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Letter to the Editor: New Observation

Relapsing GABA(A) Receptor Encephalitis After Stem Cell Transplant for Acute Myeloid Leukaemia

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Auto-antibodies against the γ-aminobutyric acid A receptor [GABA(A)R] disrupt inhibitory synaptic transmission, resulting in a rare encephalitic syndrome characterised by seizures, cognitive impairment, psychiatric symptoms, and movement disorders.[1,2]

The pathomechanisms of anti-GABA(A)R encephalitis remain to be elucidated. However, emerging reports on its associations with haematological malignancies and autologous haematopoietic stem cell transplant (HSCT) implicate immune dysregulation as a potential factor.[3,4]

We describe a case of relapsing anti-GABA(A)R encephalitis in a patient who underwent allogenic HSCT for acute myeloid leukaemia (AML). Encephalitic events coincided with COVID-19 exposure through vaccination and infection.

In June 2021, a fifty-six-year-old male presented with a one-week history of headache, altered behaviour, forgetfulness, and apraxia. He was diagnosed with AML in 2018 and underwent an allogenic HSCT in 2020, after which he was maintained on tacrolimus as prophylaxis against transplant rejection. There was no recent infective event, but he received his first COVID-19 (mRNA-based) vaccine dose a week before symptom onset. Brain MRI revealed multiple cortical and subcortical T2/FLAIR hyperintensities over bilateral frontal and temporal regions without diffusion restriction or contrast enhancement (Fig. 1: Panel 1).

Electroencephalogram demonstrated generalised background slowing. Standard blood investigations were unremarkable, and COVID-19 tests were negative. Serological testing for anti-myelin oligodendrocyte (MOG), anti-aquaporin 4, and paraneoplastic antibodies (Hu; Yo; Ri; Ma2; Amphiphysin; CV2) were negative. CSF analysis revealed an acellular picture without malignant cells, protein of 0.39 g/L, and glucose ratio of 0.6. Gram stain, cultures, and workup for tuberculosis and cryptococcus were unrevealing. Viral PCR analysis for herpes simplex viruses 1&2, human herpesviruses 6&7, human parvovirus B19, cytomegalovirus, enterovirus, adenovirus, human parechovirus, along with varicella-zoster, mumps, Epstein-Barr, John Cunningham, and Burkitt viruses were negative. CSF autoimmune encephalitis (AIE) panel test [NMDAR; LGI1; CASPR2; AMPAR-1&2; DPPX; GABA(B)R] was negative. Serum and CSF oligoclonal bands were detected.

He was treated for acute disseminated encephalomyelitis with intravenous methylprednisolone 1g o.d. for three days and intravenous immunoglobulin (IVIG) at 2g/kg over five days. He attained complete recovery and was discharged with an oral prednisolone taper (over two months). His tacrolimus was withheld. Follow-up MRI four weeks from symptom onset showed diminishing lesions (Fig. 1: Panel 2). This episode was previously included in a case series of patients with central nervous system demyelination following COVID-19 vaccination.[5]

Seven weeks later, while still on prednisolone, he developed severe COVID-19 requiring eight weeks of hospitalisation and treatment with tocilizumab and dexamethasone. He was discharged with a prednisolone taper (over two months) for post-COVID-19 organising pneumonia. Upon assessment in November 2021, after completion of steroids, he was completely well.

In December 2021, he experienced palpitations, anxiety, along with right facial twitching and foot jerking. Brain MRI showed new T2/FLAIR hyperintensities over frontal and occipital regions which appeared less confluent relative to the index event (Fig. 1: Panel 3). Electroencephalogram revealed slow background, bilateral independent periodic lateralised discharges, and seizures. He developed epilepsia partialis continua and eventually super refractory generalised status epilepticus. All investigations performed during index admission were repeated but were unrevealing. Additional testing of CSF for viral PCR (measles; rubella; COVID-19), anti-MOG, and anti-aquaporin 4 antibodies were negative. Flow cytometry and bone marrow aspirate and trephine biopsy were unrevealing. Full-body contrasted CT scans demonstrated no tumours.

