Original Article

Gluten Sensitivity And Epilepsy In Children; Review Article

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Abstract

Background; Celiac disease is the inflammatory entropy caused by hypersensitivity to gluten, which occurs in susceptible individuals. Some studies have suggested a link between celiac disease and epilepsy in children; Gluten-related disorders (GRDs) represent a spectrum of diverse clinical manifestations triggered by the ingestion of gluten. **Aim and objectives;** the aim of this review was to establish the prevalence of epilepsy in patients with coeliac disease (CD) or gluten sensitivity (GS) and vice versa and to characterise the phenomenology of the epileptic syndromes that these patients present with, **Subjects and methods:** A systematic computer-based literature search was conducted on the PubMed database. Information regarding prevalence, demographics and epilepsy phenomenology was extracted by keywords as epilepsy; celiac disease; prevalence**;** children, **Conclusion;** The data indicate that the prevalence of CD or GS is higher amongst particular epileptic presentations including in childhood partial epilepsy with occipital paroxysms, in adult patients with fixation off sensitivity (FOS) and in those with temporal lobe epilepsy (TLE) with hippocampal sclerosis. A particularly interesting presentation of epilepsy in the context of gluten-related disorders is a syndrome of coeliac disease, epilepsy and cerebral calcification (CEC syndrome) which is frequently described in the literature, greater attention is required to the possible coexistence of celiac disease in epileptic children. Children with various idiopathic types of epilepsy, and especially children with persistent seizures, should be screened for silent celiac disease in order to prevent nonreversible complications,
Keyword; epilepsy; celiac disease; prevalence; children.

Introduction

Celiac Disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. It is characterised by the presence of a variable combination of gluten-dependent clinical manifestations, CD specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy. **(1)**

In a systematic review and meta-analysis, celiac disease was reported worldwide. The prevalence of CD based on serologic test results was 1.4% and based on biopsy results was 0.7%. The prevalence of celiac disease varies with sex, age, and location. There is a need for population-based prevalence studies in many countries. **(2)**

Neurological conditions such as cerebellar ataxia, polyneuropathy, headache, and epilepsy have been reported in patients with CD. Immunoglobulin A (IgA) anti-tissue transglutaminase was determined to be highly sensitive (93.1%) and specific (96.3%) for the diagnosis of CD**.** However, the diagnosis should be confirmed by mucosal biopsy and histological examination. **(3)**

Screening CD among epilepsy patients is important to prevent long-term complications of CD. On the other hand, Gluten-free diet is an effective management of epilepsy in those with epilepsy due to CD. **(4)**

The aim of this study is to establish the prevalence of epilepsy in patients with coeliac disease (CD) or gluten sensitivity (GS) and vice versa and to characterise the phenomenology of the epileptic syndromes that these patients present with.

Celiac Disease

Celiac Disease (CD) is defined as a systemic immune-mediated disorder responsible for a permanent inflammatory enteropathy, caused by the ingestion of proteins contained in some cereals (gliadin in wheat, hordein in barley and secalin in rye) that are called prolamines, in people with specific human class II leukocyte antigen (HLA haplotype DQ2 and/or DQ8) **(5).**

However, as only a fraction of HLA- DQ2-positive and/or HLA- DQ8-positive individuals consuming gluten develop the disorder, it is likely that other genetic and/or environmental factors play a role in the disease onset. CD is more prevalent in females, may develop at any age after the introduction of dietary gluten and can affect almost any ethnicity **(2).**

Celiac Disease primarily affects the small intestinal mucosa, and the ingestion of gluten by predisposed individuals results in the development of a mucosal immune response, including an increased intraepithelial lymphocyte (IEL) count, and such immune responses eventually lead to structural changes in the gut, characterized by villous atrophy (blunting or flattening of the villi) and crypt hyperplasia (elongation of the crypts) **(5).**

Epidemiology:

Before the 1990s, CD was considered an uncommon disorder that mainly affected children and was limited to western Europe. Improved diagnostics, including the implementation of CD specific serological tests (transglutaminase 2 antibodies (TG2-Abs) and endomysial antibodies (EmAs), have led to increased recognition of CD, in addition to making it possible to estimate the true prevalence of the disorder in the general population **(6).**

