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NEUROLOGICAL MANIFESTATIONS OF GLUTEN RELATED DISORDERS

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ABSTRACT

Objective: To determine the frequency and pattern of neurological features in patients diagnosed with gluten related disorder (GRD).

Study Design: Cross sectional analytical study.

Place and Duration of Study: Pak Emirates Military Hospital Rawalpindi, from Jan 2016 to Jun 2018.

Patients and Methods: This study included cases who presented initially with neurological manifestations and later diagnosed having GRD, including coeliac disease (CD) or non-coeliac gluten sensitivity (NCGS). Cases fulfilling inclusion and exclusion criteria were selected. Record of patients was obtained from the hospital stats office. Cases were analyzed for clinical symptomatology, laboratory and neuro-radiological findings. Data was collected using performa and analysis was done using SPSS version 20.

Results: Out of 31 patients, 18 (58.1%) were male and 13 (49.9%) were females. Mean age was 28.8 ± 10.4 years. Nineteen (61.3%) were diagnosed with CD while 12 (38.7%) had NCGS. Anti-TTG antibodies were detected in 17 out of 19 patients with CD, while anti Gliadin antibodies were positive in 11 out of 12 patients with NCGS. These results were statistically significant with *p*-value <0.001. Headache was the commonest manifestation in GRD, in 17 (54.8%) patients while 11 (34.5%) had seizures. Six cases (19.3%) presented with variable generalized weakness. Moreover 10 (32.2%) patients had MRI brain abnormalities.

Conclusion: CD and NCGS should be kept in differential diagnosis, in various central and peripheral nervous system clinical manifestations. Moreover even if biopsy is negative for CD even then gluten sensitivity can be present in the form of NCGS with neurological manifestations.

Keywords: Anti Gliadin antibodies, Coeliac disease, Gluten sensitivity, Non-coeliac gluten sensitivety.

INTRODUCTION

Coeliac disease (CD) was initially considered to be a disease of pediatric age group but now it is well recognized in adult population with varied symptoms ranging from mild gastro-intestinal symptoms to debilitating neurological involvement. However non-coeliac gluten sensitivity (NCGS) is relatively new entity with extra-intestinal features of CD, including nervous system involvement. Spectrum of neurological manifestations in CD in adults and pattern of neurological features in NCGS is not largely different[1]. Although CD is a well-known disease worldwide but its diagnosis in third world countries like Pakistan is still vivid particularly if disease manifest with extra intestinal neurological features and especially in adult population. The prevalence of NCGS is (0.5-13%)[2] compared to CD (0.5-1%) with slight variation in different regions of the world[3]. However, the exact prevalence of CD in Pakistan still need to be determined[4] and NCGS is hardly reported from Pakistan.

The purpose of this study was to understand the neurological, radiological and laboratory features in adults, with gluten related disorders and to subcategorize these cases into CD and NCGS in a third world country like Pakistan where wheat is among staple diet. Perhaps to the best knowledge this is, of its kind first study done on gluten related disorders in adults in Pakistan.

PATIENTS AND METHODS

This was a, cross sectional analytical study conducted at Pak Emirates Military Hospital Rawalpindi, in the department of neurology. The cases included in this study consisted of patients, who initially presented with various neurological

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or neuropsychiatric manifestations and later on diagnosed with either coeliac disease (CD) or non-coeliac gluten sensitivity (NCGS) as a cause of neurological symptoms.

Diagnosis of CD constituted positivity of mucosal structural changes on duodenal biopsy in the form of triad of villous atrophy, cryptal hyperplasia and increased intraepithelial lymphocytes with or without positivity of auto-antibodies against gluten. While NCGS diagnosis required lack of enteropathy on duodenal biopsy in the presence of auto-antibodies against gluten.

Those cases who were previously diagnosed with CD or NCGS and later presented with neurological symptoms were not included in this study. Moreover, any patient with an alternative diagnosis or explanation for neurological or neuro-psychiatric manifestations, was also excluded from this study. Record of patients fulfilling above criteria and hence diagnosed with the gluten related disorders, from the department of neurology and hospitals stats office, over the period from January 2016 to June 2018, was obtained. Non-probability consecutive sapmling was done. Approval from the hospitals ethical committee was obtained before data collection.

The cases were analyzed for clinical symptomatology regarding the type of neurological & psychiatric symptoms. Moreover, laboratory data such as the anti-TTG antibodies, anti-Gliadin antibodies, cerebrospinal fluid (CSF) pressure & analysis was gathered. Magnetic resonance imaging (MRI) findings, EEG, NCS and EMG results, along with demographic data, such as gender & age of the patients was also obtained. Data was collected using performa filled by registrar neurologist. Data analysis was done using SPSS version 20.

