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Case report

Postencephalitic syndrome with immune-mediated psychosis in an adult with meningitis due to *Streptococcus pneumoniae*: A case report

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ABSTRACT

Introduction: A first psychotic episode may be related to neurological diseases, especially encephalitis of infectious or autoimmune origin. It is remarkable that an immune-mediated encephalitis triggered by a confirmed subacute bacterial meningitis is documented, and this is the case we will present.
Clinical case: A 22-year-old woman with no previous medical history, immunocompetent, with three months of behavioral, affective and cognitive symptoms with subsequent compromise of sensory perception and psychosis. Examination of cerebrospinal fluid showed inflammatory signs with positive FilmArray© for *Streptococcus pneumoniae.* She received anti-psychotic and antibiotic treatment for 2 weeks without clinical improvement. Postencephalitic syndrome with immune-mediated psychosis was considered as a diagnosis, and immunosuppressive management with corticosteroid and plasmapheresis was initiated with complete resolution of symptoms. After one year of follow-up no neurological relapse has been identified.
Discussion: Encephalitis is a neurological syndrome due to brain parenchymal damage that can result in psychiatric symptoms including psychosis and behavioral changes. Its causes are usually infectious (usually viral) or autoimmune (Anti NMDA, AMPA, LGI1 or others). A psychiatric condition in bacterial meningitis without improvement with antibiotic treatment is remarkable, its presence should suggest an immune-mediated post-infectious syndrome that may respond to the use of immunomodulators even in the absence of identification of autoimmune encephalitis-associated antibodies. No similar cases have been reported in the literature.
Conclusion: Immune-mediated psychosis may be a manifestation of post-encephalitic syndrome associated with bacterial meningitis and its treatment with immunosuppressants may offer benefit in cases where the use of antipsychotics and antibiotics shows no improvement.

Introduction

A first psychotic episode is a diagnostic challenge that makes it necessary to exclude organic causes of neurological nature. Encephalitis is the first etiology to be considered, with infectious and autoimmune conditions being the most prominent [1,2]. *Streptococcus pneumoniae*

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infection in the central nervous system (CNS) usually presents as acute meningitis [3]. Cortical symptoms in that type of infection are unusual, and psychiatric symptoms are remarkable findings. If they occur, they usually improve with appropriate antibiotic treatment or remain as long-term neurological sequelae [4,5]. We present the case of a patient with subacute psychiatric symptoms associated with confirmed *S. pneumoniae* meningitis, with no improvement with the use of antibiotics or antipsychotics, and with a response to immunosuppressants.

Clinical case

A 22-year-old woman, a medical student, a drawer and a violinist, immunocompetent, with no pathological, psychiatric, family or toxicological history, without premorbid personality for mental illness. She visited the clinic for 3 months due to changes in feelings and behavior (social isolation, emotional lability), cognitive changes (attention and memory problems), concrete thinking, laconic language, insomnia and an episode of complex hallucinations. One month prior to consultation, she developed global insomnia associated with episodes of temporo-spatial disorientation. She did not have headaches, spiking fevers or other neurological symptoms during the course of the disease.

On admission to the Emergency Room she showed psycho-motor agitation that required physical immobilization and pharmacological containment. Mental examination revealed partial disorientation in time, suspicious attitude, hypoprosexia, concrete thinking, question-answer time extension, bradypsychia and bradylalia. Poor sense of judgement and no introspection, she did not verbalize delusions, death or suicide. Intelligence assessment showed errors in calculation and abstraction. There were no relevant clinical findings, neurological examination without additional abnormalities, no focal or meningeal signs were identified.

Laboratory tests excluded systemic causes including metabolic (TSH, T4L, Vitamin B12, folates, renal and liver function), infectious (HIV, VDRL, Hepatitis B) and toxic (drugs of abuse) diseases (Table 1), consequently antipsychotic management with Olanzapine was initiated. The 24-hour EEG register was made without evidence of abnormal discharges or any remarkable finding. The brain MRI showed a temporo-occipital-left cavernoma with prominent venous developmental

Table 1
Case Differential Diagnosis. The different diagnoses considered in the clinical evaluation of the patient are listed, excluding nutritional, toxic, infectious, neoplastic and autoimmune etiologies. The CSF results are enlisted and the infectious studies are included.