A systematic review of screening studies indicates that CD is now a major public health problem, as the pooled global seroprevalence measured by TG2-Abs or EmAs in the general population can be as high as 1.4% (95% CI: 1.1–1.7%) **(2).**

Population based data on the prevalence of CD have also been reported from India and some countries in middle- eastern Asia and Africa **(7).**

Taken together, CD is now known to affect people worldwide. In some geographical areas such as Far East Asia and sub- Saharan Africa, the disease is still rare, although large epidemiological studies from these sites are still lacking **(8)**.

Most population- based epidemiological studies on CD prevalence are based on serological data, and the diagnosis of CD in all seropositive patients has not been confirmed by invasive small intestinal mucosal biopsies. Therefore, the global pooled prevalence of biopsy- proven CD, which is 0.7% (95% CI: 0.5–0.9%), is lower than the seroprevalence **(2).**

Although the prevalence of CD in the general population has increased, the disorder still remains heavily unrecognized. The seroprevalence figures of CD suggest that for each clinically diagnosed patient with CD, an average of five to ten seropositive individuals remain undiagnosed, usually because of atypical, minimal or even absent symptoms **(9).**

The diagnostic rate mostly depends on the level of physician awareness, and with an active search for patients, a clinical prevalence for CD of up to 0.7% may be reached, which still clearly falls behind the corresponding seroprevalence **(10).**

Risk factors: The factors that explain the varying and increasing prevalence of CD remain vague. Variation exists in the frequency of the CD predisposing HLA haplotypes worldwide, but the prevalence of CD also varies in populations with a similar HLA background **(5).**

Such variance may be explained by environmental factors rather than genetics. Potential environmental factors include the consumption of gluten- containing cereals, infection in the early years of life and lower economic status as well as an inferior hygienic environment **(11).**

Genetics: The development of CD requires both the ingestion of gluten and genetic predisposition. The genetic susceptibility of CD is evidenced by the fact that the average prevalence of CD among first-degree relatives of patients exceeds that of the general population, being ~8% **(12).**

Of the genetic factors identified to date, the HLA- DQ haplotypes HLADQ2 and HLA- DQ8 impart the strongest risk, and these variants have been estimated to contribute ~25–40% of the genetic risk **(13).**

Immune mechanisms

Gluten peptides that result from incomplete digestion in the gut lumen gain access to the lamina propria through the epithelial barrier via the transcellular or paracellular route. In patients with CD, these harmful peptides launch the activation of both adaptive and innate immune responses **(5).**

Generation of gluten- specific T cell responses: The adaptive immune response in CD is characterized by small intestinal mucosal gluten- specific CD4+ T cell responses and antibodies towards wheat gliadin and the enzyme TG2 (encoded by TGM2) **(14).**

Historically, pro- inflammatory dendritic cells, which readily express HLA-DQ molecules, have been considered as the key APCs in CD. However, it has been proposed that gliadin- specific and TG2-specific B cells might exert similar functions **(15).**

Once activated, the gluten- specific CD4+ T cells secrete various cytokines, including IFNγ and IL-21, thereby creating an inflammatory milieu in the small intestinal lamina propria that is conducive to tissue damage **(16).**

Remarkably, autoantibody responses targeting other members of the transglutaminase family have been associated with specific manifestations of CD. Antibodies targeting TG3 and TG6, which occur in the context of dermatitis herpetiformis and gluten ataxia, respectively, have been considered as potential contributors in the pathogenesis of these extraintestinal manifestations **(17).**

Cytokines in the intestinal mucosal immune response: A subset of the cytokines including IFNγ and IL-21 produced by gluten- specific CD4+ T cells as a result of adaptive immune activation serve as links between adaptive and innate immunity **(18).**

Environmental factors

Dietary gluten is the most important environmental factor involved in the development of CD. However, the great majority of humans are exposed to gluten, and only a subset of individuals who carry the genetic risk alleles will develop the disease. Therefore, other environmental factors have been suggested to be involved. Of these, microorganisms have been the target of recent research **(8).**

