

Gluten sensitivity and Epilepsy in Children

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ABSTRACT

Background: Gluten sensitivity leads to the inflammatory entropy known as celiac disease (CD), which develops in those who are susceptible to it. Some research has suggested a connection between childhood epilepsy and CD.

Objective: The aim of the current study is to compare epileptic children and control as regard the development of gastrointestinal manifestations and gluten sensitivity.

Patients and methods: A case-control study was conducted at Children's Hospital, Zagazig University. Children diagnosed with idiopathic epilepsy based on International League against Epilepsy 2017 classification had been included. The control group consists of 42 children, age and gender-matched with the case group. Medical history and complete physical examination were done for all children in both groups.

Results: There is statistically a non-relationship between serum anti-tissue transglutaminase II (TTG) antibody and either number of drugs, control, presence of GI manifestations or duration of illness of the studied patients.

Conclusion: It is important to pay more attention to the possibility of CD in children who are epileptic. To avoid irreversible problems, children with different idiopathic forms of epilepsy, and in particular children with frequent seizures, must be checked for silent CD.

Keywords: Epilepsy, Celiac disease, Prevalence, Children, Case control study, Zagazig University.

INTRODUCTION

Gluten and related prolamines can cause Celiac Disease (CD), an immune-mediated systemic illness, in people who are genetically predisposed to it. It is identified by the existence of various combinations of enteropathy, HLA-DQ2 and HLA-DQ8 haplotypes, CD-specific antibodies, and gluten-dependent clinical symptoms ⁽¹⁾. The terms "classical," "atypical," "asymptomatic," "latent," and "potential CD" have all been used to describe different types of CD. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition working group decided to use the following terminology because atypical symptoms could be significantly more frequent than traditional symptoms: gastrointestinal symptoms and warning indications, such as persistent diarrhoea, persistent constipation, stomach discomfort, nausea, and vomiting. Extraintestinal symptoms and indicators include anaemia from iron insufficiency, low stature, delayed puberty, dermatitis herpetiformis, epilepsy, neuropathy, reduced bone density, and higher risk of fractures ⁽²⁾.

Comprehensive review and meta-analysis found that CD had been present everywhere. According to serologic test outcomes, the prevalence of CD had been 1.4%, and depending on biopsy data, it was 0.7%. Age, geography, and gender all affect how often CD is. In several nations, population-based prevalence research is required ⁽³⁾.

Studied cases with CD were noted to have neurological problems including cerebellar ataxia, polyneuropathy, headaches, and epilepsy. Ability to diagnose CD using immunoglobulin A anti-tissue transglutaminase had been found to be extremely

sensitive (93.1%) and specific (96.3%). Nevertheless, mucosal biopsy and histological examination ought to be used to confirm the diagnosis ⁽⁴⁾. To avoid long-term CD consequences, epilepsy-studied cases should be screened for CD. However, for people with epilepsy brought on by CD, the gluten-free diet is an efficient method of managing conditions ⁽⁵⁾.

The aim of the current study is to compare between epileptic children and control as regard development of gastrointestinal manifestations and gluten sensitivity.

PATIENTS AND METHODS

A case control study was conducted at Children's Hospital, Zagazig University.

Inclusion criteria: Children diagnosed with idiopathic epilepsy based on International League against Epilepsy 2017 classification ⁽⁶⁾ had been included.

Exclusion criteria: Children who also had cerebral abnormalities, metabolic conditions, infections, head injuries, tumours, and cerebral palsy had been not included.

Sample size: Assuming that the attendance rate of idiopathic epilepsy is 7 cases per month, the comprehensive sample was 42 cases per 6 months of the study and the same number in the control group.

Sampling technique: The approach of systematic random sampling had been employed.

The control group consists of 42 children, age and gender-matched with the case group. They have no neurologic disorders and admitted to Zagazig

University Hospitals (e.g. Upper respiratory tract infections).

