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Severe Relapsing Autoimmune Encephalitis with $GABA_A$ Receptor, Titin, and AchR Antibodies in a Patient with Thymoma: A Case Report

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Keywords
Autoimmune encephalitis · $GABA_A$ receptor antibodies · Thymoma · Case report

Abstract
Introduction: We report a challenging case of autoimmune encephalitis in a patient with a thymoma harboring titin and acetylcholine receptor antibodies, who experienced multiple relapses despite thymectomy and aggressive first-line immunotherapy, and for whom $GABA_A$ receptor antibodies were ultimately identified. ***Case Presentation:*** This 40-year-old man presented with headaches, weakness, diplopia, hearing loss, and seizures progressing to status epilepticus. Brain MRI showed multifocal cortical and subcortical T2/fluid attenuated inversion recovery hyperintense lesions without enhancement. Initial neural antibody testing identified only acetylcholine receptor and titin antibodies. He presented multiple severe relapses despite complete thymoma resection, intravenous methylprednisolone with immunoglobulins or plasmapheresis, and mycophenolate mofetil. Second-line immunotherapy with rituximab was successful to alleviate symptoms and normalize the EEG and MRI after identification

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of anti-GABA$_A$ receptor antibodies on more comprehensive neural antibody testing for autoimmune encephalitis. ***Conclusion:*** This case demonstrates the complexity and importance of identifying pathogenic antibodies and selecting 2nd line treatment accordingly in patients with autoimmune encephalitis when multiple antibodies coexist. Despite tumor resection, aggressive immunotherapy may be needed to prevent further deterioration in anti-GABA$_A$ receptor encephalitis.

Introduction

Timely diagnosis and management of rare autoimmune encephalitis (AE) remain challenging. GABA$_A$ receptor (GABA$_A$R)-IgG represent an uncommon cause of AE with refractory seizures and are not commonly tested in neural antibody panels for AE [1–3]. In patients with thymoma, simultaneous presence of different autoantibodies can act as confounding factors [4, 5]. We report a case of AE in a patient with thymoma who experienced severe relapses despite immunotherapy and complete tumor removal and had only serum anti-acetylcholine receptor (AChR) and serum and CSF anti-titin identified on initial neural antibody testing. More comprehensive neural antibody testing for AE identified anti-GABA$_A$R, prompting aggressive immunosuppression with addition of anti-CD20 agent for surface antigen-directed antibodies, resulting in clinical improvement.

Case Presentation

A previously healthy 40-year-old man of Algerian descent experiencing worsening headaches over 6–8 weeks followed by right eyelid twitching and mild confusion for 48 h was hospitalized abroad for generalized tonic-clonic status epilepticus (Fig. 1). His brain MRI showed multifocal cortical and subcortical T2/fluid attenuated inversion recovery (FLAIR) hyperintense lesions without enhancement. CSF cell count and biochemistry were unremarkable. A diagnosis of acute disseminated encephalomyelitis was made, and he was successfully treated with levetiracetam, intravenous methylprednisolone (IVMP), and intravenous immunoglobulin (IVIG). Three days following discharge, he was re-hospitalized for generalized tonic-clonic seizures/status epilepticus, severe generalized weakness, diplopia, and sudden bilateral conductive hearing loss, showing good response to lacosamide, IVMP, intra-aural steroids (transtympanic tubes with local administration of methylprednisolone 40 mg/mL twice daily for 5 days) and IVIG. A CT-scan revealed a mediastinal mass. Serum AChR antibodies (Abs) were detected at high titers, suggesting myasthenia gravis (MG) in the context of weakness in the upper and lower limbs and diplopia but no neurophysiological study was done. Complete resection of a large (32 × 17 × 8 cm) thymoma type AB was performed a month later. Seizures and neurological deficits subsided and the patient came back to Canada.