Differential Diagnosis	Result	Differential Diagnosis	Result
Complete blood count	Leukocytes 9,470, neutrophils 6,360, lymphocytes 2,280, hemoglobin 14.0, hematocrit 42.2, platelets 243,000.	**Infectious studies**	• PCR for herpes simplex virus types I and II: Not detectable. • Hepatitis B surface antigen: < 0.1 (non-reactive <1). • Hepatitis C antibody: 0.12 (non-reactive <0.8). • Hepatitis B surface antibodies: < 0.1 (non-reactive <1). • HIV: Negative. • RPR in serum: non-reactive.
Electrolytes	Na 141, K 3.6, Cl 108.		
Liver function	ALT 11. 6, AST 13, PT 11. 4, INR 1. 07.		
Kidney function	BUN 13, Cr 0.7.		
Metabolic profile	TSH: 2.2, T4: 1.25 (Normal). Serum Cortisol: Normal. PTH: Normal. Serum glucose: 85 (Normal). HbA1c: 5.2 %.	**Abuse drugs**	Negative for amphetamines, cannabinoids, barbiturates, benzodiazepines and opiates.
Nutritional studies	• Folic acid: 10.12 (normal >5.38) • Vitamin B12: 597 (normal 211 −911) • Vitamine B1 and B6: Normals • Vitamine D and E: Normals	**Autoimmune encephalitis studies**	• AntiNMDA: Negative • Anti-AMPA: Negative • Anti LI1: Negative • Anti GABA: Negative • AntiGAD 65: Negative
Onconeural Antibodies	• Onconeural antibodies IgG: Serum sample. • Titina: Negative • SOX1: Negative • Recoverin: Negative • Hu: Negative • Yo: Negative • R1: Negative • PNMA2 Ma 2/Ta: Negative • CV2: Negative • Amphiphysin: Negative	**Autoimmune studies**	• Anti-DNA: negative • ANAs: negative • Rheumatoid factor: 5.13 (normal <14) • C3: 103 (normal 82 −160) • Lupus anticoagulant: 32.6 (control 33.2) • MPO and PR3: Negative • Thyroglobulin: Normal • Anti-TSHR: Negative • Thyroglobulin antibodies: Negative • ECA: Negative

Oncology labs	• Protein electrophoresis: hypoalbuminemia, decrease in beta−1 fraction
	• Tumoral markers: Negative
	• Flow cytometry of 2000 μL of CSF with transfix showed:
	  • Pathological population: 0 %
	  • Diagnosis: no blasts or mature neoplastic B lymphocytes in the analyzed sample.
		Other studies	• **Electroencephalographic Monitoring Report**: 12-hour video EEG study, normal. No epileptic seizures, asymmetries, or interictal epileptiform activity were recorded
			• **Transvaginal pelvic ultrasound;** Uterus in AVF (anteverted and flexed) with regular contours, trilaminar endometrium of 8.9 mm, normal ovaries.
			• **Chest CT with contrast:** Normal
			• **Abdominal and pelvic CT with contrast**: Biliary sludge
			• **PET scan:** Normal

Lumbar puncture studies	First lumbar puncture: ● Leukocytes 225 (Mononuclear 26%, polymorphonuclear 74%), Proteins 212, glucose 56. ● Cryptococcus antigen: Negative. Gram staining: No organisms. China Ink: Negative. Gram: Normal ● VDRL serology: Non-reactive. ADA: 2.7. PCR TBC: Not detectable ● Meningitis panel detected: *Streptococcus pneumoniae.* ● Other pathogens not detected: E. coli, H. influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Cytomegalovirus, Enterovirus, Herpes simplex virus types 1 and 2, Parechovirus, Varicella zoster. Control lumbar puncture (7 days): ● Opening pressure: 14 ● Leukocytes: 100, monocytes: 90 %, Proteins: 58, glucose: 57. Infectious studies: negative Last Lumbar Puncture (14 days): ● Opening pressure: 25 ● CSF Aspect xanthochromic, slightly turbid, pH 7.0, leukocytes 7 (mononuclear 90, polymorphonuclear 10), erythrocytes 10, proteins 42.42, glucose 40.81 ● Common germ culture: No growth after 48 h of incubation.		