Microorganisms: In 2004, the intestinal microbiota was first linked to CD when a study described the presence of rod- shaped bacteria associated with the mucosa of patients with active or treated CD. A follow- up study determined increases in the abundance of Clostridium, Prevotella and Actinomyces species in patients with CD **(19).**

Diagnosis, screening and prevention

Clinical signs and symptoms

CD is heavily underdiagnosed, due to the variable clinical signs and symptoms (fig. 5). Over time, the most common clinical presentation of CD has shifted from symptoms of malabsorption in childhood to milder multi- organ manifestations that present in both childhood and adulthood, reflecting the systemic nature of the disease **(20).**

CD serology

A combination of CD serology testing and the determination of small intestinal mucosal morphology forms the basis for the diagnosis of CD **(8).**

The clinical diagnosis of CD is proceeding towards non- invasive procedures; for example, in a subgroup of children, the diagnosis can be established without the need for small intestine biopsy **(21).**

Biopsy: A biopsy should be performed on children with positive TGA-IgA but lower titers (<10 times upper limit of normal). Patients should have ≥4 biopsies from the distal duodenum and ≥1 from the bulb, during a gluten-containing diet. Evaluation of biopsies should be performed on optimally orientated biopsies. In cases of differing results between TGA-IgA-results and histopathology, re-cutting of biopsies and/or second opinion from an experienced pathologist should be requested.

CD can eventually be diagnosed without duodenal biopsies in asymptomatic children, using the same criteria as in patients with symptoms.

Non- coeliac gluten sensitivity

The symptoms of CD are far from being disease specific, and patients with, for example, irritable bowel syndrome or cereal allergy, may present with similar abdominal symptoms. Interestingly, it has long been known that a large number of patients experiencing functional gastrointestinal symptoms benefit from the avoidance of wheat even in the absence of CD (table 2). Recent randomized intervention studies indicate that some patients experiencing symptoms from gluten- containing cereals have a true noncoeliac gluten sensitivity (NCGS) **(22).**

The prevalence of NCGS probably exceeds that of CD, as it has been estimated to affect ~2–5% of individuals in the general population. Currently, there is no reliable biomarker for NCGS, and NCGS diagnosis requires the careful exclusion of CD **(23).**

Refractory CD

The clinical effects of a gluten-free diet are in most cases rapid and convincing, but the recovery of the intestinal mucosal morphology can take months or even years **(24).**

According to recent population- based studies, RCD affects 0.3% of patients with diagnosed CD and its prevalence in the general population is 0.002% **(10).**

Epilepsy

The word "epilepsy" comes from the Greek and means to be taken, seized or attacked. Epilepsy is a condition characterized by repeated seizures due to a disorder of the brain cells. It is a life-long tendency, though the seizures may start at any time during life and occur sporadically or frequently **(25).**

Epidemiology

Epilepsy is a common disorder, the highest incidence occurs in childhood; with a second peak of increased incidence occur in elderly. Approximately75% of persons who develop epilepsy does so before the age of 20 years **(WHO, 2019).**

Etiology

The cause of an individual's epilepsy can be divided into three categories: symptomatic, idiopathic and cryptogenic, according to the ILAE the largest group consists of patients with idiopathic epilepsy. In developed countries, etiology of epilepsy is also age-dependent. In children, about 20% are remote symptomatic. 50% are cryptogenic while 30% are idiopathic. However, in elderly, about 55% is remote symptomatic while 45% are idiopathic/cryptogenic **(Saavalainen et al., 2015).**

Genetic causes including mutation in ion and non-ion channel genes and mutations in genes involved in antioxidant system have been suggested to be responsible for idiopathic epilepsy **(Guerrini, 2012).**

Pathophysiology and genetics

The pathophysiology of epilepsy and seizures is diverse, accounting for the many different types of seizure disorders. However, one commonality across epilepsies is a disrupted balance between excitatory (via glutamatergic signaling) and inhibitory (via GABAergic signaling) drive at the synaptic level that can result in seizure activity **(29).**

