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Case Report

An Enigmatic Case of Altered Sensorium

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Abstract

Altered mentation is a frequent but challenging clinical presentation with causes comprising infections, trauma, stroke, toxins, dyshomeostasis and very rarely, autoimmune encephalitis (AIE). AIE is characterized by neuropsychiatric symptoms and antibodies against several neural proteins; one such protein being contactin-associated protein-like 2 (CASPR2).

Here, we present one such case of a 50-year-old hypertensive male presenting with worsening mental haziness since three months, difficulty walking and burning sensation of feet since one month and decreased responsiveness since 20 days. Prior evaluation at a private facility was inconclusive and psychiatric medications were initiated but to no avail. Initial assessment at current institution showed elevated blood pressure, incoherent speech and prosopagnosia. The patient was conscious, agitated and disoriented, limiting further neurological assessment. Lab investigations showed neutrophilic leucocytosis, elevated C-reactive protein levels, hypouricemia and hypotonic hyponatremia, suggestive of SIADH. MRI of the brain revealed diffuse cerebral atrophy. EEG reported diffuse slowing of cortical activity. Pathological and microbiological analysis of CSF was unremarkable. Treatment for SIADH as per protocol proved futile. Further investigation into autoimmune causes established a diagnosis of CASPR2-positive autoimmune encephalitis. After treatment with IV immunoglobulins as per protocol, the patient significantly improved and upon follow-up, regained independence in daily activities (mRS-2).

AIE, though rare, should be considered in cases of unexplained encephalopathy. Quick and precise management are key to preventing diagnostic delays and reducing long-term effects.

Keywords: AIE; CASPR2; VGKC; IV Immunglobulins

Introduction

Altered mentation is a commonly encountered clinical presentation, yet can be one of the most challenging cases for the physicians to tackle [1]. Altered sensorium or change in the mental status could be stupor, delirium, depression, dementia or coma [1,2]. The underlying pathology in case of a patient with altered mental status can range from systemic infections, localized infections, trauma, stroke, intracranial haemorrhages or even ingestion of certain toxins, metabolic disturbances, enzyme defects, immune reactions, paraneoplastic syndromes, drug induced or iatrogenic causes [3,4]. Identifying the source of the offending agent in patients with altered mental status can be challenging, furthermore due to relative inability to take a detailed history from the patient or the relatives.

Studies estimate that altered mental status can be present in about 5-10% of all adults visiting the emergency or seeking immediate medical care, with the underlying pathology in a majority of the cases being stroke, infections or drug interactions [5-7]. However, a small fraction of the cases turn out to be AIE.

Autoimmune encephalitides /Antibody-mediated encephalitides refers to a cohort of inflammatory brain diseases characterized by prominent neuropsychiatric symptoms and associated with antibodies against neuronal cell-surface proteins, ion channels or receptors [8]. Autoimmune encephalitis (AIE) could be triggered by infections, malignancy or other autoimmune conditions [9]. The rarity of the condition, vagueness of symptoms, variety of clinical presentations and the imminent threats if left untreated, make AIE

tremendously challenging. Antibodies against several receptors have been identified in this particular disease entity with one of them being the cell adhesion protein of the neurexin family, contactin-associated protein-like 2 (CASPR2) or also called the voltage-gated potassium channel (VGKC) [10]. Here we present one such case of CASPR2 positive autoimmune encephalitis.

Case Report

A 50 year old gentleman who was a known case of long-standing essential hypertension presented to the emergency department with complaints of worsening mental haziness since three months, difficulty in walking since one month and decreased responsiveness since 20 days. On assessing his initial situation, he was unable to speak coherently, had difficulty in recognizing familiar faces and also complained of burning sensation in his feet. The gentleman was a farmer and cattle herder hailing from Shivamogga, Karnataka. With only the background of long-standing hypertension and his profession, the symptoms could most possibly be attributed to cerebrovascular accident or an unknown poison. The importance of these differential diagnoses at this juncture was that both situations are time crucial and demand a high level of speed and accuracy with regards to management. On probing, it was revealed that the patient had no history of fever, trauma, involuntary movements or history of toxin exposure. The medication history of the patient was significant for daily consumption of tablet Amlodipine 10 mg, once a day for essential hypertension. It was reported that in view of chronic knee pain, the patient would consume over the counter pain killers quite frequently. However, there were no reports of high risk sexual behavior, blood transfusion, alcohol consumption, smoking, tobacco consumption or other deleterious habits.

