

Neurological manifestations Of Patients with Coeliac disease

Akram M.Al-mahdawi, CABM, MRCP (London), FRCP (London, Edinburgh),
FACP

Anmar O. Hatem FIBMS

Mohammed S. Dahir FIBMS

BACKGROUND: *Celiac disease (CD Non tropical sprue, gluten-sensitive enteropathy) is a malabsorption disease due to an allergic reaction to gluten (cereal grain protein) which is presenting in wheat, rye and barley and causing small intestine mucosal injury.*

The onset is in the first four decades of life mainly. It may be associated with a wide spectrum of neurological manifestations including cerebellar ataxia, epileptic seizures, dementia, neuropathy, myopathies and multifocal leucoencephalopathy.

METHODS: *The study enrolled Seventy-five unselected consecutive patients with CD(The diagnosis of CD was confirmed by serologic tests (antiendomysial, anti transglutaminase antibodies and antigliadin antibodies and biopsy of the small intestine) attended the department of Gastroenterological out patient, medical and neurological wards in Baghdad Teaching Hospital from November2009 to July2010.. All patients were on gluten-free diet at recruitment and median duration of disease (2.56±1.670) years.*

Patients with associated conditions that could cause neuropathy (diabetes mellitus ; thyroid disease, alcohol abuse, vitamin B12 deficiency, exposure to neurotoxin drugs) or ataxia (alcohol abuse, genetic disorders ,syphilis, or B12 deficiency) were excluded, in order to minimize the possible confounding effect on neurological symptoms.

RESULTS: *We report 13 patients with neurological manifestations related with CD: two with cerebellar ataxia, two with epilepsy, two with migraine, and two with carpal tunnel syndrome, two with myopathies, two with peripheral neuropathy and one with cognitive impairment.. In two patients the neurological symptoms preceded the gastrointestinal abnormalities.*

Conclusins: *We need to think of CD in the differential diagnosis of neurological dysfunction of unknown cause, including ataxia, epilepsy, peripheral neuropathy and dementia. There is no association between immunological marker of celiac disease and appearance of neurological symptoms.*

KEY WORDS: *celiac disease, cerebellar ataxia, epilepsy, cognitive impairment*

I. INTRODUCTION

Celiac disease is an immune-mediated disorder that involves the small intestine It is characterized by an inflammatory process, especially in the proximal small bowel. This causes altered mucosal architecture, reduced absorptive surface area and results in impaired absorption of macro- and micronutrients. Removal of dietary gluten usually results in reversal of the mucosal inflammatory process in the small intestine and normalization of the processes involved in the assimilation of various nutrients⁽¹⁾

The diagnosis depends on demonstration of the characteristic pathological changes in the small bowel and evidence of a gluten-free diet response(1) Celiac disease has been estimated to occur in up to 1% of most populations evaluated in screening studies and may appear at any age, including the elderly (2>3) Clinical presentations of celiac disease are highly variable. Diarrhea and weight loss are usually present, but extra intestinal symptoms may occur, sometimes without any obvious gastrointestinal changes. As a result, celiac disease may be recognized late in the clinical course, often after treatment for other clinically overt disorders has been pursued.

In recent years, different neurological disorders have been identified in patients suffering from celiac disease. In some, these disorders may be the initial manifestation of celiac disease, leading to its recognition ^(4,5).

Some disorders may be the result of micronutrient malabsorption, particularly vitamins, while others may share an immune-mediated etiology or other pathogenesis that requires elucidation. Neuropathy, ataxia, seizure disorders and impaired cognitive function (or dementia) have most often been described. In some patients, vitamin deficiency has been hypothesized or a concomitant immune-mediated mechanism may be responsible. For most patients, however, the precise mechanism is unknown and requires elucidation. For many, the response in neurological changes to a gluten-free diet has either been poor or fails to occur⁽⁶⁾.

