A 27-YEAR-OLD FEMALE WITH ELEVATED CSF PROTEIN, DYSPHAGIA, TACHYCARDIA AND PSYCHOSIS REFRACTORY TO ANTIPSYCHOTIC TREATMENT WITH AN EXTENSIVE NEGATIVE WORKUP

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ABSTRACT There are many causes of psychosis. Some of them are medically related, while others are psychiatric. In this case, we explore causes of psychosis related to mildly elevated CSF protein in a 27 yo patient with unique physical exam findings: dysphagia, tachycardia, and psychosis refractory to antipsychotic treatment (including a moderate 200 mg dose of Clozapine). Ultimately we did not discover any medically known cause of her psychosis. Still, our final differential diagnosis included immune-mediated encephalitis, possibly due to COVID-19 or an unknown medical cause. We find it unlikely that this patient has a primary psychiatric disorder as they had no clinical benefit from Invega Sustenna, Olanzapine, and a moderate 200 mg dose of Clozapine.

KEYWORDS Psychosis, encephalitis, COVID-19, treatment refractory

Introduction

Elevated CSF protein with CSF oligoclonal bands is a nonspecific finding that indicates possible dysfunction in the blood-brain barrier, CSF flow, CSF inflammation, or intrathecal immunoglobulin production (Tandon 2021). Abnormal CSF findings (elevated LDH, protein, glucose) are often present in both medical and psychiatric illnesses, so changes in the CSF parameters are not pathognomonic for any illness (Giné-Servén 2022; Endres 2020; Graus 2016, Orlovska-Waast 2019; Zetterberg 2014). Oddly, it is also possible to have autoimmune encephalitis and have completely normal CSF (Hébert 2020). Still more perplexing, coronavirus has previously been implicated in psychosis as early as 2011, and, since the COVID-19 pandemic has begun, several studies have shown that it too can precipitate psychosis (Smith 2021) as well as alter CSF markers (Tandon 2021).

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Case Report

A 27-year-old Hispanic female presented to the ED for psychosis. She has a medical history significant for premature birth (@~24 weeks with 2 months in the ICU), developmental delay (mother reports patient should have been in special education classes), mild symptomatic COVID infection January 2022, and Hx of left oophorectomy for an unknown ovarian cancer in her teen years. She had no prior psychiatric hx and no family psychiatric Hx of severe mental illness.

Her family states that she was in normal health, could hold a job packing at a warehouse, and had a good relationship with her boyfriend, family, and friends until she was discovered unconscious on the floor from an unwitnessed fall in her house February 2022 by her 5-year-old son. It was unclear what precipitated this fall and for how long she experienced a loss of consciousness.

After her fall, she began acting bizarrely, staying up late at night, pacing her room, talking about shooting from her past, and saying she would "kill herself because I cannot sleep." She was hospitalized at an inpatient psychiatric hospital for 1 week in March 2022, given two paliperidone injections (254 mg IM and 156 mg IM), and subsequently discharged, but her psychosis

persisted. Finally, she was brought to our ED after biting her boyfriend. At the same time, he was asleep, and her family reported that she had increasingly unprovoked and unexplained aggressive behaviour.

The patient was admitted to neurology to rule out encephalitis. Bush Francis's catatonia scale was initially 22, so she was started on Ativan 1 mg PO TID which resulted in respiratory depression and no improvement in apparent catatonia, so this was discontinued. However, 26-minute EEG was normal (despite administration of lorazepam), and her MRI brain with contrast was unremarkable, with no change in signal intensity to suggest autoimmune encephalitis. US abdomen showed absent left ovary with normal right ovary as did MRI abdomen and pelvis with contrast.

Extensive laboratory testing (CBC, CMP, UA, UDS, cortisol, urine hCG, AFP, TSH, vitamin B12, folate, syphilis Ab, thiamine, phosphate, magnesium, ANA, CRP, ESR) were all normal.

LP showed elevated protein (56), but glucose, opening pressure, and cell studies were normal; CSF meningitis panel, coccidiomycosis, and west Nile ab were also negative. In addition, paraneoplastic and autoimmune encephalitis labs were negative (both in CSF and serum) with send-out to Mayo Clinic. CSF and serum Oligoclonal bands are at present pending.

The patient was started on empiric treatment for encephalitis after lumbar puncture, Methylprednisone 1000 mg IV for 5 days and IVIG with no improvement in symptoms. Due to dysphagia and weight loss, a peg tube was placed by general surgery, which was subsequently removed by the patient and required replacement. Since the patient continued pulling on her peg tube, she was intermittently placed in 4-point restraints the following month.

