Gluten Sensitivity: Associated Sporadic Cerebellar Ataxia in Taiwan

Chin-San Liu[1,2,3], Bing-Wen Soong[4,5], Yi-Chung Lee[4,5], Woan-Ling Chen[1], Chen-Ling Kuo[1], Wen-Ling Cheng[1], Ching-Shan Huang[1], Wei-Ting Lin[1]

Abstract-

Purpose: Gluten sensitivity (GS) is related to the pathogenesis of sporadic or hereditary ataxia.

Methods: Total of 194 healthy controls and patients with either hereditary ataxia (n=207) or sporadic ataxia (n=361) were tested for the circulating gluten-related autoantibodies which serve as biomarkers to interpret the existence of GS.

Results: The incidences of GS in each population were 1% in normal subjects, 2% in hereditary ataxia patients and 9% in sporadic ataxia patients. High serum level of anti-gliadin IgG/IgA and t-transglutaminase IgA were disclosed at the sporadic ataxia patients compared with normal subjects. However, the anti-gliadin IgG is more specific to the disease of sporadic ataxia.

Conclusion: Relatively higher incidence of GS was found in the population of sporadic ataxia patients but not in either normal subjects or hereditary ataxia patients in Taiwan. Anti-gliadin IgG still is a very powerful indicator to implicate the immune-related sporadic ataxia and we conclude that GS-related sporadic ataxia exists in Taiwan with linkage to autoimmune events.

Key Words: sporadic cerebellar ataxia, gluten sensitivity

Acta Neurol Taiwan 2010;19:263-269

INTRODUCTION

The etiology of sporadic cerebellar ataxia is mostly unclear and suspected to involve dietary and genetic factors. Ingestion of wheat gluten and related cereal proteins triggers the gluten sensitivity (GS). The intolerance of diet gluten, which is alcohol-insoluble protein of wheat, rye and barley, causes damages to mucosal surface of the small intestine and typically evokes celiac disease (CD). Sensitive and specific serological

From the Departments of [1]Vascular and Genomic Center; [2]Neurology, Changhua Christian Hospital, [3]Graduate Institute of Integrative Chinese and Western Medicine, China Medical University Hospital, [4]Department of Neurology, National Yang-Ming University, [5]Department of Neurology, Taipei Veterans General Hospital.

Accepted June 8, 2010.

Correspondence to: Chin-San Liu, MD. Department of Neurology、Vascular and Genomics Center, Changhua Christian Hospital, No. 135, Nanhsiao Street, Changhua 500, Taiwan.
E-mail: 26602@cch.org.tw

antigliadin antibody tests demonstrated a high diagnostic value in detection of CD including IgA/IgG against tissue transglutaminase (t-TG IgA/ t-TG IgG) and gliadin (Gliadin IgA/Gliadin IgG) as well as those from small intestine biopsies[1-4].

As well as in CD, GS is also intensively studied in progressive neurologic deficits including Huntington's disease, and sporadic or hereditary cerebellar ataxia[5-6]. The majority of GS patients with ataxia showed no significant enteropathy, which implicated that sporadic/ hereditary ataxia might be part of an immune-mediated syndrome of GS without classic CD manifestation[6].

GS is thought to be genetically determined as mostly Western, but not Eastern, in patients with CD or GS-related sporadic ataxia[6,7] and the role of gliadin or t-GT autoantibodies in patients with either sporadic or hereditary ataxia is still controversial. The aims of the present study were to massively assess the prevalence and association of serological AGA related GS in normal subjects and patients with hereditary or sporadic ataxia in Taiwan. This is the first massive survey study to investigate the correlation analysis among gluten related autoantibodies in the Taiwan.

METHODS

2.1 Patients and controls

Healthy controls (n=194), hereditary ataxia (n=207), and sporadic ataxia (n=361) were recruited from Health Evaluation Center and Department of Neurology of Changhua Christian Hospital, Taichung and Taipei Veterans General Hospitals, Taiwan, from September 2004 to October 2009. All patients and control individuals received a complete neurologic examination and history taking including family history of diseases (by Dr C-S Liu, Dr Y-C Lee, Dr B-W Soong). Demographic data are listed in Table 1. All of the human experimental procedures followed the medical ethics guidelines of the Department of Health, Executive Yuan of Taiwan. All patients and control individuals included in this study were given informed consents and this study was approved by the institutional ethics committee. Cerebellar ataxia was proved by the neurologic examination and cerebellar atrophy by brain magnetic resonance imaging (MRI) study. Normal subjects were enrolled from the outpatient clinic with no evidence of any neurologic or systemic diseases. Hereditary ataxia was determined by the positive results of genetic tests including spinocerebellar ataxia type 1 (SCA1), SCA 2, SCA 3, SCA 6, SCA 7, SCA 8, SCA 17 and SCA 22. Sporadic ataxia was defined by 3 diagnostic criteria including absence of family ataxia history, negative genetic test of ataxia panel and cerebellar atrophy in brain MRI study.

