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The Final thesis

Gluten Ataxia in Older Adult Patients. Case Report and Literature Review

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Summary

Late onset cerebellar ataxias have many possible aetiologies, immune mediated gluten ataxia being one of them. Gluten ataxia is autoimmune disorder characterised by cerebellar injury caused by exposure to gluten in sensitive and genetically susceptible individuals. Celiac disease is a gluten-induced autoimmune disorder causing intestinal and extraintestinal symptoms. Gluten ataxia is one of the extraintestinal manifestations. Gluten ataxia manifests with progressive neurological symptoms, like gait ataxia, dysarthria, and nystagmus without autonomic dysfunction. Most patients deteriorate gradually but in rare cases onset is rapid with devastating outcomes. Pathophysiology of gluten ataxia is the damage of mainly Purkinje cells due to inflammatory and immunological processes. Also, anti-gliadin antibodies can have a clinically significant direct or indirect neurotoxic effect. Malabsorption of vitamin E due to villous atrophy is shown to cause spinocerebellar degeneration and damage to the serotonin-containing neurons in the cerebellum and brainstem. Comorbidity with multiple autoimmune diseases is often associated in immune-mediated cerebellar ataxia. Gluten sensitivity relates to glutamic-acid decarboxylase antibody associated disease. There are also other specific antigenic triggers and pathogenic antibodies that are still unidentified. Diagnostic approach to gluten ataxia includes serum serology testing for anti-gliadin antibodies and other antineuronal antibodies, possible biopsy aiming to confirm celiac disease, and head magnetic resonance imaging study. Treatment for gluten ataxia is strict gluten free diet, which can lead to clinical improvement of the symptoms. In rapid-onset course patients can benefit from immunosuppressive medication and immunoglobulin therapy. Sometimes the damage for neuronal cells is irreversible.

Keywords: gluten ataxia, cerebellar ataxia, celiac disease, autoimmune ataxia, late-onset ataxia, anti-gliadin antibody, glutamic acid decarboxylase antibody.

Introduction

Clinically, cerebellar ataxia denotes a loss of balance and coordination. In addition, ataxia can be caused by abnormalities in multiple regions of the nervous system (for example, cerebellum, brainstem, spinal cord, and peripheral nerves) (1).

Cerebellar ataxia is a frequent discovery in neurological field and its causes are diverse. Ataxias can be classified into six main categories: autosomal dominant spinocerebellar ataxias, autosomal recessive ataxias, congenital ataxias, mitochondrial ataxias, X-linked cerebellar ataxias, and sporadic or acquired ataxia (1). Early onset ataxia has either congenital or

autosomal etiology. When ataxia has a late onset, there is a very wide amount of differential diagnosis which sometimes makes challenges to get to the diagnosis.

The aim of the thesis is to discuss the differential diagnosis of late onset cerebellar ataxias, to present the rare immune mediated gluten ataxia form and its manifestation in elderly patient.

International cases of patients who were diagnosed with gluten ataxia, the symptoms they experienced, their medical history including their initial symptoms, diagnostic tests, and treatment options that were considered and applied will be discussed in this thesis. Comparison of the cases found by the search from databases are compared to the case report from Lithuania.

The challenges of diagnosing and managing gluten ataxia, as well as the potential impact of the condition on the patient's daily life are discussed. This complex condition and its potential irreversible neurological consequences of gluten sensitivity are looked thorough the literature and case review. The importance of early diagnosis and appropriate treatment are discussed as well as the prognosis of this condition.

Researches and material for the work that were searched from the Pubmed, UpToDate, New England Medical Journal, Cochrane Library and Medscape by using terms gluten ataxia, cerebellar ataxia, gluten ataxia in elderly, celiac disease, celiac disease and neurological complications, autoimmune ataxia, anti-glutamic acid decarboxylase antibody, anti-GAD antibodies, Glutamic acid decarboxylase 65 autoimmune ataxia.

While preparing the material for this work, both cases and literature were searched from the above-mentioned databases. “Gluten ataxia case” keyword was used in Pubmed without limiting the publication year. Systematic search yielded 36 articles from the database. Two case reports of adult-onset gluten ataxia and one case series that was containing three separate cases was found and used in the work. Searching was also made by using keywords “gluten ataxia in elderly case” but that search provided fourteen articles from which two were cases already found by the previous search. Cases which were covering celiac disease and some other neurological manifestations like neuropsychiatric symptoms or cases in which the patient was juvenile were excluded. Since gluten ataxia is a rare neurological disease, not many cases are published about that disease.

Patient of the clinical case report from Lithuania has given her informed consent to use her medical data, imaging study materials and pictures and laboratory test results in this work.

Late (adult) onset cerebellar ataxias and its differential diagnosis

Cerebellar ataxia refers to large pool of neurological disorders among which ataxia is the main symptom. Clinically we see this as a loss of balance and coordination. Ataxia may be caused by dysfunction in many parts of the nervous system like cerebellum, brainstem, spinal cord, and peripheral nerves. (1).

Cerebellar ataxia is frequently encountered in neurological practice and has a wide variety of etiologies (Table 1). Ataxias have six major groups: autosomal dominant spinocerebellar ataxias, congenital ataxias, mitochondrial ataxias, autosomal recessive ataxias, X-linked cerebellar ataxias and sporadic or acquired ataxia (1).

There are two main types of ataxia: those that are inherited (whether or not there is a family history of the disease) and those that are learned or get worse over time. "Sporadic" term means that there is no history of it in the family. Progressive acquired ataxias can be immune-mediated (e.g., paraneoplastic spinocerebellar degeneration, gluten ataxia), degenerative (e.g., cerebellar variant of multiple systems atrophy (type C)), caused by nutritional deficiencies (e.g., vitamin B12, vitamin E, etc.), caused by toxicity (e.g., alcohol-related ataxia, phenytoin), or linked to infections (HIV, sporadic Creutzfeldt-Jakob disease, progressive multifocal leucoencephalopathy, and so on). Ataxias that are passed down can be passed down through the X chromosome, the mitochondria. Even though metabolic disorders like Niemann-Pick type C and Tay-Sachs disease are "inherited," they can show up as late-onset ataxia in people who don't have a family history of them. This shows how important it is to carefully look at the patient and do thorough and proper laboratory testing (2).

Table 1. *Etiology of ataxia.*

ETIOLOGY OF ATAXIAS	
Congenital, hereditary	AD, AR, X-linked
Mitochondriopathies	
Toxic origin	Alcoholic degeneration, CO, medicinal, insecticides, other toxins, extrapontine demyelination, hepatocerebral degeneration
Metabolic origin	Hypomagnesemia, hypoparathyroidism, hypothyroidism
Infectious origin	

Vascular	Stroke, superficial siderosis, vertebo-basilar insufficiency, AV stenosis, Steal syndrome
Hypovitaminosis	Vitamin B12, Vitamin E, Wernicke-thiamine, Zn deficiency
Neoplasms and paraneoplastic	
Autoimmune diseases	Acute disseminated encephalomyelitis, Bickerstaff brain stem encephalitis, Miller Fischer syndrome, Celiac disease (gluten enteropathy with ataxia), GAD Ab related, Hashimoto's thyroiditis, Histiocytosis X, Neurosarcoidosis, Vasculitis.
Neurodegenerative diseases	Multiple sclerosis atrophy, Progressive supranuclear palsy, Neuroacanthocytosis, Pantothene kinase neurodegeneration

As table 1 presents, there is a wide pool of different etiologies of cerebral ataxia from hereditary to acquired etiology. That creates a challenge for a clinician to consider possible etiologies in a given symptoms of a patient, run necessary investigation and set a correct diagnosis for a prompt and timely treatment (3). Onset and duration of an ataxia is an important factor directing physician towards diagnosis. Careful interview of the patient and relatives helps to rule out less possible causes of ataxia (4). In table 2 is described different causes of cerebellar ataxia in the light of time, from acute presentation of symptoms to chronic.

