Autoimmune encephalitis associated with two antibodies

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1. Introduction

The initial report of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in 2007 paved the way for the discovery of other antibodies including those that target voltage-gated potassium channel (VGKC), AMPA receptors (AMPAR), γ-aminobutyric acid-B receptor (GABAB-R), glutamic acid decarboxylase (GAD) among many others [1,2]. The two most common antibodies in these cases are directed to NMDAR and VGKC, and they share common features such as cognitive impairment and seizures. However, several differences still exist. Anti-NMDAR encephalitis is frequently associated with ovarian tumors and may manifest with behavioral changes, movement disorders, hyperventilation and dissociative responses to stimuli. Anti-VGKC-mediated disease may present as faciobrachial dystonic seizures (FBDS), sleep disturbances, neuromyotonia or a combination of these symptoms (Morvan syndrome) [1]. In this study, the authors describe a case of a female patient with an ovarian teratoma who tested positive for both antibodies. This study also describes the management approach for autoimmune encephalitis with coexisting antibodies and reviews the literature on its pathogenesis and response to immunotherapy.

2. Case

A 25 year old, right-handed female was brought to the emergency room due to behavioral changes. Prior to her admission, she had a one week history of fever, bitemporal headache, memory lapses, bizarre behavior (i.e., talking to herself, laughing for no apparent reason, irritability), auditory hallucinations, and two generalized-onset tonic-clonic seizures. She had no personal or familial history of epilepsy, and had no other medical illnesses prior to her admission.

On examination, the patient was hemodynamically stable. She was awake, had tangential responses to questions, and did not follow commands. She had no cranial nerve nor other focal deficits, and had no signs of meningeal irritation. Computed tomography (CT) of the brain, and chest radiograph were completed upon arrival which did not reveal any abnormalities. She was initially given oral valproic acid 500 mg twice daily and intravenous acyclovir 800 mg every 8 h. Cerebrospinal fluid (CSF) analysis for bacterial, tuberculous, cryptococcal infection, as well as cell cytology was unremarkable. The patient also had a negative CSF herpes simplex virus polymerase chain reaction (HSV PCR) result. Thus, acyclovir was discontinued.

Aside from tonic-clonic movements, the patient also manifested with sleep–wake reversal, orofacial and limb dyskinesias, lip smacking, and one episode of gelastic seizures. Electroencephalogram (EEG) showed three runs of electrographic focal seizures arising from the right fronto-temporal region with spread towards adjacent regions, lasting 110–140 s (Fig. 1). Her seizures persisted and necessitated adjustment of oral valproic acid to 500 mg thrice daily, as well as addition of oral levetiracetam 1 g twice daily, oral phenytoin 100 mg thrice daily, and clonazepam 1 mg thrice daily.

The neurologic manifestations of limbic encephalitis with unremarkable CSF findings raised suspicion for an autoimmune etiology. Serum thyroid function test and antinuclear antibody (ANA) were done yielding normal results. Taken together, the convulsive seizures, rapid cognitive impairment, psychiatric symptoms, movement disorders involving the face and the limbs, and sleep–wake reversal suggested overlapping manifestations of anti-NMDAR and anti-VGKC-associated limbic encephalitis. Serum and CSF samples were then sent for autoantibody testing which revealed positive NMDAR antibody in the serum (titer 1/10) and CSF, and positive voltage-gated potassium channel (VGKC) complex antibody in the serum (antibody titer: 346 pmol/L, normal range: 0–69 pmol/L). Further testing of anti-VGKC yielded negative results for antibodies against leucine-rich glioma-inactivated 1 (LGI1), contactin associated protein-like 2 (Caspr2), and dipeptidyl-peptidase-like protein 6 (DPPX). Due to the presence of positive anti-NMDAR result, a transvaginal ultrasound was subsequently done revealing a 7.5 × 5.1 × 1.2 cm right ovarian mass.

The patient underwent operative laparoscopy, right salpingo-oophorectomy and excision of the ovarian mass. Histopathologic study of the said mass showed mature cystic teratoma. She also underwent intravenous high dose methylprednisolone therapy (MPPT) at 1 g daily for five days with administration of oral prednisone 60 mg daily (1 mg/kg) after pulse therapy. However, the patient still had involuntary movements of the feet and fingers even after corticosteroid therapy.