GS was defined either with the positive response from the serum from individual patients or by the cut-values of gluten-related autoantibodies provided by manufacturers (Gliadin IgG, 12 U/mL; Gliadin IgA, 16 U/mL; t-TG IgG, 20 U/mL; t-TG IgA, 20 U/mL).

2.2 Detection of AGA and t-TG IgA/IgG autoantibodies

Subjects recruited were tested for AGA IgA/IgG using a commercial enzyme-linked immunoabsorbent assay (ELISA) kit (IBL-Hamburg GmbH, Germany) and t-TG IgA/IgG autoantibodies using a commercial ELISA kit (INOVA Diagnosis, Inc, San Diego, CA, USA).

2.3 Statistic analysis

Student's t-test, Chi-square test and Mann—Whitney U test were applied to each comparison including GS vs. non-GS normal subjects, sporadic ataxia, or hereditary ataxia patients. P-values < 0.05 were taken to be statistically significant. Statistical analyses were performed by use of the SPSS statistical package, version 15 (Chicago, IL).

RESULTS

The clinical demographic data of normal subjects (N=194), hereditary ataxia (N=207) and sporadic cerebellar ataxia (N=361) patients are shown in Table 1. The incidences of GS in each population were 1% in normal subjects, 2% in hereditary ataxia patients and 9% in sporadic ataxia patients. According to the characteristics of sporadic ataxia patients without and with GS (Table 2), we found the early onset of disease progress in patients

Table 1. *Demographic data of normal subjects and ataxia patients*

	Normal Subjects	Hereditary Ataxia	Sporadic Ataxia
	N = 194	N = 207	N = 361
Age (year)	46 ± 17	43 ± 12	47 ± 13
Onset age (year)	-	36 ± 17	43 ± 19
Sex (M/F)	103/91	132/75	195/165
Duration (year)	-	6 ± 5	3 ± 5
Chronic diarrhea	-	0	0
Cog rigidity	-	20	33
Dysarthria	-	112	111
Dysphagia	-	69	94
Hyperreflexia	-	86	40
Hyporeflexia	-	43	59
Nystagmus	-	68	49
Cog pursuits	-	62	116
Saccade slow	-	74	55
Posture hand tremor	-	56	46
Gluten Sensitivity (N[%])	2[1]	4[2]	31[9]

Table 2. *Characteristics of sporadic ataxia subjects without and with Gluten sensitive*

Sporadic Ataxia	Non — Gluten Sensitivity	Gluten Sensitivity	#*P*
	N = 330	N = 31	
Age (year)	48±17	35±21	*
Sex (M/F)	181/148	14/17	
Onset Age (year)	35±16	28±24	
Chronic diarrhea (N; [%])	[0]	[0]	
Cog rigidity (N; [%])	25[8]	8[26]	
Dysarthria (N; [%])	89[27]	22[71]	
Dysphagia (N; [%])	70[21]	24[77]	
Hyperreflexia (N; [%])	30[9]	10[32]	
Hyporeflexia (N; [%])	40[12]	19[61]	*
Nystagmus (N; [%])	36[11]	13[42]	
Cog pursuits (N; [%])	95[29]	21[68]	
Saccade slow (N; [%])	46[14]	9[29]	
Posture hand tremor (N; [%])	30[9]	16[52]	*

#non-GS vs, GS: *P<0.05, by Student's t-test or Chi-square test.

with GS (48±17 vs 35±21, P < 0.05). Significantly higher percentages of hyporeflexia (12% vs 61%, P < 0.05) and postural hand tremor (9% vs 52%, P < 0.05) were disclosed in the sporadic ataxia patients with GS. No classic CD was impressed in the patients with sporadic ataxia.