anomaly located in the posterior periventricular area associated, no other relevant findings (Fig. 1**A-1B**). Suspecting encephalitis, a lumbar puncture was performed, the cerebrospinal fluid (CSF) examination found pleocytosis of 212 cells, polymorphonuclear 70 % associated with hyperproteinorrachia (225 mg/dL) and hypoglycorrhachia (CSF/serum ratio 0.48), Film array© was positive for *Streptococcus pneumoniae*, other CSF infectious studies were negative (Table 1). Antibiotic treatment was started (ceftriaxone + vancomycin), a lumbar puncture one week later showed improvement of the inflammatory findings.

Despite two weeks of antibiotic and antipsychotic (Olanzapine) management at maximum dose, the patient's mental examination was still upset, with apathetic, defiant attitude, hypo-modulated affect with irritability, disorganized, concrete thinking, irrelevant responses and perseverations, frequent hallucinatory attitude, failures in memory fixation, poor sense of judgment and no introspection. Neuropsychological testing evidenced severe multi-domain cognitive impairment, and a significant impact on her drawing, and instrument playing skills was identified as shown in Fig. 1**C - 1D.** Due to the continued symptoms, further studies were performed to exclude neoplasms (contrasted thoracoabdominal CT scan, transvaginal ultrasound, tumor markers, protein

