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GABA-B ENCEPHALITIS IN PAKISTAN: A RARE BUT TREATABLE ENTITY

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ABSTRACT:
Autoimmune and paraneoplastic encephalitides are a group of neurologic disorders that present with cognitive decline, neuropsychiatric symptoms, movement disorders, or seizures. These diseases can present before, with, or after the diagnosis of malignancy. We report two cases of GABA-B encephalitis from Pakistan. The first patient was a 67-year-old gentleman presented with cognitive decline and neuropsychiatric symptoms. His CSF analysis showed increased protein levels and GABA-B receptor antibodies. He was treated with pulse steroids, which improved his symptoms. The second patient was a 34-year-old lady with cognitive decline and psychomotor symptoms. Her serum autoimmune antibody panel showed antibodies against GABA-B receptors. She was treated with pulse steroids followed by plasma exchange, but did not improve. A low threshold should be kept for testing for autoimmune and paraneoplastic encephalitides because they are potentially treatable.

KEYWORDS: autoimmune encephalitis, paraneoplastic encephalitis, GABA-B, cognitive decline, neuropsychiatric manifestations.

INTRODUCTION:

Autoimmune encephalitides are a group of neurologic diseases that affect the limbic system in response to infectious or autoimmune triggers. Some of these diseases have an association with cancers, and may present as paraneoplastic syndromes[1]. Several autoimmune encephalitides are characterized by antibodies that target neuronal cell surface receptors or synaptic proteins[2]. Many of these tumors may be treated by steroids, intravenous immunoglobulins, plasma exchange, rituximab, or cyclophosphamide[3]. Because these diseases are potentially treatable, a high index of suspicion is required to prevent neurologic morbidity. One such autoimmune encephalitis is GABA-B encephalitis, which presents with symptoms of limbic encephalitis, such as seizures, cognitive decline, and behavioral problems. It may also present with ataxia or opsoclonus-myoclonus[4]. Although the exact cause of GABA-B encephalitis is unclear, it may be preceded by systemic or neurologic viral infections or have no obvious trigger[5]. This diagnosis should be particularly considered in middle-aged or older adults with new-onset seizures and multiple neurologic manifestations[6]. Here, we present two cases of GABA-B encephalitis.

CASE REPORTS:

Patient 1:

A 67 year old gentleman presented with increasing forgetfulness, difficulty recognizing familiar people, reduced verbal output, visuospatial dysfunction, visual hallucinations and sleepiness for one month. He had a history of diabetes, hypertension, Bell's palsy, benign prostatic hyperplasia, presbycusis and hypothyroidism. He had been prescribed antipsychotics and antidepressants by a psychiatrist with some improvement in his behavior. However, his cognition had not improved. The neurologic examination was significant for orofacial dyskinesia and a mini-mental state examination score of 24, with impaired registration, recall, and attention and calculation. He had a normal EEG. His contrast enhanced MRI brain showed chronic microvascular changes and age related atrophy. His CSF analysis showed a normal white cell count (<5 cells/μL), normal glucose 64 mg/dL), raised proteins (83.2 mg/dL) and antibodies positive against GABA-B receptors (shown in Figure). All other laboratory and CSF markers were normal. There was no evidence of an underlying neoplasm on a CT chest with contrast. He was treated with pulsed methylprednisolone (1 gram/day) for 3 days followed by

oral prednisolone (1 mg/kg/day). His symptoms improved rapidly and he was started on azathioprine with gradual tapering of prednisolone. However, tapering of prednisolone led to relapse of symptoms so he is being managed on fortnightly methylprednisolone with azathioprine and a gradual tapering of the oral steroids. At the last follow-up, the patient's neurologic and psychiatric symptoms had markedly improved.