All studied cases had been subjected to the following:
Full history taking including age in years, gender, existence of parental consanguinity, age at the onset of diabetes, family history, comorbidities, associated complications drug history, and age of diagnosis of disease.

Complete clinical examination: Physical appearance, including assessment of weight, height, arterial blood pressure and other vital signs. Blood pressure, temperature, heart rate, and other vital statistics had been noted.

The 2017 classification of epilepsy by the International League against Epilepsy (ILAE) was used for the diagnostic classification of cases ⁽⁶⁾. Three diagnostic stages, involving seizure type, epilepsy type, and epilepsy syndrome, were established by the 2017 ILAE Classification of Epilepsies.

Long before the 1985 proposal of the 1st ILAE Classification of Epilepsies and Epilepsy Syndromes; Epilepsy syndromes were recognised as unique electroclinical entities. 2017–2021 Nosology and Definitions Task Force had been tasked with creating an officially recognised ILAE taxonomy of epilepsy syndromes because one was lacking at the time. ILAE position papers are broken down into three categories: (1) Syndromes that start in newborns and babies (up to years old 2), (2) Syndromes that start in childhood, and (3) Syndromes that could start at any year old (meaning in both paediatric & adult studied cases).

Laboratory investigations:

All subjects had been screened for IgA anti-tissue transglutaminase II antibody, total IgA, CBC, and Ferritin ⁽⁷⁾ Subjects with confirmed positive TTG II antibody and those with clinical possibility and IgA deficiency were presented with endoscopic small intestinal biopsy. The evaluation of biopsy samples followed the modified Marsh classification.

Technique for this research is described by **Julian et al. (2019)** ⁽⁵⁾ with the list of symptoms. In addition to English, translated list of syndromes is also available in Arabic, Chinese, French, Greek, Italian, Japanese, and Korean.

Ethical Approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. All of the participants' parents were introduced to the investigator, who then asked them to take part in the research by outlining its objectives. All chosen parents of participants received thorough

information about the research's purpose & anticipated advantages. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and Monte Carlo test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and SD, and independent sample t-test/ Mann Whitney U test was used for comparison between groups. To evaluate the relationship between 2 normally distributed variables, Pearson correlation coefficients had been used. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

No statistical significant differences were between the 2 studied groups regarding sex, age and socioeconomic class (Table 1).

Table (1) Comparing among studied groups regarding demographic data

Parameter	Groups		Test	
	Case group	Control group	χ^2/t	P-value
	N=42 (%)	N=42 (%)		
Gender:				
Women	18	19	0.048	0.826
Men	(42.9%) 24 (57.1%)	(45.2%) 23 (54.8%)		
Age in years:				
Mean \pm SD	6.28 \pm 2.53	6.69 \pm 2.83	-	0.492
Range	2.5 – 12	2.5 – 12	0.69	
Social class:				
High	0 (0%)	1 (2.4%)	1.327	0.249
Moderate	38 (90.5%)	39 (92.9%)		
Low	4 (9.5%)	2 (4.8%)		

χ^2 Chi square test. t independent sample t-test

One-third of the studied patients received dual drug therapy. Concerning the type of AEDs used, 59.5% received Levitracetam, 38.1% received valproic acid, 21.4% received carbamazepine and 14.3% of them gad phenytoin (Table 2).

Table (2): Distribution of studied cases based on therapeutic data.

	N=42	%
Therapy:		
Single	28	66.7%
Dual	14	33.3%
Type:		
Valproic acid	16	38.1%
Levitracitam	25	59.5%
Phenytoin	6	14.3%
Carbamazepine	9	21.4%
Control of attacks:		
No	7	16.7%
Yes	35	83.3%
Type of epilepsy:		
Absence	6	14.3%
Generalized tonic	2	4.8%
Generalized tonic-clonic	26	61.9%
Myoclonic	1	2.4%
Myoclonic photoparoxysmal	7	16.7%
MRI (normal)	42	100%
Duration of illness	Mean ± SD	Range
	3.54 ± 1.98	0.5 – 8.5