Genetic pathologies leading to epilepsy can occur anywhere from the circuit level (eg. abnormal synaptic connectivity in cortical dysplasia): to the receptor level (eg. abnormal gamma ammo-butyric acid (GABA) receptor subunits in Angelman syndrome): to abnormal ionic channel function (eg. potassium channel mutations in benign familial neonatal convulsions **(Wong and Roper, 2016).**

Factors Predisposing the Developing Brain to Hyperexcitability and Seizures (31): Early development of excitatory sodium and calcium channels, earlier development of excitatory synapses and neurotransmitters, delayed development of inhibitory synapses and neurotransmitters, exuberant axonal branching pattern early in life (more excitatory synapses), paradoxical depolarizing action of GABA early in development and delayed ability of glia to clear extra cellularly accumulated potassium ions.

II- Epilepsy syndromes in childhood:

An epileptic syndrome is defined as a complex of signs and syndromes that define a unique epilepsy condition with different etiologies. A syndrome must involve more than just a seizure type. One important characteristic of syndromes is the characteristic age at onset. The most recent revision

recommended that the term syndrome be restricted to a clinical entity that is reliably identified by a cluster of electro clinical characteristics **(32).**

a) Generalized epilepsy syndromes:

A- Idiopathic generalized epilepsy syndromes:

1) Benign familial neonatal convulsions (BFNC): This syndrome has been reported to occur in 14.4 per 100,000 live births. Benign familial neonatal convulsion now called benign familial neonatal epilepsy. This rare, dominantly inherited disorder is due to mutations affecting voltage-gated potassium channel genes (KCNQ2. KCNQ3). Affected infants are usually full term and appear normal at birth. In 80% of cases, seizures start on the second or third day of life, although some infants may-develop seizures later in the first month of life. The seizures are typically clonic, but often preceded by a tonic component. They are more often unilateral, but can also be bilateral. The interictal EEG is usually normal. Spontaneous resolution typically occurs within 2 to 6 months. There is a slight increase in the risk of later epilepsy (11-15%) **(33).**

2) Generalized epilepsies with febrile seizure plus (GEFS+): Generalized epilepsies with febrile seizure plus (GEFS+) is a recently described disorder in which children have febrile seizures beyond the age at which febrile seizures usually stop (5 years) **(33).**

3) Childhood absence epilepsy: Childhood Absence Epilepsy (CAE) is a form of idiopathic, genetically-determined, generalized epilepsy that is characterized by absence seizures and in 10% of cases, generalized tonic-clonic seizures. Absence seizures start between the ages of 4 and 10 years of age with the peak age of occurrence 6 to 7 years **(33).**

4) Juvenile myoclonic epilepsy (JME): Myoclonic seizures in children may occur as a part of anepileptic syndrome called Juvenile myoclonic epilepsy of Janz (Juvenile myoclonic epilepsy, JME) **(33).**

5) Juvenile Absence Epilepsy: Juvenile Absence Epilepsy (JAE) is classified as an idiopathic generalized epilepsy. The age of onset is typically at or after puberty between the ages of 10-17. Unlike in Childhood Absence Epilepsy (CAE) where absence seizures can occur hundreds of times per day. absence seizures in JAE may only occur sporadically **(33).**

B- Cryptogenic or symptomatic generalized epilepsy syndromes:

1) Infantile spasms: Infantile Spasms (IS) is an age-specific convulsive disorder of infancy and early childhood. The triad of epileptic spasms, arrest or deterioration of psychomotor development and a characteristic EEG pattern called hypsarrhythmia; is known as west syndrome. West syndrome has a later age at onset: the peak incidence of onset (50-77%) is between 3 and 7months of age. The disorder is heterogeneous in its etiology. Approximately two-thirds of infants have brain lesions. Psychomotor development may be abnormal prior to onset, but there is a clear deterioration after onset **(33).**

2) Lennox-Gastaut syndrome: Lennox-Gastaut Syndrome (LGS) is classified as an epileptic encephalopathy. The age of onset is usually before age 8 with a peak age of onset between 3-5 years of age **(33).**