Up to 50% of celiac disease patients may develop peripheral neuropathy⁽⁷⁾. Importantly, neuropathy may precede the diagnosis of biopsy-defined celiac disease⁽⁸⁾, and should be considered especially if a symmetric distal form of sensory neuropathy is evident⁽⁸⁾. Other neuropathic processes that can occur in celiac disease include a pure motor neuropathy, a form of mononeuritis multiplex, a Guillain-Barre-like syndrome and an autonomic neuropathy⁽⁸⁻¹⁶⁾.

Gait ataxia occurs, often associated with neuropathy⁽¹⁷⁾. In other individuals with ataxia, cerebellar involvement may occur^(18,19) with low vitamin E levels⁽²⁰⁾. In some, recognition of celiac disease may be preceded by cerebellar changes, but there are no clinical features of the ataxia that are distinctive for underlying adult celiac disease⁽³¹⁾.

Seizure disorder (i.e., epilepsy) appears to be associated with celiac disease^(36,40), most often, but not exclusively, in pediatric celiac disease, rather than in adults. The effect of a gluten free diet is not clear. Some studies⁽³⁴⁾ have reported better seizure control in children that resulted from a reduction in seizure-control medications. A specific seizure disorder syndrome has been recorded in celiac disease with bilateral occipital calcification.

Dementia may occur in celiac disease, particularly in the form of memory impairment⁽⁴¹⁾. In most patients, a gluten-free diet does not appear to result in an improvement of neurological Disability⁽⁴¹⁾. In a case series⁽⁴²⁾ the most common presenting neurological features were amnesia, acalculia, confusion and personality changes. In subjects with a deficiency of folic acid, vitamin B12 or vitamin E, subsequent supplementation had no effect in reversing the neurological findings. However, some patients appeared to stabilize after removal of dietary gluten. Pathology studies⁽⁴³⁾ demonstrated a nonspecific gliosis.

II. PATIENT ENROLLMENT:

Seventy-five unselected consecutive patients with histological proven CD Attended the department of Gastroenterological out patient, medical and neurological wards in Baghdad Teaching Hospital from November 2009 to July 2010, were collected. All patients were on gluten-free diet at recruitment. The median duration of disease was (2.56 ± 1.670) years. Age range between 5-50 year, male account 32 (42.7%) and female were 43 (57%)

Patients with associated conditions that could cause neuropathy (diabetes mellitus; thyroid disease, alcohol abuse, vitamin B12 deficiency, exposure to neurotoxin drugs) or ataxia (alcohol abuse, genetic disorders, syphilis, or B12 deficiency) were excluded, in order to minimize the possible confounding effect on neurological symptoms.

In our study, patients were divided into 3 groups:

- a. Those who had Intestinal manifestations
- b. Those who had neurological manifestations
- c. Those who had extra Intestinal non neurological manifestations

All patients received a questionnaire with a checklist on which they were asked to report on neurologic symptoms or conditions that required medical attention or treatment. Patients with suspected neurologic signs or symptoms underwent a full neurologic evaluation and laboratory examinations, including brain imaging and electroencephalogram if required. All investigations were performed after obtaining informed consent from patients.

III. RESULTS:

Our study consisted of 75 subjects; CD who answered the questionnaires and agreed to take part in this study. The mean ages of the patients with CD were 25.1 ± 8.4 years. 32 male (42.7%), 43 (57.3% female).

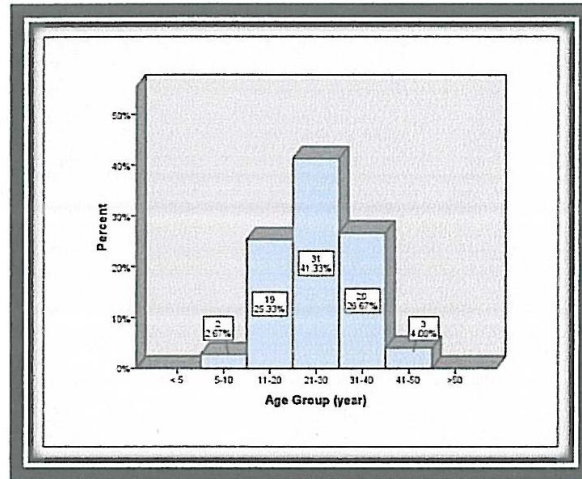


Figure 1: Distribution of study sample according to age.

