reports

MDPI

Case Report

Gluten Ataxia Associated with Dietary Protein Cross-Reactivity with GAD-65

Datis Kharrazian [1,2,3]

[1] Department of Neurology, Harvard Medical School, Boston, MA 02155, USA; Datis_Kharrazian@hms.harvard.edu
[2] Department of Neurology, Massachusetts General Hospital, Charlestown, MA 02155, USA
[3] Department of Preventive Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA

Received: 22 June 2020; Accepted: 24 August 2020; Published: 26 August 2020

Abstract: Cross-reactivity occurs when antibodies formed against an antigen have amino acid sequence homology with another target protein. This allows antibodies formed against the antigen to also bind to similar proteins that share structural similarity. Autoimmune reactions to gluten can lead to sporadic ataxia in susceptible genotypes due to cross-reactivity. With gluten ataxia, dietary consumption of gluten proteins induce immunological cross-reactivity with glutamic-acid decarboxylase-65 (GAD-65) target proteins found in the cerebellum. Implementation of a strict gluten-free diet has been shown to improve the expression of this form of ataxia with most patients in this subgroup. However, there are some subjects that have limited clinical responses to only a strict gluten-free diet. Dietary protein cross-reactivity to other food proteins, besides gluten, that also share structural similarity to GAD-65 may also play a role in this reaction. In this case report, we report of a patient suffering from gluten-ataxia in which a gluten-free diet alone did not generate significant clinical outcomes until other foods that cross-react with GAD-65 were also removed from their diet.

Keywords: idiopathic sporadic ataxia; GAD-65; cross-reactivity

1. Introduction

Gluten ataxia results from immunological damage to the cerebellum from gluten antibodies that cross-react with cerebellum tissue in genetically susceptible subgroups. Individuals suffering from gluten ataxia have been found to clinically improve when implementing a gluten-free diet due to cross-reactivity of dietary proteins with ataxia target sites, such as GAD-65 within the cerebellum in clinical settings [1].

Gluten ataxia should be considered in all patients with sporadic ataxia, regardless of whether they have abdominal symptoms; early diagnosis and treatment may result in neurological improvement [2]. Many patients with gluten ataxia do not demonstrate gastrointestinal manifestations but instead exhibit only cerebellum neurological deficits, while progressed individuals demonstrate cerebellum atrophy on MRI [3]. The diagnosis of gluten ataxia is vital as it is one of the very few treatable causes of sporadic ataxia.

Early diagnosis and treatment with a gluten-free diet can improve ataxia and prevent its progression [4]. However, there are subgroups of patients suffering from gluten ataxia that only have a partial resolution of their symptoms while implementing a gluten-free diet. It is not clear why these patients do not respond. It is possible that cross-reactivity to food proteins with GAD-65 other than gluten may be responsible for triggering sporadic ataxia and explain why a gluten-free diet alone is not sufficient for some gluten ataxia subjects. Patient consent was received to present this case report.

In this case report, we present a patient that had been diagnosed with gluten ataxia, celiac disease, and latent autoimmune diabetes of adulthood. His clinical presentation included sporadic truncal

ataxia, postural instability, progressive dizziness, vertigo, and fatigue. He only had a partial resolution of his ataxia and instability symptoms on a strict gluten-free diet.

2. Case Report

A 42-year-old male with chief complaints of dizziness, instability, nausea, and cognitive decline was previously diagnosed with celiac disease and type 2 diabetes at UCLA Medical Center. The patient had adopted a gluten-free diet for the past 3 years. These dietary changes had improved his gastrointestinal complaints, cognitive function, and his overall health significantly. In recent months he has noted limb tremor, postural instability especially while walking downstairs, and sporadic ataxia.

The patient has a family history that includes type 2 diabetes, cardiovascular disease, and autoimmunity. Both parents are living and suffer from obesity and diabetes. The father suffers from chronic depression and mood disorders, and his mother also has rheumatoid arthritis. The patient has no siblings, and there are no other relevant findings in the patient's family history.