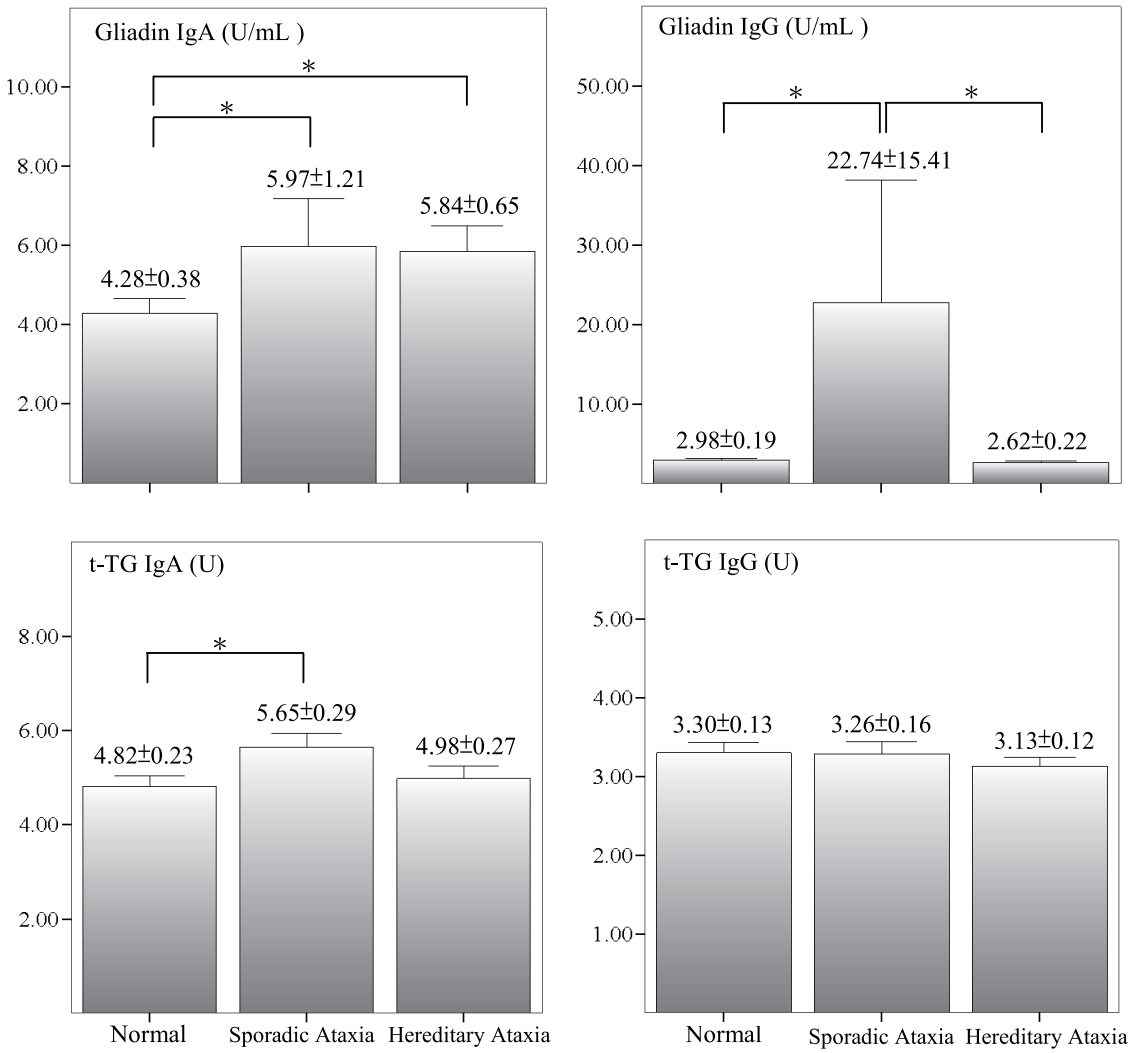

Figure 1. Anti-gliadin and anti-tissue transglutaminase antibodies in normal controls (N=194), sporadic ataxia (N=361) and hereditary ataxia (N=207). Each value above the bar indicates the value of mean ± SE of the gluten related autoantibodies. *P-value was determined by Mann—Whitney U-test.