Previously, the patient was evaluated thoroughly at a different private facility where the underlying pathology could not be determined even with metabolic tests and neuroimaging studies. In view of unremarkable MRI of the patient, organic brain disorders were ruled out and he was hence started on treatment with psychiatric medications. Along with Amlodipine, the medications prescribed to the patient included Pregabalin, Mecobalamin, Duloxetine, Clonazepam and Escitalopram. The initial treatment proved to be inadequate since there was no improvement in his condition and hence sought further evaluation in our institution.

On initial assessment, his vital parameters were as follows; pulse rate was 110 beats/min with regular rhythm, normal in volume and character, no radio-radial or radio-femoral delays and all peripheral pulses were palpable. His blood pressure was 140/90 mmHg as measured in the right arm in supine position. Respiratory rate was 22 cycles/min and axillary temperature was 98^0 F. His general physical examination was unremarkable. CNS examination revealed that the patient was conscious, agitated and disoriented. His speech was irrelevant. Both pupils were reactive to light normally and the patient was able to move all 4 limbs spontaneously. Due to non-cooperation from the patient as well as his agitated and confused state, further neurological evaluation could not be done. However, it is to be noted that after systemic examination, the cardiovascular, respiratory and gastrointestinal systems were unremarkable. The patient's GRBS was 171 mg/dL.

At the end of detailed history and physical examination, the patient was suspected to have encephalopathy which could be metabolic, vascular, or infectious in origin.

The initial panel of investigations showed leucocytosis (19240 cells/cubic mm) with predominant neutrophilia (93.5%) with significantly less lymphocytes (5.6%) and monocytes (0.7%). Remaining parameters of the haemogram were well within normal limits. Liver function tests, serum ammonia levels, procalcitonin and vitamin B12 levels were normal. Although, C reactive protein levels were elevated (2.04 mg/dL). Interestingly, renal function tests revealed hypouricemia (2.2 mg/dL) and severe hyponatremia (117 mEq/dL). Serum osmolality was low (250 mOsm/L) and the values of urine osmolality and urine spot sodium were elevated (210 mOsm/L and 165 mEq/L respectively) (Table 1).

Test	Component	Value	units
Complete blood counts	Hemoglobin	13.9	g/dL
	Total leucocyte counts	19240	cells/cumm
	Platelet Count	3.86	lakhs/cumm
Differential counts	Neutrophils	93.5	%
	lymphocytes	5.6	%
	Eosinophils	0.1	%
	Monocytes	0.7	%
	Basophils	0.1	%
Renal Function Test	Blood urea nitrogen	3.83	mg/dL
	Creatinine	0.33	mg/dL
	Uric Acid	2.2	mg/dL
	Sodium	117	mEq/L
	Potassium	3.9	mEq/L
	Chloride	93	mEq/L
Serum Osmolality		250	mMol/L
Urine Osmolality		210	mMol/L
Urine spot sodium		165	mMol/L
TSH		1.06	µU/mL
Liver Function Test	Total Bilirubin	0.96	mg/dL
	Direct Bilirubin	0.07	mg/dL
	Aspartate Transaminase	25	mg/dL
	Alanine Transaminase	27	mg/dL
Vitamin B12		475	pg/mL
CRP		2.04	mg/dL
Procalcitonin		0.07	ng/mL
Antinuclear Antibody		Negative	

Table 1: Blood Investigations.

MRI imaging of the brain showed diffuse cerebral atrophy consistent with small vessel disease (Figure 1). Chest radiograph and ultrasonography of abdomen and pelvis showed no remarkable abnormalities. Electroencephalogram (EEG) demonstrated diffuse slowing of the background cortical activity. Lumbar puncture was done in order to assess the CSF (cerebrospinal fluid) and the only abnormality found was low chloride levels (116 mEq/L) (Table 2). Anaerobic culture of CSF along with CBNAAT for MTB, HSV 1, HSV 2 and cryptococcal antigen yielded negative results.

