The Cerebellum
2008, 494–498

Springer

INVITED REVIEW

Gluten ataxia

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Abstract
Gluten ataxia is an immune-mediated disease triggered by the ingestion of gluten in genetically susceptible individuals. It should be considered in the differential diagnosis of all patients with idiopathic sporadic ataxia. Early diagnosis and treatment with a gluten free diet can improve ataxia and prevent its progression. Readily available and sensitive markers of gluten ataxia include antigliadin antibodies. IgA deposits against TG2 in the small bowel and at extraintestinal sites are proving to be additional reliable and perhaps more specific markers of the whole spectrum of gluten sensitivity. They may also hold the key to its pathogenesis.

Key words: *Gluten ataxia, cerebellum*

Introduction

It is now widely accepted that gluten sensitivity is a systemic illness with diverse manifestations. Such manifestations can occur independent of the presence or not of the classic small bowel lesion that defines celiac disease (CD), also known as gluten sensitive enteropathy (triad of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes). Cerebellar involvement in the context of gluten sensitivity, also known as gluten ataxia (GA), is one of such extraintestinal manifestations that have only been recognized in the last decade (1,2). Some still consider this entity controversial (3,4). Currently GA is defined as sporadic cerebellar ataxia associated with the presence of circulating antigliadin antbodies, in the absence of an alternative aetiology for ataxia. This review aims to bring the reader up to date on recent developments in understanding gluten ataxia as a disease entity.

Prevalence and definition

Gluten ataxia is probably one of the commonest causes of idiopathic sporadic ataxia. A number of studies looking at the prevalence of antigliadin antibodies in patients with ataxia have been published and are summarized in Table I. The common finding in all of these studies is the consistently high prevalence of these antibodies in sporadic ataxias when compared to healthy controls. Some have found a high prevalence of these antibodies in patients with genetically determined ataxias and in patients with Huntington's disease (3–5). This finding, if confirmed by larger studies, should not necessarily challenge the existence of gluten ataxia as a disease entity, but rather should stimulate interest on the possible mechanism by which a genetically determined ataxia or other neurodegenerative process can result in the generation of antibodies against gluten. Understanding the correct use of antigliadin antibody assays, requires knowledge of the definition of gluten sensitivity and its relationship to CD. Gluten sensitivity represents a spectrum within which CD is a part. Most antigliadin assay kits are marketed with their sensitivity and specificity defined and optimized for gluten enteropathy. Given that the extraintestinal manifestations of gluten sensitivity can exist in the absence of an enteropathy, the sensitivity and specificity of antigliadin antibody assays must be redefined for each manifestation. This factor may well partly explain the variation in the prevalence of antigliadin antibodies in sporadic ataxias reported in different studies.

The prevalence of antigliadin antibodies in the 'healthy' population varies from 5 to 12%, depending on the assay used as well as the local prevalence of CD. The prevalence of CD in most European

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ISSN 1473-4222 print/ISSN 1473-4230 online
DOI: 10.1007/s12311-008-0052-x
Online first: 12 September 2008

Table I. List of studies looking at the prevalence of antigliadin antibodies in patients with ataxia and controls (studies with no control groups are not included).

	Sporadic ataxia	Familial ataxia	Normal controls
Hadjivassiliou et al. UK (2)	90/221 (41%)	12/78 (15%)	149/1200(12%)
Pellecchia et al. Italy (24)	3/24 (13%)	0/23 (0%)	?
Burk et al. Germany (25)	12/104 (11.5%)	?	(5%)
Bushara et al. USA (5)	7/26 (27%)	9/24 (37%)	?
Abele et al. Germany (26)	13/98 (13%)	1/15 (6%)	(5%)
Luostarinen et al. Finland (27)	8/44 (17%)	?	(2%)
Ihara et al. Japan (28)	5/14 (36%)	1/27(4%)	1/47(2%)

countries is at least 1% (6). Geographic variations in the prevalence of CD between European countries, however, do exist and this may be another factor contributing to the variation in the prevalence of antigliadin antibodies in sporadic ataxia between different countries. We do not know what proportion of the remaining 'healthy' 4–11% of individuals with positive antigliadin antibodies without enteropathy has occult gluten sensitivity. The HLA class II type DQ2 (found in 90% of patients with CD) is overrepresented in individuals with circulating antigliadin antibodies and normal small bowel biopsy (2). Such antigliadin positivity cannot therefore simply be dismissed as an epiphenomenon. Antigliadin antibodies are allied with the HLA genotype associated with CD and may well signify gluten sensitivity without overt clinical evidence of end organ involvement. As antigliadin antibodies are present in up to 12% of the 'healthy' population it is possible that in a subgroup of patients with idiopathic sporadic ataxia who fulfil the criteria for gluten ataxia using the proposed definition, the ataxia is coincidental rather than causally linked to gluten sensitivity.

