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Case Report

Celiac disease and catatonia: more than a coincidence?

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ABSTRACT

Background. Catatonia is a complex neuropsychiatric disorder involving stupor, waxy flexibility, and mutism lasting more than 1 hour. It has arisen mostly from mental and neurologic disorders. Organic causes are more prominent in children.

Case. A 15-year-old female who had refused to eat and drink for 3 days, had not talked, and had stood in a fixed position for long periods was admitted to the inpatient clinic, and she was diagnosed with catatonia. Her maximum score on the Bush-Francis Catatonia Rating Scale (BFCRS) was 15/69 on day 2 of her stay. On neurologic examination, the patient's cooperation was limited, and she was apathetic to her surroundings and stimuli and inactive. Other neurologic examination findings were normal. To investigate catatonia etiology, her biochemical parameters, thyroid hormone panel, and toxicology screening were conducted but all parameters were normal. Cerebrospinal fluid examination and autoimmune antibodies were negative. Sleep electroencephalography showed diffuse slow background activity, and brain magnetic resonance imaging was normal. As a first-line treatment for catatonia, diazepam was started. With her poor response to diazepam, we continued to evaluate the cause and found the transglutaminase levels were 153 U/mL (normal values, <10 U/mL). The patient's duodenal biopsies showed changes consistent with Celiac disease (CD). Catatonic symptoms did not benefit from a gluten-free diet or oral diazepam for 3 weeks. Then, diazepam was replaced with amantadine. With amantadine, the patient recovered within 48 hours, and her BFCRS retreated to 8/69.

Conclusions. Even without gastrointestinal manifestations, CD may present with neuropsychiatric symptoms. According to this case report, CD should be investigated in patients with unexplained catatonia, and that CD may only present with neuropsychiatric symptoms.

Key words: amantadine, catatonia, Celiac disease, child, gluten-free diet.

Celiac disease (CD), an immune-mediated enteropathy, is precipitated by dietary gluten consumption in genetically susceptible individuals.[1] The prevalence is approximately 0.3% to 2.9% in children, with increasing rates in recent years.[2]

CD affects the small intestine, but it is accepted as a systemic disease. There is a wide range of extraintestinal manifestations in CD, such as neurologic and psychiatric disorders, including headache, seizure, ataxia and neuropathy, mood disorders, anxiety, and attention deficit hyperactivity.[3-5] Previous studies showed a 1.4-fold increased risk of developing a future psychiatric disorder in children and adolescents with CD compared with the general population.[5]

Catatonia is a complex neuropsychiatric disorder involving stupor, waxy flexibility, and mutism. It can arise from a variety of medical and psychiatric conditions.[6] Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) requires three of the following 12 symptoms for diagnosis: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing,

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mannerisms, stereotypy, agitation, grimacing, echolalia, and echopraxia.[6] Twenty percent of catatonia has a general medical cause.[7] However, little is known about the etiology and physiopathology of catatonia in children and adolescents. Here, we present the case of a 15-year-old female patient who presented with catatonia as the first symptom and was diagnosed with CD. According to this case report, CD should be included in the etiology of catatonia.

Case Report

A 15-year-old female patient was brought to the outpatient clinic. She had refused to eat and drink for 3 days, had not talked, and had stood in a fixed position for long periods. Her family history was unknown because she was an adopted child. Her foster parents did not notice any food allergens. The patient's vital signs and physical examination were normal. Before this presentation, she maintained weight and height above the 25th centile. In her neurological examination, the patient's cooperation was limited, she was apathetic to the surroundings and stimuli, and she was inactive. Other neurologic examination findings were normal, but sense and cerebellar examinations could not be performed. The symptoms of mutism, negativism, and posturing were detected in the psychiatric examination, and she was diagnosed with "catatonia associated with other mental disorders" and "schizophrenia" according to DSM-5. We performed a diazepam challenge test, which was positive, confirming the catatonia diagnosis. Her maximum score on the Bush-Francis Catatonia Rating Scale (BFCRS) was 15 on day 2 of her hospitalization. She was accepted by the inpatient clinic to investigate the organic causes of catatonia. Her vital follow-ups were normal. A nasogastric tube was placed. Complete blood counts, serum electrolytes, liver, and renal function tests, and thyroid hormone panels were performed, and no pathology was detected. Biochemical parameters and toxicology screening to exclude drug-related catatonia were normal. The cerebrospinal fluid (CSF) revealed normal protein and glucose levels. The CSF culture and serology for viruses were negative. The tests for Epstein bar virus, cytomegalovirus, herpes simplex virus, and respiratory tract viruses were negative. Antinuclear antibodies, antiphospholipid antibodies, anti-myelin oligodendrocyte glycoprotein antibodies, paraneoplastic encephalitis antibodies (anti-NMDA, anti-LGI), and anti-thyroid antibodies were also negative. Sleep electroencephalography (EEG) showed diffuse slow background activity, and brain magnetic resonance imaging (MRI) was normal.