Table 2. *Causes of cerebellar ataxia according to the timeframe.*

Acute Causes of Cerebellar Ataxia (Minutes to a Few Days)	**Subacute Causes of Cerebellar Ataxia (Weeks to Months)**
Vascular causes: ischemic or hemorrhagic cerebellar strokes	Paraneoplastic cerebellar degeneration
Ethanol intoxication	Brain tumors
Toxins (mercury, thallium, toluene, solvents)	Creutzfeldt-Jakob disease
Medication (phenytoin, carbamazepine, phenobarbital, lithium)	Superficial siderosis
Multiple sclerosis	Anti–glutamic acid decarboxylase ataxia
Meningitis, particularly basilar meningitis	
Viral cerebellitis	
Cerebellar abscess	

Wernicke encephalopathy/thiamine deficiency	
Chronic Causes of Cerebellar Ataxia (Months to Years)	**Episodic Causes of Cerebellar Ataxia**
Ataxia associated with gluten sensitivity	Genetic episodic ataxia
Genetic ataxia	Psychogenic ataxia
Mitochondrial disease	Mitochondrial disease
Multiple system atrophy	
Idiopathic late-onset cerebellar ataxia	

Celiac disease and its neurological complications

Gluten sensitivity develops in genetically predisposed individuals in response to wheat gluten and related proteins. Patients with this disorder exhibit a wide range of manifestations, from clinically asymptomatic features to incapacitating disorders such as celiac disease. Celiac disease is an autoimmune enteropathy induced by the gluten sensitivity in people who are prone to it. Celiac disease is a multisystemic dietary, gluten-induced autoimmune disorder usually characterized by the presence of transglutaminase (TG) 2 serum autoantibodies. Autoantibodies that target members of the TG enzyme family (TG2, TG3, and TG6) are deposited in the small-bowel mucosa and extraintestinal tissues. Patients with untreated celiac disease develop autoantibodies to other self-antigens in their serum (5). Celiac disease is a common gluten related disease (GRD) in which genetic and environmental factors and gluten intolerance are the major causes of innate and adaptive immune responses. Celiac disease is characterized by small intestine mucosal lesions, subtotal, or total intestinal villi atrophy and nutrient malabsorption. The global prevalence of celiac disease is estimated at 1–2% in the general population and 0.3–2.9% in children (6).

Gluten related diseases are estimated to have a global prevalence of approximately 5%. Until two decades ago, celiac disease and other gluten related diseases were considered to be almost exclusively found in European populations. Advances in the manufacture of sensitive and specific serological tests have resulted in an increase in the diagnosis of gluten-related diseases and recognition of these conditions as a major global health concern (7). Collin et al. (8) showed in their research that celiac disease not uncommonly presents for the first time in older patients and is an important diagnosis to make. In their review was noted that approximately 25 percent of all diagnoses of celiac disease are made for patients at age 60 or more and 20 percent for

patients over 65 years of age. Approximately 4 percent is diagnosed for patients at 80 or above. They concluded that celiac disease is often not detected in elderly people and active serological screening for risk groups who would benefit of following gluten free diet would prevent severe complications like bone fractures (8).

It is important to mention non-celiac gluten sensitivity (NCGS) which is a clinical entity characterized by the absence of celiac disease and wheat allergy in patients that trigger reproducible symptomatic responses to gluten-containing foods consumption. Since NCGS was recently recognized as a clinical entity, more studies are needed to clear out NCGS pathogenesis, for instance, the molecular interactions between the suspected cereal grain components that trigger NCGS. Yet the prevalence and relevance of NCGS in different populations is still studied, the clinical importance of NCGS might be high (9).

Neurological manifestation of celiac disease was first described by Cooke and Smith (10) in 16 patients in 1966. Since then, several conditions have been reported in association with celiac disease, such as sensory ataxia or mixed type ataxia, epilepsy, anxiety, depression, encephalitis, occipital calcification, peripheral neuropathy, neuromuscular disorders, dementia, learning disorders such as attention deficit hyperactivity disorder, developmental delay and migraine (10).

Manifestations of celiac disease can include a broad spectrum of musculoskeletal, neurological, cardiovascular, and autoimmune disorders. Most notably, peripheral neuropathies and gluten ataxia are frequent neurological manifestations of celiac disease. Many patients who present with neurological manifestations of celiac disease have no gastrointestinal symptoms (11).

Celiac disease patients with ataxia often present with difficulty with arm and leg control, gait instability, poor coordination, loss of fine motor skills such as writing, problems with talking, and visual issues. Other neurological symptoms include encephalopathy, myopathy, myelopathy, ataxia with myoclonus, and chorea (11).

Gluten ataxia

Gluten ataxia (GA) typically manifests gradually, with a mean onset age of 53 years. Patients with gluten ataxia may exhibit signs of irreversible and difficult-to-treat cerebellar atrophy. GA is a type of cerebellar ataxia induced by gluten exposure in genetically susceptible and gluten-sensitive individuals. Gluten ataxia was first defined in 1996 as idiopathic sporadic ataxia in patients with anti-gliadin antibodies (AGA) positivity. Patients with Celiac disease and gluten ataxia have oligoclonal bands in their cerebrospinal fluid, evidence of perivascular

inflammation in the cerebellum, and antibodies against Purkinje cells (11). GA is an autoimmune disorder that results in a cerebellar damage that primarily affects Purkinje cells (12). In most cases there has been a previous diagnosis of celiac disease or non-celiac gluten sensitivity with digestive symptoms. Taraghikhah et al. (7) refer to several studies which have identified possible mechanisms for the development of gluten ataxia in celiac disease. Impaired intestinal absorption can cause vitamin E deficiency and further spinocerebellar degeneration. Malabsorption can also harm the serotonin-containing neurons in the cerebellum as well as brainstem. Immunological and inflammatory processes may also be important in the aetiology of gluten ataxia. There is a cross-reactivity between antigenic epitopes located at the level of Purkinje cells and gluten-related antibodies. Anti-gliadin antibodies may be toxic to neurones directly or indirectly that is clinically significant in susceptible individuals. (7). In the review of autoantibodies that occur in the relation of celiac disease Caja et al. (5) mention that GA patients have celiac-specific TG2-targeted IgA deposits in the duodenal mucosa as well as in brain blood vessels. Also, serum autoantibodies in GA patients recognize a neuronal transglutaminase, TG6. Hadjivassiliou et al. (12) estimated that GA is responsibe for approximately 15% of all ataxias and 40% of all idiopathic sporadic cerebellar ataxias. Gluten ataxia is more common in the USA and Europe compared to Asia. It most commonly affects males and females that are above 50 years of age (7).

