GAD antibody-spectrum disorders: case report

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

AntiGAD-SD has various phenotypic manifestations, however there is little published data on the features of the clinical course. There is also little data of therapy efficacy.

Introduction

GAD (glutamic acid decarboxylase) is a pyridoxal-5'-phosphate-dependent enzyme, widely expressed in the central nervous system and beta cells of the pancreas, which catalyzes the conversion of the excitatory neurotransmitter l-glutamate into the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Autoantibodies against GAD are found in patients with stiff person syndrome (SPS), epilepsy and type 1 diabetes mellitus (DM-1). In recent years, a link has been revealed with other autoimmune neurological diseases associated with excitability of neurons, which currently include "GAD antibody-spectrum disorders " (antiGAD-SD) and include SPS, autoimmune epilepsy, cerebellar ataxia, limbic encephalitis, myoclous and nystagmus. In all antiGAD-SD, there is impaired GABAergic neurotransmission resulting in neuronal excitability, presumably by the GAD-targeting antibodies. In spite of their overlapping symptomatology, however, each disease within the spectrum maintains a distinct phenotype.

Anti-GAD antibody-associated cerebellar ataxia is the second most frequently seen GAD-related neurological disorder. It affects more women than men, often with comorbid diabetes or polyendocrine autoimmunity. Patients exhibit gait and limb ataxia, nystagmus, often severe dysarthria, and oculomotor dysfunction, most often overlapping with the typical SPS symptomatology that worsens the overall clinical picture. CSF can show oligoclonal bands and intrathecal antiGAD antibody synthesis. Importantly, there is no cerebellar atrophy on the MRI imaging, except of mild changes in rare instances, implying a functional blockade of cerebellar pathways rather than a destructive neuronal process.

For SPS and antiGAD-SD, two strategies of treatment are implemented: symptomatic and immunologic interventions either independently or in combination. Intravenous immunoglobulins (IVIg), corticosteroids, rituximab, autologous stem cell transplantation are used as immunotherapy. In a randomized, double-blind, placebo-controlled trial, IVIg resulted in significant improvements in GAD-positive SPS patients. The drug clearly improves stiffness and muscle flexibility especially in the paraspinal muscles, improves gait preventing falls and reduces even anxiety-triggered spasms.

However for other phenotypes there are less information about effectiveness of immunologic treatment and therefore it is extremely difficult to judge the effectiveness of therapeutic strategies.

Additional information on the specifics of therapy can help in the subsequent selection of the optimal strategy.

Case report

Female, 10 y.o., disease started in May 2019, after sinusitis. Symptoms include: progressive vertigo, drowsiness, weakness of the eyelids, tetraparesis (patient unable walk independently), and urinary incontinence. Four relapses occurred over the course of six months, with varying degrees of severity. Brain and cervical MRI: normal. Lumbar puncture: normal. Oligoclonal bands: negative. AntiNMDR, antiLGI-S, and antiCASPR-S: all negative. AntiGAD: 49.5 IU/ml (high level). In December 2020, intravenous immunoglobulins were started (0.8 g/kg every 4-6 weeks) with clinical stabilization. After two months therapy discontinuation relapse occurred, manifesting in gait ataxia and muscle weakness. Since August 2021, IVIG therapy has been resumed (1 g/kg every 4-6 weeks).

The neurological status outside of exacerbations is represented by a slight paresis in the legs in the proximal groups on both sides (up to 4 points), enhanced reflexes, Babinsky sign on both sides, a slight diffuse decrease in muscle tone.

During this time, two mild exacerbations (vertigo and gait ataxia up to 5 days) after respiratory infections were noted. The patient continues to receive therapy (Image1).

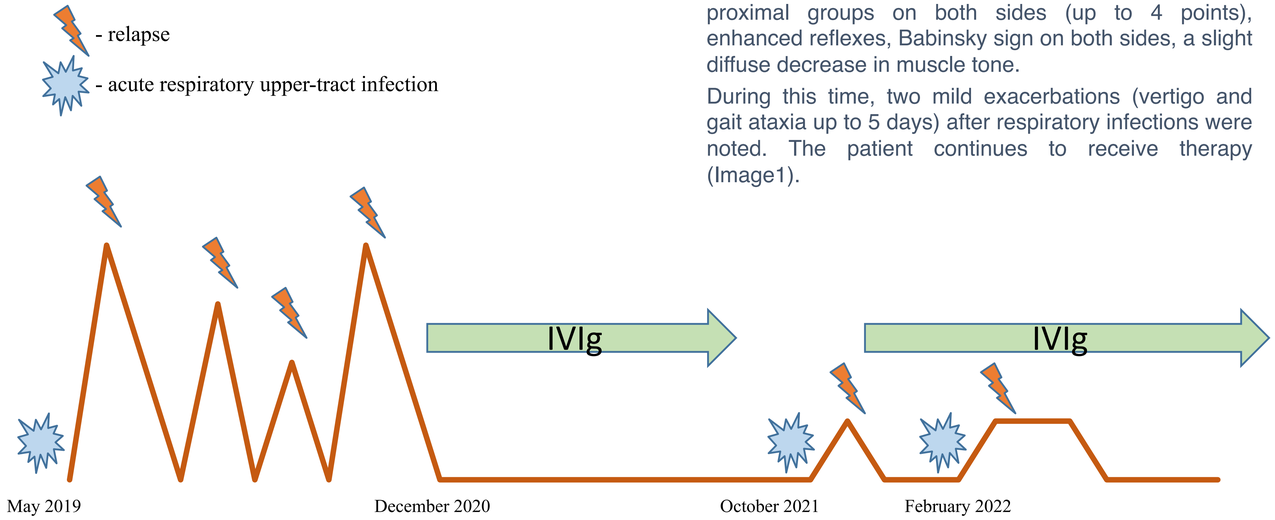

Image 1

Concusion

In cases with episodes of vertigo, ataxia, muscle weakness and normal MRI, antiGAD-SD must be excluded. IVIG therapy may be the best option for children to reduce the frequency and severity of exacerbations.

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