As a first-line treatment for catatonia, we started diazepam, and the dose was gradually increased. After getting a poor response from her to diazepam treatment, we continued to search for catatonia's etiology, and the deamidated gliadin protein antibody (AGA) level was 33 U/mL (normal values, <10 U/mL), and the transglutaminase level was 153 U/mL (normal values, <10 U/mL). The patient's duodenal biopsies showed changes consistent with gluten-sensitive enteropathy, including subtotal villous atrophy, intraepithelial lymphocyte infiltration, and crypt hyperplasia (Marsh-Oberhuber 3c). The histological findings and positive tissue IgA anti-tissue transglutaminase antibody testing supported the presumptive diagnosis of CD. After CD was diagnosed, the patient began a gluten-free diet with oral diazepam. This dual treatment continued for 3 weeks, but her BFCRS did not improve (15/69). Ultimately, amantadine was added and titrated over 2 days to a maximum (200 mg, twice a day), and oral diazepam was weaned. The patient's response to amantadine was dramatic; within 48 hours, she was alert and communicative. At that time, she scored 8/69 on the BFCRS. Throughout the subsequent 4 months of amantadine treatment and a gluten-free diet, her situation continued to improve, and showed progress in speech, and her EEG was normal. Informed consent was received from the family.

Discussion

Celiac disease is a systemic immune-mediated enteropathy characterized by injury to mostly the small intestinal mucosa. This autoimmune response to gliadin leads to an inflammatory reaction and causes many extraintestinal manifestations, such as neuropsychiatric disorders, including mood disorders, eating disorders, anxiety, and attention deficit hyperactivity.[4,5]

Catatonia is a group of symptoms that involve a lack of movement as well as a lack of communication. It coexisted with several mental disorders, yet it has also presented with other medical conditions.[8] Although previously it was often categorized as schizophrenia, with the new changes in DSM-5, catatonia is not just associated with psychiatric disorders.[8] Recognizing catatonia and determining its etiology protects the patient from possible complications.

Twenty percent of catatonia has a general medical cause, of which central nervous system inflammation, including infective and immune causes, accounts for 29%.[7] In a systematic review, catatonia caused by an autoimmune disorder was reported. Most cases were observed with NMDAR encephalitis, systemic lupus erythematosus, autoimmune thyroid disorders, or demyelinating disorders.[6,7] The exact reason why some medical conditions lead to catatonia is not understood well; however, direct neurotoxic effects, the patient's psychological reaction to the insult, or mediation by acute phase reactants have all been suggested as potential causes.[9] Benarous et al.[6] reported that autoimmune investigations should be conducted for young patients with catatonia. Because of the higher morbidity and mortality rates in patients with catatonia, detection of the underlying cause of catatonia becomes critical.[10]

In a recent study, CD and some other autoimmune disorders (hypothyroidism, alopecia areata) were reported in 3 of 7 patients with Down syndrome diagnosed with catatonia. The authors underlined a high prevalence of autoimmune disorders (57%) in their patients.[11] Given that the current evidence on pediatric catatonia that advice autoimmune investigations should be conducted[6], it may be a reasonable strategy to screen for celiac disease in children with unexplained catatonia[11] The most recent hypothesis suggests that different manifestations of CD depend on the role of transglutaminase antibodies in the humoral immune response. Transglutaminase 6 seems to be important in brain damage.[12] With the support of functional neuroimaging studies, previous studies have shown that the γ-aminobutyric acid (GABA)-ergic inhibition response decrease in the cortical regions plays a crucial role.[6] This also explains the quick response to GABA-A agonists during treatment. Hypothetically, in CD, immune-mediated dysregulation of inhibitory GABAergic interneurons may cause catatonia.[13] In the catatonic brain, there is a neural excitatory/inhibitory imbalance, and we hypothesize that CD may have an effect similar to the mechanism proposed in anti-NMDAR encephalitis.[13] Further studies will help improve the understanding of immune-mediated triggers in catatonia.

Even though the specific pathophysiologic mechanisms underlying catatonia has yet to be defined, they are thought to primarily involve dysfunction in dopamine, GABA, glutamate, and acetylcholine circuits. GABA-A agonists such as benzodiazepines are frequently used for the treatment of catatonia because dopamine antagonists induce catatonia-like symptoms.[14] Previous studies showed that almost all patients initiated first-line treatment with oral lorazepam as soon as catatonia was diagnosed.[15] Deficiencies in GABA, dysfunction of the GABA receptors, and dysfunction and/or hyperactivity of NMDA receptors are believed to contribute to the motor symptoms and inhibition seen in patients with catatonia. The imbalance in the GABAergic inhibitory and glutamatergic excitatory pathways is thought to impair motor planning and execution, leading to motor symptoms, such as stupor

and ambitendency.[16] The NMDA antagonists amantadine and memantine are currently being studied in the treatment of catatonia.[17]

To the best of our knowledge, the patient is one of the few cases in the literature under the age of 18 who used amantadine for catatonia and who presented with catatonia as the first symptom of CD. To conclude, this case underlines the rare but possible associations between CD and catatonia as the onset symptom, even in the absence of gastrointestinal manifestations. Autoimmune investigations and early detection of the etiology of catatonia are crucial and may decrease further complications. In addition, the patient is important as one of the rare pediatric cases in the literature in which amantadine was used in the treatment of catatonia.

Ethical approval

Written informed consent was obtained from the patient's relatives as institutional review board accepted.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: PÖ, KG; data collection: PÖ, AEK, DKM, HÖ; analysis and interpretation of results: PÖ, AEK, DKM, HÖ, KG; draft manuscript preparation: PÖ, KG. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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