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She was then given a short course of intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg for five days with no noted adverse or untoward events. After MPPT and IVIG therapy, the patient had no recurrence of seizures and involuntary movements. A repeat EEG did not reveal any epileptiform discharges or other abnormalities. She remained seizure free even after discontinuation of valproic acid, phenytoin and clonazepam. She had gradual improvement in memory, orientation, mental status and had no recurrence of auditory hallucinations. She was discharged improved but decided to have her follow up at the province instead.

### 3. Discussion

More recently, there has been an increase in the recognition of autoimmune encephalopathies and antibody-mediated limbic encephalitis. The exact mechanisms leading to CNS dysfunction remain unclear, but evidence suggests that these autoantibodies exert their pathogenicity through (1) blockade of channel ligand of ionic channels or receptors, (2) cross-linking, internalization and depletion of receptors, or (3) complement-mediated neuronal death [1].

The limited evidence report that the incidence of NMDAR encephalitis ranges between 1 and 4% in all cases of encephalitis [3,4]. The antibodies target the NR1 subunit of NMDAR and the general pathogenic mechanism involves receptor cross-linking and internalization [2,5]. The disease is characterized by a prodrome of nonspecific symptoms followed by psychiatric changes, cognitive decline (particularly memory loss and disintegration of language), movement disorders, autonomic dysfunction, and motor or complex seizures. It may also manifest with decreased responsiveness, hypoventilation and dissociative responses to stimuli. Anti-NMDAR encephalitis is frequently associated with ovarian tumor although the absence of which does not preclude its diagnosis [1–3,6]. EEG may disclose epileptiform discharges and nonspecific slow, disorganized activity. MRI may also reveal nonspecific T2 of FLAIR signal hyperintensities in specific areas of the brain, but these abnormal findings are found in less than half of the patients with the disease. The definitive diagnosis rests on the finding of antibodies in serum, CSF or ovarian mass [2]. Retrospective and large cohort studies recommend treatment approach with tumor resection and first-line immunotherapy with corticosteroids, IVIG, or plasma exchange (PLEX) alone or in combination. Second-line immunotherapy with rituximab or cyclophosphamide is recommended for refractory cases or for those with disease relapse [1,2,6,7].

Anti-VGKC antibodies encompass a spectrum of diseases including limbic encephalitis, neuromyotonia and Morvan syndrome, reflecting the presence of the VGKC complex in the central and peripheral nervous system [1,6,8,9]. These antibodies are thought to induce complement-mediated neuronal cell death and destruction [6]. Retrospective, as well as prospective studies have shown that nonparaneoplastic autoimmune encephalitis associated with VGKC/LGI1 respond well to immunotherapy [7,10,11].

Recent studies reveal that the antibodies do not target VGKC but are rather directed to proteins associated with the channel complex giving rise to four subgroups [12]. The first subgroup is associated with LGI1 antibodies which frequently associated with limbic encephalitis [1,9,13,14]. The second subgroup is associated with antibodies to contactin-associated protein-like 2 (Caspr2) and usually manifests as neuromyotonia or Morvan syndrome. Another subgroup includes those with reactivity to dipeptidyl-dipeptidase-like protein 6 (DPPX). The last subgroup includes VGKC-positive patients with absent LGI1 and Caspr2 antibodies. There are still controversies on the clinical significance of positive VGKC titers in the absence of LGI1 and Caspr2 antibodies. The disease is characterized by a prodrome of nonspecific symptoms followed by psychiatric changes, cognitive decline (particularly memory loss and disintegration of language), movement disorders, autonomic dysfunction, and motor or complex seizures. It may also manifest with decreased responsiveness, hypoventilation and dissociative responses to stimuli. Anti-NMDAR encephalitis is frequently associated with ovarian tumor although the absence of which does not preclude its diagnosis [1–3,6]. EEG may disclose epileptiform discharges and nonspecific slow, disorganized activity. MRI may also reveal nonspecific T2 of FLAIR signal hyperintensities in specific areas of the brain, but these abnormal findings are found in less than half of the patients with the disease. The definitive diagnosis rests on the finding of antibodies in serum, CSF or ovarian mass [2]. Retrospective and large cohort studies recommend treatment approach with tumor resection and first-line immunotherapy with corticosteroids, IVIG, or plasma exchange (PLEX) alone or in combination. Second-line immunotherapy with rituximab or cyclophosphamide is recommended for refractory cases or for those with disease relapse [1,2,6,7].