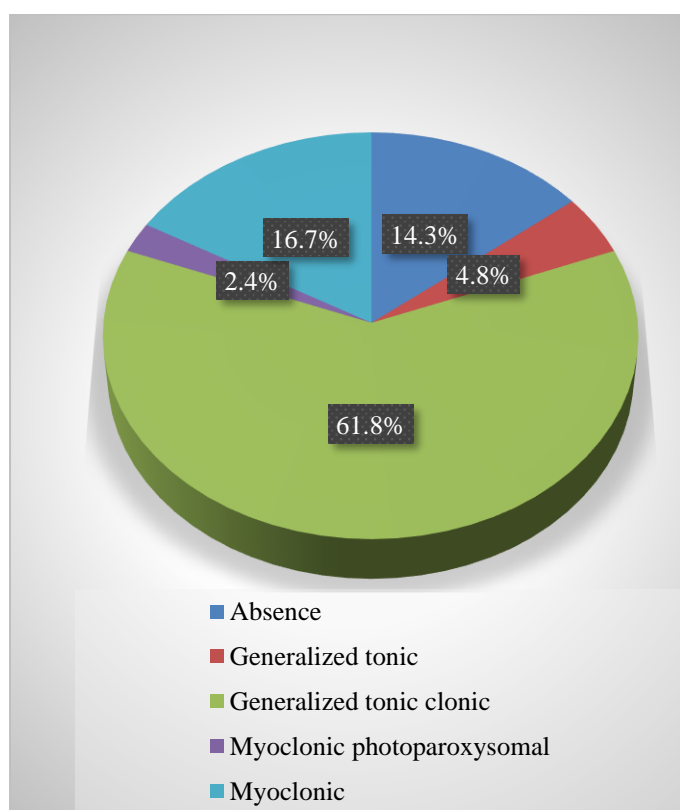


Figure (1) Pie chart finding the distribution of studied cases based on the type of therapy

There is no variation among studied groups regarding GI manifestations (**Table 3**).

Table (3): Comparing among studied groups regarding gastrointestinal manifestation.

Parameter	Groups		Test	
	Case group N=42 (%)	Control group N=42 (%)	χ^2	P-value
Gastrointestinal manifestation:				
No	28 (66.7%)	34 (81%)	M	0.869
Constipation	3 (7.1%)	1 (2.4%)	C	
Diarrhoea	2 (4.8%)	1 (2.4%)		
Abdominal Distension	3 (7.1%)	2 (4.8%)		
Nausea	1 (2.4%)	1 (2.4%)		
Recurrent aphthous	1 (2.4%)	0 (0%)		
Recurrent abdominal pain	4 (9.5%)	3 (7.1%)		

χ^2 : Chi square test. MC: Monte Carlo test.

There is no variation among studied groups regarding weight, height and BMI (**Table 4**).

Table (4): Comparing among studied groups regarding anthropometric data.

Parameter	Groups		Test	
	Casegroup Mean ± SD	Control group Mean ± SD	t-test	P-value
Weight (kg)	24.52 ± 8.97	26.35 ± 10.67	-0.847	0.399
Height (cm)	116.49 ± 17.54	119.39 ± 19.02	-0.727	0.469
BMI (kg/m²)	17.45 ± 1.49	17.63 ± 2.01	-0.463	0.644

t independent-sample t-test. BMI body mass index.

There is statistically a non-variation among studied groups regarding serum ferritin that was non-greater in the control group (**Table 5**).

Table (5): Comparing among studied groups regarding serum ferritin.

Parameter	Groups		Test	
	Case group Median (range)	Control group Median (range)	Z	P-value
Ferritin (ng/mL)	43.43 (3.94 – 179.95)	48.35 (4.2 – 120)	-1.209	0.304

Z Mann Whitney test

There is no variation among studied groups regarding serum IgA or anti-tissue transglutaminase II (TTG) antibodies (all those within each group had normal antibody levels) (**Table 6**).