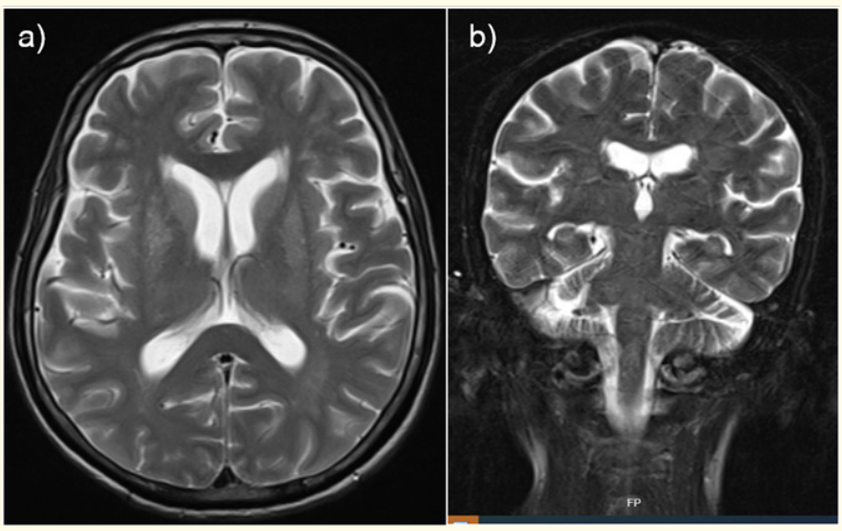

Figure 1: Application of Finger-O-Ring test.

CSF Parameters	Recorded Value	Reference Values
Color	Clear	Clear
Glucose	69 mg/dL	60-80 mg/dL
Protein	44 mg/dL	15-45 mg/dL
Chloride	116 mEq/L	120-130 mEq/L
Cell Count	2 (Lymphocytes)	<5 cells (Lymphocytes)
Aerobic Culture	Negative	-
GeneXpert for MTB	Negative	-
HSV-1,2	Negative	-
Cryptococcal Antigen	Negative	-

Table 2: CSF analysis findings.

With these results, it was quintessential to achieve homeostasis in the patient with adequate correction of sodium levels as well as determine the underlying pathology. The picture of hypotonic hyponatremia along with hypouricemia led to the diagnosis of SIADH (Syndrome of inappropriate Anti-diuretic hormone secretion). Hence, the corrective measures namely hypertonic saline and fluid restriction were started along with antibiotic coverage with IV Ceftriaxone 2g BD and IV Doxycycline.

Over the course next few days, the sodium levels were brought to normal (117→ 127 → 128→ 131→ 138 mEq/L) and not rapidly so in order to avoid CPM (Central pontine myelinolysis). But to the dismay of the patient and the treating physicians, he showed no improvement in symptoms. There was increasing haziness, not in the condition of the patient, rather the treating physicians as the microbiological reports were all negative; blood culture, urine culture, CSF culture, Viral serology (HIV, HbSAg, Anti HCV), VDRL, Brucella antigen were all negative. With the panel of tests ruling out infective, toxic, metabolic and structural abnormalities, one thing that caught the eye was raised CRP levels. Tests for Systemic autoimmune disorders were negative. That left us with focal autoimmunity and paraneoplastic etiologies.

The ironically rapid clinical decline and negative test reports of the patient prompted aggressive measures as a result of which autoimmune and paraneoplastic encephalitis panel was investigated. Antibodies against 16 out of the 17 antigens tested were negative except for the rare, vague and bothersome contactin – associated protein 2/ VGKC associated or also known as CASPR2 (Table 3). Finally, in accordance in with International Encephalitis Consortium 2013 diagnostic criteria for encephalitis, diagnosis of CASPR 2 positive AIE was established [11] (Figure 2). Following the opinion of the neurology team, treatment with IV immunoglobulins was initiated as per the established guidelines (0.4 g/kg body weight/ day). At the rate of 10g IV BD over the next 5 days, a total of 100 g of IV immunoglobulins were administered.