The clinical manifestations of gluten ataxia are similar to those of other ataxias and include ocular signs like gaze-evoked nystagmus (84%), dysarthria (66%), upper limb ataxia (75%), lower limb ataxia (90%), gait ataxia (100%) and additional movement disorders, for example myoclonus, chorea, palatal tremor and opsoclonus myoclonus. Gluten ataxia is characterized by gradual onset of gait ataxia, associated with peripheral neuropathy. Sometimes, however, its progression can be comparable to that of paraneoplastic cerebellar degeneration. The absence of autonomic dysfunction distinguishes these patients from those with multiple system atrophy of the cerebellum (MSA-C) (7).

Gluten ataxia in elderly patients

By systematic search from the medical databases we found five consistently described case reports of adult-onset gluten ataxia.

Khwaja et al. (13) presented a case of a 35-old male, who had a one year history of gradually progressive slurring of speech, clumsiness of hands and gait disturbance. His condition was worsening in months, and he needed support for walking and his speech became progressively

difficult to understand. In addition to neurological complaints, he was suffering from chronic diarrhea without abdominal pain. Routine laboratory blood tests were all in the normal range. Blood test was positive for antigliadin antibody but negative for anti ATTG (tissue trans-glutamase) antibody. Magnetic resonance imaging study of the brain showed pancerebellar atrophy. Duodenal biopsy was without villous atrophy. A strict gluten free diet was started for the patient and his clinical condition with gait ataxia and dysarthria improved in 3 months follow up around 40 % (13).

Newrick et al. (14) present in their case series three patients with rapid-onset gluten ataxia, an immune-mediated cerebellar ataxia due to gluten sensitivity. 34-year-old male with a one year history of progressively blurring speech, difficulty of walking and frequent vomiting. When presenting, he had had a two-week lasting period of ear pain, vomiting and unsteadiness. These symptoms were thought initially to be a viral infection. Serum autoimmune and paraneoplastic antibody testing were unremarkable. There were marked vermis abnormalities in MRI and magnetic resonance spectroscopy (MRS). Duodenal biopsy showed no enteropathy. Results showed an elevated IgG anti-gliadin antibody (3.6 U/ml, abnormal > 3) and he was positive for HLA-DQ2 (DQB1*02). 34-year-old patient started treatment with prednisolone (20 mg once daily), a course of intravenous immunoglobulin (IVIG) and mycophenolate, and gluten free diet. Gradual and sustained clinical improvement was noted (14).

In a case of a 19-year old male (14), patient presented with 12-month history of progressive speech disturbance, difficulties swallowing, coordination impairment, imbalance and intermittent abdominal pain and diarrhoea. At the time of referral he was using thickened fluids and needed the assistance of one and a frame to be able to move. In physical examination he had cerebellar syndrome with pyramidal signs and pseudobulbar affect. He was dysarthric and could only use the words yes and no. IgA anti-transglutaminase type 6 (TG6) antibodies were positive (11.1 U/ml, normal range < 4), referring to gluten sensitivity. An MRI of the head and MRS demonstrated mild cerebellar vermian and hemispheric atrophy with spectroscopic abnormalities (N-acetylaspartate/Creatine ratio (NAA/Cr) superior vermis 0.63 and right cerebellar hemisphere 0.67). There were significant brainstem changes with signal change affecting the midbrain and extending into the thalamus and corticospinal tracts bilaterally, with no enhancement. Gluten ataxia was diagnosed and patient started a gluten free diet and mycophenolate following an induction course of IVIG, approximately 14 months after symptom onset. Neurorehabilitation was started. 3 months later MRI spectroscopy was done and there was evidence of improvement (NAA/Cr vermis 0.79 and right cerebellar 0.85) with

persistent cerebellar atrophy and diencephalic signal changes. In 3 year follow up the patient had significant improvement of mobility and speech. He has only a minimal dysarthria and recidual gait ataxia is shown only in tandem walking (14).

A 48-year-old man (14) was referred to the Sheffield Ataxia Centre following rapid onset of double vision, slurred speech and imbalance 2 years prior. His symptoms were previously static but couple of weeks after onset his mobility decreased to a level in which he needed to use wheelchair to moving. He was diagnosed with viral cerebellitis and treated with IV methylprednisolone, aciclovir, and later oral steroids. This treatment provided only a minimal improvement of symptoms. He received no further immunosuppression. MRI imaging demonstrated cerebellar signal change referring to cerebellitis with later progressive cerebellar atrophy. In patients family history his mother had dermatitis herpetiformis and brother coeliac disease. Before the referral, he had started a gluten free diet. On referral, physical examination demonstrated a cerebellar syndrome with gaze-evoked nystagmus, downbeat nystagmus in primary gaze, hypometric saccades, broken pursuit, severe dysarthria, severe limb dysmetria with mild asymmetry and gait ataxia. He required the assistance of two people to transfer. There also of myoclonus, prominent in the left upper limb, but not stimulus sensitive. As he had already been on a strict gluten free diet, all antigliadin antibodies were negative. Autoimmune and paraneoplastic antibodies, including glutamic-acid decarboxylase antibody (GAD), onconeuronal, anti-glycine receptor (anti-GlyR) and IgG dipeptidyl-peptidase–like protein 6 (anti-DPPX) were negative. MRI head and MRS performed on referral (2 years into the illness), showed established cerebellar vermian and hemispheric atrophy with spectroscopic abnormalities (superior vermis NAA/Cr 0.7, right hemisphere 0.89). Duodenal biopsy, that was performed after 12 months of a gluten free diet, demonstrated increased intraepithelial lymphocytes consistent with a gluten sensitive enteropathy (Marsh grade 1) but without evidence of refractory coeliac disease. A diagnosis of gluten ataxia was made and a tapering dose of steroids was continued. No more immunosuppression was given, since patient had static symptoms and an antibody/endoscopic response to a gluten free diet with stable MRS. His mobility has stayed stable over 5 years (14).

Jain et al. (15) presented a 45-year-old female with a speech and walking impairment over the past two years with exacerbation for the last 2 months. She could not stand without support, her speech was shortening into syllables and later became impossible to understand by the hearers. She had no history of chronic illnesses or gastrointestinal symptoms like diarrhea. The patient had bilateral cerebellar signs, with nystagmus, dysdiadochokinesia, scanning speech,

inability to complete point-to-point movement evaluation tests (finger-nose-finger test, heel to shin coordination test). In the laboratory tests both Ig ATTG and IgG anti-gliadin antibodies were markedly elevated. Endoscopic examination and histopathological evaluation revealed marked villous atrophy with presence of intraepithelial lymphocytosis consistent with celiac disease. Patient started gluten free diet which led to drastic improvement in the follow up. Her speech improved and to some extent her gait showed improvement as well. She could now take few steps with support (15).