The patient was evaluated in a private clinical practice approximately one year after evaluation at UCLA Medical Center. Physical examination findings identified patterns associated with both midline and lateral cerebellum degenerative disease that included a positive Romberg's test, termination tremor with targeting of the limbs, dysdiadochokinesia with repeated coordinated movements, and moderate ataxia. The patient exhibited no patterns of nystagmus or nystagmus with provocation of gaze, darkness, head position, head-shaking, hyperventilation, or sound. Hypometric saccades were identified in all fields of gaze. There were no abnormalities of the oculomotor system or patterns of dysarthric speech. There were no abnormal findings associated with motor or sensory pathways. Cognitive function was intact with no impairments in the following: attention, psychomotor speed, verbal memory, visuospatial function, emotions, or executive functions. Despite the abnormal cerebellar disease findings, the patient was in good health and displayed no other abnormalities during a comprehensive physical examination.

Non-contrast, T1 and T2-weighted images were conducted, and the images were found to be unremarkable. Normal signal intensity patterns and volume of the cerebellum, cerebellar hemispheres, and brainstem were reported. There were no shifts of midline structures or basilar invagination. Neurological autoantibodies were tested. The patient was tested for autoantibodies associated with latent autoimmune diabetes of adulthood, blood–brain barrier permeability, and neurological autoimmunity. The results found that myelin basic protein, synapsin, alpha and beta-tubulin, and asialoganglioside antibodies were all within normal reference ranges GAD-65; islet antigen antibodies (IA-2) and S100B autoantibodies were significantly elevated.

The clinical impression, at this time, was the development of both latent autoimmune diabetes of adulthood and cerebellum ataxia associated with GAD-65 antibodies that express in both cerebellum and pancreatic tissue with increased risk due to blood–brain barrier permeability. GAD-65 autoimmunity is associated with cerebellum disease and ataxia [2,3]. Antibodies to GAD-65 are also involved with autoimmune diabetes [5–9]. S100B is a neuromodulatory protein of astrocytes, and S100B antibodies are elevated during neuroinflammatory mechanisms that include injury to neurons and also with permeability of the blood–brain barrier [10]. Enzyme-linked Immunosorbent assay was used for all antibody measurements at a clinical laboratory improvement amendments (CLIA) certified laboratory.

The concern for cross-reactivity with other food proteins to GAD-65 and IA-2 have been reported in the literature. There are nine food proteins that share amino sequence protein homology with GAD-65 and 24 food protein antibodies that have been found to cross react with IA-2 [11,12]. This mechanism in combination with his findings of a compromised blood-brain barrier leads to the clinical investigation of other dietary proteins that may also cross-react with GAD-65.

A dietary protein profile using combined forms of IgA + IgG antibodies was conducted with 200 foods to evaluate for any dietary protein interactions. Enzyme-linked Immunosorbent assay was used for all antibody measurements at a CLIA certified laboratory. Positive dietary protein antibodies were compared to known cross-reactive dietary proteins with GAD 65 and IA-2 autoantibodies. Several

cross-reactive foods were identified including gluten, casein/milk AGF78, egg proteins, rice proteins, seaweed protein, spinach protein, and zucchini protein. A summary of all of the essential laboratory and imaging studies during the patient's chief complaints are listed in Table 1.

Table 1. Patients test results during presentation of chief complaints.

