CASE REPORT

A case of possible autoimmune encephalitis with complex neuropsychiatric presentation

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INTRODUCTION

Autoimmune encephalitis (AE) challenges diagnostic boundaries as it often presents with a myriad of symptoms that range from subtle cognitive impairments to overt psychiatric manifestations. This report aims to shed light on AE that first presented with depressive phenomenology in an elderly male wherein neurological assessment revealed preserved memory with occasional cognitive slowing, leading to a provisional diagnosis of Agitated Depressive Stupor. Upon discovering fluctuating levels of consciousness and focal clonic seizures, we describe the diagnostic journey, clinical course and subsequent therapeutic interventions in a steroid-responsive possible seronegative AE. As we delve into the complexities of this case study, we hope to contribute to the growing body of knowledge surrounding this enigmatic form of encephalitis whilst emphasising the importance of early recognition, accurate diagnosis and targeted management for improved patient outcomes. Through a comprehensive examination of this case report, we seek to enhance our understanding of the complexities surrounding AE, fostering awareness and considering future clinical approaches in the ever-evolving landscape of neuropsychiatry.

CASE PRESENTATION

An 86-year old White Caucasian male was reported to be feeling distressed and having episodes of 'disorientation' following difficulties with the use of his credit card while on a cruise ship from the Middle East to Australia. While initially expressing anxiousness without overt sadness, he later manifested with symptoms of agitation, pacing about and having sleep disturbances. There were no associated physical symptoms such as fever, vomiting or feeling imbalanced. There was no reported history of trauma to the head and there was no slurring or limb weakness. He was taken to a hospital in Bangkok and computed tomography (CT) brain imaging was unremarkable. He was subsequently allowed to return to the ship with the recommendation to rule out potential organicity if there was no clinical improvement. He unfortunately did not improve and was deemed unfit to continue his cruise journey and thus disembarked in Penang. On being admitted into a private specialist hospital, he was noted to exhibit reduced alertness (possibly following an earlier administration of a low-dose neuroleptic quetiapine for his agitation) but there were no fluctuating levels of consciousness. There was near complete psychomotor inhibition and impaired reaction to external stimuli by way of reduced responsiveness, but with consciousness retained and he would then return to the unresponsive state if undisturbed. Some grimacing with negativism was observed, as well as protective actions to prevent his hand from dropping on his face, but there was an absence of posturing, rigidity or waxy flexibility. There was no observation of any self-talking or suspicious behaviour and he instead exhibited a lack of mobility and speech.

There was no notable past history except for a recent shift towards a less talkative demeanour and increased fatiguability over two months prior to him being seen here and approximately a month after that, he exhibited an obsession with organising tasks in a meticulous and orderly manner. This behaviour escalated about eight days prior to admission when he was already on the cruise ship whilst demonstrating the similar preoccupations. There was no preceding history of memory loss or a decrease in his ability to execute activities of daily living (ADL). Premorbidly, he was described by his wife as a talkative and jovial person. He had retired as a banker years ago and there were no financial or family issues. They have two daughters. He was active in playing golf three times a week and was a social drinker. A thorough mental state examination could not be conducted at first contact due to his perceived stuporose state.

During his admission, he began to exhibit brief periods of increased verbalisation followed by a return to his persistently negative and depressed demeanour. A sense of impending doom emerged, accompanied by heightened agitation, especially in response to phone calls from his concerned daughters. Although he denied harbouring negative thoughts, he displayed restlessness and continuous murmuring. He refused feed during the initial part of the admission and his physical condition deteriorated, leading to unsteadiness and a notable decrease in confidence to mobilise. Initially, his fears displayed both nihilistic and paranoid elements. While the nihilistic thoughts diminished over time, the paranoid ideation persisted. Surprisingly, he attributed his condition at the time to his wife. His daughter later confirmed that he had shown a loss of interest in activities he once enjoyed, dating back as far as a year before the episode. No manic symptoms were reported.

Neurological assessment revealed relatively normal memory function although his responses were noticeably slowed.

This article was accepted: 12 August 2025
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There were no signs of neck stiffness or features suggestive of extrapyramidal system involvement. Muscle strength was generally good although occasional twitching over certain muscles was suggestive of myokymia. Deep tendon reflexes were within the normal range and no nuchal pain was elicited during neck flexion. Tests for Babinski and Hoffmann reflexes were negative and his electroencephalogram (EEG) was reported as normal. A provisional diagnosis of Agitated Depression with Stupor was considered. During the initial four days of admission, antidepressant therapy with vortioxetine was initiated and his level of consciousness appeared to remain normal. However, on the fifth day, he began experiencing fluctuations in awareness and consciousness. He was found wandering around the ward and unable to recall his actions or behaviour afterwards. Around the same time, he experienced several episodes of focal seizures, characterised predominantly by the semiology of clonic seizures involving both lower limbs in the form of characteristic rhythmic twitching that lasted only a few seconds.