The argument by some, that antigliadin antibodies cannot be used as a marker of gluten ataxia because of their high prevalence in the 'healthy' population should be challenged. An analogous argument can be had for rheumatoid factor and its use in the diagnosis of rheumatoid arthritis. Despite the fact that rheumatoid factor has a high prevalence in the healthy population, it's use in the appropriate clinical scenario (i.e., the presence of inflammatory arthropathy) is universally accepted as valuable in diagnosing rheumatoid arthritis. Until a more specific marker becomes available, antigliadin antibodies remain the most sensitive marker for GA in those patients with otherwise idiopathic sporadic ataxia.

Clinical features

There are no unique features that distinguish GA from other types of ataxia. The following clinical characteristics are based on more than 147 patients diagnosed and followed up over the last 12 years. GA is characterized by insidious onset of predominantly gait ataxia, often associated with symptoms and signs suggestive of peripheral neuropathy. The mean age at onset is 53 years. It affects both sexes equally. Rarely GA presents with a rapidly progressive ataxia mimicking paraneoplastic cerebellar degeneration. Evidence of limb ataxia is seen in up to 90% of patients with lower limbs more often affected than upper limbs. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases. The lack of autonomic dysfunction distinguishes these patients from patients with cerebellar variant of multiple system atrophy. Indeed, the prevalence of antigliadin antibodies in patients with clinically probable MSA-C was 5/35 (14%) which is no different to that found in the healthy population. Patients with clinically probable MSA-C and positive antigliadin antibodies do not respond to a gluten free diet. Additional movement disorders encountered in gluten ataxia include myoclonus, chorea, palatal tremor and opsoclonus myoclonus (7,8). These additional features however are rare. Up to 60% of patients have neurophysiological evidence of a sensorimotor axonal neuropathy. As with coeliac disease, patients with GA are often found to have an increased prevalence of additional autoimmune diseases the commonest of which include hypothyroidism (patients with GA frequently have thyroid antibodies even if they are biochemically euthyroid), type 1 diabetes mellitus and pernicious anaemia. Vitamin E deficiency is rare (only seen in 2 patients from a cohort of 147 patients with GA). Gastrointestinal symptoms are seldom seen and are not a reliable indicator of the presence or absence of enteropathy. In this respect, gluten ataxia resembles dermatitis herpetiformis where gastrointestinal symptoms are not prominent despite the presence of an enteropathy.

Small bowel biopsy in patients with GA reveals evidence of enteropathy in just under a third. By

definition all patients will have positive IgG and/or IgA antigliadin antibodies. Antiendomysium antibodies are present in only 22% of patients. These antibodies have high specificity for the presence of enteropathy but lack sensitivity for the whole spectrum of gluten sensitivity. Tissue transglutaminase antibodies are positive in up to 56% of patients with GA, often at lower titres than those seen in patients with coeliac disease. Therefore endomysium and tissue transglutaminase antibodies cannot be used in isolation to diagnose GA. The HLA type DQ2 is seen in 70% of these patients (seen in 90% of patients with coeliac disease) with the remaining 30% having the HLA DQ8 (10%) and HLA DQ1 (20%). HLA DQ1 has not been reported in patients with CD but may represent an additional HLA susceptibility genotype associated with the neurological manifestations. Table II summarizes the clinical and immunological characteristics of 147 patients with gluten ataxia.

Imaging

Up to 60% of patients with gluten ataxia have evidence of cerebellar atrophy on MR imaging. Some patients will, in addition, have evidence of white matter abnormalities which are often extensive and confluent. Such abnormalities have been described in a subgroup of patients with or without gluten ataxia who also have episodic severe headaches often with focal transient neurological dysfunction mimicking severe migraine with aura (9). The headaches resolve with the introduction of a gluten-free diet. Even in those patients with gluten ataxia who have no evidence of cerebellar atrophy on MRI, proton MR spectroscopy of the cerebellum reveals abnormalities supporting the hypothesis that cerebellar neuronal physiology is abnormal. Investigation of the metabolic status of the cerebellum in 15 patients with gluten ataxia and 10 controls using proton MR spectroscopy demonstrated significant differences in mean N-acetyl aspartate levels at short echo-time and N-acetyl aspartate/choline ratios at long echo-time between patients with gluten ataxia and healthy controls (10).