She remained selectively mute and non-verbal, answering questions with grunts throughout her stay in April and May. Notably, she was also tachycardic during this time with HR in the low 90s. Because of her continued agitation, she was trialled on Depakote 750 mg PO TID with a trough level of 76. Still, Depakote was discontinued when the patient developed thrombocytopenia and when it had little effect on her agitation and altered mental status. She was subsequently tried on Ambien 10 mg qHS PRN for sleep and Haldol, Propranolol 20 mg q6 PRN, and Olanzapine 5 mg PO BID, all with little effect, so the team decided to rapidly titrate Clozapine to 200 mg daily. Unfortunately, this also had no clinical effect and was tapered and discontinued after another two weeks.

Discussion

What do we make of a 27-year-old female unresponsive to antipsychotics with a mild change in their CSF protein and an otherwise completely unremarkable and extensive workup?

We believe several clinical signs point to a primarily medical rather than psychiatric aetiology. These include unresponsiveness to antipsychotics (especially at an adequate dose for an adequate duration: olanzapine 5 BID, Invega sustenna with adequate loading, and Clozapine titrated to 200 mg), physical exam findings consistent with medical illness (dysphagia and tachycardia), acute onset of psychosis after a fall, no family Hx of primary psychiatric disorder, and no prodromal symptoms consistent with schizophrenia or other primary psychiatric psychotic disorder. The psychiatric attending managing this case even saw a video of the patient weeks prior to her illness; she seemed happy, personable, and outgoing, with no perceptible illness.

Beyond the thought that this patient's illness is medical rather than psychiatric, there is very little evidence to point to any known illness. The patient did not meet the clinical criteria for encephalitis (Graus 2016). Their autoimmune panel was normal, their EEG showed only diffuse wave slowing, which is non-specific, MRI brain as well as abdomen were normal, and an extensive laboratory workup (including lumbar puncture) was also normal, except for a mildly elevated protein–which by itself is very non-specific.

Conclusion

We are left feeling very unsettled by this case. Sometimes, it seems like there is no clinical evidence to point to a specific diagnosis or treatment. Here is a patient with a very extensive workup and empiric encephalitis treatment in addition to schizophrenia treatment with very little clinical improvement.

Summaries of Studies

Zetterberg 2017

Mental disorders or antipsychotic treatment can cause dysfunction in the BBB or cerebrospinal flow and a resultant elevation in CSF protein.

Graus 2017.

Absence of antibodies does not exclude the possibility that a disorder is immune mediated.

Classic symptoms of NMDA encepahlitis: abnormal behavior (psychosis) with irritability and insomnia followed by speech dysfunction, dyskinesia, memory deficits, autonomic instability and decreased level of consciousness.

Three levels for autoimmune encephalitis: possible, probable and definite:

- Possible criteria she meets: (1) subacute onset, AMS, or psychotic symptoms; (2) new focal CNS findings (i.e. dysphagia) and (3) reasonable exclusion of other causes
- Probable criteria for NMDA she meets if oligoclonal bands are positive
- For patients with negative autoantibodies and meeting probable criteria "detection of new antibodies in serum and CSF in reference labs is important."

Bauer 1987

Overall conclusion was that schizophrenics prior to prolonged antipsychotic antipsychotic have blood brain dysfunction with elevated CSF protein, however only 1 patient in this study of 15 patients had a total protein value higher than our patient.

Orlavska-Waast 2019

(systematic review and meta-analysis of studies on mental illness and CSF)

Schizophrenia spectrum disorders is associated with BBB dysfunction and even intrathecal production of immunoglobulin

- Total protein (3 studies with 97 patients)
  - Standard mean difference was 0.41 (95% CI was 0.15 - 0.67); no difference from normal controls
- Oligoclonal bands in 12.5% of cases

Zemen 1993

- OCB of IgG provides evidence of the production of antibodies but it does not tell you where the antibodies are being produced (CSF vs. Plasma).

  - If present in CSF and absent in serum then strong evidence of intrathecal response
  - If present in serum and not CSF then production is in serum
  - If present in both CSF and serum then likely serum except if CSF has additional bands that serum does not contain
- Causes of OCB: infection, inflammation, paraneoplastic, neoplastic, GBS, peripheral neuropathies, MS, vasculitis, degenerative disorders.

Tandon 2021 CSF studies and COVID 19

- COVID 19 can result in an encephalitis
- CSF protein elevated in all fatal cases (average protein 61) and in 74% of non-severe cases (average protein 56)
- In many cases PCR for COVID was negative for CSF

Seyfurt 2002 (determinants of CSF protein concentration)

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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Table 1 Occurrence of OCB patterns in major categories of disease.