Newrick et al. (14) state that the cerebellum appears particularly susceptible to autoimmunity. Emerging evidence suggests that a substantial proportion of idiopathic sporadic cerebellar ataxias may be immune-mediated disorders, with implications for early diagnosis and immunotherapy. While paraneoplastic cerebellar degeneration and gluten ataxias are well characterized immune-mediated cerebellar ataxias (IMCAs) for many diseases, a specific antigenic trigger or pathogenic antibody has not yet been defined. In these cases, an immune etiology is inferred based on the presence of autoimmunity markers (such as non-pathogenic autoantibodies, CSF-restricted oligoclonal bands, or pleocytosis), the co-occurrence or family history of autoimmune disease, and no evidence of a family history that would indicate a genetic ataxia. Rather than being pathogenic, associated antibodies may constitute an autoimmune epiphenomenon. Associated antibodies may represent an autoimmune epiphenomena rather than be pathogenic. In contrast to the ‘global’ cerebellar dysfunction of genetic and degenerative ataxias, immune-mediated cerebellar ataxias are associated with a 'midline' cerebellar phenotype in which gait ataxia is out of proportion to limb, speech, and ophthalmic manifestations. Neuroimaging studies support a predilection for the vermis, with evidence of selective magnetic resonance spectroscopic changes NAA/Cr that correspond to clinical severity, even prior to the appearing of atrophy. Symptoms typically manifest in middle age, with a gradual onset and progression (14).

Clinical case report

On 10th of January 2023, 82-year-old woman presented to outpatient department in Republican Vilnius University hospital. She complained of progressive gait disorder, difficulty maintaining balance, impaired coordination and frequent falls. On December 19th, 2022, there was an episode when she stumbled and had weakness in all limbs therefore she was unable to get up. Her speech was clearly impaired and her articulation became disturbed. These symptoms lasted up to 10-20 minutes, after which she recovered. She was admitted to emergency room. At the

hospital high blood pressure was found, and after correction, she was discharged home. Patient also complained about loss of appetite and bad memory, and tremor in both hands and chin.

An morbi: The symptoms started about 1 year ago, when her balance worsened. After the imbalance progressed, she started tripping and falling (without loss of consciousness) and started to use a cane. Due the symptoms she avoided leaving the home. About 2 years ago, she noticed that her chin trembled with both hands at rest. During action tremor becomes more pronounced. Propranolol was prescribed without any effect. At the same time, the relatives noticed a deteriorating memory, loss of appetite and weight.

An vitae: The patient's daughter describes that in last few months, her weight dropped significantly. The patient herself does not emphasize the weight loss but claims that she has no appetite and denies other digestive disorders. 2 years ago, patient was suffering of hair loss and after the careful examination autoimmune thyroiditis was diagnosed, a course of treatment with Thyroxine was prescribed. The patient has poorly corrected arterial hypertension, and in year 2021 and in 2022 there was a paroxysm of atrial fibrillation but anticoagulant treatment was not prescribed for a long-time treatment.

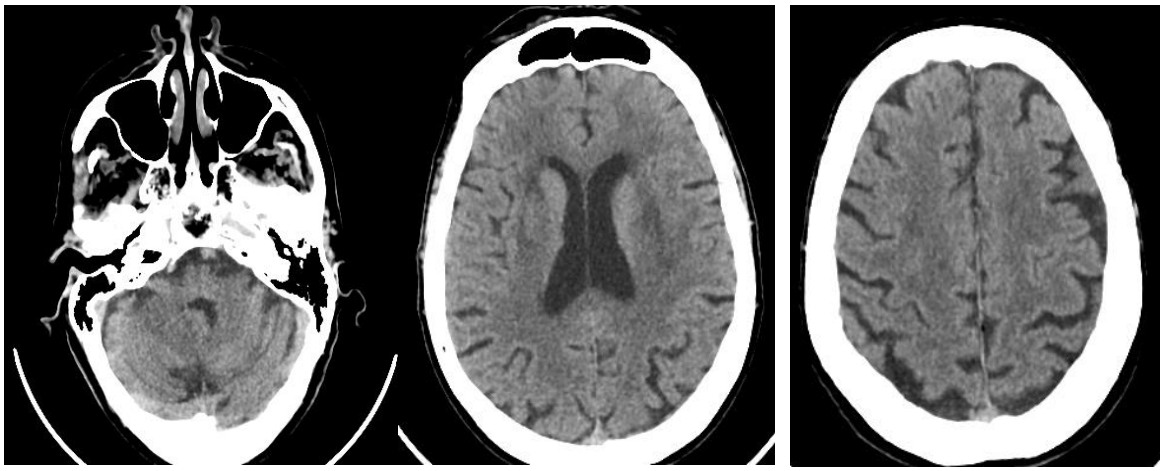
On neurological examination patient has spontaneous direction - changing horizontal and down beating vertical nystagmus. There were no sensory and autonomic disturbances. Muscle strength, tone and tendon reflexes was normal in all limbs.

Coordination tests reveal bilateral ataxia and intense tremor in limbs, pronounced static ataxia and the Romberg test was negative. Slight tremor of the chin, positional tremor of both hands was noticed. Mini mental state examination was 25 points.

Preliminary diagnosis of undetermined ataxia was made and the patient was hospitalized to the neurology department for further investigation.

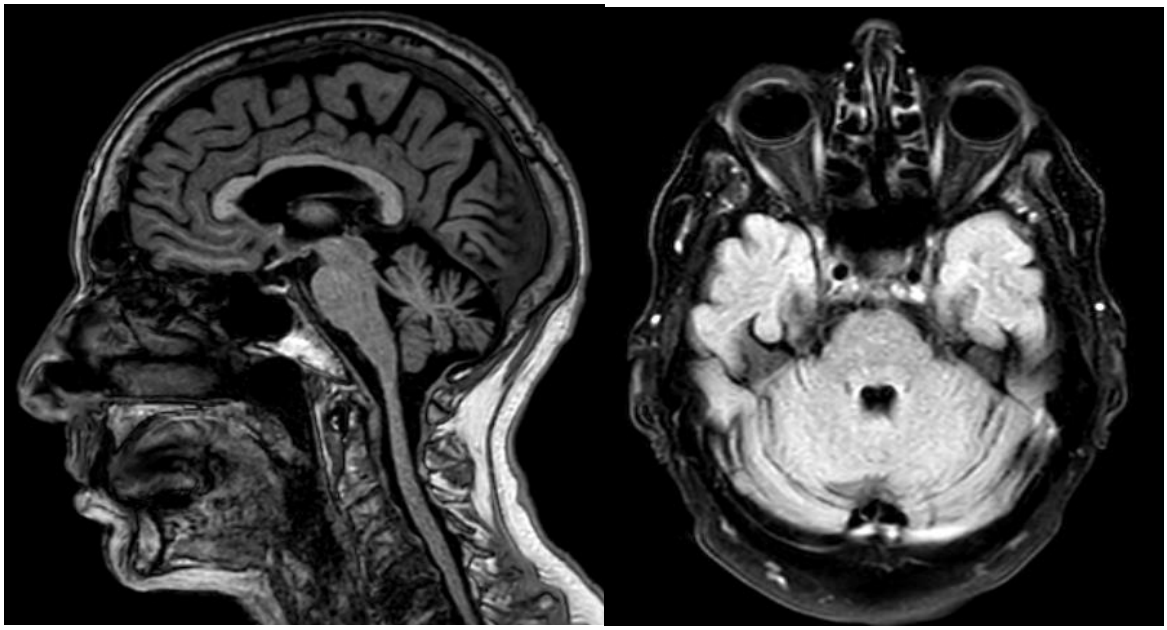
The complete blood count was normal. Biochemical blood test showed normoglycemia, normal kidney function, normal electrolytes and no rise in inflammation markers. Lipidogram revealed elevated cholesterol level (6.29 mmol/l, normal: 0.00 – 5.20 mol/l) and low-density lipoproteins LDL 4.09 mmol/l (normal 2.60 - 3.50 mmol/l. The urine, coagulation and thyroid hormone tests was normal, but antithyroid microsomal antibodies was significantly elevated (ATPO >1000kIU (normal range <5,61kIU). Level of vitamin B12 was on the lower normal range (30.90 pmol/L.normal 25.10 - 165.00 pmol/L), Folic acid was also low: 6 nmol/l (normal 7.02 – 46.43nmol/l).