Laboratory Test and Special Studies	Results
Non-Contrast Brain MRI	Normal
Myelin Basic Protein Antibodies	Normal
Glutamic Acid Decarboxylase-65 Antibodies	Elevated
Islet Antigen Antibodies	Elevated
S100B Antibodies	Elevated
Asialoganglioside Antibodies	Normal
Alpha and Beta Tubulin Antibodies	Normal
Cerebellar Antibodies (Purkinje Cell Antigens)	Normal
Anti-Nuclear Antibodies	Normal
Fecal SIgA	Elevated
Hemoglobulin A1c	Elevated (6.1%)
Fasting Glucose	Elevated (110 mg/dL)
Total Cholesterol	Normal (88 mg/dL)
High-Density Lipoproteins (HDL) Cholesterol	Depressed (35 mg/dL)
Low-Density Lipoproteins (LDL) Cholesterol	Elevated (118 mg/dL)
Triglycerides	Elevated (175 mg/dL)
Cholesterol/HDL ratio	Elevated (5.4)
Thyroid Stimulating Hormone	Normal
C-Reactive Protein	Normal (0.37 mg/dL)
Complete Blood Count (CBC) with differential	Normal
Urinalysis	Normal
Gluten Antibodies	Elevated
Casein/Cow Milk AGF78 Antibodies	Elevated
Egg Proteins GF1 and F75 Antibodies	Elevated
Rice Protein	Elevated
Seaweed Protein	Elevated
Spinach Aquaporin	Elevated
Zucchini Protein	Elevated

The patient was placed on a restrictive diet to avoid these cross-reactive food proteins. Within the first 6 weeks, the patient noted significant changes in his cognitive function and his stability. He no longer had any symptoms of dizziness. Follow-up testing identified an improvement in his serum HbA1c levels and significant changes in his physical examination findings. There was a significant improvement in his balance and patterns of both trunk and limb ataxia. The patient continued this diet for an additional 6 months with no relapses and continued to improve with no identifiable patterns of ataxia or progression of his autoimmune diabetic pattern. His HbAlc levels returned to normal ranges within this time.

3. Discussion

In 1868, Jean-Martin Charcot was the first to describe the possibility of an immune-mediated mechanism leading to cerebellum neuroinflammation with characteristic relapsing and remitting courses of nystagmus, scanning speech, and ataxia [13]. Immune-mediated reactions against the cerebellum have the potential to induce disabling ataxia, and they are also classified as treatable ataxias. Therefore, identification of the trigger is critical in the management of neuroimmune ataxia. The key feature of neuroimmune ataxia is that it presents as sporadic ataxia. One study found that 60% of patients with sporadic ataxia presented cerebellum target protein antibodies compared to 5% of genetic ataxias [14]. In recent years, the concept of autoimmune and immune-related etiology of ataxia has become a more popular area of investigation. Researchers have identified several neuroimmune

mechanisms of cerebellar ataxias, including Hashimoto's antibody cross-reactivity, infection, primary autoimmunity, autoimmunity secondary to infection, neoplasm, and gluten sensitivity [15].

Hadjivassiliou et al., in the United Kingdom, found that immune reactivity to dietary gluten was the most prevalent cause of sporadic ataxia in a prospective study of 320 subjects [16]. The mechanism of cross-reactivity with cerebellum and anti-glidian proteins have been studied due to the structural homology between anti-cerebellar amino acid sequence (EDVPLLED) and anti-gliadin amino acid sequence (EQVPLVQQ) with immunoblot and inhibition studies [17]. Experimental evidence suggests cross-reactivity may occur between antigenic epitopes on GAD-65 and other cerebellar tissue proteins with gluten peptides [18]. Furthermore, Vojdani et al. demonstrated immune reaction of monoclonal anti-gliadin 33-mer to the cerebellum and GAD-65 proteins using dot-blot analysis to demonstrate cross-reactivity [19].

Individuals with gluten ataxia have gluten cross-reactive antibodies against cerebellum tissue (GAD-65 antibodies) leading to cerebellum pathology [18]. Gluten ataxia should be considered in all patients with sporadic ataxia, regardless of whether they have abdominal symptoms; early diagnosis and treatment may result in neurological improvement [2].

Many patients with gluten ataxia do not demonstrate gastrointestinal manifestations but instead only exhibit cerebellum neurological deficits, while progressed individuals demonstrate cerebellum atrophy on MRI [3]. The diagnosis of gluten ataxia is critical as it is one of the very few treatable causes of sporadic ataxia. Early diagnosis and treatment with a gluten-free diet can improve ataxia and prevent its progression [4]. In some susceptible individuals, other dietary proteins may also cross-react with cerebellum target proteins (GAD-65) and lead to cerebellum degeneration and the presentation of cerebellar disease clinical findings, such as ataxia, intention tremor, and nystagmus, as noted with our clinical case [16].