In the next month, he experienced progressive gait imbalance and memory disturbances. Brain MRI was stable (Fig. 2). He was admitted 3 weeks later to a local hospital with seizures, mild weakness, and confusion. EEG, whole-body fluorodeoxyglucose-positron emission tomography, cerebral CT-angiogram and spinal MRI were unremarkable, but brain MRI showed marked deterioration (Fig. 2). CSF was again normal including absence of oligoclonal bands, and a comprehensive panel for autoimmune/paraneoplastic Abs was ordered. He was treated

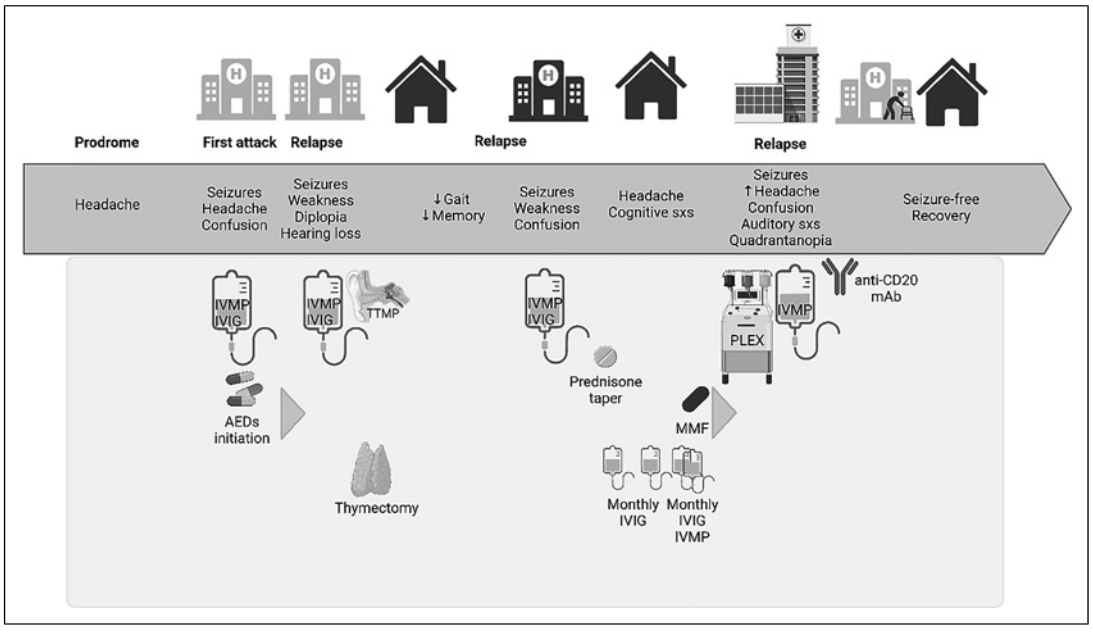

Fig. 1. Clinical timeline (created with BioRender.com). Arrow represents timeline of main clinical symptoms over 12 months. Interventions/treatments are represented below the arrow. AEDs, anti-epileptic drugs; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; mAb, monoclonal antibody; PLEX, plasma exchange; sxs, symptoms; TTMP, transtympanic methylprednisolone.

with levetiracetam, IVMP 1 g/day for 5 days followed by oral prednisone tapered over 6 weeks, and IVIG 1 g/kg monthly. Following clinical and radiological improvement, he was discharged home.

He was evaluated at our center 8 weeks later. The patient reported persisting headaches and memory difficulties but no recurrence of seizures. Mild cognitive slowing, short-term memory impairment, and difficulty switching between languages were observed. Neurological exam was normal except for equivocal plantar response, mild rapid alternative movement impairment and slow gait. Results from CSF AE and paraneoplastic Abs panel only revealed positive anti-titin. Serum and CSF anti-MOG and anti-AQP4-IgG were negative. A diagnosis of AE in the context of anti-titin was suggested and pulse IVMP 1 g/day for 3 days was added to monthly IVIG. A repeat brain MRI 2 weeks later (Fig. 2) showed new cortical lesions but regression of one lesion. EEG was normal and neurological exam stable. Mycophenolate mofetil (MMF) was added and titrated over 3 weeks.