Table II. Clinical and immunological characteristics of 147 patients with gluten ataxia.

Male:female ratio	1:1
Mean age at onset of ataxia	53
Ocular signs	80%
Upper limb ataxia	70%
Lower limb ataxia	90%
Gait ataxia	100%
Peripheral neuropathy	60%
Enteropathy on biopsy	28%
Antigliadin antibody positive	100%
Anti-endomysium antibody positive	22%
Transglutaminase antibody positive	56%
HLA DQ2	70%
Presence of oligoclonal bands	50%

Pathophysiology

There is strong evidence to suggest that the damage to the nervous system is immune-mediated. Post mortem examination from patients with gluten ataxia revealed patchy loss of Purkinje cells throughout the cerebellar cortex. The cerebellar white matter showed astrocytic gliosis, vacuolation of the neuropil and a diffuse infiltrate mainly of T-lymphocytes. Marked perivascular cuffing with inflammatory cells, mainly T-lymphocytes, with smaller numbers of B-lymphocytes and macrophages, was present within the cerebellar white matter and the posterior columns of the spinal cord. Purkinje cells were lost. The peripheral nervous system showed sparse lymphocytic infiltrate (1). Similar findings have been described in patients with established coeliac disease who then developed ataxia (11).

Experimental evidence suggests that there is antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten peptides. Serum from patients with GA and from patients with coeliac disease but no neurological symptoms, demonstrate cross-reactivity with epitopes on Purkinje cells using both human and rat cerebellum (12). This finding could also explain why some patients with genetically determined ataxia may have circulating antigliadin antibodies: Antibodies against proteins from degenerating Purkinje cells formed as an epiphenomenon, may recognize and cross-react with gliadin peptides within the gut circulation and, through a process of epitope spreading, generate antigliadin antibodies (13). In the sera of patients with gluten ataxia there is evidence of additional antibodies targeting Purkinje cell epitopes. This is shown by the failure to eliminate reactivity with Purkinje cells by removal of antigliadin antibodies from sera of patients with gluten ataxia (12). Determination of the cerebellar antigen targeted by these additional circulating antibodies in patients with GA may help in identifying a more specific marker for GA.

Treatment

The benefits of a gluten-free diet in the treatment of patients with coeliac disease and dermatitis herpetiformis have long been established. There are very few studies, mainly case reports, of the effect of gluten-free diet on the neurological manifestations of gluten sensitivity (14–17). All but one of these reports primarily concern patients with established coeliac disease who then develop neurological symptoms. In the majority of these case reports, adherence to the gluten-free diet is assumed or

assessed by improvement of gastrointestinal symptoms. Such an approach is inadequate if partial adherence to the diet is insufficient for neurological improvement to occur. The best marker of strict adherence to a gluten-free diet is serological evidence of elimination of circulating antigliadin antibodies. A small, uncontrolled study looked at the use of intravenous immunoglobulins in the treatment of 4 patients with gluten ataxia without enteropathy (18). All four patients improved. Dietary intervention, however, was not mentioned as having been considered and used prior to the use of immunomodulatory therapy. All of these case reports and small studies suggest variable but overall favourable response to gluten free diet.

Only one systematic study of the effect of gluten-free diet on a cohort of patients presenting with neurological dysfunction, with or without an enteropathy, has been published (19). Forty three patients with gluten ataxia were enrolled. Twenty six patients adhered strictly to the gluten-free diet and had serological evidence of elimination of the antigliadin antibodies. These patients comprised the treatment group. Fourteen patients refused the diet and comprised the control group. Patient and control groups were matched at baseline for all evaluated variables. There was no significant difference in the baseline performance on ataxia tests between the two groups. There was significant improvement in performance in all the tests, and in the subjective global clinical impression scale in the treatment group when compared to the control group. The significant improvement in all the tests when comparing treatment and control groups was apparent even after excluding patients with an enteropathy. The study concluded that gluten-free diet appeared to be an effective treatment for gluten ataxia. It was suggested, however that close monitoring should be undertaken using regular antigliadin antibody estimation and dietetic review to ensure strict adherence to the gluten-free diet.

