumococcal infection. Antimicrobial chemotherapy was modified to treat potentially resistant pneumococci (vancomycin associated with rifampicin). On day 4 in the ICU, the patient developed a right hemiplegia, associated with a complete loss of contact. Magnetic resonance imaging (MRI) showed numerous small lesions in the white matter and the basal ganglia (Figure 1A). Angiography showed pathological changes (vessel wall irregularities, focal dilatation and narrowing) of most cerebral arteries, particularly evident in the medial and posterior cerebral arteries, highly evocative of cerebral arteritis (Figure 1B). A new lumbar puncture showed 57/mm^3 white blood cell count, with 65% neutrophils, 30% lymphocytes, 5% monocytes, 5.1 mmol/L glucose, 2.65 g/L proteins, and no bacteria. The unfavorable evolution motivated the initiation of steroids as adjunctive therapy. Methylprednisolone, 500 mg daily, stabilized the patient's clinical condition with no new lesion on MRI. After 5 days, methylprednisolone was replaced by prednisone 1 mg/kg followed by 0.25 mg/kg/day. On day 7, after reduction of prednisone to 0.25 mg/kg/day, the patient's clinical status deteriorated. His level of consciousness dropped and only stereotyped movements were elicited by painful stimulation. MRI showed new lesions in the left occipital area (Figure 1C) and a progression of the vasculitic process on the posterior branch of both middle cerebral artery branches. High doses of steroids were reintroduced (methylprednisolone 1 g iv per day, for 5 days) and later associated with cyclophosphamid (1 g iv). Following the optimization of immunosuppressive therapy, the patient improved progressively. After 1.5 months of evolution, he was capable of directed movements of the right arm and left leg and a visual contact was again possible.

Gelatinase levels in our patient's CSF were investigated on days 0, 4, and 19 of hospitalization in the ICU. MMP measurements were performed using a classical zymographic method described elsewhere (*18,24*). Briefly, CSF samples were loaded into 10% Tris sodium dodecyl sulfate (SDS) polyacrylamide gels containing gelatin (EC61755box, Invitrogen, Carlsbad, CA). After electrophoresis, gels were washed in 2.5% Triton X-100 for 30 minutes, rinsed and incubated in 50 m*M* Tris, 0.2 *M* NaCl, 5 m*M* $CaCl_2$, buffer overnight at 37°C. Gels were stained with 0.2% Coomassie brilliant blue R-250 (Bio-Rad 161-0400, Hercules, CA), 10% acetic acid, 30% methanol and destained in 10% acetic acid, 30% methanol. White bands on a blue background indicated zones of digestion corresponding to the presence of different MMPs, identified on the basis of their molecular weight. Serial dilutions of pro-MMP-9 and -2 standards (Calbiochem-Novabiochem, La Jolla, CA) were used to draw a standard curve. Bands were scanned using a densitometer and quantifications were performed using the National Institutes of Health 1.63 image software.

Although control CSF (obtained from patients investigated for noninflammatory neurological disease) did not show any pro-MMP-9 but only pro-MMP-2 (0.54 µg/mL), the first CSF obtained from the patient at the time of ICU admission showed a dramatic increase of pro-MMP9, 0.11 µg/mL (Figure 2). The second CSF examination, at the time of the patient's neurological deterioration, showed increasing levels of pro-MMP-9 (0.13 µg/mL) and pro-MMP-2 (0.74 µg/mL). After several days of corticotherapy, a significant decrease of pro-MMP-9 (0.09 µg/mL) and pro-MMP-2 (0.5 µg/mL) CSF levels were observed. The active form of MMP-9 was also detected and decreased with corticotherapy. Whereas the number of neutrophils decreased dramatically between the first and second fluid examination, the level of MMPs increased. In accordance with CSF levels, blood levels of MMP-9 and -2 dramatically decreased after the introduction of steroids (Figure 2).