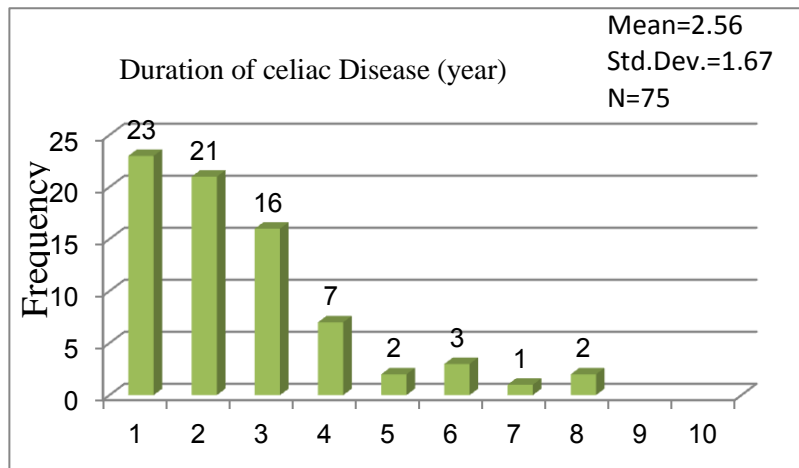


Figure 2: Distribution of study sample according to the duration of Celiac disease.

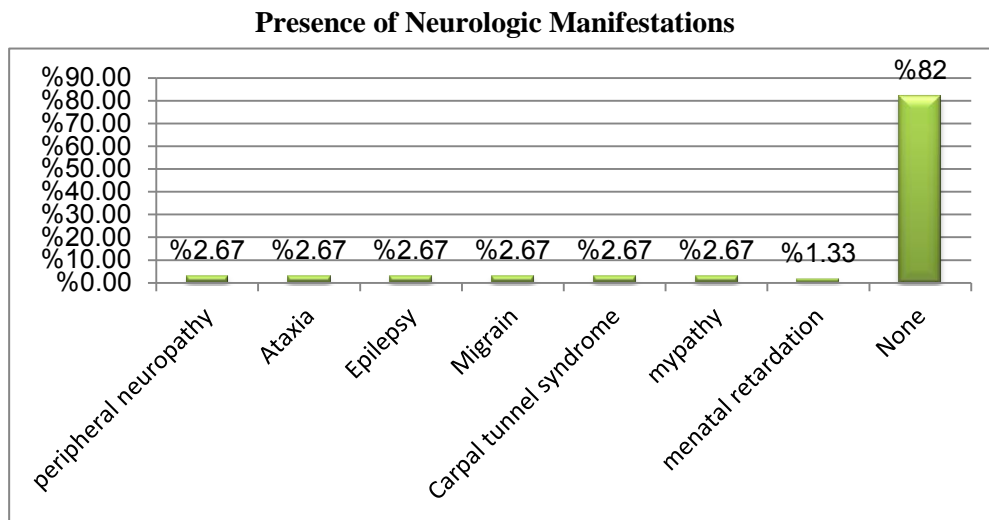


Figure 3: Distribution of participants according to their clinical manifestations

Distribution of participants according to their clinical manifestations.

1-Intestinal manifestations:

The presence of intestinal manifestations of malabsorption such as steatorrhea, weight loss or other signs of nutrient or vitamin deficiency; and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months, found in 69(92%) patients.

2-Extra-intestinal Manifestations

A. Neurological Manifestations

Prevalence of neurological manifestation or findings were 17.3 % (95%CI 12.9-21.7%) We report 13 (17.3%) patients with neurological manifestations related with CD: two (2.7%) with migraine, two(2.7%) with epilepsy, two(2.7%) with cerebellar ataxia, two (2.7%)with myopathies, two(2.7) with carpel tunnel syndrome, two(2.7%) with peripheral neuropathy and one(1.3) with cognitive impairment, see figure3.

