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Case Report

Double Negative Anti-Voltage-Gated Potassium Channel Complex Autoimmune Limbic Encephalitis Associated with Pulmonary Sarcoidosis

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Abstract

Autoimmune encephalitis comprises a myriad of conditions due to autoantibodies against neuronal surface antigens. Etiologies and prognosis vary. Limbic encephalitis often has subacute manifestation with short-term memory loss, seizures, confusion, and psychiatric symptoms. Here, we presented a rare case of non-neoplastic double negative anti-Voltage-Gated Potassium Channel Complex (anti-VGKC) limbic encephalitis that was found to have pulmonary sarcoidosis with fast recovery after Intravenous Immunoglobulin (IVIG) and steroid treatment.

Keywords: Autoimmune limbic encephalitis; Pulmonary sarcoidosis; Autoantibodies

Introduction

Autoimmune Voltage-Gated Potassium Channel Complex Limbic Encephalitis (VGKC - LE) is uncommon. The diagnostic criteria for definite autoimmune encephalitis are 1) subacute onset of less than three months with personality changes or altered mental status, 2) symptoms that suggest involvement of the limbic system, including working memory deficits, psychiatric symptoms, and seizures, 3) MRI finding suggesting limbic encephalitis, showing highly restrictive hyperintensity at the medial temporal lobe, 4) EEG with epileptic or slow-wave activity or CSF pleocytosis, and 5) a reasonable exclusion of alternative etiologies [1-4].

VGKC - LE is associated with diverse neurological diseases or syndromes, including Guillain Barre Syndrome, neruomyotonia, N-methy-D-aspartate receptor encephalitis, and Creutzfeldt-Jackson disease. VGKC-LE is not known to be associated with sarcoidosis. Here, we report a case of VGKC-LE, associated with sarcoidosis.

Case presentation

Forty-four-year-old male engineer initially complained about sore throat, coughs, rhinorrhea, tactile fever, facial pressure, vague headaches, achiness, and nausea. Eleven weeks later, patient complained about worsening headaches and episodic dizziness spells, accompanied with nausea, 3 to 4 times daily. He had no focal neurological defects, had intact cranial nerves II to XII, normal gait, coordination, and balance. He was treated for unresolved acute sinusitis and a possible eustachian tube dysfunction. Patient declined head CT at that time. Two weeks later, patient reported worsening frontal dull headache, photophobia, neck stiffness, dizziness, nausea, right eye blurry vision, no diplopia, occasional disorientation, distorted sense of time, increased fatigue, sleeping more than 12 hours a day, acute onset of short-term amnesia, confusion, distorted sense of reality, and episodic déjà vu feeling. Physical exam was significant for mild bradycardia at 54 to 56 beats per minute. He had normal C-reactive protein, complete cell count test, and basic metabolic panel. CSF analysis showed eight WBC, one RBC, normal glucose, and negative bacterial and virology. Brain MR Angiography was normal. Brain MRI images showed symmetrical bilateral enhancements in the amygdala and multiple small enhancement of foci (Figure 1), consistent with a limbic encephalitis. Further EEG test showed frequent spikes and sharp waves in the left temporal lobe, consistent with a partial seizure disorder. An extensive encephalitis panel was negative, including NMDA. Patient was treated with Keppra, empiric high-dose of corticosteroids, and five days of IVIG to prevent seizure and limbic encephalitis.

Headache was significantly improved after three days of IVIG. One week later, patient reported "sharper' mind, no dizziness, and no disorientation. He continued experiencing stiffed neck and fatigue. His autoimmune encephalitis panel (Mayo Clinic, ENS2 encephalopathy panel) revealed positive for VGKC autoantibodies (titer>400 pM), negative for anti-LGI1 and anti-Caspr2, and for other markers (NMDA-R, AMPA-R, GABA-B-R, mGluR1, N-type VGCC, CPA-Tr, etc). Other workups of autoimmune were negative, which included anti-Hu, RI, SOX-1, CRMP-5, GFAP and others. Serum ACE level was elevated to 75 unit/L (the normal range of ACE are 9 and 67, respectively). As part of tumor screening, chest X-ray showed calcified multiple granulomas in the right upper lobe. The largest one measured 9 mm in diameter. The patient was negative for tuberculosis. His chest CT images showed calcified and non-calcified nodules. His