Despite clinical and radiological features suggestive of anti-GABA(A)R encephalitis, confirmation of GABA(A)R auto-antibodies was not possible as this was not included in our AIE panel and unavailable for specific testing within our local setting. Nevertheless, he received full courses of intravenous methylprednisolone, plasma exchange, and IVIG in succession, but derived no clinical benefit. Rituximab could not be administered due to recurrent severe sepsis, which he ultimately succumbed to. Figure 2 summarises his clinical course.

Notably, a follow-up brain MRI one month from admission revealed morphologically distinct, confluent, T2/FLAIR hyperintense cortical lesions predominantly over the bilateral frontal, parietal, and temporal lobes, with no diffusion restriction or contrast enhancement. (Fig. 1: Panel 4). We considered a brain

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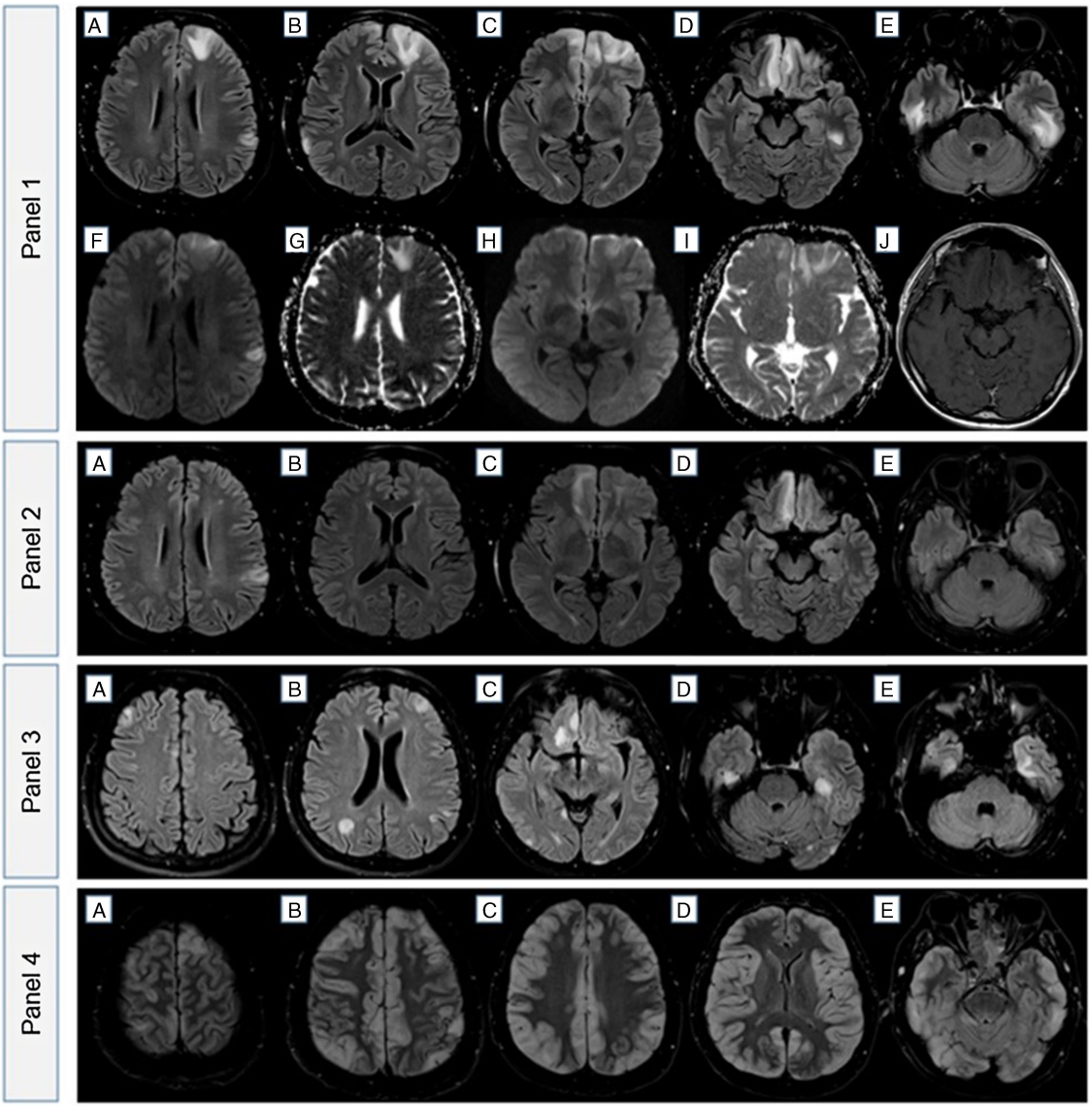