B. Presence of non Neurologic Manifestations:

The presence of non Neurologic Manifestations like iron deficiency anemia, arthritis, and osteopenia and osteoporosis found in 10(13.3%) patients
All figure3findings are highly significant(not by chance)i.e. the distribution observed was true, see figure3

4-3: Distribution of study sample according to the results of clinical examinations:

A. General and systemic examination:

28 patients was had positive finding inform of pallor(15patients),,short stature(2 patients) ,skin lesion (2 patients)in form of dermatitis herpetiformis, systolic murmur(6 patients) and arthritis(3 patients)

B. Central nervous system examination:

- 1- mental state examination: one patient positive mini mental state examination was 20/30
- 2- cranial nerve examination: no patients with abnormal finding
- 3- motor examination: two patients positive they had proximal muscle weakness more than distal about grad 4 plus powers
- 4- sensory examination: two patients positive they had gloves and stocks sensation, while other two patients had Tinel’s sign, and Phalen’s test positive

cerebellar examination: two patients positive they had abnormal ataxic gait, intention tremor and other cerebellar signs, see table (1)

Table 1: Distribution of study sample according to the results of clinical examinations.

Type of Examination	N (%)		X ²	P
	Total	75(100.0)		
General and systemic Examination				
	Positive	28(37.3)	4.813	0.028
	Negative	47(62.7)		
Mental state Examination				
	Positive	1(1.3)	71.053	0.000
	Negative	74(98.7)		
Cranial Nerve Examination				
	Positive	0(0.0)	---	----*
	Negative	75(100.0)		
Motor Examination				
	Positive	2(2.7)	67.213	0.000
	Negative	73(97.3)		
Sensory Examination				
	Positive	4(5.3)	59.853	0.000
	Negative	71(94.7)		
Cerebellar Examination				
	Positive	2(2.7)	67.213	0.000
	Negative	73(97.3)		

*Chi square test cannot be performed.

Distribution of study sample accordins to the results of investigations

We do the following investigations

- A. General Investigations: like complete blood picture and found 8 patients had anemia also we do biochemical analysis like RBS, TFT, LFT
 - B. NB. Patients Which had diabetes mellitus and positive TFT, are excluded from this study.
 - C. Immunological Investigations
 - 1- AGA were positive in 30(40%) patients
 - 2- EMA were positive in 50(66.7%) patients
 - 3- tTGA were positive in 24(32%) patients
 - D- Endoscopic examination :were positive in 75 patients
 - E- EMG: were done in 7 patients which was positive in2 patients had carpel tunnel syndrome,2 had myopathies,, 2 had peripheral neuropathy ,and 1 negative.
 - F- MRI: were done in 5 patients which was positive in 2 patients showing cerebellar atrophy
- See (Table 2)

Table (2) Distribution of study sample according to the results of investigation

Type of Investigation		N (%)
	Total	75(100.0)
General Investigations		
	positive	10(13)
	Negative	65(87)
Lmmunological Investigations		
AGA	positive	30(40.0)
	Negative	45(60.0)
EMA	positive	50(66.7)
	Negative	25(33.3)
tTGA	positive	24(32.0)
	Negative	51(68.0)
Endoscopic Examination		
	positive	75(100.0)
	Negative	0(0.0)

Distribution of studied sample according to the presence of neurological manifestations and to the results of immtmmological tests

Results of AGA, EMA & tTGA in combination were positive 13 patients in whom 5(p=0.901) patients had AGA positive,4 (p=0.003) patients had EMA positive and 4(p=0.917) patients had tTGA positive
 P is the probability of getting above findings by chance, so findings are not considered significant if the probability of chance is high (i.e. $P > 0.05$ or 5%).

It is significantly to find more positive EMA results in celiac disease without neurological manifestations.

No significant association between results of AGA and tTGA and the presence or absence of neurological manifestations in patients with celiac disease.

