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Streptococcus pneumoniae and Herpes Simplex Virus-1 Central Nervous System Co-Infection

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Abstract

Co-infections of the central nervous system (CNS) caused by bacterial and viral pathogens are considered to be rare. Herpes simplex virus type-1 (HSV-1) reactivation following *Streptococcus pneumoniae* infection is well described but most cases are related to oral or cutaneous lesions or in respiratory samples. HSV-1 CNS reactivation after *Streptococcus pneumoniae* meningitis is a very rare event and may have significant morbidity and mortality. In this case report, we describe a 71-year-old female patient that presented with a history of abdominal pain and confusion/disorientation that had tonic-clonic seizures while in the Emergency Department. The diagnostic work-up confirmed CNS co-infection caused by *Streptococcus pneumoniae* and HSV-1. Of note, beyond age, the patient had no known risk factors for both entities and recovered fully after antibiotic and antiviral therapy. This case underlines that clinicians must be aware of CNS co-infection despite being a rare diagnosis. This should be suspected particularly in patients who present an unusual clinical course of CNS infection.

Keywords

Streptococcus pneumoniae, Herpes Simplex Virus Type 1, Central Nervous System, Co-Infection

1. Introduction

Concurrent infection by different pathogens, also known as co-infection, of the central nervous system (CNS) is a rare event, both in immunocompetent and immunocompromised patients. Classical forms of CNS infection include acute meningitis and encephalitis. Acute meningitis is an inflammation of the mem-

branes lining the brain and the majority of cases in the adult population are caused by viruses and *Streptococcus pneumoniae* [1]. Encephalitis describes an inflammation of the brain parenchyma and is most frequently of viral etiology, especially herpes simplex virus type-1 (HSV-1) [2]. Usually, these cases are due to latent viral reactivation.

From a general perspective, it is unknown to what degree herpesviruses reactivate from latency in the CNS in association with other infections. In patients with severe pneumococcal disease, HSV-1 reactivation has been described [3]. These cases correspond mostly to oral herpes but there are some cases of reactivation in the respiratory tract [4] [5]. CNS HSV-1 reactivation following *Streptococcus pneumoniae* meningitis is a very rare event and only a few cases have been reported in the literature [6] [7] [8]. In two studies conducted on patients with acute bacterial meningitis, researchers found no evidence of herpes viruses' reactivation in cerebrospinal fluid (CSF) [6] [9].

In this case report, we describe a female patient that presented with abdominal pain, altered mental status, and tonic-clonic seizures, with the diagnostic work-up confirming CNS co-infection caused by *Streptococcus pneumoniae* and HSV-1. Although this case represented a diagnostic and therapeutic challenge, the patient recovered fully after antibiotic and antiviral therapy.

2. Case Description

A 71-year-old woman with a medical history of high blood pressure and type 2 diabetes mellitus presented to the Emergency Department (ED) with abdominal pain for the past eight days. The patient's next of kin also reported confusion and disorientation since the day before. In the ED, the patient had two tonic-clonic seizures within 10 minutes that ceased after diazepam. During the post ictal period, neurological examination revealed conjugate eye deviation to the right, left-sided visual neglect and left-sided hemiparesis. The patient was afebrile, blood pressure 130/65mmHg and heart rate 86 bpm. The remaining examination was unremarkable.

Blood tests showed leukocytosis (14.33 × 10^9/l) with neutrophilia (12.19 × 10^9/l) and elevated C-reactive protein (13 mg/dl) (**Table 1**). Blood cultures were drawn and the patient was started on dexamethasone (10 mg every 6 h), ceftriaxone (2 g every 12 h), ampicillin (2 g every 4 h) and acyclovir (700 mg every 8 h) due to suspected CNS infection. Head computed tomography (CT) revealed no acute intracranial lesions. CSF analysis showed 520 cells/ul (90% polymorphonuclear cells), proteins 0.59 g/l and glucose 70 mg/dl (blood glucose 120 mg/dl). CSF gram stain showed gram positive cocci and ampicillin and acyclovir were suspended. The patient was admitted to the Infectious Diseases department due to probable bacterial meningoencephalitis.