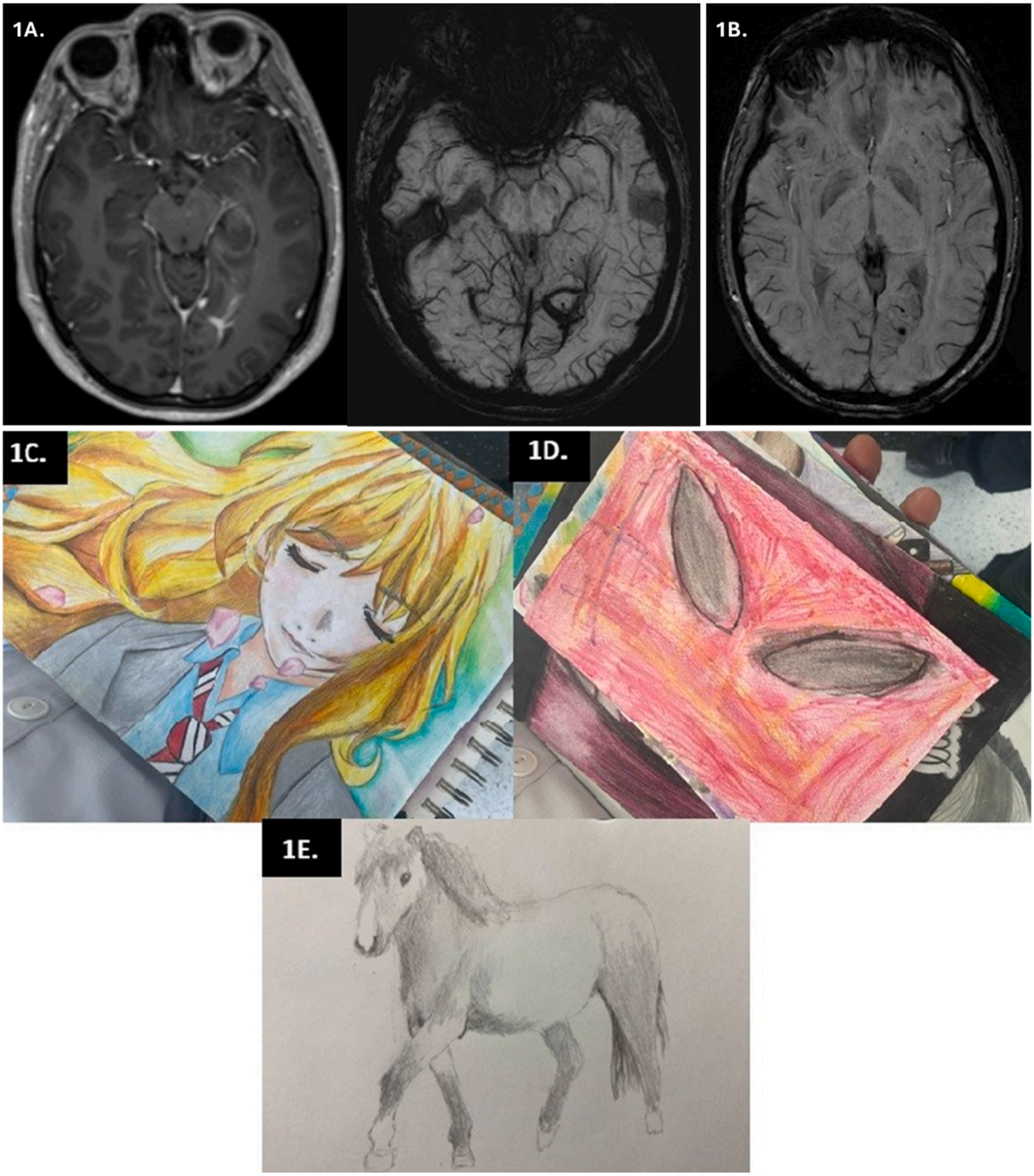

Fig. 1. 1A) Contrast enhanced T1 and Echo- gradient brain MRI. Venous developmental anomaly and small associated cavernoma in the left occipital lobe. **1B). Echo gradient MRI** Small cavernoma in occipital lobe **2A)** Artistic skills prior to symptoms (Provided by family) **2B)** Evidence of neuropsychiatric deficit through change in drawing patterns during the clinical event. **2 C)** Drawing made by the patient 72 h after the start of immunotherapy showing the recovery of her artistic skills.

electrophoresis, PET-SCAN), autoimmune diseases (ANA, ENA, Anti-DNA, complement, ANCA) and autoimmune encephalitis (NMDAR and antineuronal antibodies in serum and CSF) (Table 1**)**, all of which were negative. Other autoimmune conditions including ADEM and multiple sclerosis were ruled out because they did not meet radiological criteria.

In view of the clinical course and the results reported, it was considered probable immune-mediated psychosis in the context of a post-encephalitic syndrome triggered by bacterial meningitis, and management with immunosuppressants was decided. She received high doses of methylprednisolone for 5 days with gradual resolution of symptoms 48 h after initiation of treatment. As some neuropsychiatric findings remained, she completed additional management with plasmapheresis for 5 days without complications. The patient showed complete resolution of symptoms and reacquired drawing skills as evidenced in Fig. 1**E.** After one year of clinical follow-up and periodic neuropsychological testing there have been no relapses, the patient has resumed her professional career and artistic activities without any additional neurological symptoms or difficulties.

Discussion

Psychosis is a symptom that may be associated with psychiatric diseases, systemic medical conditions or primary neurological diseases [1,6]. A first psychotic episode, such as the one presented, requires ruling out CNS pathologies [6]. Encephalitis is a neurological syndrome characterized by brain parenchymal damage associated with an inflammatory occurrence with an incidence of 5–10 people per 100,000 population [2,7]. The main clinical signs include headache, fever, behavioral changes, seizures and focal neurological deficits [6,7]. Its most important causes are infectious (almost 50 % of cases) especially viral (Herpes simplex, West Nile Virus, Enterovirus, Chickenpox, among others); while another important percentage of these causes are associated with an immune-mediated condition (Anti NMDA, LGI1, Hu, CASPR2, etc.) [8,9]. Despite diagnostic advances, in 20–30 % of encephalitis cases the cause is still unknown [2].

Psychiatric symptoms are especially important in patients with autoimmune encephalitis, which has gained importance in recent decades as an explanation for multiple cases of encephalitis that previously remained undiagnosed and untreated [9,10]. Autoimmune encephalitis is an antibody-mediated inflammatory phenomenon that occurs in response to an antigenic stimulus at the intracellular (Hu, Ma1, Ri proteins) or cell membrane level (NMDA, AMPA, GABA, CASPR2, potassium/calcium channels) leading to CNS damage with cell destruction; an increasing number of antibodies associated with this condition are described [1,7,10]. It presents with subacute or chronic symptoms of cognitive impairment, seizures and behavioral symptoms. Its appearance is variable and is determined by the type of antibody and the brain area affected [7,9]. Among these antibodies, the presence of CASPR2, LGI1 and GAD65 have been mostly involved in the development of behavioral and neurocognitive symptoms including psychosis [11].