Patient 2:
A 34 year old lady presented with progressively worsening memory for recent events, repetition of speech, visual hallucinations, delusions, disinhibition, psychomotor agitation and urinary and fecal incontinence for a year. She did not have any past medical history of note. Her initial neurological examination and workup was normal. Her serum autoimmune antibody profile showed antibodies against GABA-B receptors (shown in Figure). It is important to note that anti-GABA-B antibodies should preferably be checked in the CSF. However, this patient had refused CSF analysis. Therefore, the antibodies were checked in the serum. She was managed with methylprednisolone (1 gram/day) for 5 days followed by oral steroids. The patient did not improve so plasma exchange was done. She was advised rituximab for maintenance therapy, but her family declined further treatment due to financial reasons. Her follow-up evaluation revealed a static neurological condition.

DISCUSSION:
The incidence of anti GABA-B antibody positivity in patients tested for autoimmune encephalitis related antibodies is around 0.2%[7]. We tested 640 samples (both sera and CSF) for autoimmune encephalitis associated antibodies from January 2015 to October 2019 and 2 (0.3%) were positive for anti GABA-B antibodies. According to the most recent published literature, the median age of patients presenting with anti GABABR encephalitis is 66 years with an almost equal incidence in males and females[8]. Similarly, in our patients, the mean age was 50.5 years with an equal gender distribution. However, this is a report of two patients only. Therefore, conclusions should be drawn with caution. The most common presenting symptom is seizures8, however, none of our patients had seizures during the disease course. Patient 1 presented with memory dysfunction and neuropsychiatric disturbances, whereas Patient 2 presented with behavioral problems.

Around 50% of the patients with anti-GABA-B antibodies have an underlying small cell lung cancer[9]. However, both our patients were negative for malignancy after extensive workup. Anti-GABA-B encephalitis is also associated with presence of antibodies against other intracellular neuronal antigens like amphyphysin, Ri (ANNA2) and SOX-1[9]. Patient 1 had negative test result for an immunoblot panel of nine antibodies against intracellular neuronal antigens PNMA2, amphyphysin, CV2, Ri, Yo, Hu, Recoverin , SOX-1 and titin.

Around 60 to 70% of patients with anti-GABA-B encephalitis show complete or partial response to immunosuppressive therapy[10]. Patient 1 showed complete recovery with parenteral and oral steroids. However, Patient 2 did not improve with steroids and plasma exchange. Because of financial issues, Patient 2 and her family refused further treatment.

CONCLUSION
In conclusion, anti-GABA-B encephalitis represents a potentially treatable cause of cognitive decline and neuropsychiatric disturbances. A high index of suspicion should be kept for GABA-B and related encephalitides as they present with a diverse range of symptoms.

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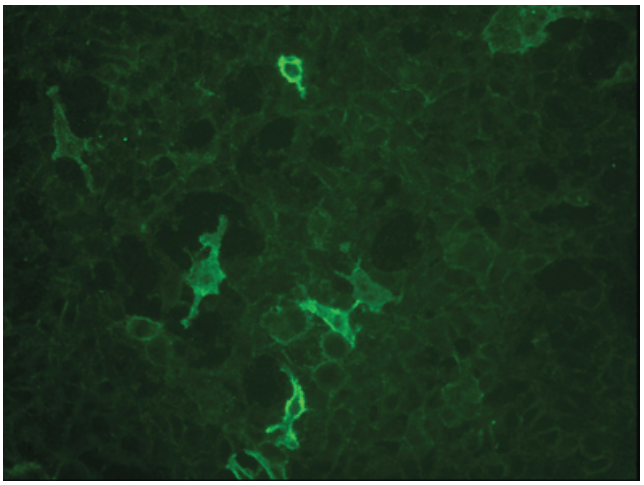

Figure. Indirect Immunofloresence using U90 cells (Euroimmun, Leubeck Germany) transfected with genes of GABAB receptors, showing anti $GABA_B$ receptor antibodies. Non transfected cells were used as negative control.

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Asfandyar Khan Niazi; data collection, data analysis, manuscript writing, manuscript review
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Arsalan Ahmad; concept, data analysis, manuscript writing, manuscript review
Ayesha Zafar; data collection, data analysis, manuscript review
Tahir Aziz Ahmed; data collection, data analysis, manuscript writing, manuscript review