Table (6): Comparing among studied groups regarding IgA and anti-tissue transglutaminase II (TTG) antibody.

Parameter	Groups		Test	
	Case group (n=42)	Control group (n=42)	Z	P-value
	Median (range)	Median (range)		
IgA (mg/dl)	82 (25 - 210)	88 (46 - 205)	- 0.872	0.383
Serum anti-tissue transglutaminase II (TTG) antibody (U/ml)	4.897 (1.1 - 9.61) 42 (100%)	5.7 (1.24 - 9.53) 42 (100%)	- 0.394	0.694

Z Mann Whitney test.

There is statistically a non-relationship among serum anti-tissue transglutaminase II (TTG) antibodies and social class, age, weight, height, or BMI of studied cases (Table 7).

Table (7): Correlation between anti-tissue transglutaminase II (TTG) antibody and demographic and anthropometric data of cases.

Parameter	R	P
Years old	0.106	0.335
Weight	0.095	0.389
Height	0.126	0.255
BMI	-0.047	0.668
Social class	0.1	0.365

r Spearman rank correlation coefficient

There is no correlation between serum anti-tissue transglutaminase II (TTG) antibodies and either haemoglobin, MCV, MCHC, white blood cells, platelet count, serum ferritin or serum IgA of the studied patients (Table 8).

Table (8): Correlation between anti-tissue transglutaminase II (TTG) antibody and laboratory data of cases.

Parameter	R	P
Hemoglobin(g/dl)	0.141	0.201
MCV (fl)	0.081	0.461
MCHC(g/dl)	0.182	0.098
WBCs (10 ³ /μl)	0.037	0.738
Platelet count (10 ³ /μl)	0.04	0.715
Serum ferritin (ng/mL)	0.162	0.141
Serum IgA (mg/dl)	0.062	0.572

Spearman rank correlation coefficient.

There is no relationship between serum anti-tissue transglutaminase II (TTG) antibodies and either number of drugs, control, presence of GI manifestations or duration of illness of the studied patients (Table 9).

Table (9): Correlation between anti-tissue transglutaminase II (TTG) antibody and disease-specific data of cases.

Parameter	R	P-value
Number of drugs	0.236	0.133
Duration of illness	-0.035	0.824
Control of attacks	-0.116	0.464
Gastrointestinal manifestations	-0.141	0.2

Spearman rank correlation coefficient.

DISCUSSION

Gluten-containing grains like wheat, rye, and barley are linked to the chronic autoimmune condition known as celiac disease, which is seen more frequently in people with a hereditary predisposition. Studied cases with CD were documented to have neurological problems including cerebellar ataxia, polyneuropathy, headaches, and epilepsy⁽⁸⁾. It's critical to screen for CD in people with epilepsy in so that CD's long-term effects. On other hand, it is hypothesised that a gluten-free diet may be protective against autoimmune diseases and seizure control⁽⁹⁾.

The goal of this research had been to detect the prevalence of CD in children with idiopathic epilepsy in Zagazig University Hospitals.

In the present research, we found that there had been non-variation among studied groups regarding gender, socioeconomic class, and age. Males represented 57.1% of the case group versus 54.8% within the control group. The mean age of the case and control group had been 6.28 and 6.69 years, respectively. Moderate social class prevailed at 90.5% and 92.9% within the case and control groups, respectively.

These results were compatible with Ghazizadeh *et al.*⁽⁸⁾ who reported that Boys made up 44 (62.9%). They were 7.8 (SD 4.8) years old on average. Average studied case years old at time of epilepsy start had been 3.6 (SD 2.1) years. In majority of instances, seizures began before age of six. Others had no other comorbidities and autoimmune disorders.

In our study, we found that one-third of the studied patients received dual drug therapy. Concerning the type of AEDs used, 59.5% received Levitracitam, 38.1% received valproic acid, 21.4% received carbamazepine and 14.3% of them received phenytoin. Concerning type of epilepsy, 61.9%, 16.7%, and 14.3% had generalized tonic-clonic, myoclonic and absence epilepsy respectively. Seizures are controlled in 83.3% of patients. Mean time of illness in the study group had been 3.54 (SD 1.98 years). MRI brain was performed for the entire study group and showed normal findings in all patients.