Treatment with immunosuppressants and intravenous immunoglobulins could be considered if strict gluten-free diet (with elimination of the antibodies) has not resulted in any improvement of the ataxia after a year or if the ataxia is rapidly progressive. In patients where the dietetic review suggests strict adherence to a gluten free diet but serological testing still shows positive antigliadin antibodies, wheat free diet should be considered first before embarking on immunosuppressive treatment. This is because gluten free products contain small amounts of gluten which, in cases of extreme sensitivity, may be enough to perpetuate the immune process, resulting in tissue damage. Additional immunosuppressive treatments used by the authors in cases of 'resistant' neurological cases include intravenous immunoglobulins, ciclosporin, cyclophosphamide and mycophenolate. Such cases however are rare and by far the commonest cause of lack of response relates to poor adherence to gluten free diet. In patients with evidence of cerebellar atrophy on MRI the dietary intervention may sometimes prevent deterioration and stabilize the condition with only minor improvements of the ataxia.

Recent advances

Recent work suggests that even in those patients with gluten sensitivity (based on serological markers) and normal bowel mucosa, there is evidence of antibodies targeting tissue transglutaminase (the auto-antigen responsible for CD) not only in the small bowel mucosa but at extraintestinal sites as well (20,21). Based on this observation, jejunal biopsy samples from nine patients with gluten ataxia and seven patients with other causes of ataxia were evaluated for the presence of tissue transglutaminase-related immunoglobulin deposits using double colour immunofluorescence. Autopsy brain tissue from one patient with gluten ataxia and one neurologically intact brain were also studied. IgA deposition on jejunal tissue transglutaminase was found in the jejunal tissue of all patients with GA and in none of the controls. The intestinal IgA deposition pattern was similar to that seen in patients with overt and latent coeliac disease and in those with dermatitis herpetiformis. Widespread IgA deposition around vessels was found in the brain of the patient with gluten ataxia but not the control brain. The deposition was most pronounced in the cerebellum, pons and medulla (22). This work has thus demonstrated that anti-tissue transglutaminase IgA antibodies are present in the gut and brain of patients with gluten ataxia, with or without an enteropathy, in a similar fashion to patients with CD and patients with dermatitis herpetiformis, but not in ataxia control subjects. This finding strengthens the contention that GA is immune-mediated and belongs to the same spectrum of gluten sensitivity as CD and dermatitis herpetiformis. It also suggests that transglutaminases may play an important role in the pathogenesis of the diverse manifestations seen in gluten sensitivity.

Patients with dermatitis herpetiformis have antibodies with low affinity for tissue transglutaminase (TG2) but very high affinity for epidermal transglutaminase (TG3). This results in an immune response and clinical manifestations in the skin, the main site of epidermal transglutaminase production (23). An analogous situation of an immune response directed towards neural transglutaminases may result in clinical manifestations primarily in the brain or the peripheral nervous system with minimal involvement of the gut, perhaps just deposition of autoantibodies against TG. Identification of specific brain transglutaminases may hold the key to the neurological manifestations and facilitate the

development of more specific markers for gluten ataxia.