Given the progression of his symptoms, an antinuclear antibody (ANA) test for autoimmune encephalitis (AE) was conducted. The results were positive for ANA via immunofluorescence assay (IFA) and indirect immunofluorescence assay (IIFA), with anti-titin antibodies at borderline levels - all other tested antibodies were negative. AE, in particular anti-leucine-rich-glioma-inactivated 1 (LGI1) antibody disease, was considered a potential diagnosis and to err on the side of caution, he was then transferred to a neurological facility after interdepartmental liaison discussions.

Magnetic resonance imaging (MRI) brain revealed T2-weighted and FLAIR hyperintensity in the bilateral anterior cingulate gyrus. The EEG was normal. A lumbar puncture (LP) showed elevated protein levels (559.9 mg/L) without any white blood cells, with normal glucose levels, and no organisms identified. Levels of Vitamin B12, folate, electrolytes, thyroid function and anti-thyroglobulin antibodies were all within normal limits. Tumour markers, including prostate specific antigen (PSA), were also normal. Paraneoplastic screening was negative except for a borderline positive result for anti-titin antibodies (anti-Ri, -Yo, -Hu, -Recoverin, -SOX1, -AMPAR 1&2, -CASPR 2, LGI1, -DPPX 6, -GABA-B and -NMDAR). A CT scan of the thorax, abdomen and pelvis showed no evidence of malignancy.

Given his subacute symptom onset of less than three months, new neuropsychiatric (agitation, insomnia, reduced alertness, psychomotor inhibition, paranoia and later confusion) and neurological (delayed development of focal clonic seizures) findings along with MRI findings of encephalitis (hyperintensities in anterior cingulate gyri bilaterally) and a reasonable exclusion of alternative causes, a working diagnosis of possible AE was made and a treatment protocol mapped out. Probable or definite AE could not be considered due to the absence of epileptic or slow-wave activity on EEG, cerebrospinal fluid (CSF) pleocytosis and evidence of typical limbic encephalitis on MRI, namely in the form of medial temporal involvement.

He was initially treated with intravenous ceftriaxone 2g twice daily and intravenous acyclovir 500mg every 8 hours for one week, along with intravenous methylprednisolone 500mg twice daily for five days. He responded well to the low dose of the intravenous steroid, becoming noticeably more cheerful and eventually regaining full consciousness and cognitive functions. His mood returned to normal state and his seizures were well-controlled with levetiracetam, titrated up to 1g twice daily. He was eventually discharged after a total admission period of 29 days. A follow-up call to his daughter eight months later reported that he was doing well - independent in all ADL and ambulating with the aid of a Zimmer frame. Three months after that, he was said to have grown stronger although he had not yet resumed playing golf. At the most recent communication, three years after the initial episode, he was reported to be doing extremely well and had returned to his baseline physical condition. There were no neuropsychiatric sequelae and he had coped well with the COVID-19 pandemic, although he remained understandably cautious about socialising. He was later diagnosed with malignant melanoma following the pandemic - he accepted the diagnosis, underwent treatment and eventually made a full recovery.

DISCUSSION

AE presents a formidable diagnostic challenge, particularly when psychiatric-like symptoms dominate the clinical picture and paint a scenario suggestive of a mood disorder with accompanying disturbances in volition and/or movement abnormalities. This case of a male in his mid-80s highlights the critical importance of being vigilant in clinical practice and adopting a multidisciplinary approach to diagnose AE promptly, especially in its early stages. The broad spectrum of clinical presentations associated with AE, spanning from psychiatric symptoms to cognitive and neurological impairments, necessitates a comprehensive and nuanced diagnostic approach.[2] The initial psychiatric presentation of AE often leads to misdiagnosis and treatment delay, as observed in this patient who exhibited symptoms of anxiety, agitation and depression without overt neurological signs.[3]

Early and comprehensive autoantibody testing plays a crucial role in the diagnostic process for AE. In this particular patient, detecting positive ANA and borderline anti-titin antibodies heightened our suspicion of possible AE.[4] Moreover, specific autoantibodies such as anti-LGI1 play a pivotal role in confirming the diagnosis, facilitating the transition from a presumed primary psychiatric disorder to a diagnosis of AE - however, this did not seem to be the case in our patient. Diagnostic tools and neuroimaging, despite being indispensable, often need to be more conclusive in the early stages of AE. Advanced imaging modalities and EEG can furnish supportive evidence for the diagnosis, albeit with limitations.[3] In our case study, initial EEG and imaging studies yielded non-specific results, complicating the diagnostic trajectory. Nonetheless, the persistence of symptoms despite standard psychiatric interventions warranted further investigation, ultimately culminating in the diagnosis of possible AE.