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(Hu, CRMP-5) antigens without evidence of malignancy. It was proposed that neuronal destruction from autoantibodies against intracellular neuronal antigens result in the secondary formation of antibodies against cell-surface antigens [15]. In a cohort study of 416 epileptic patients, only 46 yielded positive serum results in one or more antibody tests. Interestingly, only one patient had an elevated titer to two antibodies namely, VGKC and glycin receptor antibodies (Gly-R) [16]. At present, there are no published studies or data showing autoimmune encephalitis with coexisting antibodies to NMDAR and VGKC.

The study was limited in that other paraneoplastic autoantibodies, including those that target intracellular neuronal antigens, were not tested. Nevertheless, the study emphasizes the need for an organized approach to the diagnosis of autoimmune encephalitis and thorough evaluation of autoantibodies involved, as these may affect the disease course, response to therapy and relapse rate.

4. Conclusion

Autoimmune encephalopathies and limbic encephalitis are rare syndromes that may arise from several established, as well as emerging antibodies. More importantly, this case illustrates the importance of early recognition of these diseases as they are responsive to prompt initiation of immunotherapy. It also emphasizes the need for a thorough and complete autoimmune panel testing in such cases since these antibodies may coexist. In cases wherein antibodies for anti-NMDAR and VGKC coexist, tumor resection (if present) and combination immunotherapy with corticosteroids and IVIG may be effective treatment strategies.

Conflicts of interest

The authors disclose no commercial or financial relationships, as well as potential conflicts of interests in the conduct of this research.

Ethical statement

The conduct and preparation of this research followed guidelines set forth by the local ethical review board of the Philippine General Hospital. The authors declare that all details, including laboratory data and test results, are entirely original. In instances wherein comparisons have been made between these findings in this research and related literature, the authors made proper citation of the latter in the submitted manuscript.

The authors ensure that a thorough informed consent process was carried out prior to the preparation of this research manuscript. The authors have adequately explained the nature, risks, and benefits of this research to the patient and her family, and have given them the opportunity to withdraw their consent prior to its submission. The editors and reviewers of Epilepsy and Behavior Case Reports may contact the corresponding authors should they wish a furnished copy of the accomplished informed consent form.

The authors grant the editors of Epilepsy and Behavior Case Reports permission to publish the data included in the submitted manuscript.

References

[1] Gastaldi M, Thouin A, Vincent A. Antibody-mediated autoimmune encephalopathies and immunotherapies. Neurotherapeutics 2016;13:147–62.
[2] Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experiences and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10(1):63–74.
[3] Pruss H, Dalmau J, Hamls L, et al. Retrospective analysis of anti-glutamate receptor (type NMDA) antibodies in patients with encephalitis of unknown origin. Neurology 2010;75:1735–9.
[4] Gruner J, Ambrose H, Davies N, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicenter, population-based prospective study. Lancet Infect Dis 2010;10:835–44.
[5] Dalmau J, Gleichman A, Hughes E, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7(12):1081–8.
[6] Bien C, Bauer J. Autoimmune epilepsies. Neurotherapeutics 2014;11:311–8.
[7] Quek A, Britton J, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012;69(5):582–93.
[8] Vincent A, Buckley C, Schott J, et al. Potassium channel antibody-associated encephalopathies: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127:701–12.
[9] van Sonden A, Schreurs M, Wirtz P, et al. From VGKC to LGI1 and Caspr2 encephalitis: the evolution of a disease entity over time. Autoimmun Rev 2016;15:970–4.
[10] Shin Y, Lee S, Shin J, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neurommunol 2013;265:75–81.
[11] Wong S, Saunders M, Larner A, et al. An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis. J Neurol Neurosurg Psychiatry 2010;81:1167–9.
[12] Irani S, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 and contactin-associated protein-2 in limbic encephalitis, Morvan’s syndrome and acquired neuromyotonia. Brain 2010;133:273–48.
[13] Irani S, Stagg C, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 2013;136:3151–62.
[14] Frisch C, Malter M, Elger C, et al. Neuropsychological course of voltage-gated potassium channel and glutamic acid decarboxylase antibody related limbic encephalitis. Eur J Neurol 2013;20:1297–304.
[15] Kim A, Kang P, Bucelli R. Autoimmune encephalitis with multiple autoantibodies: a diagnostic and therapeutic challenge. Neurologist 2018;23(2):55–9.
[16] Brenner T, Sills G, Hart Y, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia 2013;54(6):1028–35.