See figure (4)

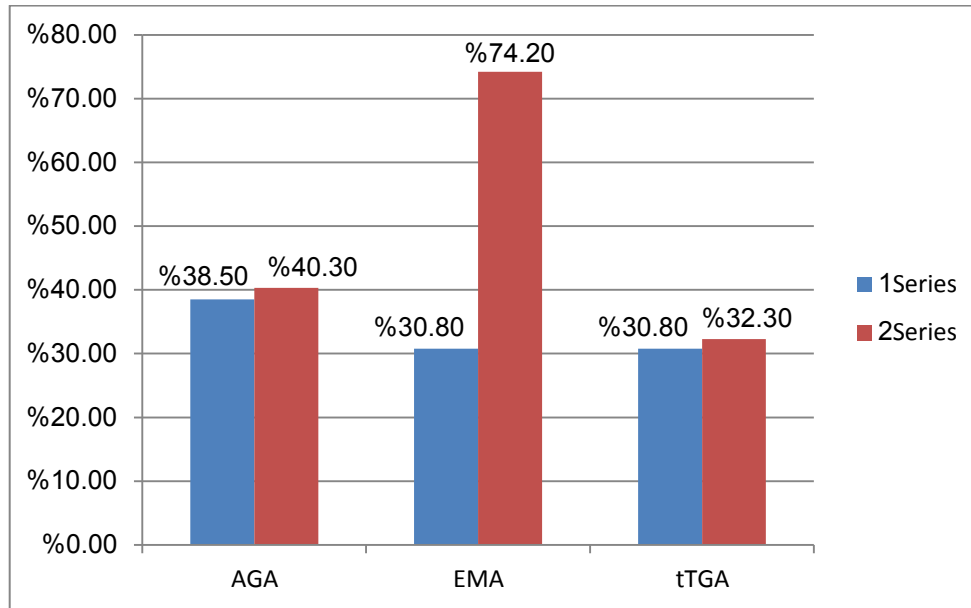


Figure 4: Distribution of positive results of immunological tests according to the presence or absence of neurological manifestations in patients with celiac disease.

IV. DISCUSSION:

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten proteins in genetically susceptible individuals, with more than 95% of patients carrying the MHC class II, human leukocyte antigen (HLA) DQ2 or DQ8 heliotype⁽⁴⁶⁾

The enzyme tissue transglutaminase (tTG, TG2) is involved in the generation of T cell stimulatory gluten peptides through deamidation of glutamine residues. It is also the main autoantigen in CD, making anti-tTG antibodies a highly specific marker of the disease⁽⁴⁷⁾. Intestinal biopsy showing varying degrees of villous atrophy of the small intestinal mucosa that improve after gluten-free diet allows for a definitive diagnosis of the disease. Approximately 50% of adult celiac patients present with extra intestinal manifestations, including iron deficiency anemia, osteoporosis, infertility, and neurological alterations. Peripheral neuropathy and cerebellar ataxia are the most common neurologic deficits in CD^(48,49,50). The pathogenesis of neurological damage is poorly understood and the response to gluten-free diet is still controversial^{^ ^}. Humoral immune mechanisms have been proposed in the pathogenesis of both ataxia and peripheral neuropathy. Antibodies to gliadin that cross react with Purkinje cells have been inconsistently reported in sera of celiac patients with ataxia,^(52,53,54) and IgG antibodies to gangliosides have been found in adult CD patients with neuropathy and other neurological manifestations⁽⁵⁵⁻⁵⁶⁾

In Our study that consisted of 75 subjects; CD which answered the questionnaires and agreed to take part in this study The mean ages of the patients with CD were 25.1 ± 8.4 years. 32male (42.7%) ,43(57.3% female)and the duration of celiac disease was 2.56 ± 1.6 years. The presence of intestinal manifestations of malabsorption such as steatorrhea, weight loss or other signs of nutrient or vitamin deficiency; and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months, found in 69(92%) patients.

