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Case Report

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A Rare Presentation of Anti-Gad Associated Neurological Disorder in A Fifteen-Year-Old Girl

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Abstract

Anti-GAD antibodies have been associated with numerous neurological conditions that have a wide variety of presentations. These conditions include limbic encephalitis, stiff person syndrome, opsoclonus-myoclonus-ataxia syndrome, cerebellar ataxia, and status epilepticus. In this paper, we aimed to present a female patient admitted with complaints of acute weakness and right peripheral facial palsy, pancytopenia, hepatosplenomegaly, and anti-glutamate decarboxylase antibody and report the diversity and clinical features of neurological diseases associated with anti-glutamate decarboxylase antibodies.

Conclusion

Besides the common primary syndromes, other new clinical and neurological manifestations have been associated with anti- anti-glutamate decarboxylase antibodies.

Keywords: Glutamic Acid Decarboxylase, Autoimmune, Fascial Palsy, Acute Weakness

Introduction

Anti-glutamate decarboxylase antibodies (anti-GAD-Ab) have been associated with numerous neurological conditions. These conditions include; limbic encephalitis, stiff person syndrome, opsoclonus-myoclonus-ataxia syndrome, cerebellar ataxia, status epilepticus, palatal tremor, and periodic alternating nystagmus. Gamma-aminobutyric acid (GABA) is formed by the conversion of glutamate to GABA and carbon dioxide. This process is catalyzed by an enzyme called glutamate decarboxylase or glutamic acid decarboxylase (GAD). GABAergic neurons in pancreatic cells usually express the GAD enzyme. Glutamate decarboxylase 67 (GAD67) enzyme diffuses throughout the cell, while glutamate decarboxylase 65 (GAD65) is trapped in nerve terminals [1, 2].

Case Presentation

A 15-year-old female patient presented with complaints of acute weakness and right peripheral facial paralysis two weeks after the upper respiratory tract infection. On physical examination, body weight was 47kg (25-50 p), height: 148 cm (10-25 P), hepatosplenomegaly was detected, and other systemic examination findings were unremarkable. In neurological examination, she was conscious with right peripheral facial paralysis grade 4; no ophthalmoparesis could be seen, low muscle strength was (3/5) experienced, which progressed in two months, DTR was not taken on all extremities, general tenderness, paraesthesia, and pain were present. Examination showed no neck stiffness, Kernig sign, or Brudzinski sign. In the abdominal USG, hepatosplenomegaly was detected, the right cervical lymph node is 1x1.2 cm, axillary and inguinal lymph nodes were considered to be normal. Based on laboratory tests, all samples were collected during the early active disease stage without any treatment, white blood count(W-BC) was 2300 cell/ml, red blood count (RBC): 2,900 cell/ml, platelet (PLT) 75,000 cell/ml and due to the presence of atypical lymphocytes in the peripheral smear, bone marrow aspiration, and biopsy were normal. Viral panel (including enterovirus and West Nile). B12, folate, vitamin D, triglyceride, immunoglobulins, and ferritin were normal. C-reactive protein was 10.5 mg/L, anti microsomal antibody and Anti-nuclear antibody titers were weakly positive., C3, C4 , NMO antibody, anti-endomysium, anti-gliadin ,and anticardiolipin were normal, anti-GAD: 494 nmol/L (N <10), vanillyl mandelic acid and neuron-specific enolase were checked to exclude neoplastic situations, and they were normal. A lumbar puncture was performed. Cerebrospinal fluid protein was 272 mg/dl and glucose: 71 mg/dL. CSF cytology and CSF culture were normal. Serum CD3, CD4, CD 45, CD8, CD 19, CD59 panel, and natural killer cells were normal. Amino acid, acylcarnitine, urine organic acid, Lactic acid, pyruvic acid, and biotinidase activities were normal. On MRI examination, leptomeningeal enhancement in the leptomeningeal tissues of the brain [Figure 1] and contrast enhancement was detected at the level of the conus medullaris and

filum terminal fibers [Figure 2]. Echocardiogram, thyroid ultrasonography, thorax, abdominal computed tomography, and bone scintigraphy were normal. The fundus, visual acuity, and area were normal, and no signs of metabolic disease were found. In the EMG performed ten days after her hospitalization, axonal and demyelinating neuropathy was detected. The patient was diagnosed with anti-Gad-related neurological disease. Plasmapheresis was applied, and pulse methylprednisolone was given for five days and tapered gradually. IVIG was given at a dose of 2 gr/kg. Intensive physical therapy and rehabilitation support were provided to the patient during this period. Some improvement was observed in the patient's clinic. Etiologies for high anti-GAD were investigated every six months. The patient adhered to IVIG treatment every month, and steroid therapy continued at a dose of 1 mg/kg /day for at least 12 months. The weakness of extremities and fascial nerve palsy were recovered at 14 and 6 months, respectively.

