$GABA_B$ receptor limbic encephalitis: Case report and a brief literature review

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Background

$GABA_B$ receptor associated encephalitis is an uncommon cause of limbic encephalitis that presents typically with early and prominent seizures along with other features of limbic encephalitis, namely memory impairment and behavioral changes[1]. Antibodies to $GABA_B$ receptor in limbic encephalitis was first described in 2009 by Lancaster and colleagues who reported on fifteen such cases, seven of whom had an underlying neoplasm[1]. Frequent co-occurrence of other antibody types in these patients likely suggest a tendency to autoimmunity and possibly an anti-tumor immune response in those cases with an underlying neoplasm[2].

Case report

A 29 year-old male was admitted to our neurology service with two weeks history of new onset multiple generalized tonic-clonic seizures, headache, and cognitive and behavioral disturbance. He denied other neurologic or systemic symptoms. He had no other significant past medical history including no prior history of seizures.

On exam, he was a well-nourished individual. There were no meningeal signs. He was alert but confused and agitated and frequently had difficulty cooperating with elements of the neurological exam. Cranial nerves II-XII were intact. He exhibited full strength in all muscle groups and sensation was normal throughout. Deep tendon reflexes were 3+ and symmetrical. Co-ordination and gait were normal. Rest of the systems exam were normal.

On investigation, his basic laboratory panel including complete blood count, metabolic profile and ESR were normal. MRI of the brain showed FLAIR hyperintensity in the limbic region along with subtle leptomeningeal enhancement in the parieto-occipital region (Fig 1 and 2) . Diffusely slow background was noted in the EEG. Cerebrospinal fluid (CSF) analysis demonstrated a lymphocytic pleocytosis with 37 wbc/mm^3 (90% lymphocytes) and mildly elevated protein of 48 mg/dl. CSF glucose was normal and viral studies were negative. Given his clinical features, CSF and MRI findings, we considered the possibility of limbic encephalitis and analyzed the CSF and serum samples for several paraneoplastic and autoimmune antibodies.

High titers of antibody against the $GABA_B$ receptor was detected in both the serum and the CSF suggesting the diagnosis of $GABA_B$ receptor autoimmune encephalitis. CT chest, abdomen and pelvis and a testicular ultrasound were done to search for any underlying neoplasm and these were all normal. PET scan was attempted on multiple occasions but was not possible because of patient's severe agitation. He was initially treated with high dose intravenous steroids and plasma exchange. As he did not respond to either of these, we treated him with a dose of Rituximab followed by an additional dose two weeks later. Unfortunately, he remains encephalopathic three months after his diagnosis.

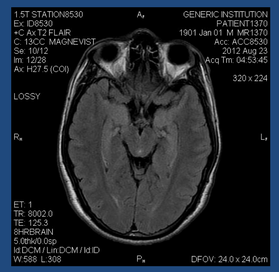

Figure 1 . MRI showing FLAIR hyperintensity in the limbic region.

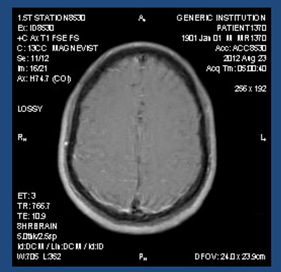

Figure 2. Leptomeningeal enhancement in in the parieto-ocipital region

Discussion

Limbic encephalitis is an inflammatory condition of the brain involving the hippocampi, amygdala, and occasionally with involvement of the frontobasal and insular regions[3]. The classic syndrome of limbic encephalitis presents with an acute or subacute onset of confusion, short-term memory impairment, mood and behavioral changes and seizures. CSF usually shows a lymphocytic pleocytosis, and antibodies to either intracellular antigens (Hu, Ma2, CV2/CRMP5) or cell surface antigens (NMDA, AMPA, $GABA_B$, LGI1, Caspr2) are identified in the serum and/or the CSF[2]. $GABA_B$ receptor associated limbic encephalitis is uncommon accounting for only about 5% of cases of limbic encephalitis[2]. These patients present with early and prominent seizures. MRI is reported to be abnormal in 66% of cases with mostly FLAIR hyperintensity in the medial temporal lobes [2].

Our patient's clinical presentation as well as the strongly positive serum and CSF antibodies to $GABA_B$ receptor was considered diagnostic of $GABA_B$ limbic encephalitis. Leptomeningeal enhancement seen on the MRI in our case is not typical of this condition, although it has been reported in another recently published case[4]. Although a PET scan was not possible in our patient because of agitation, CT scan of the chest, abdomen and pelvis and a testicular ultrasound did not identify any underlying neoplasm. In one study, about one third of cases of $GABA_B$ encephalitis were reported to harbor an underlying tumor, most commonly small cell lung cancer[2]. Another recent study identified small cell lung cancer in 8 out of 10 patients[5]. Given the frequent association of underlying tumors in this condition, an exhaustive search for a neoplasm should be conducted including a whole body PET scan.

Management of $GABA_B$ limbic encephalitis mostly comprises of immunotherapy and treatment of the underlying tumor and they often show good response to treatment. In a series of 15 patients with $GABA_B$ limbic encephalitis, of which 7 had an underlying tumor, nine patients responded to immunotherapy and/or treatment of the underlying tumor whereas four patients who received no treatment did not improve[2]. Immunotherapies that have been used in this condition and other forms of limbic encephalitis include corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, rituximab, mycophenolate mofetil and cyclophosphamide [1, 4, 6, 7]. Although there are no established guidelines on treatment, high dose steroids, IVIG and plasmapheresis are usually the first line agents with Rituximab and other stronger immunosuppresants reserved for patients who remain unresponsive.

Conclusion

$GABA_B$ receptor limbic encephalitis is uncommon. However, recognition of this condition as well as the other types of limbic encephalitis is important as prompt and aggressive treatment with immunotherapy and treatment of the underlying tumor can be effective. Further studies are required to help construct useful guidelines on treatment of the condition.

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