Ghazizadeh *et al.*⁽⁸⁾ showed that Sodium valproate (61.4%, n=43), levetiracetam (58.6%, n=41), phenobarbital (48.6%, n=34), and carbamazepine

(32.9%, n=23) had been most frequently prescribed antiepileptic drugs.

Vieira et al.⁽¹⁰⁾ reported revealed only 4% of studied cases needed 3 and more medicines, with 84.8% of participants taking no medication at all and just 1 medication. Carbamazepine (50.5%), phenobarbital (27.3%), sodium valproate (22.2%), oxcarbazepine (9.1%), and clonazepam (3%) were drugs used. Regarding therapy compliance, 83.1% of participants said they took their medication on regular basis, and 69.7% of the sample said their epileptic seizures were completely under control.

Our current findings regarding GI manifestations clearly revealed that there had been non-variation among the studied groups. About 66.7% of the study group and 81% of the control group had no GI symptoms or were very mild and not to be noticed. The marked GI symptoms in the study group were recurrent abdominal pain (9.5%), constipation (7.1%), abdominal distension (7.1%), diarrhoea (4.8%) and 1 case of recurrent aphthous. In the control group, the most marked GI symptoms were recurrent abdominal pain (7.1%) followed by abdominal distension (4.8%).

Ghazizadeh et al.⁽⁸⁾ showed that anorexia had been found in 18 (25.7%) cases and constipation in 34 (48.6%) cases. Only 15 (21.4%) studied cases had abdominal pain, 10 (14.3%) had abdominal distension, 2 (2.9%) had vomiting, and 1 (1.4%) had diarrhoea. Contrarily, anti-epileptic medications can have a variety of gastrointestinal side effects, including dysphagia, constipation, diarrhoea, nausea, and vomiting. Therefore, these gastrointestinal symptoms could be the result of medical intervention.

Vieira et al.⁽¹⁰⁾ reported that gastrointestinal symptoms were reported by at least 19% of subjects, with recurring stomach pain being the most prevalent symptom (44.4%).

Emami et al.⁽¹¹⁾ documented that in absence of celiac disease, studied cases with epilepsy frequently experienced constipation and gastrointestinal pain. Nevertheless, compared to non-celiac-studied cases, celiac-studied cases experienced much more diarrhoea.

In the present research, we found that there had been a non-variation among studied groups regarding weight, height, or BMI. The mean BMI of the case and control group were 17.45 and 17.63 kg/m², respectively. The mean weight of the case and control group had been 24.52 (SD 8.97) and 26.35 (SD 10.67) kg, respectively. Mean height in case and control groups had been 116.49 (SD 17.54) and 119.39 (SD 19.02), respectively.

Ghazizadeh et al.⁽⁸⁾ reported that the studied cases' mean BMI, weight (kg), and height (cm) had been 118.1 (SD 28.9), 26.9 (SD 18.5), and 16.9 (SD 4.1), respectively.

In the present research, we found that there had been a non-variation among studied groups regarding haemoglobin, MCV, MCHC, white blood cells or platelet count. The mean haemoglobin level (g/dl) was

11.4 (SD 1.43). The mean MCV (fl) was 76.28 (SD 7.24). The mean WBCs (10³/μl) were 9.44 (SD 2.66). The mean platelet count (10³/μl) was 292.4 (SD 84.6).

There were 204 participants in all (98 studied cases and 106 controls). Averages of haemoglobin, hematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and platelet count among studied cases and controls did not differ significantly (P-value >0.1 for all). No correlation or relationship between epilepsy and RBC indices was found in this investigation.

In our research, the comparison among studied groups regarding serum ferritin had been non-significant. Mean ferritin level (ng/mL) was 43.4 (SD 39) in the study group and 48.35 (SD 34) in the control group.