The brain imaging findings in our patient favours AE, although MRI features of autoimmune encephalitis can overlap significantly with viral encephalitis. However, certain features can help differentiate the two.[5] In autoimmune encephalitis, the location of the lesions are bilateral and symmetrical predominantly in the limbic system commonly mesial temporal lobe including the hippocampus, amygdala, hypothalamus, cingulate gyrus and limbic cortex with rare or minimal diffusion restriction or enhancement. In contrast, the lesions in viral encephalitis are unilateral single lobe, asymmetrical lesions involving the limbic system. Lobar involvement in the inferior frontal significantly favours viral or infectious encephalitis.[6,7]

We favour a diagnosis of AE over viral encephalitis in this patient, although there are overlapping clinical features including seizures and altered cognition. The patient did not exhibit fever or vomiting, which are predominant clinical features in infectious or viral encephalitis.[7] In contrast, psychosis and seizures are more commonly associated with autoimmune encephalitis (AE) compared to viral encephalitis, aligning with this patient's presentation. Additionally, the presence of myokymia, a manifestation linked to peripheral nerve hyperexcitability has been reported in AE but not in viral encephalitis.[3] MRI of the brain demonstrated symmetrical bilateral anterior cingulate gyrus hyperintensities on T2/FLAIR sequences without enhancement or diffusion restriction, findings more suggestive of AE than viral encephalitis. Notably, leptomeningeal enhancement, observed in up to 38.5% of infectious encephalitis cases, was absent.[7] CSF cultures did not reveal any microorganisms, although viral PCR testing was not performed. Based on the diagnostic criteria proposed by Graus et al. (2016), the patient meets the definition of possible autoimmune encephalitis, fulfilling the criteria of subacute onset (less than three months), new focal central nervous system findings (lower limb clonic seizures), MRI evidence of encephalitis (bilateral anterior cingulate gyrus hyperintensities albeit not in the medial temporal lobes required for a definitive AE diagnosis), and reasonable exclusion of alternative causes.[1]

The limitations of this case report include the absence of CSF samples for Real-Time quantitative Polymerase Chain Reaction (RT-qPCR) viral panel testing and viral culture. In addition, the available autoimmune encephalitis panel was limited and CSF studies for oligoclonal bands and IgG index were not performed. These constraints preclude a definitive diagnosis, allowing for only a classification of 'possible' autoimmune encephalitis.

A multidisciplinary approach, encompassing collaboration among neurologists, psychiatrists and immunologists, emerges as a paramount path in navigating the diagnostic conundrum posed by AE.[8] Early integration of these specialities facilitates a comprehensive evaluation and expedites treatment initiation, thereby averting the harmful consequences of diagnostic delay. Prompt initiation of immunotherapy, including corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis, proves to be the cornerstone in the treatment paradigm of AE.[9] Early intervention facilitates symptom resolution and portends favourable long-term outcomes, underscoring the imperative importance of expeditious diagnosis and treatment initiation.

CONCLUSION

This case study epitomises the critical importance of considering AE it in the differential diagnosis of new-onset psychiatric disorders. Undoubtedly, it can prove challenging to routinely screen those without any prior psychiatric history but since most functional illnesses begin before the ages of 45-50 years, a high index of suspicion is recommended if acute and atypical psychiatric presentations occur in those older than that range and would thereby warrant a full organic work-up. By amalgamating insights from contemporary literature and embracing a comprehensive multidisciplinary approach, clinicians can enhance diagnostic accuracy, expedite treatment initiation and thereby optimise patient outcomes.

DECLARATION

The authors certify that they have obtained the patient's and families' consent. The patient understands that neither his name nor initials will be published and due efforts will be made to protect his identity; however, complete anonymity cannot be guaranteed.

REFERENCES

1. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Celluci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurology 2016; 15(4): 391-404.
2. Patel A, Meng Y, Najjar A, Lado F, Najjar S. Autoimmune encephalitis: A physician's guide to the clinical spectrum, diagnosis and management. Brain Sciences 2022; 12(9): 1130.
3. Uy CE, Binks S, Irani SR. Autoimmune encephalitis: clinical spectrum and management. Practical Neurology 2021; 21(5): 412-23.
4. Wingfield T, McHugh C, Vas A, Richardson A, Wilkins E, Bonington A, et al. Autoimmune encephalitis: a case series and comprehensive review of the literature. QJM: Monthly Journal of the Association of Physicians 2011; 104(11): 921-31.
5. Sanvito F, Pichiecchio A, Paoletti M, Rebella G, Resaz M, Benedetti L, Massa F, Morbelli S, Caverzasi E, Asteggiano C, Businaro P, Masciocchi S, Castellan L, Franciotta D, Gastaldi M, Roccatagliata L. Autoimmune encephalitis: what the radiologist needs to know. Neuroradiology. 2024; 66(5): 653-75.
6. Tan Y, Liu M, He L. Clinical and MRI differential analysis of autoimmune encephalitis and viral encephalitis. J Taibah Univ Med Sci. 2022 Oct 11; 18(2): 271-8.
7. Vinoshini Nair Sukumaran, Khairunnisa Rashid, Suhailah Abdullah, Kartini Rahmat, Khairul Azmi Abd Kadir, Norlisah Ramli. A comparison of infectious and autoimmune meningoencephalitis: Clinical presentation, biochemical markers and MRI findings. Neurology Asia 2024; 29(3): 795-804.
8. Liu Y, Tang X. Depressive syndromes in autoimmune disorders of the nervous system: prevalence, etiology and influence. Frontiers in Psychiatry 2018; 9: 451.
9. Harris L, Griem J, Gummery A, Marsh L, Defres S, Bhoja, M, et al. Neuropsychological and psychiatric outcomes in encephalitis: A multi-centre case-control study. PloS One 2020; 15(3): e0230436.