	+	>	*	specificity?
Infection	yes (esp CNS)	yes (esp CNS)	yes (esp syst)	yes[10 13]
Inflammation	yes (esp CNS)	yes (esp CNS)	yes (esp syst)	yes[14 17]
Paraneoplastic	yes	yes	yes	yes[15 16]
Neoplastic	rare	rare	yes	no
CBS	no	no	yes	no
Other neuropathies	no	no	yes	no
Multiple sclerosis	yes	yes	no	no
Vascular	no	no	rare	no
Degenerative	no	no	rare	no

Syst = systemic, GBS = Guillain-Barré syndrome, "Specificity?" refers to the question of whether, in at least some instances, the antigenic specificity of the OCBs has been determined. + refers to isoelectric focusing patterns with OCBs in CSF only: for explanation of * and ` see figure and text.

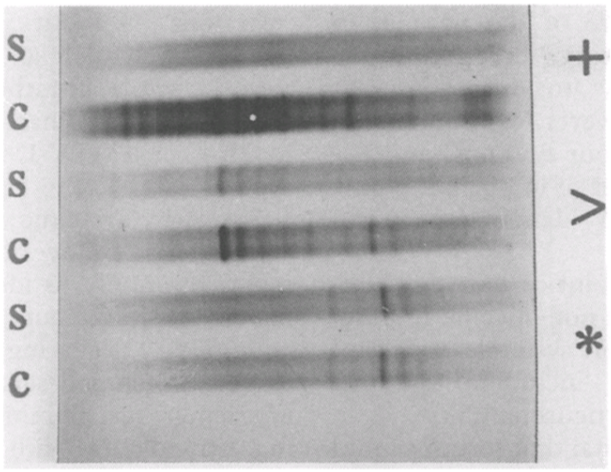

Figure 1 Three sets of paired serum (s) and CSF (c) samples illustrate the patterns of oligoclonal response (+, >, *) defined in the text.

Table 2 Frequency of pathological processes responsible for isoelectric focusing patterns (percentages in brackets.)

	*	>
Infection	8 (14)	13 (29)
Inflammation	10 (18)	4 (9)
Paraneoplastic	3 (5)	2 (4)
Neoplastic	9 (16)	1 (2)
CBS	9 (16)	0 (0)
Other neuropathies	10 (18)	0 (0)
Multiple sclerosis	1 (2)	26 (57)
Vascular	3 (5)	0 (0)
Degenerative	3 (5)	0 (0)
Totals	56 (99)	46 (100)

GBS = Guillain-Barré syndrome, other PN = other varieties of peripheral neuropathy. * refers to isoelectric focusing patterns with identical CSF and serum OCBs, > to patterns with at least one clone identical in CSF and serum and at least one unique CSF clone. See text for further details.

Table 3 General characteristics of SARS-CoV-2 ($n = 113$) patients with CSF study and neurological manifestation.

Characteristics	N(%)
Mean Age in years, SD	57 (SD = 14,3)
*Gender	
Male	57(50.40)
Female	29(25.66)
Neurological manifestation	
GBS and its variants	55(48.67)
Encephalopathy	14(12.39)
Meningoencephalitis	11(9.73)
Seizure	11(9.73)
Ischemic stroke	5(4.42)
Hemorrhagic stroke	3(2.65)
CNS demyelinating disorder	3(2.65)
Cranial nerve enhancement	3(2.65)
**Others	8(7.08)
•**Severity of CovID-19**	
Severe	35(30.97)
Non-Severe	78(69.03)
Outcomes	
Fatal	7(6.19)
Non-Fatal	106(93.81)

* 27 cases gender not available
**Other includes neuropsychiatric manifestations and delirium
• Severity based on Infectious Disease Society of America/American Thoracic Society IDSA/ATS criteria

Table 4 Demographic characteristics of 104 patients for CSF observational study on COVID-19-associated neurological complications*.

	CSF high protein**	CSF normal protein	CSF Elevated cell count***	CSF normal cell count
Age (year) mean ± SD	56.9 ± 15.0	57.3 ± 12.6	54.6 ± 17.9	58.0 ± 12.6
Gender (%)				
Female	21 (33.9)	8 (33.3)	10 (41.7)	19 (30.7)
Male	41 (66.1)	16 (66.7)	14 (58.3)	43 (69.4)
COVID-19 Severity				
Non-Severe	38 (74.5)	13 (25.5)	15 (29.4)	36 (70.6)
Severe	24 (68.6)	11 (31.4)	9 (25.7)	26 (74.3)
Fatality				
Non-Fatal	52 (65.0)	28 (35.0)	23 (28.7)	57 (71.3)
Fatal	7 (100)	0 (0.0)	3 (42.9)	4 (57.1)
Outcome				
CNS Manifestation[a]	26 (59.1)	18 (40.9)	19 (43.2)	25 (56.8)
PNS Manifestation[b]	42 (77.8)	12 (22.2)	9 (16.7)	45 (83.3)

* Severity was not reported in 27 cases, fatality was not reported in 26 cases,CNS status on PNS status was not reported in 15 cases
** Cerebrospinal fluid
*** Cerebrospinal fluid cell count
[a] Central nervous system
[b] Peripheral nervous system