In agreement with our research, **Namakin et al.** (2016) found that there had been no variation among case and control groups in terms of mean serum ferritin level (P-value 0.743), which had been 40.61 ng/mL in the case group and 41.80 ng/mL in the control group⁽¹²⁾.

In alignment with our study, **Shajari et al.** (2021) stated that there was no discernible variation between case and control groups' studied cases' median serum ferritin levels⁽¹³⁾. In the current research, we showed that there had been a non-variation among studied groups regarding serum IgA or anti-tissue transglutaminase II (TTG) antibody (all those within each group had normal antibody levels). The mean level of IgA (mg/dl) in the case group was 82 (SD 45) and 88 (SD 53) in the control group while the mean level of TTG (U/ml) was 4.8 (SD 3.6) and 5.7 (SD 4.3) in the case group and control group, respectively.

Ghazizadeh et al.⁽⁸⁾ illustrated that Except for 1 studied case, everyone had normal total IgA serum levels. TTG IgG had been employed in this instance for CD screening, and it had been normal. There had been no reports of aberrant TTG and anti-EMA. Because of negative serological testing, endoscopy and intestinal biopsy had not been done.

In agreement with our results, **Ranua et al.**⁽¹⁴⁾ stated no variations in prevalence among 2 groups, with similar rates of positive serology for anti-AGA, TTG, and anti-EMA among research sample participants and control group. In research, we found that there had been statistically no relationship between serum anti-tissue transglutaminase II (TTG) antibodies and either social class, years old, weight, height or BMI of the studied patients.

Our current findings clearly revealed that there had been no correlation between serum anti-tissue transglutaminase II (TTG) antibody and either haemoglobin, MCV, MCHC, white blood cells, platelet count, serum ferritin or serum IgA of the studied patients.

In the present research, we showed that there had been statistical non-correlation among serum anti-tissue transglutaminase II (TTG) antibodies and either number of drugs, control, presence of GI manifestations or duration of illness of the studied patients.

In our study, no case in the 2 studied groups revealed positive serology results so biopsy and histopathology had not been performed with a conclusion of 0% prevalence of CD in both groups.

Pratesi et al. ⁽¹⁵⁾ demonstrated that there had been no variation in the prevalence of CD between studied cases with epilepsy and control group.

Research by **Dai et al.** ⁽¹⁶⁾ investigated the prevalence of CD and temporal lobe epilepsy. According to research, 2.22% of 90 children had great levels of TTG and had been serologically positive. pathological analysis of biopsy specimens of these 2 children revealed signs of CD.

Research by **Antigoni et al.** (2007) on 280 healthy children and 255 epileptic children revealed that 5 epileptic children tested positive for TTG. In all 5 epileptic children's biopsy samples, alterations have been discovered ⁽¹⁷⁾. **Ertekin et al.** ⁽¹⁸⁾ did research in Turkey in 2004 that looked at CD in 1263 kids. Depending on the seropositivity of TTG and biopsy data, the prevalence of CD had been 1.1% and 0.87%, respectively. Furthermore, in epileptic studied cases seropositivity had been 15.6% and positive biopsy for CD had been 9.1%; these results pointed out that CD is more common in children with epilepsy. **Djuric et al.** ⁽¹⁹⁾ reported that there was no variation had been shown in the prevalence of CD studied cases among research (0.8%) and control groups (0.6%) ($P > 0.05$).

CONCLUSION

Increased consideration must be given to the possibility of celiac disease in children with epilepsy. To avoid irreversible problems, children with different idiopathic forms of epilepsy, and in particular children with frequent seizures, must be examined for silent celiac disease.

DECLARATIONS

- **Consent for Publication:** I attest that all authors have agreed to submit work.
- **Availability of data& material:** Available
- **Competing interests:** None
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- **Conflicts of Interest:** Regarding the publishing of this paper, the authors state that they have no conflicts of interest.

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