On day three, the CSF polymerase chain reaction (PCR) test was positive for HSV-1 and *Staphylococcus epidermidis* was isolated in the CSF. The Microbiology laboratory did not perform further PCR tests in the CSF after the first posi-

tive test due to their in-house routine protocol. The patient restarted acyclovir and was started on vancomycin (25 mg/kg loading dose and 15 mg/kg every 12 h). On day five, blood cultures came negative and ceftriaxone was suspended. At this point, both viral and bacterial pathogens were considered and a second lumbar puncture was planned to clarify the etiology of the CNS infection.

The next day, the patient became febrile and obtunded. Blood tests showed recrudescence of leukocytosis (12.73×10^9/l) with neutrophilia (9.20×10^9/l) and C-reactive protein elevation (200 mg/dl) (Table 1). Blood cultures were drawn and the second CSF analysis showed 31 cells/ul (100% mononuclear cells), proteins 0.1 g/l, and glucose 94 mg/dl (blood glucose 136 mg/dl). In this CSF sample, the PCR test was positive for *Streptococcus pneumoniae* and HSV-1. The diagnosis of *Streptococcus pneumoniae* and HSV-1 CNS coinfection was assumed.

Table 1. Laboratory and microbiology results at admission, day 4 and day 8.

Parameter	Units	Admission	Day 2	Day 4	Day 8
Blood					
Hemoglobin	g/dl	14.1	13.9	13.2	13.8
Platelets	$\times 10^9$ cells/l	268	258	233	260
WBC	$\times 10^9$ cells/l	14.33	10.98	12.73	9.1
Neutrophils	$\times 10^9$ cells/l	12.19	8.3	9.2	5.6
Urea	mg/dl	61	64	78	71
Creatinine	mg/dl	1.09	1.11	1.34	1.22
Sodium	mmol/l	139	138	133	136
Potassium	mmol/l	4.7	4.7	4.3	4.4
Chloride	mmol/l	99	98	99	97
CRP	mg/dl	13	45	200	54
CSF					
Cells	/ul	520	---	31	---
PMN	%	90	---	0	---
Proteins	g/l	0.59	---	0.1	---
Glucose	mg/dl	70	---	94	---
Microbiology					
Blood cultures		Negative	---	Negative	---
CSF gram stain		Gram positive cocci	---	Negative	---
CSF culture		S. epidermidis	---	Negative	---
CSF HSV-1 DNA		Positive	---	Positive	---
CSF SP DNA		(Not tested)	---	Positive	---

Legend: CRP: C-reactive protein, CSF: cerebrospinal fluid, DNA: deoxyribonucleic acid, HSV-1: herpes simplex virus-1, PMN: polymorphonuclear, SP: *Streptococcus pneumoniae*, WBC: white blood cell count.

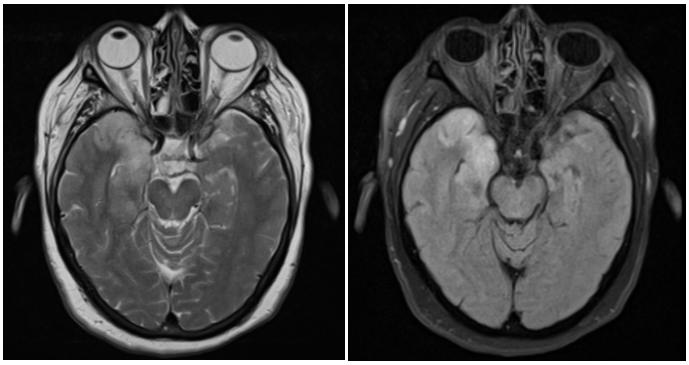
The patient was kept on acyclovir, restarted ceftriaxone, and vancomycin was suspended.

The patient became afebrile the next day and inflammatory markers decreased. The brain magnetic resonance imaging (MRI) revealed T2-hyperintense diffuse lesions on the right temporal lobe (**Figure 1**) and the electroencephalogram (EEG) described periodic lateral epileptiform activity on the right hemisphere. The second CSF sample culture and blood cultures came negative. The patient was treated with 21 days of acyclovir and 12 days of ceftriaxone, having a complete neurologic recovery. The patient was kept on anticonvulsants and no further seizures were documented. She was later discharged to a physical rehabilitation center in stable condition and followed up with outpatient Neurology appointments.

