

Anti-Tissue Transglutaminase Antibodies and EEG Pattern in Celiac Patients on Prolonged Gluten-Free Diet

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Abstract

The Authors investigate the relationship between serum anti-tTG antibodies and EEG pattern in 12 celiac patients of various age on gluten-free diet for 1-10 years. In a group of 6 patients with good compliance with the diet, anti-tTG antibodies were normal in all and EEG in 5; in another group of 6 patients with poor compliance with the diet, serum anti-tTG antibodies were raised in all; EEG abnormalities of various gravity were reported in 5 patients. The concomitance of raised anti-tTG antibodies and EEG abnormalities is stressed, as possible expression of an immune-inflammatory reaction persistent in Central Nervous System.

Celiac disease (CD) is "a state of heightened immunological responsiveness (T and B lymphocytes-based) to ingested gluten in genetically predisposed individuals" [1]. CD is associated with the HLA class II genes HLA-DQ 2 in 90% and HLA-DQ 8 in 10% of patients. Today the concept of CD has been expanded and this disease is considered a multisystem autoimmune disorder [2] sometimes with extraintestinal complications as neurological symptoms [3]. Immune response against gluten is associated with activations of specific T cells with production of pro-inflammatory cytokines (INFgamma, TNF α , IL-1 α , IL-2, IL-6)

with a response against tissue transglutaminases (tTG), one isoform of which (tTG 6) is present in the Central Nervous System (CNS) (cerebral cortex, cerebellum, hippocampus). In addition there is a cellular and humoral immunologic response against tTG. It was hypothesized that an immune response against different tTG isoenzymes may explain the different manifestations of CD [4]. Patients with CD may be at increased risk of late epilepsy [5] i.e. of a disorder of the brain characterized by enduring predisposition to general seizures in subjects which had at least one epileptic seizure [6]. In these patients inflammation may have a role [7,8]. Epilepsy in CD is classified as focal symptomatic epilepsy [6] with abnormal electroencephalographic (EEG) patterns attributed to gluten [8]. Patients with CD present with anti-gladiadin antibodies in serum (which are specific in the manifestations of gluten sensitivity) and anti-tTG antibodies which are a marker for untreated CD, more specific in the diagnosis of gluten-related enteropathy and useful as screening test for CD.

The relationship between anti-tTG antibodies and EEG in CD patients on gluten free diet, to our knowledge, is scarcely reported in the medical literature. In this study, we investigated the relationship between anti-tTG antibodies and EEG pattern in 12 CD patients of various ages (10-44 years) diagnosed by laboratory testing and/or duodenal biopsy, on gluten free diet for 1-10 years. Anti-tTG serum antibodies were estimated by current laboratory methods; EEG pattern was obtained by 16 channels polygraphic system with Ag-AgCl electrodes according to International Systems. No patients reported seizures. The results are reported in table 1.

Table 1. CD patients with normal/raised anti-tTG antibodies and concomitant EEG patterns.

Group A: CD patients with normal anti-tTG antibodies

Patient number	Associated disease	anti-tTG antibodies R.units/ml	EEG pattern
1	Thyroiditis	N	N
2	Thyroiditis	0.2 (nv 0-7)	Epileptic discharges: right parieto-central sharp waves
3	Thyroiditis	11.7 (nv 0-20)	N
4		N	N
5	Diabetes	6 (nv 0-20)	N
6		0.36 (nv 0-20)	N

Group B: CD patients with raised anti-tTG antibodies

Patient number	Associated disease	anti-tTg antibodies R.units/ml	EEG pattern
7		200 (nv 0-20)	Ubiquitarious low voltage fast activity
8		84.6 (nv 0-20)	-
9		19.9 (nv 0-7)	Right centro-temporal fast activity on hyperpnoea
10		53 (nv 0-7)	Focus of sharp waves over right temporal region
11		17.5 (nv 0-7)	moderate right posterior slow background; fronto-temporal sharp waves after hyperpnoea
12		342 (nv 0-7)	Left temporal fast activity (moderate)

In group A of 6 subjects with good compliance with the diet, 5 patients on prolonged gluten-free diet showed normal anti-tTG antibodies in serum and normal EEG pattern. This concomitance may be due to a favourable response to treatment without CNS complications. In three subjects thyroiditis autoimmune coexisted, one of whom showed hyper-hypothyroidism and epileptic EEG record. Given that CD and thyroiditis are both autoimmune disorders, we can hypothesize that, in this case, autoimmunity might have a role in the development of hyperthyroidism and in the consequent EEG epileptic pattern [9,10] without involvement of tTG autoantibodies. This condition was observed in other metabolic diseases with anti-thyroidal [11] autoimmunity. Alternatively, the EEG pattern may be independent of CD and due to other unknown factors (Cryptogenetic epilepsy); or independent of tTG antibodies and due to a chronic inflammatory CNS process [12].