Figure 1: Brain MRI findings of our patient taken at four separate intervals. n.b.: Panel 1: MRI brain at the onset of the index event. (a – e): Axial T2/FLAIR images demonstrating multiple cortical and subcortical lesions involving the bilateral frontal and temporal lobes. Lesions appear confluent with poorly demarcated borders. (f – g): Axial DWI and ADC images demonstrating the absence of diffusion restriction corresponding to lesions in (a). (h – i): Axial DWI and ADC images demonstrating the absence of diffusion restriction corresponding to lesions in (c). (j): Axial T1 + gadolinium images demonstrating the lack of contrast enhancement. Panel 2: Follow-up MRI brain 1 month after the onset of the event. (a – e): Axial T2/FLAIR images showing that lesions previously seen in Panel 1 are diminishing. Panel 3: MRI brain at the onset of relapse. (a – e): Axial T2/FLAIR images demonstrating multiple new cortical and subcortical lesions involving the bilateral frontal, temporal, and occipital lobes. Lesion borders are better defined and more circumscribed relative to lesions in Panel 1. Panel 4: MRI brain performed one month after the onset of relapse. (a – e): Axial T2/FLAIR images demonstrating confluent lesions.

biopsy for further interrogation then but surgery was deemed clinically unsuitable for him. The family later withdrew their consent for an autopsy upon his demise.

Posthumously, stored serum and CSF samples (from second episode) were tested for GABA(A)R IgG auto-antibodies at the Clinical Immunological Laboratory Prof. Stöcker, Groß Grönau. Indirect immunofluorescence assay revealed strong positive results (titres 1:320) for both serum and CSF, demonstrating reactivity with fixed HEK293T cells transfected with plasmids encoding alpha-1 and beta-3 subunits of GABA(A)R.

This case emphasises that relapses are possible in anti-GABA(A)R encephalitis and that symptoms, lesion characteristics, and response to treatment may vary between episodes.

The differential MRI findings during his relapse pose a diagnostic challenge. Possible explanations we considered, like hypoxic ischaemic encephalopathy (HIE), prolonged-seizure changes, and metabolic insults, lacked convincing evidence. No documented evidence of hypoxic events or typical basal ganglia changes associated with HIE were identified and achievement of satisfactory burst suppression within 72 hours suggests that prolonged seizures may not be the primary cause. One potential consideration is the contribution of anti-GABA(A)R encephalitis itself (and its progression) to this intriguing evolution. A recent case series revealed that patients with anti-GABA(A)R encephalitis may display extensive confluent lesions, deviating from the usual pattern of multiple spotted cortical and

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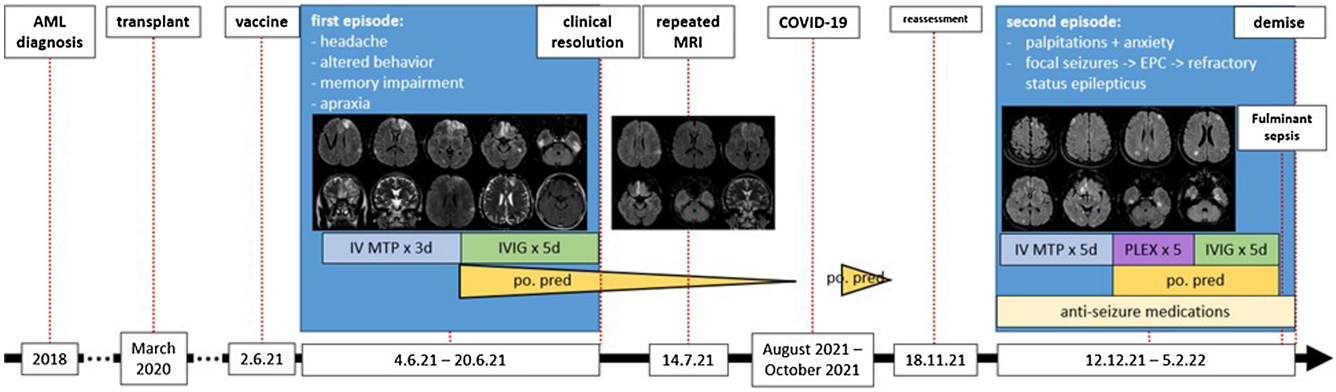