References

1. Hadjivassiliou M, Grünewald RA, Chattopadhyay AK, Davies-Jones GAB, Gibson A, Jarratt JA, et al. Clinical, radiological, neurophysiological and neuropathological characteristics of gluten ataxia. Lancet. 1998;352:1582–85.
2. Hadjivassiliou M, Grünewald RA, Sharrack B, Sanders D, Lobo A, Wood N, et al. Gluten ataxia in perspective: Epidemiology, genetic susceptibility and clinical characteristics. Brain. 2003;126:685–91.
3. Abele M, Schols L, Schwartz S, Klockgether T. Prevalence of antigliadin antibodies in ataxia patients. Neurology. 2003;60:1674–5.
4. Bushara KO, Nance M, Gomez C. Antigliadin antibodies in Huntington's disease. Neurology. 2004;62:132–3.
5. Bushara KO, Goebel SU, Shill H, Goldfarb LG, Hallett M. Gluten sensitivity in sporadic and hereditary ataxia. Ann Neurol. 2001;49:540–43.
6. Sanders DS, Patel D, Stephenson TJ, Milford-Ward A, McCloskey EV, Hadjivassilou M, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastro Hep. 2003;15:407–13.
7. Pereira AC, Edwards MJ, Buttery PC, Hawkes CH, Quinn NP, Giovannoni G, et al. Choreic syndrome and coeliac disease: A hitherto unrecognised association. Mov Disord. 2004;19:478–82.
8. Deconinck N, Scaillon M, Segers V, Groswasser JJ, Dan B. Opsoclonus-myoclonus associated with celiac disease. Pediatr Neurol. 2006;34:312–14.
9. Hadjivassiliou M, Grünewald RAG, Lawden M, Davies-Jones GAB, Powell T, Smith CML. Headache and CNS white matter abnormalities associated with gluten sensitivity. Neurology. 2001;56:385–8.
10. Wilkinson ID, Hadjivassiliou M, Dickson JM, Wallis L, Grunewald RA, Coley SC, et al. Cerebellar abnormalities on proton MR spectroscopy in gluten ataxia. J Neurol Neurosurg Psychiatry. 2005;76:1011–13.
11. Cooke WT, Thomas-Smith W. Neurological disorders associated with adult coeliac disease. Brain. 1966;89:683–722.
12. Hadjivassiliou M, Boscolo S, Davies-Jones A, Grunewald R, Not T, Sanders D, et al. The humoral response in the pathogenesis of gluten ataxia. Neurology. 2002;58:1221–6.
13. .Hadjivassiliou M, Williamson CA, Woodroofe N. The immunology of gluten sensitivity: Beyond the gut. Trends Immunol. 2004;25:278–82.
14. Ward ME, Murphy JT, Greenberg GR. Coeliac disease and spinocerebellar degeneration with normal vitamin E status. Neurology. 1985;35:1199–1201.
15. Kaplan JG, Pack D, Horoupian D, DeSouza T, Brin M, Schaumburg H. Distal axonopathy associated with chronic gluten enteropathy: A treatable disorder. Neurology. 1988;38:642–5.
16. Bhatia KP, Brown P, Gregory R, Lennox GG, Manji H, Thompson PD, et al. Progressive myoclonic ataxia associated with coeliac disease: The myoclonus is of cortical origin, but the pathology is in the cerebellum. Brain. 1995;118:1087–93.
17. Pellecchia MT, Scala R, Perretti A, De Michelle G, Santoro L, Filla A, et al. Cerebellar ataxia associated with subclinical celiac disease responding to gluten-free diet. Neurology. 1999;53:1606–07.
18. Bürk K, Melms A, Schulz JB, Dichgans J. Effectiveness of intravenous immunoglobulin therapy in cerebellar ataxia associated with gluten sensitivity. Ann Neurol. 2001;50:827–8.
19. Hadjivassiliou M, Davies-Jones GAB, Sanders DS, Grünewald RAG. Dietary treatment of gluten ataxia. J Neurol Neurosurg Psychiatry. 2003;74:1221–4.
20. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;7: 797–801.
21. Korponay-Szabo IR, Halttunen T, Szalai Z, Laurila K, Kiraly R, Kovacs JB, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut. 2004;53:641–8.
22. Hadjivassiliou M, Maki M, Sanders DS, Williamson C, Grunewald RA, Woodroofe N, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. Neurology. 2006;66:373–7.
23. Sardy M, Karpati S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (Tgase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med. 2002;195:747–57.
24. Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci C, Barone P. Idiopathic cerebellar ataxia associated with celiac disease: Lack of distinctive neurological features. J Neurol Neurosurg Psychiatry. 1999;66:32–5.
25. Bürk K, Bösch S, Müller CA, Melms A, Zuhlke C, Stern M, et al. Sporadic cerebellar ataxia associated with gluten sensitivity. Brain. 2001;124:1013–19.
26. Abele M, Bürk K, Schöls L, Schwartz S, Bessenthal I, Bessenthal I, Dichgans , et al. The aetiology of sporadic adult-onset ataxia. Brain. 2002;125:961–8.
27. Luostarinen LK, Collin PO, Paraaho MJ, Maki MJ, Pirttila TA. Coeliac disease in patients with cerebellar ataxia of unknown origin. Ann Med. 2001;33:445–9.
28. Ihara M, Makino F, Sawada H, Mezaki T, Mizutami K, Nakase H, et al. Gluten sensitivity in Japanese patients with adult-onset cerebellar ataxia. Intern Med. 2006;45: 135–40.