3. Discussion

HSV-1 usually persists as a latent infection in the trigeminal ganglion and viral reactivation during severe bacterial infections is thought to be a consequence of the immune paralysis associated with the complex immune response to such infections [10]. HSV-1 reactivation following *Streptococcus pneumoniae* infection is well described in animal studies, including CNS involvement [11]. In humans, most HSV-1 reactivation episodes after bacterial infection are related to oral or cutaneous lesions or in respiratory samples [3] [4] [5].

To the best of our knowledge this is the first case of HSV-1 CNS reactivation following pneumococcal meningitis in an elderly patient without classic risk factors for *Streptococcus pneumoniae* meningitis or HSV-1 reactivation. In this case, HSV-1 reactivation was documented first and the patient was diagnosed with encephalitis based on altered consciousness, seizures, EEG and brain MRI findings suggestive of encephalitis [2]. CSF PCR for HSV-1 has a sensitivity and specificity of over 95% for HSV-1 encephalitis in immunocompetent adults, which in this case, established the etiology [12]. The diagnosis of pneumococcal



(a) (b)

Figure 1. Brain magnetic resonance showing diffuse hyperintense signal in the right medial temporal lobe, including in the amygdala and hippocampus, in T2 and T2 fluid-attenuated inversion recovery (FLAIR) sequences ((a) and (b), respectively).

meningitis was confirmed later by detection of *Streptococcus pneumoniae* by PCR in the second CSF sample, in addition to the presence of gram positive cocci in the gram stain of the first CSF sample, and two reasons can be presented for that. The first was the administration of antibiotics prior to the lumbar punctures that achieves CSF sterilization within 4 h of antibiotics administration [13]. The second was the Microbiology laboratory routine protocol, which, by default, does not perform further PCR tests after a first positive test. Noteworthy, after the diagnosis of coinfection was made, the isolation of *Staphylococcus epidermidis* in the first CSF sample was considered a contamination, because this pathogen is found mostly in skin flora and rarely causes CNS infections, with exception of patients with invasive neurosurgical procedures or devices [14].

Coinfections of the CNS with microorganisms of different taxa, such as bacterial and viral pathogens, are rare. Two studies evaluated herpes viruses' reactivation in CSF samples following acute bacterial meningitis, including 77 CSF samples in total. There were no reported cases of viral deoxyribonucleic acid (DNA) detection by PCR in both studies [6] [9]. In the literature, HSV-1 CNS reactivation following pneumococcal meningitis is described in only three patients [6] [7] [8]. In one report, a 67-year old female patient with a history of recurrent otitis media was diagnosed with *Streptococcus pneumoniae* meningitis and HSV-1 CNS reactivation within 24 h [6]. In a second report, a splenectomized 41-year old male patient, diagnosed initially with *Streptococcus pneumoniae* meningitis, was also diagnosed with HSV-1 encephalitis six days later [7]. Both patients recovered fully after antibiotic and antiviral therapy. Finally, a case of a 67-year old male patient with pneumococcal meningitis complicated with cervical myelitis was also described to have HSV-1 CNS reactivation [8].

This case underlines that, despite being an extremely rare event, an unusual clinical course of CNS infection could be related to a concurrent undiagnosed infection, even in patients without previously known risk factors. In this case, after ceftriaxone was suspended the patient's condition worsened with fever and decreased consciousness. Fortunately, *Streptococcus pneumoniae* was detected by PCR in the second CSF sample and the diagnosis was established.

4. Conclusion

Coinfections of the CNS with bacterial and viral pathogens are considered to be rare. HSV-1 reactivation following *Streptococcus pneumoniae* infection is well described but HSV-1 CNS reactivation is a very rare event. This is the first case of HSV-1 CNS reactivation following pneumococcal meningitis in a patient without previously known risk factors for both entities. This case underlines that clinicians should be aware of CNS co-infection, particularly in patients who present an unusual clinical course of CNS infection, even if without risk factors.

Statement of Ethics

The study is exempt from ethics committee approval. It is a retrospective case report. Informed consent was obtained from the patient for publication of this

study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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