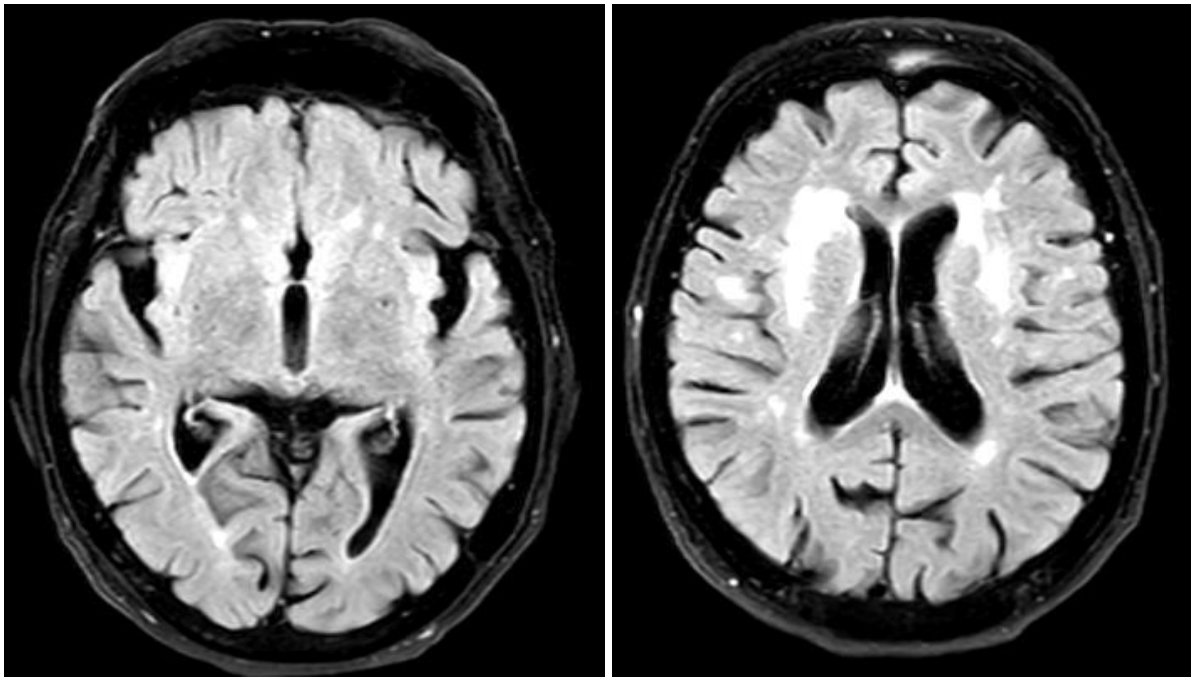
Several instrumental studies were performed. Patient went through a non contrast head computer tomography (CT) imaging. Any of acute pathology were not visible in the brain. Vascular leukoencephalopathy was seen (Picture 1).



Picture 1. *Computer tomography image of the patient's head in January 2023. In the sub- and supratentorial brain there were no focal changes. Periventricularly lower density zones. The ventricular system is moderately dilated.*

After the negative CT, the brain magnetic resonance imaging (MRI) was peformed. The MRI showed vascular leukoencephalopathy (Fazek II). Acute focal foci were not observed. In angiograms right posterior cerebral artery of fetal type, hypoplasia of its P1 segment was found.





Picture 2. *MRI of the brain in January 2023. Multiple hyperintense foci of various sizes are observed in T2 sequences in the deep white matter of the cerebral hemispheres/periventricularly, more bifrontally, converging foci without positive diffusion restriction. Similar small foci in the bridge. The ventricular system is moderately dilated.*

Color sonography of extracranial arteries was made showing atherosclerotic plaques on both sides of internal carotid arteries. Abdominal ultrasound examination revealed kidney cysts and calcified uterine fibroids. Thyroid ultrasound examination showed nodular goiter and suspected thyroiditis. Electroencephalography was performed showing a variation of the age norm.

Esophagogastroduodenoscopy was performed and lead to diagnosis of candida esophagitis, mucosal atrophy in the fundus and body areas of the stomach. Duodenal biopsy for celiac disease was taken.

Blood serum sample for antineuronal antibody (picture 3) were negative.

Picture 3. *Antineuronal antibody investigation was performed.*

Autoantikūnų tyr.

Antineuroniniai antikūnai: - anti-amfifizinas	Neigiamas	NEIGIAMAS
- anti-CV2	Neigiamas	NEIGIAMAS
- anti-PNMA2(Ma2/Ta)	Neigiamas	NEIGIAMAS
- anti-Ri/ANNA-2	Neigiamas	NEIGIAMAS
- anti-Yo/PCA-1	Neigiamas	NEIGIAMAS
- anti-Hu/ANNA-1	Neigiamas	NEIGIAMAS
- anti-rekoverinas	Neigiamas	NEIGIAMAS
- anti-SOX1	Neigiamas	NEIGIAMAS
- anti - titinas	Neigiamas	NEIGIAMAS

Atliko: Biomed. tech. Irena Simkovičiūtė; Med. biol. Nijolė Gerčiukaitė; 2023-01-17 13:51;
Patvirtino: Med. biol. Nijolė Gerčiukaitė; 2023-01-17 14:21;

Nutritionist was consulted due to patient's weight loss that was approximately 9 kg in few months. Patient didn't follow any special diet or took vitamin supplements. Objectively depletion of the subcutaneous fat layer and sarcopenia was noted. Recommendations for satisfactory diet fulfilling the daily nutritional needs were made.

During the hospital stay the neurological symptoms unchanged, the treatment of cardiovascular risk factors, including arterial hypertension, dyslipidemia was prescribed, the anticoagulants was started, supplementary treatment with vitamins B complex and folic acid started. Diagnosis at discharge were idiopathic late-onset cerebellar ataxia. Transient ischemic attack (2022.12.19). Arterial hypertension. Persistent atrial fibrillation (CHA2DS2-VASc = 6).

Patient was discharged from the hospital with referral to rehabilitation treatment, warned of possible gluten intolerance and follow up in a week for the biopsy response was recommended.

Patient's status was controlled by phone after a week. Patient was living under the care of her daughter. The patient's well-being had slightly improved: the incidence of ataxia was decreased. It was noticed that after the wheat side dish served to the dinner, the patient felt bad: she felt nauseous, she vomited and her general well-being worsened.