Figure 1 illustrates the alteration of serum levels of each gluten related autoantibodies among normal subjects, hereditary or sporadic ataxia patients. The serum level of AGA IgA were increased in sporadic ataxia (5.97±1.21 vs 4.28±0.38, $P < 0.05$) and hereditary ataxia patients (5.84±0.65 vs 4.28±0.38, $P < 0.05$) compared with normal subjects. However, the serum level of AGA IgA failed to reveal the difference between sporadic and hereditary patients. Increased level of AGA IgG can effectively differentiate sporadic ataxia patients from normal subjects (22.74±15.41 vs 2.98±0.19, $P < 0.05$) and from hereditary ataxia patients (22.74±15.41 vs 2.62±0.22, $P < 0.05$). The higher serum level of t-TG IgA was disclosed in patients with sporadic ataxia (5.65±0.29 vs 4.82±0.23, $P < 0.05$) compared with normal subjects, but not with hereditary ataxia patients. Nevertheless, we failed to inspect any difference of t-TG IgG level among normal subjects, hereditary ataxia or sporadic ataxia patients. No relationship was found between the levels of gluten-related autoanti-

bodies and disease onset in the patients with sporadic ataxia.

DISCUSSION

Our study in gluten sensitivity and the incidence of hereditary and sporadic ataxia is a clinical research with the largest number of cases around the world, and is the first in Taiwan to address this topic.

It was reported that CD patients have mucosal atrophy in intestinal walls, which is resulted from the defense to intestinal antibodies. Other researches found that cerebellar neurons also contain antigenic proteins similar to those in intestinal walls, and as a result autoantibodies in CD patients attack not only intestinal mucosa but also cerebellar neural cells[8,9]. Few cases of CD were reported in Asia, and thus low prevalence of CD related cerebellar ataxia had been inferred in Asian countries until recent reports that CD patients may reveal no clinical gastrointestinal manifestation. GS is thus proved to include a hidden type of CD which does not evoke gastrointestinal disorders but may induce sporadic ataxia[7]. Our study discovered that in Taiwan 9% of sporadic ataxia patients have gluten sensitivity, all of whom revealed no clinical manifestation of CD, and meanwhile a very low incidence of GS was found in normal subjects and patients with hereditary ataxia. Although several reports demonstrated a higher incidence of GS in hereditary ataxia and hereditary neurodegenerative disorders[6], our study does not support this observation.

On the question whether related autoantibodies can be used to indentify hereditary or non-hereditary ataxia, some reports demonstrated the high detectability of T-TG antibodies[10,11], whereas AGA did not have high specificity[12,13]. However, the findings of our research indicated that AGA IgG, instead of T-TG, was the only marker with high sensitivity and specificity. Although patients with sporadic ataxia showed higher serum levels of T-TG IgA, the value was not significant enough to differentiate from that of hereditary ataxia patients. In addition, T-TG IgG was of no significance among normal subjects, hereditary ataxia and sporadic ataxia patients. Therefore, our research indicates that serum AGA IgG is a biomarker for the link between autoimmunity and cerebellar ataxia.

This study discovered that cerebellar ataxia patients tested positive for GS have a high incidence of neuropathy[14], and tremor. The finding provides a lead for neurological professionals if patients with sporadic ataxia are accompanied by obvious tremor.

Our research also provides a biomarker for follow up for sporadic ataxia patients who undergo immunoglobin therapy, which was found to partly recover cerebellar neural functions, and we thus propose that in the future patients with sporadic ataxia accompanied by GS may receive intravenous immunoglobin therapy[15-17].

Although research found that serum antibodies positive for GS do not necessarily represent the occurrence of neuronal autoantibodies[14] and several researchers doubted the association of GS and cerebellar ataxia[12,18,19], our future research will continue to investigate the incidence of these neuronal antibodies and compare them with GS antibodies in serum.

Gluten sensitivity has been considered as a neurological illness and gluten ataxia is the most common neurological manifestation of gluten sensitivity[20]. Sporadic ataxia has been reported to be associated with anti-gliadin antibodies[12]. Prevalence studies in European and USA population have shown that gluten sensitivity related celiac disease affects up to 1% of the normal population[21]. In this study, we first reported the incidence of GS in normal subjects, hereditary ataxia or sporadic ataxia patients. Positive results of GS indicate the possible pathogenesis directly or indirectly related to the pathogenesis of cerebellar neuron degeneration.

Though identification of mucosal abnormalities in intestinal biopsy is required, invasive biopsy sampling and inconclusive immunohistochemical staining results become the common pitfalls for diagnosis of gluten associated atypical CD. AGA is widely applied as a biomarker in gluten sensitivity screening, and the measurement of t-TG antibodies may be added to offer specific and sensitive initial screening for CD including the accompanied disease of sporadic cerebellar degeneration[20].