Comment

This case report illustrates that central nervous system (CNS) vascular inflammation is a key issue in pneumococcal meningitis. Although bacteria are responsible for triggering host inflammatory response, the latter may last and perpetuate despite correct antimicrobial therapy and early bacterial disappearance from CNS. Our observation showed that CSF and blood levels of MMP-9 and -2 paralleled the patient's vascular complications and clinical evolution. Corticotherapy

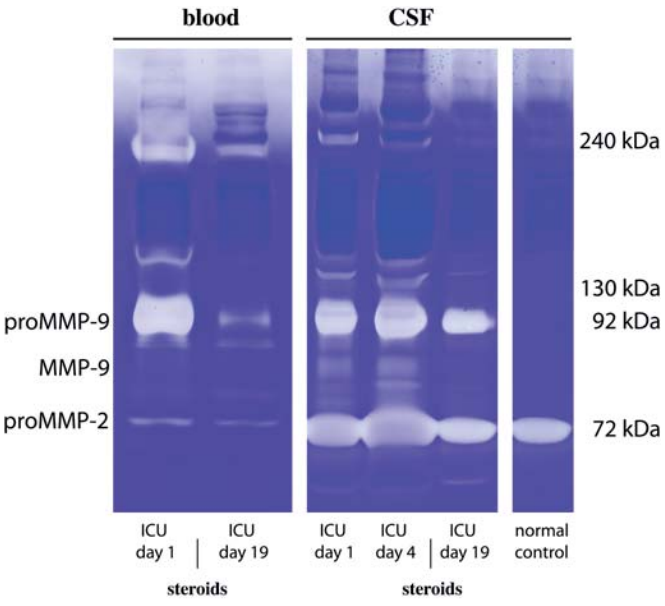

Fig. 2. Zymographic analysis of gelatinase levels in blood and CSF samples obtained from the patient at his admission. Pro-MMP-9 is not detectable, whereas pro-MMP-2 is constitutively produced in the CSF obtained from patients with noninflammatory neurological disease (a representative sample is shown, normal control). High CSF and blood levels of the proform of MMP-9 and MMP-2 and of the active form of MMP-9 are observed in the meningitic patient, at the admission in the ICU. Increasing CSF levels of both gelatinases are detected at the time of ischemic complications. Decreased but persisting levels of pro-MMP-9 are osbserved during corticosteroid treatment.

initiation stabilized the patient's clinical condition and was associated with a reduction in MMP-9 and -2 levels. The reduction of steroids was followed by a rapid clinical deterioration caused by vasculitis relapse, suggesting some efficacy of the treatment. According to one meta-analysis *(23)* and recent randomized study *(3)*, corticosteroid treatment is efficient and indicated only very early in the course of bacterial meningitis, prior or at the time of the first dose of antibiotics. No scientific evidence supports delayed or prolonged (>4 days) treatment in pneumococcal meningitis. Our report suggests that immunosuppressive therapy could be beneficial for delayed complications related to vascular inflammation. It also suggests that MMPs, in particular MMP-9, could be a potential target of new adjunctive therapies. However, our isolated observation needs confirmation in a large prospective study. Recently, Leib et al. showed that the association of a broad-spectrum inhibitor of MMPs to antibiotics reduced neuronal necrosis and apoptosis in a model of experimental meningitis *(13,14)*. These results were challenged by Bottcher et al., who showed that MMP-9-deficient mice infected with *S. pneumoniae* were not protected as compared with wild-type animals. Nevertheless, there is growing experimental evidence that the neurological sequelae observed in bacterial meningitis *(25,26)* are related to the inappropriate inflammatory host response. Our report shows that, at the time of neurological complications, although no bacteria and only a few inflammatory cells were detected in the patient's CSF, CSF and blood levels of MMP-9 were elevated. This suggests that MMPs might be actively involved in the vasculitic process or be a potential marker of this vascular complication. If this is the case, MMP-9 detection could help to identify patients susceptible to benefit from aggressive and prolonged immunosuppression.

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