Current diagnostic criteria for autoimmune encephalitis include clinical features, neuroimaging findings and identification of positive serum or CSF antibodies (associated with improved performance) [1, 10]. Treatment aims to reduce inflammatory activity and secondary neuronal damage by immunomodulation with either corticosteroids, plasmapheresis, immunoglobulin, rituximab, or cyclophosphamide [9, 10]. Prognosis can range from recovery of neurological function to severe sequalae and even death [7].

On the other hand, *S. pneumoniae* remains a frequent CNS infection in immunocompetent patients and a leading cause of bacterial meningitis worldwide [4,5]. Its involvement in the CNS is framed by virulence factors of the agent and the host response, leading to a severe neutrophil-dependent proinflammatory cascade [12]. Neurological manifestations usually include meningeal involvement (fever, headache, disturbance of consciousness and meningeal signs), occasionally leading to encephalitis with brain parenchymal damage [4,5]. In adults, it rarely causes neuropsychiatric symptoms; when it does occur, it is expected to improve with antibiotic treatment [3]. Other bacterial agents such as *Neisseria meningitidis, Listeria monocytogenes, Treponema pallidum* and *Borrelia burgdorferi* have also been associated with encephalitis at a low frequency [2].

Given the above, the occurrence of subacute psychiatric symptoms in *S. pneumoniae* meningitis is remarkable, although CSF findings confirm the presence of an acute bacterial infection, the clinical features are more similar to autoimmune encephalitis. Differential psychiatric diagnoses should be evaluated when there is no strong evidence of an infection or CNS autoimmune process, and therefore, the use of antipsychotics is necessary [13]. However, the presence of psychiatric symptoms in bacterial meningitis unresponsive to antipsychotics and antibiotics should raise suspicion of an immune-mediated origin, even with negative antineuronal antibody results, which does not conclusively exclude autoimmune encephalitis [10,13].

Para-infectious or post-infectious encephalitis is a poorly understood and not clearly established condition in the literature, especially in the context of primary CNS infections. Physio-pathologically, it is assumed that there is a molecular mimicry between the epitopes of the microorganism and the patient's cellular antigenic proteins that triggers an immune reaction that not only damages the pathogen, but also the host cells [1,7]. The strain of *Streptococcus* has been associated with autoimmune phenomena, mainly in the pediatric population such as Sydenham's Chorea or the Group of Pediatric Neuropsychiatric Autoimmune Disorders associated with Streptococcal Infections (PANDAS) [14]. The involvement of carbohydrate-binding antibodies in neurological conditions associated with *Streptococcus pneumoniae* infections or vaccines has also been described [15]. Despite this, data on immune-mediated events in immunocompetent adults following streptococcal infection is non-existent. Immunosuppressive treatment has a plausible pathophysiological basis, but there is no strong clinical evidence for an infectious or post-infectious event such as ours.

We present a case of immune-mediated psychosis in the context of post-encephalitic syndrome secondary to *Streptococcus pneumoniae* bacterial meningitis, with response to immunosuppressive measures and no response to antibiotic or antipsychotic management. To date, a case similar to ours has not been documented in the literature.

Conclusion

Streptococcus pneumoniae infection in the CNS typically shows up as meningitis, rarely associated with psychosis or neuropsychiatric symptoms; in such cases, autoimmune encephalitis is the most likely differential diagnosis. This report suggests an immune-mediated occurrence (post-encephalitic syndrome) secondary to Streptococcal meningitis that may respond to immunosuppressive therapy, and it should be a diagnosis to consider in patients with psychiatric symptoms and meningitis, who do not respond to standard management, even with negative studies for autoimmune encephalitis, before categorizing the patient as a psychiatric pathology.

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. All information has been appropriately identified.

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Author Agreement Statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Bibiana Briceno: Writing – original draft. **Michael Ariza-Varon:** Writing – review & editing. **Nicole Pinzón:** Visualization, Project administration. **Juan Castro:** Investigation. **Laura Oviedo:** Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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