Two weeks later, the patient was hospitalized at our center for worsening headaches and seizures. He showed deterioration of memory and language, auditory hallucinations, apraxia, and left superior quadrantanopia. Brain MRI showed progression of multiple lesions with improvement of one lesion (Fig. 2). EEG revealed right frontal focal status epilepticus. CSF showed no abnormality and extensive infectious studies were negative. A whole-body fluorodeoxyglucose-positron emission tomography scan, testicular ultrasound, and chest CT did not reveal any tumor or residual thymoma. Phenytoin and lacosamide were added. IVMP and plasma exchange were repeated for a total of 10 days over the next 2 weeks. Oral prednisone was started after IVMP, and mycophenolate mofetil increased to 1 g bid. Clinical improvement was observed with reduction of seizures, but moderate cognitive deficits remained. Follow-up MRI showed improvement of some lesions but evolution of others (Fig. 2).

Based on the MRI and clinical presentation, anti-GABA$_A$R-associated AE was suspected, an antibody not screened for by the initial extensive neural antibody testing performed.

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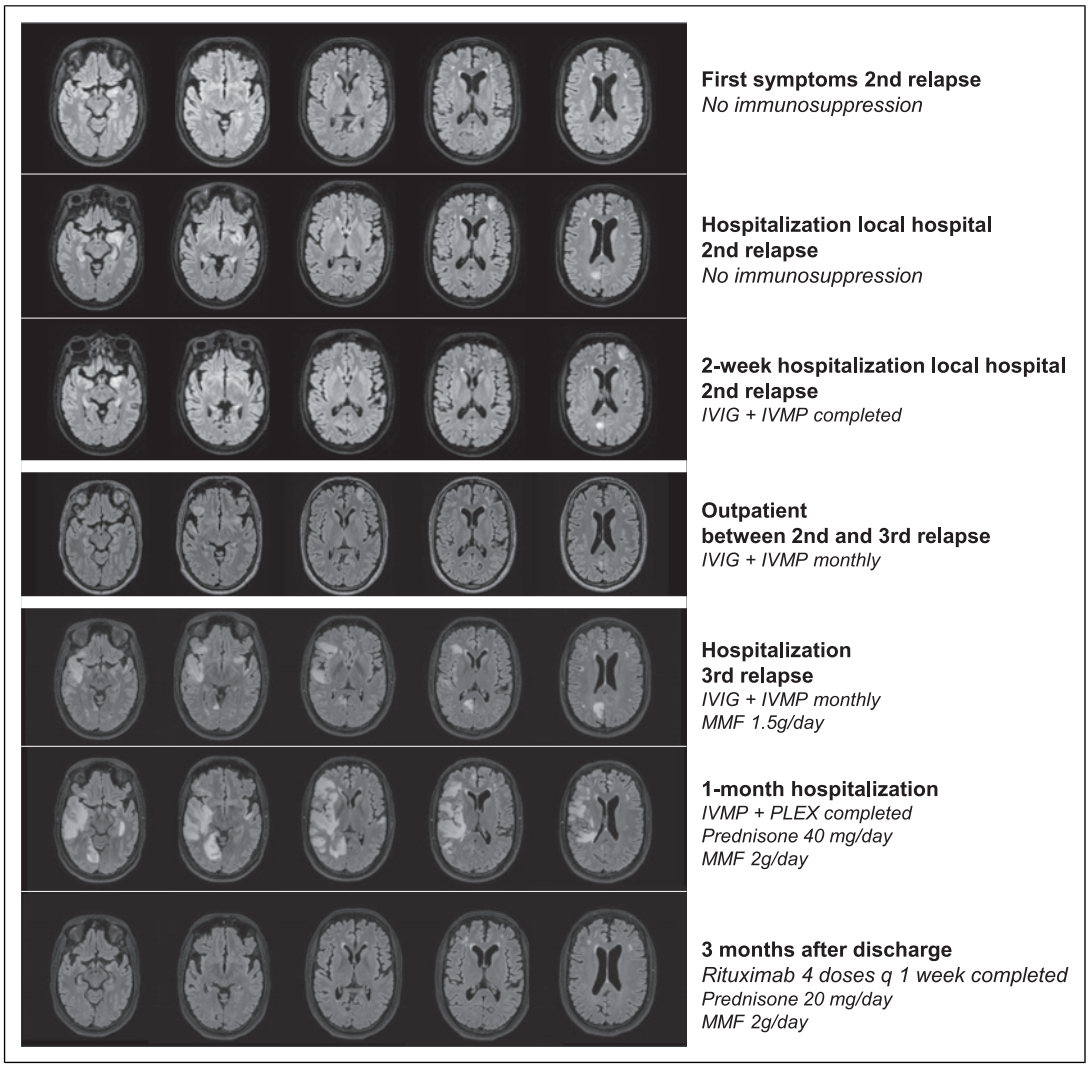