Results were expressed as the mean ± standard deviation for continuous variables such as age, and frequencies and percentages for categorical data such as gender, the type of neurological manifestations, laboratory tests, and MRI brain findings, EEG, NCS and EMG. Moreover chi square test was used to see any significant difference among two groups (CD and NCGS) for anti TTG and gliadin antibodies and neurological as well as neuro-radiological findings on MRI. A *p*-value less than or equal to 0.05 was considered significant.

RESULTS

Total number of patients included in study was 31, out of these, 18 (58.1%) were male and 13 (41.9%) were females. Mean age was 28.8 ± 10.4 years. Maximum age reported was 53 years. Number of patients diagnosed with CD was 19 (61.3%) while 12 (38.7%) patients had NCGS.

Overall out of 31 patients, anti TTG abs were present in 19 (61.3%) patients while anti gliadin antibodies were positive in 14 (45.2%) patients. However, anti-TTG antibodies were positive significantly in CD in 17 out of 19 patients while NCGS group had only 2 patients with positive results for anti TTG antibodies out of 12 patients,

Table-I: Anti-TTG antibodies positivity in different gluten related disorders (n=31).

		Anti TTG antibodies	
		Positive	**Negative**
Gluten related disorder	CD	17 (89%)	2 (11%)
	NCGS	2 (20%)	10 (80%)

p-value <0.001

Table-II: Anti-Gliadin antibodies positivity in different gluten related disorders (n=31).

		Anti-Gliadin antibodies	
		Positive	**Negative**
Gluten related disorder	CD	3 (15.7%)	16 (84.2%)
	NCGS	11 (91.6%)	1 (8.3%)

p-value <0.001

this was statistically significant with *p*-value <0.001 (table-I). Similarly anti Gliadin antibodies were positive in 11 patients diagnosed with NCGS but in only 3 patients of CD, which is also statistically significant with *p*-value <0.001 (table-II). Both anti TTG and anti Gliadian antibodies were positive in only 4 (12.9%) patients, However 2 (6.4%) patients did not show any kind of antibodies in serum.

Thirteen (41.9%) patients had single neurological manifestation while 18(58.1%) patients manifested with more than one neurological features. Among neurological

features migraine like headache was found the most common manifestation in gluten related disorders, in 17 (54.8%) cases, while only 2 (6.5%) patients had intracranial hypertension along with headache (table-III). Moreover statistically no neurological symptom was found preferably more common in either CD or NCGS group.

Out of 6 (19.3%) patients who presented with variable generalized weakness, 4 (12.9%) were diagnosed with chronic polyneuropathy and 2 (6.5%) patients were confirmed to have inflammatory myopathy on muscle biopsy. In all these patients EMG/NCS findings were consistent with diagnosis of polyneuropathy or myopathy. Only 11 (35.5%) patients presented with various types of seizures and later on diagnosed with either CD or NCGS while 20 (64.5%) patients did not seize during course of disease. Among 11 patients with seizures, 5 had complex partial seizures, 4 patients had generalized tonic clonic seizures (GTCS) while only 2 had myoclonic seizures (table-IV). Moreover 10 (32.2%) patients had various findings on MRI Brain, with subcortical hyper-intensities being most common finding in 5 (16.1%) patients (figure).

DISCUSSION

Gluten-related disorders (GRD) are divided into classic celiac disease and NCGS. In these disorders body becomes intolerant to gliadin present in gluten-containing foods like barley, rye, and wheat. Immune response may result in enteropathy which occurs in CD or result in sensitivity to gluten without enteropathy known as NCGS with mostly extra intestinal features. Classical CD is diagnosed on duodenal biopsy along with or without presence of serological markers. Improvement of symptoms on a gluten-free diet (GFD) in the presence of positive serology and normal duodenal biopsy defines NCGS[5].

Neurological manifestations occur in almost equal frequency in CD and NCGS[1] involving both central and peripheral nervous system. In a recent study cerebellar ataxia was the commonest finding followed by the peripheral neuropathy and encephalopathy in both CD and NCGS but mild difference in the severity of these symptoms was present[1,6].

Our predominant finding was of headache which was present in 17 (54.8%) of the patients followed by neuropsychiatric symptoms 13 (41.9%) in the form of mood disorder and anxiety disorder, while we observed ataxia in only 4 (12.9%) of the patients which is reported previously a very common finding in GRD particularly CD. CD patients are more prone to headache-related visits to health care facilities[6] and we have observed that our patients met ICHD criteria for migraine as being the most frequent type of headache. While intracranial hypertension was found in only 2 (6.5%) patients as cause of headache.

Table-III: Frequency and percentages of different neurological features in Gluten related disorders (n=31).

Neurological Features	Frequency (n=31)*	Percentage (%)
Migraine like headache	17	54.8
Seizures	11	35.4
Mood disorder	7	22.6
Anxiety	6	19.4
Polyneuropathy	4	12.9
Ataxia	4	12.9
Inflammatory myopathy	2	6.5
Intracranial HTN	2	6.5

*Many patients had more than one neurological manifestations

Table-IV: Different types of seizures in gluten related disorder (n=31).