Gluten ataxia is one of the rare forms of ataxias in which a gluten-free diet alone can effectively stop the progression of the disease. Removal of the antigenic trigger can effectively reduce the neuroinflammatory response to the cerebellum, however some degree of cerebellum injury persists, and ongoing refractory symptoms associated with cerebellum injury can persist, such as postural instability, dizziness, dysmetria, etc. [20].

Early detection and removal of the antigen is essential to preserve cerebellum tissue integrity and to avoid refractory patterns of cerebellum injury. Immunosuppression and pharmacotherapy are not standard forms of treatment for gluten ataxia; however, physical rehabilitation to improve cerebellum plasticity may have some promise [21].

4. Conclusions

In conclusion, this case report highlights two important clinical considerations. First, the clinical presentation of latent autoimmune diabetes of adulthood in combination with idiopathic sporadic ataxia suggests the possibility of GAD-65 autoimmune reactivity, since this target protein is co-expressed in both pancreatic and cerebellum tissue. Second, the role of dietary protein cross-reactivity with specific autoimmune target sites, such as GAD-65 may have a potential role in diet modification in susceptible individuals.

Although gluten protein immune reactivity in susceptible individuals has received much of the focus regarding food proteins triggers for ataxia, current cross-reactive research suggests other food proteins may also play an antigenic role in cerebellum neuroimmune reactions to dietary proteins. Potential antigen–antibody epitope binding with food antigens at specific cerebellum target sites leads to possibilities that may explain the etiology of some cases of idiopathic ataxia and why some individuals with gluten ataxia who implement a gluten-free diet do not improve.

A novel finding of this case report is that dietary proteins besides gluten may also cross-react with gluten-ataxia target sites. The current literature has only emphasized the implementation of a gluten-free diet alone for gluten ataxia. This case study illustrates the potential need to implement