Antibody Test	Result
Anti-Hu (ANNA-1, anti-neuronal nuclear autoantibody, type 1)	Negative
Anti-Ri (ANNA-2, anti-neuronal nuclear antibody, type 2)	Negative
Anti-Yo (PCA-1, Purkinje cell antibody 1)	Negative
Anti-CV-2 (Anti-CRMP5)	Negative
Anti-PNMA2 (Ma2/Ta)	Negative
Anti-SOX1 (Anti-glial nuclear antibody - AGNA)	Negative
Anti-Tr (PCA-Tr)	Negative
Anti-GAD65	Negative
Anti-Zic4 (immunoblot only)	Negative
Anti-Titin (immunoblot only)	Negative
Anti-Recoverin (immunoblot only)	Negative
Glutamate receptor, NMDA	Negative
Glutamate receptor, AMPA1	Negative
Glutamate receptor, AMPA2	Negative
CASPR (contactin-associated protein 2/VGKC associated)	Positive
LGI-1 (Leucine-rich glioma-inactivated protein 1/ VGKC associated)	Negative
GABA_B receptor (GABAB1, B2)	Negative

Table 3: Autoimmune encephalitis panel.

Major Criterion	
Patients presenting to medical attention with altered mental status lasting ≥24 h with no alternative cause identified.	
Minor Criteria	
Documented fever ≥38° C (100.4°F) within the 72 h before or after presentation	
Generalized or partial seizures not fully attributable to a preexisting seizure disorder	
New onset of focal neurologic findings	
CSF WBC count ≥5/cubic mm	
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset	
Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.	
Interpretation	
Major criterion + 2 minor criteria	possible encephalitis
Major criterion + ≥3 minor criteria	probable or confirmed encephalitis

Figure 2: International Encephalitis Consortium 2013 diagnostic criteria for encephalitis [11].

The patient's previously mentioned symptoms improved significantly. After completing the IV Ig treatment, his sensorium returned to normal, and he regained full orientation to time, place, and person. His speech was spontaneous, coherent, and appropriate in content. He was able to move independently and perform daily activities with minimal difficulty (mRS-2).

Discussion

The incidence of autoimmune encephalitis (AIE) globally has significantly increased over a short duration of time; from 0.4/100,000 people between 1995-2005 to about 1.2/100,000 people between 2006-2015 [12]. While these statistics could indicate absolute increase in the incidence of the disease, researchers do argue that this could be due to the advancement in the field of molecular biology and neurosciences which has led to identification of more and more types of autoantibodies [13,14]. Depending on the target antigen of these autoantibodies, AIE is broadly classified as intracellular or extracellular. The common target antigens and the features have been tabulated in (Table 4). Intracellular antigens include Hu, Ma2, and Yo. These encephalitides are strongly associated with malignancies and attributing to irreversible neuronal damage, the prognosis is poor despite immunomodulatory therapy. In contrast, the extracellular group comprises of cell-surface proteins, ion channels and receptors one of which is a voltage gated potassium channel of the neurexin group of proteins named contactin-associated protein-like 2 or CASPR2.

Autoantibody	M:F ratio	Clinical features	Tumor association
NMDAR	1:4	Neuropsychiatric manifestations, Seizures, Movement and Language disorders, Autonomic dysfunction, Central apnea, Coma	Ovarian teratoma
LG1	2:1	LE, Hyponatremia, classical Fasciobrachial dystonic seizures	Thymoma, lung, renal, and thyroid cancer
CASPR2	9:1	LE, Morvan syndrome, Peripheral nerve excitability.	Thymoma
GABA-a	1:1	LE, Seizures, Refractory status epilepticus	Thymoma
GABA-b	1.5:1	LE, Seizures	Small cell lung carcinoma
AMPA	1:2	LE, Confusion, Amnesia, Seizures, Psychiatric complaints	Thymus, lung, breast, and ovarian cancers
DPPX	1.6:1	Multifocal encephalitis, Amnesia, Delirium, Myoclonus, weight loss and diarrhea	GI lymphoma and CLL
Glycine	1:1	Stiff person spectrum syndrome, PERM, Encephalitis	Thymoma, B -cell lymphoma
MOG	1:1	Optic neuritis, Seizures, Encephalitis	not known
Neurexin	1:2	Prodromal fever, Weight loss, GI symptoms, Confusion, Seizures, Decreased level of consciousness	not known
IgLON	1:1	Sleep disorders, bulbar dysfunction, Gait abnormalities. HLADRB1*10:01/ HLADQB*05:01 alleles in 87%.	not known