Biopsy of duodenum result was obtained: morphological changes correspond to the stage of destructive celiac disease (stage III according to Marsh). For the patient, the final clinical diagnosis of gluten enteropathy with ataxia was made. For the treatment for the patient was ordered gluten free diet and outpatient consultation. Neurologist control for the dynamics of neurological condition was planned. In February 2023 the additional laboratory results were received (Picture 3): in immunological testing the amount of anti-GAD (Glutamic Acid Decarboxylase) antibodies was 814,5 IU/ml *(>=5* IU/ml *means positive)*. As a conclusion patient had a gluten ataxia caused by celiac disease with an anti-GAD autobody involvement.

Discussion

It is evaluated in the studies (12) that GA is responsible of 15% of all ataxias and 40% of idiopathic sporadic cerebellar ataxias (CA). After reviewing the published case reports we found consistently described five cases. Our case adds to the literature one case of an elderly patient that was suffering with progressive gait ataxia, disturbances of balance and reciprocal and vertical nystagmus as well as dysarthria. Patient was also having a loss of appetite and loss of weight but no other gastrointestinal complaints. Important information was get from anamnesis – previously she was diagnosed with autoimmune thyroiditis. According to literature, the comorbidity with other autoimmune diseases is often found in CA (7). Basic laboratory tests revealed a folic acid deficiency which could been a sign of malabsorption. Brain magnetic resonance imaging showed vascular encephalopathy (Fazek II). All these changes raised suspicions about celiac disease and gastroduodenoscopy with duodenal biopsy with pathological morphological changes corresponding to celiac disease (Marsh III) confirmed the diagnosis. Anti-gliadin antibodies were not tested in this patient but several other antineuronal antibodies were with negative results. Later anti-GAD antibodies test showed markedly elevated levels. Our clinical case showed gluten enteropathy with extraintestinal symptoms with positive anti-GAD antibodies. The patient started gluten free diet and is under observation.

Our clinical patient in report was 82-years of age. In the literature described patients (13,14,15) were all less than 50 years old. Collin et al. (8) are stating that it is common to underdiagnose celiac disease in elderly patients. In their review, fifth of diagnoses was done to patients over 65 years and 4 percent for patients over 80 years (8).

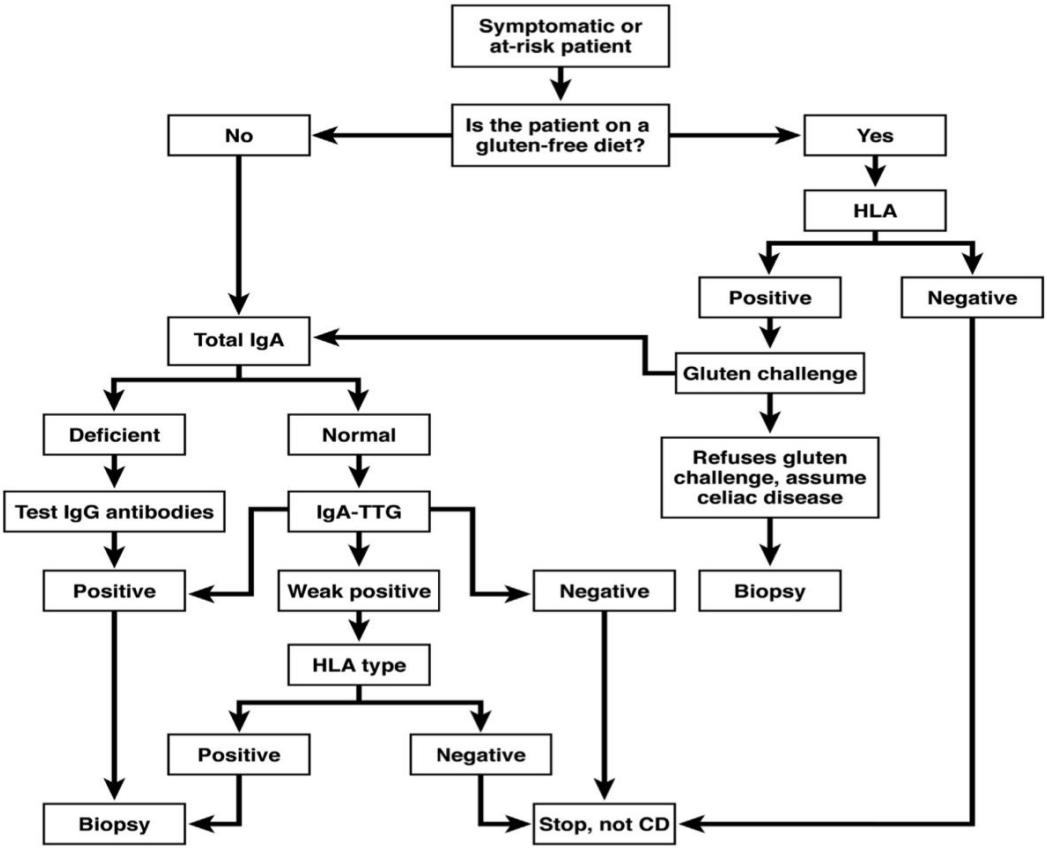
As well as described in the literature case reports, clinical symptoms in patients started prior to referral. Patients were having gradual onset of the neurological symptoms. In the case series, patients faced a rapid deterioration of the symptoms in few weeks. In all patients ataxia effected dramatically to their mobility and speech. Clinical case patient had frequent falls due to impairment of balance and gait.

Diagnostic approach of gluten ataxia

The diagnosis of gluten ataxia is supported by the presence of anti-gliadin (IgA, IgG), anti-tTG (anti-tissue transglutaminase antibodies) and, when available, anti-TG6 (anti-transglutaminase 6 antibodies). The optimum diagnostic strategy for patients with suspected gluten ataxia remains uncertain (7). Taraghikhah et al. (7) went though several researches that were

suggesting that the IgA anti-gliadin antibody is more specific than the IgG anti-gliadin antibody test, but referred also to Hadjivassiliou et al. (16) who reported that IgG anti-gliadin antibody has high sensitivity and therefore is a better marker of gluten ataxia. The level of anti-gliadin antibodies is evaluated to be 5–12% in the general population, and because of that some medical professionals claim that anti-gliadin antibody tests cannot be used for the diagnosis of gluten ataxia. Studies of gluten ataxia patients have shown that anti-tTG antibodies are present in the brain, supporting a possible pathogenic role in the etiology of the condition (17). Hadjivassiliou et al. (17) studied autopsy brain tissue from one patient with gluten ataxia and one neurologically intact brain. The brain of a patient with gluten ataxia contained widespread IgA deposition around blood vessels, which was not observed in the brain of a healthy control. Cerebellum, pons, and medulla exhibited the most prominent deposition. Anti-tissue transglutaminase IgA antibodies are present in the intestine and brain of patients with gluten ataxia with or without enteropathy, similar to patients with celiac disease, latent celiac disease, and dermatitis herpetiformis, but absent in ataxia control subjects. They stated that this finding strengthens the contention that gluten ataxia is immune mediated and belongs to the same group of gluten sensitivity as celiac disease and dermatitis herpetiformis. If celiac disease serology is positive, then obtaining intestinal biopsies to look for evidence of celiac disease should be considered (17). IgA tTG has high sensitivity and specificity of ~ 98% and is the best serologic marker for evaluating celiac disease. IgA deficiency affects 2%–3% of celiac disease patients (18). In Table 5 is presented a diagnostic algorithm for diagnosing celiac disease.