In conclusion, we found lower incidence of GS in

population of sporadic ataxia patients but relatively higher than the incidence in normal subjects or hereditary ataxia patients. Especially, anti-gliadin IgG is still a very powerful indicator to implicate the immune-related sporadic ataxia. To the best of our knowledge, we first reported the prevalence of gluten ataxia in Taiwan and our data suggests that detection of circulating gluten associated autoantibodies could provide one of effective indicators in the screening of sporadic ataxia susceptibility. Additional studies with a larger number of patients and HLA genotyping could be helpful to intensify the significance of these associations.

REFERENCES

1. Cummins AG, Thompson FM, Butler RN, Cassidy JC, Gillis D, Lorenzetti M, Southcott EK, Wilson PC. Improvement in intestinal permeability precedes morphometric recovery of the small intestine in coeliac disease. Clin Sci (Lond) 2001;100:379-386.
2. Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol 2001;96:3237-3246.
3. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005;40:1-19.
4. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroofe N, Aeschlimann D. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase.Ann Neurol 2008;64:332-343.
5. Bushara KO, Nance M, Gomez CM. Antigliadin antibodies in Huntington's disease. Neurology 2004;62:132-133.
6. Ihara M, Makino F, Sawada H, Mezaki T, Mizutani K, Nakase H, Matsui M, Tomimoto H, Shimohama S. Gluten sensitivity in Japanese patients with adult-onset cerebellar ataxia. Intern Med 2006;45:135-140.
7. 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; 126:685-691.
8. Hadjivassiliou M, Boscolo S, Davies-Jones GA, Grünewald RA, Not T, Sanders DS, Simpson JE, Tongiorgi E, Williamson CA, Woodroofe NM. The humoral response in the pathogenesis of gluten ataxia. Neurology 2002;58: 1221-1226.
9. Boscolo S, Sarich A, Lorenzon A, Passoni M, Rui V, Stebel M, Sblattero D, Marzari R, Hadjivassiliou M, Tongiorgi E. Gluten ataxia: passive transfer in a mouse model. Ann N Y Acad Sci 2007;1107:319-328.
10. Hadjivassiliou M, Sanders DS, Woodroofe N, Williamson C, Grünewald RA. Gluten ataxia. Cerebellum 2008;7:494-498.
11. Hadjivassiliou M, Mäki M, Sanders DS, Williamson CA, Grünewald RA, Woodroofe NM, Korponay-Szabó IR. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. Neurology 2006;66:373-377.
12. Abele M, Schols L, Schwartz S, Klockgether T. Prevalence of antigliadin antibodies in ataxia patients. Neurology 2003;60:1674-1675.
13. Wong D, Dwinnel M, Schulzer M, Nimmo M, Leavitt BR, Spacey SD. Ataxia and the role of antigliadin antibodies. Can J Neurol Sci 2007;34:193-196.
14. Lock RJ, Tengah DP, Williams AJ, Ward JJ, Bingley PJ, Wills AJ, Unsworth DJ. Cerebellar ataxia, peripheral neuropathy, "gluten sensitivity" and anti-neuronal autoantibodies. Clin Lab 2006;52:589-592.
15. Nanri K, Okita M, Takeguchi M, Taguchi T, Ishiko T, Saito H, Otsuka T, Mitoma H, Koizumi K. Intravenous immunoglobulin therapy for autoantibody-positive cerebellar ataxia. Intern Med 2009;48:783-790.
16. Nanri K, Otsuka T, Takeguchi M, Taguchi T, Ishiko T, Mitoma H, Koizumi K. A case of anti-gliadin-antibody-positive cerebellar ataxia effectively treated with intravenous immunoglobulin in which voxel-based morphometry and FineSRT were diagnostically useful. Rinsho Shinkeigaku 2009;49:37-42.
17. Burk K, Melms A, Schulz JB, Dichgans J. Effectiveness of intravenous immunoglobin therapy in cerebellar ataxia associated with gluten sensitivity. Ann Neurol 2001; 50:827-828.
18. Lock RJ, Pengiran Tengah DS, Unsworth DJ, Ward JJ,

Wills AJ. Ataxia, peripheral neuropathy, and anti-gliadin antibody. Guilt by association? J Neurol Neurosurg Psychiatry 2005;76:1601-1603.

19. Serratrice J, Attarian S, Disdier P, Weiller PJ, Serratrice G. Neuromuscular diseases associated with antigliadin antibodies. A contentious concept. Acta Myol 2004;23:146-150.
20. Hadjivassiliou M, Grünewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, Kandler RH, Lobo A, Powell T, Smith CM. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998;352:1582-1585.
21. Fasano A. Celiac disease: the past, the present, the future. Pediatrics 2001;107:768-770.