Table 4: Summary of characteristic features of autoimmune encephalitides [8].

*LE: Limbic Encephalitis; GI: Gastrointestinal; PERM: Progressive Encephalitis with Rigidity and Myoclonus

Further it is vital to note that most cases of AIE associated with certain malignancies, which could be the triggers for widespread neuronal inflammation. Although cancers originating in the ovaries, lungs, pancreas, uterus, prostate and kidneys are strongly associated, the malignancy most commonly associated with AIE was seen to be thymoma [15,16]. Anti-CASPR2 however is not known to be associated commonly with malignancies and when it is, the most common malignancy is thymoma.

Further, most subtypes have been reported to have a strong male preponderance but the reason remains unknown at large [17]. Another frequent association seen in these patients is other autoimmune conditions as evidenced by positive tests for certain autoantibodies like thyroid peroxidase or antinuclear antibody [18,19]. The propensity to other autoimmune conditions may or may not be linked to AIE and may not indicate cross reacting antigens in the central nervous system. The evidence of this lies in a study done by Petit-Pedrol et al., who demonstrated that while the patients' serum and CSF contained autoantibodies to specific neuronal proteins, the CSF showed no trace of the other autoantibodies that were present in the serum [19]. With regards to our patient particularly, his autoimmunity screening showed no significant results.

With the incidence of AIE being about 1 in 100,000 the rarity of CASPR2 positive AIE is even higher. A study conducted in NIMHANS (National institute of mental health and neurosciences), Bangalore demonstrated that among the 1475 patients admitted and treated for encephalitis, 238 patients tested positive for one or more autoantibodies with only 16 of them testing positive for CASPR2 antibody. The clinico-demographic profile of those who tested positive for CASPR2 antibody was that of elder male presenting with

complaints consistent with limbic encephalitis, Morvan syndrome or peripheral nerve excitability [20]. Although studies suggest that the presentation of this entity can range from short term memory deficits to behavioural symptoms, psychiatric manifestations and seizures.

Our patient having a history of progressive decline in sensorium, difficulty in recognizing familiar faces and agitation was in favour of limbic encephalitis with the complaints of burning sensation in feet suggesting peripheral nerve excitability. Even with these pointers and in accordance with International Encephalitis Consortium 2013 diagnostic criteria (Figure 1) for encephalitis, a probable diagnosis of encephalitis was made, which was confirmed and established with CASPR2 positivity.

The first-line therapy for AIE consists of immunomodulation and resection of tumour if applicable, unlike in our patient. Immunomodulation includes intravenous corticosteroids, intravenous immunoglobulins, plasmapheresis or a combination of these 3 modalities. Since our patient was a long standing hypertensive, corticosteroids were withheld and was treated with intravenous immunoglobulins accordingly. Plasmapheresis is considered in patients with dysautonomia, refractory seizures or central apnea. Since our patient drastically improved, the necessity of second-line therapy was negated. In case of failure to improve with first line therapy, rituximab and/or cyclophosphamide dosed according to the patients' age and body weight is recommended [17].