Fig. 2. MRI evolution (2nd and 3rd relapse) in relation to treatment. Axial FLAIR sequences demonstrating the evolution over 8 months in relation to current therapeutic regimen. IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; MMF, mycophenolate mofetil.

Serum AE antibody testing at London Health Sciences Centre was remarkable for equivocal staining on mouse brain tissue indirect immunofluorescence (TIIF), for which submission of CSF for testing was recommended. Using CSF, TIIF staining compatible with anti-GABA$_A$R was observed, and confirmatory serum and CSF testing for anti-GABA$_A$R by EUROIMMUN fixed cell-based assay (CBA) was positive (Fig. 3). Rituximab 375 mg/m^2/week for 4 weeks was initiated. At 1-month and 3-month follow-up the patient demonstrated improvement of memory and language, as well as of left superior visual field at 3 month, and reported no recurrence of seizures or headaches, while MRI showed improvement and then near-complete resolution of lesions (Fig. 2). At 1 year, the patient showed no recurrence and no adverse event on rituximab, while formal neuropsychological evaluation revealed marked improvement with only mild impairment of lexical access, visual memory and short-term memory remaining.

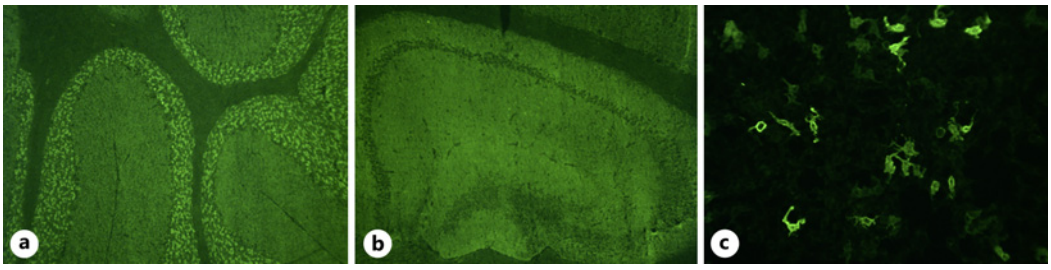

Fig. 3. Positivity for anti-GABA$_A$R by mouse brain TIIF and CBA in our patient. Mouse brain tissue indirect immunofluorescence (TIIF) shows staining of (**a**) the cerebellum and (**b**) hippocampus compatible with anti-GABAAR. **c** Confirmatory positivity for anti-GABAAR by EUROIMMUN fixed cell-based assay (CBA).