Prevalence of neurological manifestation or findings were 17.3 % (95%CI 12.9-21.7%) and these compatible to study dome by (Chiara Briani, Gabriella, Zara, Armin Alaedini) which had been found the prevalence of neurological complication 22.5%⁽⁵⁷⁾

Celiac disease and the central nervous system:

1-MIGRAINE:

In our study we found two patients (2.7%) with migraine, which were symmetrical to study done by the (Katrin Bu"rk, MD, Marie-Louise Farecki) which found migraine(3.2%).⁽⁵⁸⁾

Patients with history of migraine are improve in gluten free diet in which attacks are decrease in frequency and severity and that agreement with Italian study (Department of Internal Medicine, Catholic University of the Sacred Heart, Gemelli Hospital, Rome, Italy.)⁽⁵⁸⁾

2-EPILEPSY:

In our study we found two patients (2.7%) with epilepsy one of them had generalize tonic clonic fit, and the other one had partial complex fit. Both of them responded to carbamazepine .MRI in both of them were negative.

This finding is in concordance with the result of (Katrin Bu"rk, MD, Marie-Louise Farecki)⁽⁵⁸⁾ and (LIISA Luostarnen)⁽⁵⁹⁾ In which Prevalence of epilepsy 4% .

Epilepsy in association with celiac disease has been focal with or without evolving to bilateral convulsion seizure in most cases (Gobbi and Labate et al.)^(60,61)

Localization has been often temporal, but many cases with occipital lobe epilepsy have also been described, especially in connection with occipital calcifications (Chapman et al, Labate et al.)^(61, 62). The classification of epilepsy type in CD in most studies inadequate.

3-ATAXIA:

We found two patients (2.7%) with ataxia and that agreement with (Combarros *et al.*)⁽⁴³⁾ and Turkish case reports⁽⁶³⁾ There is some controversy as to the concomitant occurrence of celiac disease and ataxia of unknown origin.. Hadjivassiliou and colleagues reported 16% of patient with ataxia of unknown origin to be suffering from celiac disease.⁽⁶⁴⁾

Pellecchia and colleagues⁽⁴⁰⁾ found three (12.5%) celiac disease cases among 24 ataxic syndromes of indefinite origin. Burk and associates found celiac disease frequency of 1.9% in patient with idiopathic cerebellar ataxia. In conflict with this finding, a group under combarros⁽⁴³⁾ failed to find any cases of celiac disease in cohort of 32 patients with idiopathic cerebellar ataxia. As a summary, the frequency of celiac disease was significantly increased only in the studies by. Hadjivassiliou⁽⁶⁴⁾ and Pellecchia⁽⁴⁰⁾. The others could not confirm this finding of an increased frequency of celiac disease in association with ataxia of unknown origin.

4-DEMENTIA:

We reported one case that has decrease state of cognitive function Intellectual deterioration ranged from moderate to severe and diffuse cerebral or cerebellar atrophy was found in brain CT. In contrast, Hallert and Astrom⁽⁶⁵⁾ found no consistent signs of cognitive impairment in patients with untreated celiac disease Frisoni found no difference in the prevalence of celiac disease in Alzheimer's disease or cognitively unimpaired elders suggesting that the immune changes in celiac disease are unlikely to play a role in Alzheimer's disease⁽⁶⁶⁾ The question of possibly increased frequency of dementia in patient with celiac disease and mechanism behind the possible association remains open.

B- Celiac disease and the peripheral nervous system

1- Celiac disease and neuropathy:

In our study we found two cases (2.7%) with carpal tunnel syndrome, also we found two cases (2.7%) with peripheral neuropathy and that was symmetrical to study done by the (Chiara Briani ,Gabiella Zara and Katrin Bu"rk, MD, Marie-Louise Farecki)^(57,58).

The combination of reduced deep tendon reflexes and sensory deficits in patients with CD is compatible with peripheral neuropathy. Actually, peripheral neuropathy of the axonal or demyelinating type has often been reported in patients with CD⁽⁵⁹⁾ The presence of neuropathy seemed to be independent of gluten-free diet, considering that patients with neuropathy had been on gluten-free diet since the establishment of the CD diagnosis, The presence of neuropathy in patients with gluten-controlled CD has already been reported (Luostarinen et al.). These results question a direct neurotoxic effect of gluten exposure, and point to different mechanisms that might be responsible for the development of peripheral neuropathy in CD.⁽⁵⁹⁾ In a study by Hadjivassiliou and associates the role of gluten free diet was uncertain in modifying symptom and findings of neuropathy in celiac disease.⁽⁶⁷⁾ In some case reports the symptoms have disappeared after introducing gluten free diet (Kaplan et al., Polizzi et al.)^(68,69)