Table 5. *Celiac Disease diagnosis algorithm.*



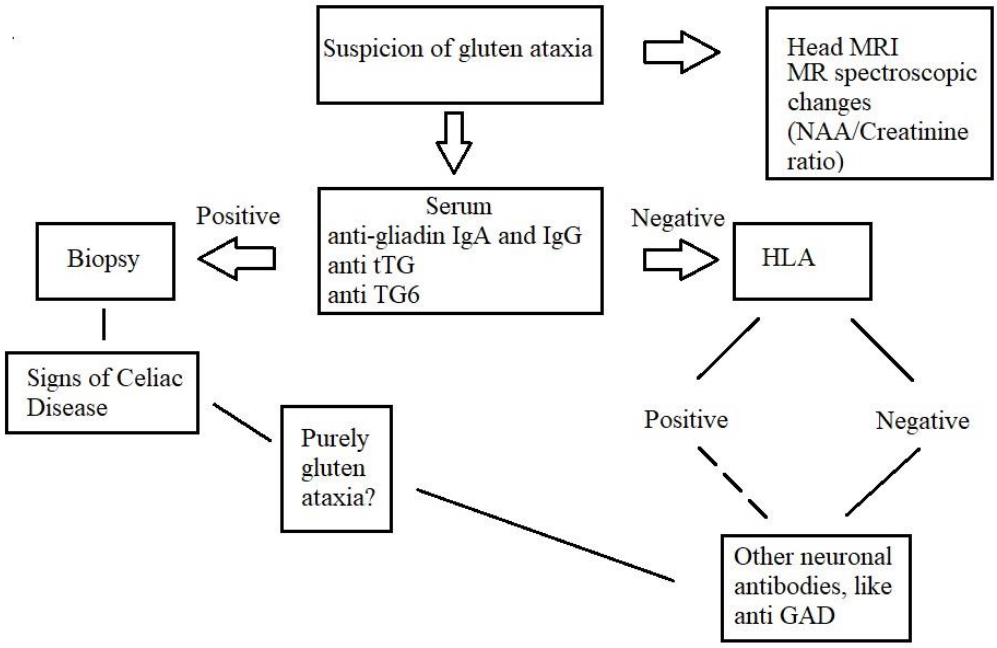
If IgA deficiency is noted proceed to check IgG anti-gliadin antibody. If the patient is already on a gluten free diet it is recommendable to check HLA DQ2 or DQ8 to identify which patient needs further testing. A negative test rules out celiac disease. A positive test however, does not confirm diagnosis because it can be seen in the general population (18). Permission to use the Celiac disease diagnosis algorithm provided by the creator.

The presence of gluten-related immune markers in normal population however complicates the reliable diagnosis of gluten related neurological disorders as presented in Table 5 and clinical improvement on gluten free diet can serve as a diagnostic tool for this disease (13).

Magnetic resonance imaging (MRI) is also a usable tool for diagnosis of gluten ataxia. Magnetic resonance imaging studies of gluten ataxia patients show the presence of moderate cerebellar atrophy in up to 60% of patients. (7) Magnetic resonance spectroscopic changes (NAA/creatinine ratio) correspond to clinical severity and may show the degeneration of the vermis. These changes can be seen before atrophy (14). In table 6 we modelled a diagnostic approach to gluten ataxia suspicion.

In Lithuanian patient the diagnostics started from the head computer tomography to rule out more common reasons of cerebellar ataxia. Brain magnetic resonance imaging study showed vascular encephalopathy. Esophagogastroduodenoscopy was performed and duodenal biopsy was investigated histopathologically confirming diagnosis of a celiac disease. In Lithuanian patient also several antineuronal antibodies were tested with negative results. Anti-GAD antibody testing revealed markedly elevated levels which was a prove that case was not purely a gluten ataxia but had also anti-GAD antibody involvement.

Table 6. *Diagnostic approach to gluten ataxia.*

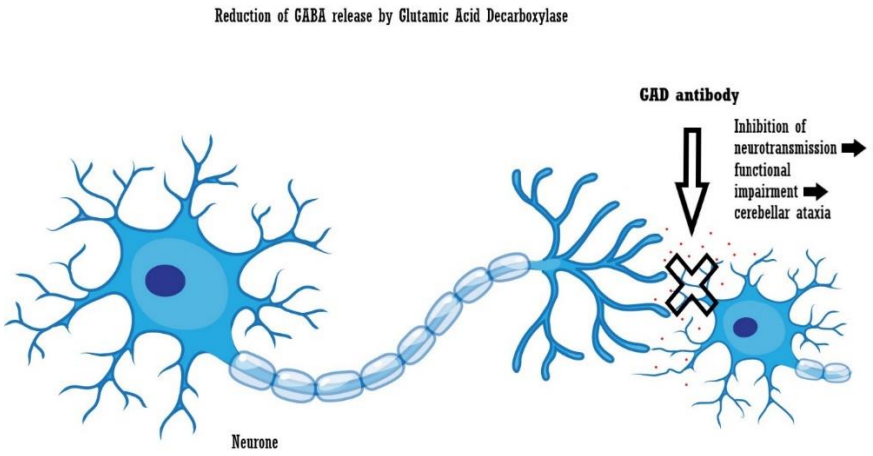


In clinical suspicion of gluten ataxia head MRI should be performed and MR spectroscopic changes evaluated (NAA/Creatinine ratio). Serum antibodies of anti-gliadin, anti-tTG and anti-TG6 should be measured. If no antibodies from the serum is found, HLA should be investigated. Negative HLA DQ2 or DQ8 result rules out celiac disease. In positive result other antibody testing also should be considered. If serum antibodies are positive, biopsy sample for histopathological evaluation should be taken. In presence of signs of celiac disease, other autoantibodies should be tested.

Gluten ataxia relation with other autoimmune diseases

Hadjivassiliou et al. (19) made a retrospective review of all patients with anti-GAD ataxia that were treated at the Sheffield Ataxia Centre over the last 25 years. He identified 50 patients (62% females) with anti-GAD ataxia. The prevalence of this condition was 2.5% amongst 2000

patients with progressive ataxia of various etiologies. There was a great overlapping between anti-GAD ataxia and gluten ataxia. 35 patients (70%) had serological proof of gluten sensitivity. All 35 started gluten-free diet (GFD). 18 (51%) improved, 13 (37%) stabilized, 3 have started the GFD too recently to draw conclusions and one deteriorated. For those patients with anti-GAD ataxia and gluten sensitivity, strict GFD alone can be an effective treatment. Patients with anti-GAD ataxia and no gluten sensitivity respond well to immunosuppression. In picture 3 is illustrated the pathophysiology of anti-GAD antibodies inhibiting the neurotransmission leading to functional impairment.



Picture 3. The mechanism by which GAD antibody induces presynaptic impairment of cerebellar Purkinje cells through inhibition of GABA is shown in the picture. Picture is created using models from Takenoshita et al. (20).