Discussion

Anti-GABA$_A$R AE is an uncommon entity, and relapsing cases are exceedingly rare with only five cases reported [3]. GABA$_A$R Abs structurally block the GABA$_A$R and cause hyperexcitability [6, 7]. As such, anti-GABA$_A$R AE manifests with rapidly progressive encephalopathy and seizures, often with status epilepticus as observed in our patient [2, 4, 8]. Prodromal headache and hearing loss, prominent early symptoms in our case, are less common but reported [2, 4, 8, 9]. Characteristic MRI features are multifocal cortical-subcortical FLAIR hyperintense lesions that can mimic acute disseminated encephalomyelitis, and a spotted or patchy pattern similar to our case, as opposed to a confluent bilateral multifocal pattern, is associated with a better prognosis [8]. Standard CSF studies are usually normal in adults [2]. GABA$_A$R Abs can be associated with other Abs in 36% of patients and/or with tumors in 28% [3]. Of those patients, 64% have thymoma [3], as did our patient.

Thymoma is commonly associated with autoimmune diseases. Neurological presentations encompass MG, neuromyotonia, neuromyelitis optica, myositis, and AE. GABA$_A$R Abs represented 10% of thymoma-associated AE in a case series and in another over half of cases with multifocal T2/FLAIR hyperintense lesions [4, 5]. Concomitant detection of other autoantibodies is frequent in thymoma-associated AE, and clinical MG is reported in around 25% [4, 5] but is not correlated with a specific neuronal antibody [4]. Of note, MG manifestations usually precede thymoma-associated AE [4, 10] but can develop after resolution of encephalitis [11] and in the absence of thymoma in the context of GABA$_A$R AE [2]. Our case is therefore typical for thymoma-associated and anti-GABA$_A$R AE, except for the multiple severe relapses after IVMP, IVIGs, and thymectomy. Interestingly, in our patient symptoms suggestive of MG did not recur after thymectomy but AE relapses became more severe. Titin Abs are common in thymoma-associated MG and are associated with more frequent severe relapses [12]. Whether the presence and persistence of anti-titin after thymectomy reflects sustained autoimmune processes that could influence prognosis of AE is unknown.

In a recent study of 64 thymoma-associated AE cases, 95% received first-line therapy, and only 15% required second-line therapy [5]. For GABA$_A$R Abs AE, 23/42 patients received only first-line immunotherapy, of which 31% entirely recovered, while 13 received second-line therapy, of which 70% completely recovered [3]. In contrast to our patient who experienced three relapses after the first attack, in 88% of cases GABA$_A$R Abs AE was monophasic [3]. MMF was initiated in our patient before identification of GABA$_A$R Abs but was insufficient to control neuro-inflammatory processes in combination with steroids and PE. After identification of anti-GABA$_A$R, we administered rituximab and our patient responded favorably like has been observed in previously reported cases [9, 13, 14], but a delayed therapeutic response to previous therapeutic interventions cannot be excluded.

In summary, we present a patient with relapsing severe anti-$GABA_AR$ encephalitis with a delay in identification of the neural antibody most relevant to their clinical presentation. Comprehensive neural antibody testing for AE was critical to the identification of anti-$GABA_AR$ in our case and illustrates the value of TIIF-based testing using serum and CSF to maximize clinical sensitivity. The identification of anti-$GABA_AR$ in our case prompted administration of rituximab and led to clinical improvement, highlighting the utility of neural antibody detection in clinical decision-making. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539186).

Statement of Ethics

Ethics approval was not required as determined by the Institutional Ethics Committee of the Centre Hospitalier de l'Université de Montréal. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

M.B., C.R., A.K., H.C., L.L.-G., G.M., and C.L. report no conflict of interest in relation to this work. A.B. reports that he holds the London Health Sciences Centre and London Health Sciences Foundation Chair in Neural Antibody Testing for Neuro-Inflammatory Diseases, and receives support from the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO).

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Author Contributions

M.B. and C.R. contributed to the acquisition and interpretation of data and drafting the manuscript. A.B., H.C., and G.M. contributed to the acquisition and interpretation of data and reviewing the manuscript critically. A.K. and L.L.-G. contributed to the interpretation of data and reviewing the manuscript critically. C.L. contributed to the acquisition and interpretation of data and drafting and reviewing the manuscript critically. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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