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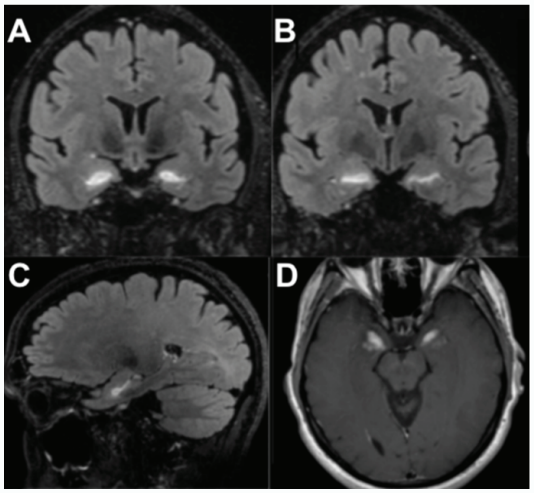

Figure 1: Brain MRI without contrast, showing bilateral regions of hyperintensity within the amygdala closely associated with the temporal horns of the lateral ventricles measuring 1.3 cm × 0.9 cm on the right and 1.2 cm × 0.8 cm on the left. A and B) coronal, C) Sagittal and D) Axial images.

PET-CT images showed several hypermetabolic mediastinal and hilar lymph nodes. The patient was diagnosed with sarcoidosis after a confirmed biopsy result carried out by Mayo Clinic. The biopsy samples were obtained from bronchoscopy. Brain MRI images from two months follow-up showed an almost complete resolution of bilateral enhancement at the temporal and occipital lobes, consistent with a favorable response to the treatment of VGKC - LE.

Presently, two years after the initial workup, patient is neurologically stable. He is treated with rituximab for autoimmune limbic encephalitis as well as sarcoidosis. He is managed by a multidisciplinary team, comprising neurologists, a pulmonologist, an oncologist, and patient's primary care physician. His baseline pulmonary functional test has been normal.

Discussion

Here, we report a case of double negative non-paraneoplastic VGKC-LE that is histologically positive for pulmonary sarcoidosis with a rapid symptomatic relief from IVIG and steroids and has a negative workup for an extensive screening for tumors and other autoimmune diseases. Studies suggested that over fifty percent of VGKC-LE is oftenanti-LG1 positive and often presents with intractable hyponatremia (~60%), seizure with a relapse rate of up-to ~20%, and a positive tumor screen of up to ~11% [5]. Seizure associated with LG1-VGKC-LE often precedes cognitive decline. When a seizure is recognized, a prompted initiation of treatment can effectively improve prognosis. Among all associated seizures in LG1-VGKC-LE, ~50% is of a specific type, called Facio Brachial Dystonic Seizures (FBDS). FBDS is a very brief (<3 seconds) unilateral contraction of the arm with possible involvement of ipsilateral face at a frequency of up to 100 times onset daily. Recognizing FBDS can help pointing to the diagnose of VGKC-LE. The second common subgroup of VGKC-LE (~20%) is anti-Caspr2 positive VGKC-LE (Caspr2-VGKC-LE). It is often found in older males of an average age of ~70, while the average age of patient group in LG1-VGKC-LE is ~60 years-old. Caspr2-VGKC-LE often presents with peripheral nerve hyperexcitability, muscle fasciculation and cramp, autonomic dysfunction syndromes, insomnia, weight loss, and pain [6]. Both LG1-VGKC-LE and Caspr2-VGKC-LE affect predominately males (1:2 ratio *versus* 1:4-5, respectively) and have good prognoses.

The subgroup of VGKC that is negative for both anti-LGI1 and anti-Caspr2, as presented here, is also called "double negative-VGKC-LE". Double negative-VGKC-LE is a heterogenous group that is not well characterized and understood due to very limited cases. Previously, most of all VGKC-LE were lumped together for analysis [7,8]. It was not until recent years that the characteristics of this double-negative subgroup of VGKC - LE started to be unveiled. The heterogenicity of this group may be explained by unknown novel autoantibodies. The targeted antigens in VGKC-complex remain to be discovered. However, not until we have more cases of double negative VGKC-LE, will we be able to have a better understanding of the clinical relevance of this disease group.

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