Hadjivassilou et al. (21) studied 32 patients. The titer of anti-GAD reduced following the introduction of a gluten-free diet in patients with stiff person syndrome (SPS) who had serological evidence of gluten sensitivity. As a result of the study, they noticed positivity for anti-GAD*:* six of seven (86%) patients with SPS, mean titer 109 U/ml. This compared with 9/90 (11%) patients with idiopathic sporadic ataxia, mean titer 32 U/ml. 16/40 (40%) patients with gluten ataxia, mean titer 25 U/ml, and 6/10 patients with type 1 diabetes only, mean titer 8 U/ml. None of 32 patients with celiac disease only, and of 40 patients with genetic ataxia were positive for anti-GAD (21).

Hadjivassilou et al. (21) concluded in their research that the findings of their work suggest a link between gluten sensitivity and GAD antibody-associated diseases.

Graus et al. (22) found that there is not still clear evidence that GAD antibodies are pathogenic in CNS syndromes like stiff person syndrome, cerebellar ataxia and temporal lobe epilepsy.

They are suggesting that the diagnosis should be based on the spectrum of symptoms, levels of the serum GAD antibodies and demonstration of the GAD antibody production intrathecally. Therefore, the cerebrospinal fluid and intrathecal synthesis of GAD antibodies should be determined in patients which are having suspected to have forementioned CNS syndromes or have high serum anti-GAD levels. Yet no criteria exist to establish when a neurological syndrome is pathogenically linked to GAD antibodies and the writers are proposing further research and animal models to prove whether neurological syndromes are directly caused by specific disruption of GAD function by GAD antibodies.

Kharrazian et al. (23) showed in his case study that autoimmune reactions to gluten can lead to sporadic ataxia in susceptible genotypes due to cross-reactivity. With gluten ataxia, dietary consumption of gluten proteins causes immunological cross-reactivity with glutamic-acid decarboxylase-65 (GAD-65) target proteins that are present in the cerebellum. A strict gluten-free diet has been shown to lessen the manifestation of this form of ataxia in the majority of patients in this subgroup. Nevertheless, there are some subjects whose clinical responses to a strict gluten-free diet are limited. Cross-reactivity between gluten and other food proteins that share structural similarity with GAD-65 could additionally have a role in this reaction. In case report Kharrazian et al. Report of a patient with gluten-ataxia for whom a gluten-free diet alone did not produce significant clinical improvement until other substances that cross-react with GAD-65 were also eliminated from the diet (23).

Vojdani (24) presents in his study that in the patients with neurological manifestations, who also have an enteropathy, the prevalence of these antibodies is 96%. These observations imply that the presence of these antibodies in the context of enteropathy might predispose individuals to the development of neurological disease. However, this cannot explain entirely the whole variabilities of gluten sensitivity because the antibodies are still present in some patients with gluten-related neurological dysfunction and absent enteropathy. The prevalence of GAD within the nervous system correlated with the clinical presentation of ataxia and/or peripheral neuropathy. Those were the commonest neurological manifestations of gluten sensitivity.

The challenges of diagnosis of the rare etiologies of immune-mediated cerebellar ataxias are presented in Hadjivassiliou et al. (3) review. They describe the multiple possible etiologies that are only partially known and are manifesting neurological clinical features. The term primary autoimmune cerebellar ataxia (PACA) refers to ataxic conditions which are suspected to have an autoimmune etiology in the absence of specific well-characterized pathogenic antibody markers. In the revies is underlined the importance of diagnosing the rare etiologies since they

are potentially treatable and very likely underdiagnosed and may lead to severe clinical syndrome if treatment is not induced early.

Treatment

Gluten ataxia patients should be treated with a strict gluten free diet as soon as possible. Hadjivassiliou et al. (25) studied 117 patients with gluten ataxia to evaluate the effect of gluten free diet on magnetic resonance spectroscopy of the cerebellum. 63 of them where on strict gluten free diet without antigliadin antibodies, 35 were also on gluten free diet but still having antigliadin antibodies and 19 were not on gluten free diet. As their result N-acetylaspartate/creatinine area ratio from the cerebellar vermis increased in 98% of the patients that were following the strict gluten free diet, in 26% of the patients that were following the diet but positive for the antibodies and only 5% in those who were not on the diet. The research demonstrated the increased NAA/Cr ratio on those patients following the strict gluten free diet which were strengthening earlier findings of clinical improvement of the ataxia in gluten ataxia patients (25).

In the published cases all presented patients were starting gluten free diet. Gluten free diet alone improved neurological symptoms like gait, balance and speech but did not provide full recovery for all the patients described in the literature (14). In addition, Newrick's (14) case series have shown that immunotherapy (steroids, intravenous immunoglobulins (IVIG)) can be an effective treatment for patients with rapid-onset symptoms and provided in addition of gluten free diet. As gluten ataxia is a progressive condition in which neurons and Purkinje cells perish over time, the response to treatment is dependent on the time between gluten ataxia onset and treatment (7). Lithuanian patient was starting a gluten free diet under the control of nutritionist. Clinically this treatment alone led to some improvement of the gait and balance as well as the speech. The patient should come for observation visit after the rehabilitation period.

Prognosis of gluten ataxia

There is a enlarging retrospective and observational research-based evidence which supports the use of different immunotherapy treatments in the management of immune-mediated cerebral ataxias, in addition to remove any antigenic stimulus. In this category are corticosteroids, intravenous immunoglobulins, mycophenolate, and rituximab. Regardless of modality, it appears that clinically significant outcomes are contingent on initiating treatment early to prevent the loss of cerebellar cells beyond an irreversible threshold, sometimes referred to as cerebellar reserve. Use of steroids and intravenous immunoglobulins to deliver fast

induction prior to mycophenolate and then a gluten-free diet attaining full efficacy is recommended in cases with rapid progression (14).

Conclusions and recommendations

Gluten ataxia patients present a spectrum of atypical celiac disease with extraintestinal symptoms, cerebellar ataxia being one of them. Our patient was an elderly person and is a notable example how advanced age should not limit the diagnostic thinking. Celiac illness is many times thought to be an illness of children and young adults. However, celiac disease can be detected in any age and since the symptoms often are not specific, there is a possibility that this illness is overlooked and diagnosis delayed. This can lead to devastating outcomes (8).

In addition to enteropathy and dermatitis, gluten sensitivity can also manifest with neurologic symptoms. Neurologic dysfunction related to gluten can occur with or without gastrointestinal symptoms and can be neglected if it occurs in isolation. Gluten ataxia is a potentially treatable and reversible disorder; therefore, all patients with sporadic, unexplained subacute or chronic cerebellar ataxia should be examined for serological evidence of gluten sensitivity. Celiac serology should always be tested in patients for ataxic symptoms after ruling out all other possible etiologies because gluten-free diet might be as a cure from the ataxic symptoms. Since gluten ataxia is an autoimmune mediated illness, it may be that not all the cases are purely anti-gliadin based but have also other autoimmune etiologies, like anti-glutamic acid decarboxylase, should also be considered and tested since gluten ataxia may have also other autoimmune involvement (3,13,15)

Patients who are testing positive for antigliadin and anti transglutaminase antibodies, should start a strict gluten free diet to minimize damage and stop the further disease progression. In addition to remove antigenic stimulations, some patients might benefit from steroids, intravenous immunoglobulins and mycophenolate (14). If patient would have limited response to strict gluten free food, diet should be evaluated from the cross-reactivity point of view and other cross-reactive dietary proteins should be excluded from the diet (23).

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