One major highlight of this report is that while the globally established diagnostic criteria for a particular disease does aid in giving a definitive diagnosis, not satisfying the criteria might not always be a sufficient reason to rule out the diagnosis. Our patient satisfied the major criteria and 2 of the minor criteria (suggestive neuroimaging features and abnormal EEG) which can be interpreted as "possible encephalitis" but the presence of one more minor criterion could have changed the interpretation, namely "New onset of focal neurologic findings". Inability to perform a complete neurological examination in this patient due to non-cooperation and agitation cannot be ruled as an absence of new onset focal neurological deficit. The intention of the authors here is not on the lines of invalidating or questioning the well-researched and established criteria but is only to highlight that in certain situations, one may not be able to elicit the criteria for diagnosis of a particular condition, but the treating physician must still strongly have a suspicion of the same. Especially with time being of essence in cases of encephalitis, quick decision skills pertaining to diagnosis and treatment is fundamental in order to reduce the morbidities and mortality.

Conclusion

Although rare, it is imperative that one considers the possibility of AIE in a patient with no probable explanation of encephalopathy even with inconclusive investigations. AIE, albeit primary or secondary, must be promptly investigated and the management be adjudicated promptly in case of suspicion. A thorough compare and contrast of various forms of encephalitis is pivotal in preventing the analysis paralysis as well as mitigation of residual effects.

Bibliography

1. Patti L and Gupta M. "Change in mental status". Statpearls, treasure island (fl): statpearls publishing (2024).

2. Rummans TA., *et al*. "Delirium in elderly patients: evaluation and management". *Mayo Clinic Proceedings* 70 (1995): 989-998.

3. Huff JS., *et al*. "Emergency neurological life support: approach to the patient with coma". *Neurocritical Care* 17.1 (2012): s54-59.

4. Grover S and Kate N. "Assessment scales for delirium: a review". *World Journal of Psychiatry* 2 (2012): 58-70.

5. Simkins TJ., *et al*. "A clinical decision rule predicting outcomes of emergency department patients with altered mental status". *Journal of the American College of Emergency Physicians Open* 2 (2021): e12522.

6. Inouye SK. "Delirium in older persons". *The New England Journal of Medicine* 354 (2006): 1157-1165.

7. Hosker C and Ward D. "Hypoactive delirium". *BMJ* 357 (2017): j2047.

8. Gole S and Anand A. "Autoimmune encephalitis. Statpearls, treasure island (fl): statpearls publishing (2024).

9. Dutra LA., *et al*. "Autoimmune encephalitis: a review of diagnosis and treatment". *Arquivos de Neuro-Psiquiatria* 76 (2018): 41-49.

10. Saint-Martin M., *et al*. "Contactin-associated protein-like 2, a protein of the neurexin family involved in several human diseases". *European Journal of Neuroscience* 48 (2018): 1906-1923.

11. Venkatesan A., *et al*. "Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium". *Clin infect dis off publ infect* dis *soc am* 57 (2013): 1114-1128.

12. Dubey D., *et al*. "Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis". *Annals of Neurology* 83 (2018): 166-177.

13. Varley JA., *et al*. "Autoimmune encephalitis: recent clinical and biological advances". *Journal of Neurology* 270 (2023): 4118-4131.

14. Graus F., *et al*. "A clinical approach to diagnosis of autoimmune encephalitis". *The Lancet Neurology* 15 (2016): 391-404.

15. Leypoldt F., *et al*. "Autoimmune encephalopathies". *Annals of the New York Academy of Sciences* 1338 (2015): 94-114.

16. Bost C., *et al*. "Malignant tumors in autoimmune encephalitis with anti-nmda receptor antibodies". *Journal of Neurology* 265 (2018): 2190-200.

17. Titulaer MJ., *et al*. "Treatment and prognostic factors for long-term outcome in patients with anti-n-methyl-d-aspartate (nmda) receptor encephalitis: a cohort study". *Lancet Neurology* 12 (2013): 157-165.

18. Lai M., *et al*. "Ampa receptor antibodies in limbic encephalitis alter synaptic receptor location". *Annals of Neurology* 65 (2009): 424-434.

19. Petit-Pedrol M., *et al*. "Encephalitis with refractory seizures, status epilepticus, and antibodies to the gabaa receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies". *Lancet Neurology* 13 (2014): 276-286.

20. Shivaram S., *et al*. "Clinical profile and treatment response in patients with caspr2 antibody-associated neurological disease". *Annals of Indian Academy of Neurology* 24 (2021): 178.