Group B including 6 patients with high anti-tTG antibodies in serum presented with variable EEG abnormalities. In one case with CD and apraxia, dysgraphia, dyslexia and symptoms of temporal epilepsy, the EEG presented a focus of sharp waves over the right temporal region which documented a true epilepsy; 3 patient showed fast activity (2 involving the temporal lobe); 1 presented moderate slow wave background and fronto-temporal sharp waves after hyperpnoea; in 1 case EEG was normal. All these cases showed poor compliance with the gluten-free diet. The concomitance of high anti-tTG serum antibodies and abnormal EEG pattern was present. This observation was attributed to insufficient compliance with the diet, with a pathologic effect of gluten on anti-tTG antibodies and EEG pattern due to persistent CNS autoimmune inflammation. The EEG normal pattern of the patient with high serum anti-tTG antibodies may be attributed to the absence of CNS complications in CD.

Ataxia, peripheral neuropathy and seizures are the most common neurological complications in CD patients [13,14]. Leukoencephalopathy with seizures and EEG abnormalities in CD was reported by some Authors [15-18].

This condition was attributed to autoimmunity in genetically predisposed subjects [19]. In a group of 53 patients with neurological dysfunction of unknown cause,

Hadjivassiliou et al. [3] reported on 30 cases with positive antigliadin antibodies. Nine of these 30 patients were positive for CD at duodenal biopsy, and the Authors concluded that gluten sensitivity in these patients had aetiological significance and that gluten could play a role in some neurological disorders of unknown cause. Positive serum IgG antigliadin antibodies were demonstrated in 2 patients of 7 with epilepsy, with normal duodenal biopsy [3]. In a group of 255 patients with idiopathic epilepsy, Antignoni et al. [20] found 2 cases with elevated anti-tTG antibodies and positive duodenal biopsy for CD. On this basis a relationship between CD and epilepsy was proposed [20] but it is still debated [4].

Many Authors reported on neurological symptoms and epilepsy in celiac disease patients without gastrointestinal manifestations, who presented with "silent" or "latent" CD, diagnosed by intestinal biopsy and serum antigliadin and/or anti-tTG antibodies [4]. Statistically, the prevalence of epilepsy in CD patients varied in some reports between 1.1% [21] and 5.5% [22,23]. This range appears slightly higher compared to the prevalence of epilepsy in the general population (i.e. 1%) [22]. In children with CD the risk of epilepsy is increased (2.1 fold) [22]. Some autoimmune disorders (IDDM, Dermatitis herpetiformis, autoimmune thyroiditis) are prominent disorders in CD-associated epilepsy.

Neurological manifestations in late forms of CD are attributed to prolonged exposure to gluten with its immunologic and inflammatory effects on many structures [23-25]. It was hypothesized that gliadin, digested by the duodenal mucosa, produces peptide(s) which, having high affinity to the tTG, form(s) a complex tTG-peptide, able to induce autoimmunity and cause both humoral and T-cell mediated immune-response against tTG [24-26]. This autoimmunity should be responsible of tissue inflammation.

At CNS level, chronic immune-mediated inflammation, lymphocytic infiltration or vasculitis may cause neuronal, glial or amonal damage and, possibly, epilepsy. Actually, epilepsy in CD and epilepsy with cerebral calcification in CD (Gobbi syndrome) are considered autoimmune disorders that may be reverse with a gluten-free diet in some patients [26] in whom tTG are target of autoantibodies.

The importance of anti-gliadin and anti-tTG antibodies in brain damage of celiac patients is now accepted by many Authors. Hadjivassiliou et al. [27] reported that serum samples from a patient with gluten-related ataxia targeted tTG in gut biopsy, in brain parietal specimens and in cerebellar tissue of a dead patient with gluten intolerance and ataxia. In this case, anti-endomysium IgA granular deposition which co-located with anti-tTG 2 antibodies was demonstrated. Intrathecal production of anti-tTG 2 antibodies has been reported, showing the possibility also of a cell-mediated mechanism, instead of a passive antibody transfer, with infiltration of nervous tissue and presence of CD4⁺T cells, specific for the gut in the cerebrospinal fluid.

The association of CD with epilepsy and anti-tTG antibodies in serum [28] was reported, but the possibility that autoantibodies against tTG 2 or tTG 6 (another isoform) are specifically involved in epilepsy needs further confirmation [4].

In celiac patients gluten may cause EEG abnormalities, as first demonstrated by Emanuel and Lieberman [7]. Further cases of EEG alterations in gluten-related encephalopathies with epilepsy were reported [4,14,15,18].

Interictal centro-temporal or parietal sharp waves (7-9 c/sec), fronto-temporal or posterior bi-occipital spike-wave discharge and temporal slowing were reported, but no EEG finding was specific for gluten-related encephalopathies [14].

The EEG response to gluten withdrawal in CD patients with EEG alterations may be positive [7,26], but it is not uniform, a condition likely due to low compliance with the diet [29] and perhaps with other unknown mechanisms. Gluten-free diet in CD with epilepsy may cause a reduction of seizure frequency, but the possibility of seizure freedom is dependent on the age when the diet was started and on diet compliance [29].

In our cases we observed a concomitance of normal/abnormal anti-tTG antibodies and normal/abnormal EEG pattern. It seems obvious that high serum anti-tTG antibodies denotes a general stimulation of the immune system by gluten. Pathological EEG may denote poor compliance with diet or, alternatively, the presence of pathological/inflammatory reaction in brain that must be identified with laboratory and radiological methods. Further studies may elucidate the role of slight EEG alterations, present in our cases and associated with anti-tTG antibodies, in the development of serious complications and, eventually, of epilepsy in CD.

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