Figure 2: Timeline of clinical events, main imaging findings, and treatment rendered. n.b.: IV MTP: intravenous methylprednisolone, IVIG: intravenous immunoglobulin, po. pred: oral prednisolone, PLEX: plasma exchange therapy, x 3d: three days, x 5d: five days. Image of an isosceles triangle depicts a tapering dose of medication with doses reducing in the direction of the narrowest edge.

subcortical lesions. These are associated with poorer prognosis.[6] It is possible that imaging features of this disease might evolve within a single episode, alongside the aforementioned inter-episode variability.

Like other AIE, viral prodromes and vaccinations have been associated with anti-GABA(A)R encephalitis. These include cases following herpetic viral encephalitis in children, and one case after yellow fever vaccination.[2,7] Our patient's index event occurred shortly after COVID-19 vaccination, and the second event followed the discontinuation of prednisolone for COVID-19 pneumonia. Although conclusive evidence of causality is lacking, the close temporal correlation between his encephalitic events and vaccination/COVID-19 raises interest and would benefit from further investigation in larger patient cohorts.

Recent reports have described anti-GABA(A)R encephalitis in patients who underwent autologous HSCT for multiple myeloma, expanding the spectrum of post-transplant autoimmune complications associated with immune dysregulation.[3] Our case further develops this concept by suggesting that an altered immunological milieu, such as post-HSCT status, not only predisposes individuals to anti-GABA(A)R encephalitis but may also increase the risk of relapses. It is plausible that the history of HSCT and discontinuation of immunotherapy post-COVID-19 might have lowered the threshold for his relapse.

In managing this patient, we faced significant limitations with our panels' restricted inclusion of auto-antibodies, none of which included anti-GABA(A)R. Limited outsourcing options due to logistical and financial constraints further complicated the situation. These likely contributed to the delayed diagnosis. When working up for AIE in general and including its rarer forms, comprehensive testing is crucial and should ideally incorporate tissue-based Indirect Immunofluorescence followed by confirmatory cell-based assays for improved sensitivity and specificity of testing.

Reference labs must expand their services, making comprehensive testing more accessible, especially to under-represented populations. This will ensure equitable access to accurate diagnoses and appropriate management worldwide while improving the current skewed understanding of such diseases based solely on patients from developed countries. Meanwhile, clinicians in similar resource-limited settings should familiarise themselves with clinic-radiological features of AIE and strongly advocate for comprehensive neural antibody testing in patients with highly suspicious clinical presentations.

The timing of second-line immunotherapy initiation is crucial and delays while monitoring for response to first-line therapies may be detrimental in aggressive cases like ours. Given the high risk of nosocomial infections in these immunosuppressed patients who typically require prolonged ventilation and hospitalisation, prompt escalation of therapy is vital to seize the treatment window. Additionally, we advocate for the consideration of longer-term immunosuppression as secondary prophylaxis in patients with persistent immune dysregulation (i.e., post-transplant) or those who have experienced relapses. Longitudinal studies investigating long-term outcomes, relapse rates, and factors contributing to relapses are required to substantiate this recommendation.

In conclusion, this important association between anti-GABA(A)R encephalitis, AML, and allogenic HSCT underscores the role of immune dysregulation as a pathomechanistic factor. As COVID-19 transitions into an endemic state, it is imperative to further investigate the potential relationship between events and exposure to the virus. Our case highlights the importance of considering anti-GABA(A)R encephalitis in the differential diagnosis of encephalopathy post-HSCT, the significance of employing more comprehensive AIE testing, and the need for early initiation of second-line immunotherapy in aggressive cases. For a select group of patients, longer-term immunotherapy may be warranted as secondary prophylaxis.

Competing interests. None.

Ethics statement. The patient and his next of kin provided informed consent for the use of de-identified data for publication purposes. This study was approved by the National Medical Research Register of Malaysia (NMRR ID-23-00378-JQH) and was granted exemption from requiring additional ethics approval as per local protocol.

Statement of authorship. JCEO is the main author of this manuscript. PP, SL, SAMO, KLK, and YKC contributed equally to the management of the patient and drafting of the manuscript.

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