1- Celiac disease and myopathies

In our study we found two cases (2.7%) with myopathies in which proximal muscle effected more than distal and features goes with inflammatory myopathies These result compatible with (LIISA Luostarnen)⁽⁵⁹⁾ There is little information concerning muscle disease in association with Celiac disease . Bannerji and Hurwitz described myopathies in five cases (11.9%) out 42 patients with celiac disease .all of them had vitamin D deficiency, which was considered to be the etiological factor⁽⁷⁰⁾.

There are recent case reports deal with an association of celiac disease with Osteomalacia or rickets and myopathies (Hardoff et al., Russel, Cimaz et al)^(71,72, 73) in these case, myopathy improved after gluten free diet. Celiac disease has also been described in association with inflammatory myositis (vilppula and aine,and marie et al),^(74,75) inclusion body myositis, neuromyotonia (Hadjivassiliou et al) but these observations may be only coincidental⁽⁶⁷⁾.

C -Immunological mechanism:

In our study we significantly found more positive EMA results in celiac disease without neurological manifestations. Our study did not detected any significant association between results of AGA and tTGA and the presence or absence of neurological manifestations in patients with celiac disease. These finding agree with (Chiara Briani ,Gabriella Zara)⁽⁵⁷⁾ but not agree with (Hanagasi *et al.*)⁽⁴¹⁾ (Pellecchia *et al.*, Hadjivassilliou *et al*)^(40,50).

In which immunologic abnormalities were suggested as causes of the neurological involvement of the disease^(40,41,42). Abnormal immunological reactions may be responsible for the occurrence of the neurological complications. Antigliadin antibodies are suggested to be neurotoxic. The mechanism of the neurological complications is not definite (Pellecchia *et al.*)⁽⁴⁰⁾. Malabsorption was thought to be the cause of neurological complication. However, nutritional, toxic and immunologic abnormalities were suggested as causes of the neurological involvement of the disease. They found that abnormal immunological reactions may be responsible for the occurrence of the neurological complications (Hanagasi *et al.*)⁽⁴¹⁾. Antigliadin antibodies are suggested to be neurotoxic (Pellecchia *et al.*)⁽⁴⁰⁾. Hadjivassilliou *et al.* reported a series of patients with neurological complications of celiac disease. In these patients there were positive correlations between the duration of the ataxia and cerebellar atrophy. It is suggested that the continuous intake of gluten and its products may be harmful to cerebellar cells in gluten sensitive patients.⁽⁴²⁾ The neurological manifestations are immune mediated and not related to vitamin deficiencies. Pathological data obtained from nerve and muscle biopsies and brain tissue from post mortem examinations demonstrate evidence of inflammation around arteries with predilection for the cerebellum (balance centre) and/or the peripheral nerves.

Patients with gluten ataxia without enteropathy have evidence of IgA deposits against tissue transglutaminase type 2 (the autoantigen in CD) within the small bowel mucosa. This finding has been shown to be a reliable marker of the whole spectrum of GS and has been described in patients with DH and CD before the development of enteropathy. Such deposits have also been found on arterial wall within the brain of patients with gluten ataxia. This suggests that transglutaminase may play an important role in the pathogenesis of the neurological manifestations. Of interests the discovery of a new transglutaminase, TG6, that is primarily expressed in brain, but shares genetic and structural similarities with TG2, the autoantigen in CD and TG3 the autoantigen in DH. Antibodies against TG6 may become a useful marker for the neurological spectrum of the disease.⁽⁴⁵⁾

CONCLUSION

1. Celiac disease may be initially defined after presentation with a neurological disorder.
2. CD should be ruled out in the differential diagnosis of neurological dysfunction of unknown cause, including ataxia, epilepsy and dementia.
3. There is no association between immunological marker of celiac disease and appearance of neurological symptoms.

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