Seizures type	Frequency (n=31)	Percentage (%)
Complex focal seizures	5	16.1
GTCS	4	12.9
Myoclonic seizures	2	6.5
No. seizures	20	64.5
Total	31	100

Association of schizophrenia with coeliac disease is long known[7], but CD has also been implicated in various other psychiatric conditions

like anxiety state, depression, attention deficit hyperacute disorder, and autism-related spectrum disorders[8-10]. Mood disorder was present in 7 (22.6%) patients as being most common psychiatric condition followed by the generalized anxiety disorder in 6 (19.3%) patients while psychosis was not found in any patient in our study, which has been reported previously in CD and gluten related disorders. Psychiatric symptoms are better controlled in those with GFD.

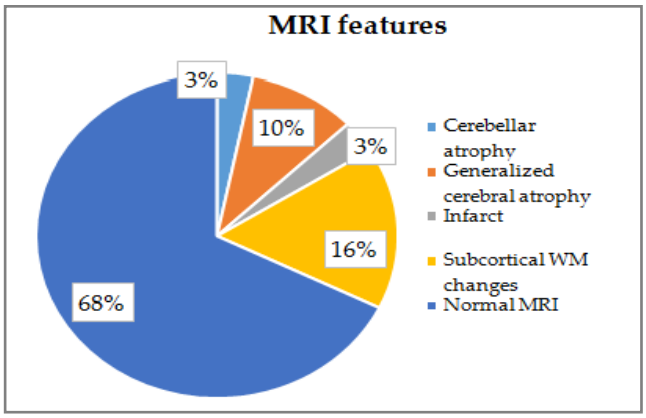

Figure: MRI brain findings in gluten related disorders.

In patients with the CD, MRI of brain can depict white matter abnormalities (WMA) and significant atrophy of various parts of brain like cerebellum and caudate nucleus[11]. WMA were found in 5 (16.1%) of the patients with gluten sensitivity in this study. Even these findings can be present in neurologically asymptomatic patients in CD[12].

Various kind of nerve disorders can occur in gluten related disorders. Patients may present with neuropathic symptoms like numbness and burning sensation in distal extremities while others manifest with weakness. They may have sensory motor axonal polyneuropathy, axonal motor peripheral neuropathy or mononeuritis multiplex[13-17]. Four (12.9%) patients had polyneuropathy, all these patients had weakness, predominantly in proximal muscles in only 2 cases which were diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). While other two cases had mild distal weakness. These cases also had paresthesia and numbness in hands and feet, just like reported by chin *et al*[14]. Patients with chronic inflammatory demyelinating polyneuropathy were treated with plasmapheresis and chronic immunosuppression as these patients showed poor response to gluten free diet only. While patients with paresthesia were kept only on GFD. In addition to sensory ganglionopathy[15], amyotrophic lateral sclerosis like syndrome[16,18] and peripheral nerve hyperexcitability has also been reported previously.

Inclusion body myositis has been reported[17], but interestingly we managed 2 cases of inflammatory myositis, one case being necrotizing myositis, who presented with acute generalized weakness, and later on developed significant weight loss. During work up of weight loss, duodenal biopsy was done which was consistent with diagnosis of CD. His anti-inflammatory myopathy panel was positive and muscle biopsy was diagnostic of necrotizing myositis. He responded very well to steroids and immunomodulatory therapy with rituximab.

Neurological symptoms can precede long before enteropathic symptoms causing delay in diagnosis unless there is a high index of suspicion. In our study, all the patients initially presented with different neurological features and subsequently were diagnosed either having coeliac disease or NCGS. After having ruled out all other possible causes we screened them for GRD as a possible cause. This screening was done with anti-TTG antibodies, anti-gliadin antibodies and duodenal biopsy.

Duodenal biopsy should be considered even if the serological markers are negative. In our study biopsy was consistent with diagnosis of CD in 19 (61.3%) patients. Even if duodenal biopsy is negative with neurological manifestations in the presence of positive auto antibodies, such patients should be diagnosed with NCGS, as in our case 12 (38.7%) had NCGS, and such cases should be considered for GFD. This is important because, if diagnosis is made early in patients

with neurological manifestations, it may be possible to halt the progression of symptoms by introducing GFD. In this way, patients can be saved from disabling deficits if intervened timely.

CONCLUSION

Coeliac disease/NCGS should be kept in differential diagnosis, in various central and peripheral nervous system involvement, especially if the disease turn out to be idiopathic or refractory to standard treatment. Moreover even if biopsy is negative for CD even then gluten sensitivity can be present which can manifest in the form of NCGS with neurological manifestation. We have emphasized role of serological markers in gluten related disorders even despite non conclusive duodenal biopsy for coeliac disease.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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