dietary restrictions of other cross-reactive dietary proteins in addition to gluten, especially when patients have a limited response to a strict gluten-free diet.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Hadjivassiliou, M.; Aeschlimann, D.; Grünewald, R.A.; Sanders, D.S.; Sharrack, B.; Woodroofe, N. GAD antibody-associated neurological illness and its relationship to gluten sensitivity. *Acta Neurol. Scand.* **2011**, *123*, 175–180. [CrossRef]
2. Ghazal, F.A.; Singh, S.; Yaghi, S.; Keyrouz, S.G. Gluten ataxia: An important treatable etiology of sporadic ataxia. *Int. J. Neurosci.* **2012**, *122*, 545–546. [CrossRef] [PubMed]
3. Hadjivassiliou, M.; Grünewald, R.A.; Chattopadhyay, A.K.; Davies-Jones, G.A.; Gibson, A.; Jarratt, J.A.; Kandler, R.H.; Lobo, A.; Powell, T.; Smith, C.M. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. *Lancet* **1998**, *352*, 1582–1585. [CrossRef]
4. Hadjivassiliou, M.; Sanders, D.S.; Woodroofe, N.; Williamson, C.; Grünewald, R.A. Gluten ataxia. *Cerebellum* **2008**, *7*, 494–498. [CrossRef] [PubMed]
5. Vianello, M.; Tavolato, B.; Giometto, B. Glutamic acid decarboxylase autoantibodies and neurological disorders. *Neurol. Sci.* **2002**, *23*, 145–151. [CrossRef] [PubMed]
6. Mitoma, H.; Nanri, K. Autoantibodies associated with autoimmune-mediated cerebellar ataxia. *Brain Nerves* **2013**, *65*, 355–364.
7. Narayanan, S. Molecular mimicry: Basis for autoimmunity. *Indian J. Clin. Biochem.* **2000**, *15* (Suppl. 1), 78–82. [CrossRef]
8. Moinuddin; Ansari, N.A.; Shahab, U.; Habeeb, S.; Ahmad, S. Immuno-chemistry of hydroxyl radical modified GAD-65: A possible role in experimental and human diabetes mellitus. *IUBMB Life* **2015**, *67*, 746–756. [CrossRef]
9. Jayakrishnan, B.; Hoke, D.E.; Langendorf, C.G.; Buckle, A.M.; Rowley, M.J. An analysis ofthe cross-reactivity of autoantibodies to GAD65 and GAD67 in diabetes. *PLoS ONE* **2011**, *6*, e18411. [CrossRef]
10. Koh, S.X.; Lee, J.K. S100B as a marker for brain damage and blood-brain barrier disruption following exercise. *Sports Med.* **2014**, *44*, 369–385. [CrossRef]
11. Kharrazian, D.; Herbert, M.; Vojdani, A. Detection of Islet Cell Immune Reactivity with Low Glycemic Index Foods: Is This a Concern for Type 1 Diabetes? *J. Diabetes Res.* **2017**, *2017*, 4124967. [CrossRef] [PubMed]
12. Banchuin, N.; Boonyasrisawat, W.; Vannasaeng, S.; Dharakul, T.; Yenchitsomanus, P.T.; Deerochanawong, C.; Ploybutr, S.; Sriussadaporn, S.; Pasurakul, T. Cell-mediated immune responses to GAD and beta-casein in type 1 diabetes mellitus in Thailand. *Diabetes Res. Clin. Pract.* **2002**, *55*, 237–245. [CrossRef]
13. Charcot, J.M. Séance du 14 mars. *CR Soc. Biol.* **1868**, *20*, 13.
14. Hadjivassiliou, M.; Boscolo, S.; Tongiorgi, E.; Grünewald, R.A.; Sharrack, B.; Sanders, D.S.; Woodroofe, N.; Davies-Jones, G.A. Cerebellar ataxia as a possible organ-specific autoimmune disease. *Mov. Disord.* **2008**, *23*, 1370–1377. [CrossRef]
15. Mitoma, H.; Adhikari, K.; Aeschlimann, D.; Chattopadhyay, P.; Hadjivassiliou, M.; Hampe, C.S.; Honnorat, J.; Joubert, B.; Kakei, S.; Lee, J.; et al. Consensus Paper: Neuroimmune Mechanisms of Cerebellar Ataxias. *Cerebellum* **2016**, *15*, 213–232. [CrossRef]
16. Hadjivassiliou, M.; Grünewald, R.; Sharrack, B.; Sanders, D.; Lobo, A.; Williamson, C.; Woodroofe, N.; Wood, N.; Davies-Jones, A. Gluten ataxia in perspective: Epidemiology, genetic susceptibility and clinical characteristics. *Brain* **2003**, *126 Pt 3*, 685–691. [CrossRef]
17. Vojdani, A.; O'Bryan, T.; Green, J.A.; Mccandless, J.; Woeller, K.N.; Vojdani, E.; Nourian, A.A.; Cooper, E.L. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. *Nutr. Neurosci.* **2004**, *7*, 151–161. [CrossRef]
18. Hadjivassiliou, M.; Boscolo, S.; Davies-Jones, G.A.; Grünewald, R.A.; Not, T.; Sanders, D.S.; Simpson, J.E.; Tongiorgi, E.; Williamson, C.A.; Woodroofe, N.M. The humoral response in the pathogenesis of gluten ataxia. *Neurology* **2002**, *58*, 1221–1226. [CrossRef]

19. Vojdani, A.; Tarash, I. Cross-reaction between gliadin and different foods and tissue antigens. *Food Nutr. Sci.* **2013**, *4*, 20–32. [CrossRef]
20. Mitoma, H.; Manto, M.; Hampe, C.S. Immune-mediated Cerebellar Ataxias: Practical Guidelines and Therapeutic Challenges. *Curr. Neuropharmacol.* **2019**, *17*, 33–58. [CrossRef]
21. Manek, S.; Lew, M.F. Gait and Balance Dysfunction in Adults. *Curr. Treat Options Neurol.* **2003**, *5*, 177–185. [CrossRef] [PubMed]