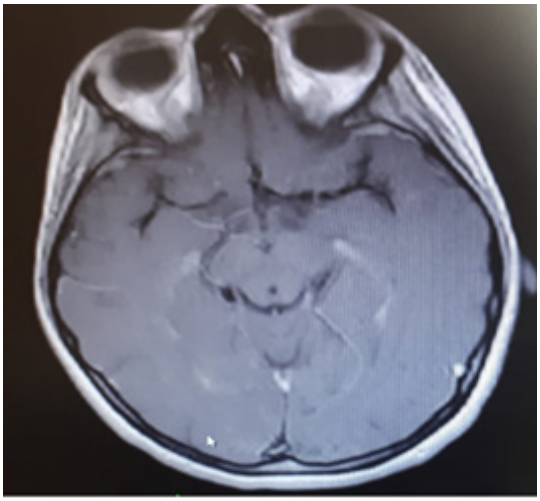

Figure 1: MRI of brain T1 findings of leptomeningeal enhancement of the brain

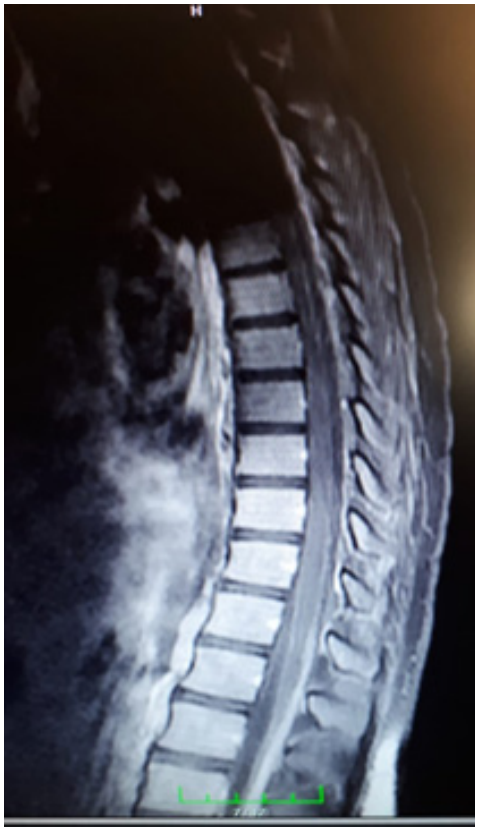

Figure 2: MRI of spine T1 sequence with gadolinium enhancement showing enhancement of conus medullarıs and filum terminal fibers

Discussion

As the name suggests, this antibody attacks the GAD 65 enzyme, thereby inhibiting GABA conversion. According to a study, very high titers of GAD65 antibodies in serum were associated with recurrent myelitis, which also provided quantitative data on GAD65 antibodies in the course of relapse and remission. It was suggested that an increase in serum levels of GAD65 was associated with relapses in this patient and a decrease in levels occurred during remission, thus suggesting that anti-GAD65 antibodies may play a role in the pathogenesis of the disease. Only 1 study has examined GAD antibodies and spinal cord abnormalities. In a study of 98 patients with neuromyelitis optica spectrum disorder (NMOSD), no patients were positive for GAD antibody. Our patient presented with Gullian- barre-like, detecting high titreş of anti-Gad and deterioration of the symptoms even after two months showed us that this neurological disease is a new entity related to high titers of anti-GAD [3-5].

The anti-GAD antibody can be a paraneoplastic or an autoimmune marker. It has been reported in the literature that GAD expressed by tumors can immunize mature T cells and B cells, thereby activating humoral and cellular immunity. On the other hand, Chang et al. argued that although GAD is an intracellular protein, it can undergo extracellular humoral immunity during exocytosis of GABAergic neurons, thereby inducing specific cellular-humoral immunity. In our patient high level of Anti-GAD was detected, all the neoplastic and paraneoplastic panels were screened, bone marrow aspiration and biopsy were done and repeated every six months. Despite the two years follow -up the results were normal. This experience may suggest that anti-Gad might not always be neoplastic in children, but This paper supports that GAD antibodies could play a pathogenic role in neurological disease [1, 6, 7].

According to a study in adults, all five patients with high anti-GAD were female. The mean age was 41.5 years. The neurological symptoms included stiff person syndrome (SPS), encephalitis, myelitis, cramping, vision loss, and paresthesia. Three patients (60%) were diagnosed with tumors. In immunohistochemistry for tumor pathology, GAD65 expression was found in only one patient. Four patients (80%) had abnormal brain MRI findings. All patients received immunotherapy and improved significantly after treatment, but 4 (80%) had relapses. Although different combinations of immunotherapy were used, all patients responded to the treatment. Interestingly, four patients developed relapses, including the patient with both thymic abnormalities. This situation suggests that patients with GAD65 antibodies, especially those with abnormal thymic glands, should be followed up regularly and receive immunotherapy [1, 8-10]. Our patient had abnormal cerebral and spinal MRI findings that entirely became normal within one month. At the same time, she responded to IVIG and steroid treatment almost in one year. Firstly facial nerve palsy symptoms improved with heavy physical therapy support; she could walk again without any aid. She didn't experience any relapses. Such a case of neurological disease associated with anti-GAD to the best of our knowledge, has not been reported in any patient. The follow-up control is screenings are going on.

Conclusion

Anti-GAD antibodies are known to cause anti-GAD syndrome and related disorders. However, it is not fully understood why the presence of an antibody causes variable symptoms and why different conditions exist rather than a particular disorder. Future research will uncover this mystery.

Informed consent statement

The parents or the child's legal guardians provided informed written consent before study enrollment.

The authors declare no conflict of interest for this article.

Data sharing statement

No additional data are available.

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Strobe Statement

The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items

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