The diagnosis may be difficult to do at first because not all features of the syndrome may be present. The seizures are typically refractory to medical treatment **(Rudzinski et al., 2013).**

b) Localization-related epilepsy syndromes:

A. Idiopathic localization-related epilepsy syndromes: Benign childhood epilepsy with centrotemporal spikes (Rolandic epilepsy): The most common such syndrome is benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy) which typically starts during childhood and is outgrown in adolescence. The child typically wakes up at night owing to a focal seizure causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness **(Mikati, 2011).**

B. Symptomatic localization-related epilepsy syndromes

Symptomatic localization-related epilepsy syndromes are those that arise in a particular region of brain due to an acquired or congenital lesion. **(Scheffer et al., 2017).**

C. Indeterminate epilepsy syndromes:

Landau-Kleffner syndromes: The common features of Landau Kleffner Syndrome (LKS) are a decline in cognitive function in association with an EEG pattern of continuous spike and-wave activity during slow wave sleep. In Landau Kleffner syndrome, the cognitive decline is specifically in the area of speech **(37).**

Drug-resistant epilepsy (intractable epilepsy):

The ILAE consensus definitions of drug resistant epilepsy:

The proposal defines drug-resistant epilepsy as failure of adequate trials of two (or more) tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom **(Saad, 2014).**

The patients categorized as intractable when they developed at least 1 seizure or more per month in a 6-month period despite being treated with ' at least 2 antiepileptic drugs **(Sirven et al., 2014).**

Epidemiology of intractable epilepsy: Because of unstandardized definitions as well as misdiagnoses, the incidence and prevalence of intractable epilepsy are somewhat uncertain. Estimates of the proportion of epilepsy cases that are or become medically resistant vary between 20 and 40 percent **(Sirven et al., 2014).**

Neurological manifestation of Celiac Disease

Over the last several decades, the clinical presentation of CD has changed with the proportion of patients presenting with classical CD symptoms decreasing and a corresponding increase in the frequency of extra-intestinal symptoms in children and adults **(40).**

This increasing proportion of extra-intestinal symptoms at presentation can result in lengthened diagnostic delay **(41).**

Active case finding to facilitate prompt detection of CD and life-long adherence to a strict gluten-free diet (GFD) among patients with confirmed CD is recommended to reduce symptoms and the likelihood of disease of potentially serious manifestations **(9).**

CD patients with ataxia often present with difficulty with arm and leg control, gait instability, poor coordination, loss of fine motor skills such as writing, problems with talking, and visual issues. Gluten ataxia usually has an insidious onset with a mean age at onset of 53 years **(42).**

The association between CD and epilepsy is less clear and the precise mechanism of association is unknown. Recent data have been less consistent. In children with CD the prevalence of epilepsy has varied greatly (0%, 0.5%, 1.1%, 1.3%, and 7.2%), which can be partly explained by differences in definitions of epilepsy (e.g., febrile convulsions have been included in some studies **(43).**

Although these neurological manifestations of CD have been described over the last 30 years in the literature, there are still diagnostic delays often resulting in permanent neurological disability. Such delays are attributed to “controversies” arising from some variation in reported prevalence and poor understanding of the use of appropriate serological testing **(42).**

A systemic review had concluded that Epilepsy is 1.8 times more prevalent in patients with CD, compared to the general population. CD is over 2 times more prevalent in patients with epilepsy compared to the general population. Further studies are necessary to assess the prevalence of GS in epilepsy. In this review the author recommended that Patients with epilepsy of unknown aetiology should be investigated for serological markers of gluten sensitivity as such patients may benefit from a GFD **(44).**

Conclusions

This review has identified the following key points: There is an increased prevalence of CD amongst patients with epilepsy and an increased prevalence of epilepsy amongst those with CD or gluten sensitivity. Patients with CD presenting with neurological symptoms often suffer no gastrointestinal symptoms. There appears to be a stronger link between some epileptic presentations and GS or CD than others. Future studies should not treat epilepsy as though it is homogenous when investigating its relationship with GS or CD. Gluten-free diet is an effective management of epilepsy in those with epilepsy due to GS/CD. CEC syndrome is the best characterised epileptic presentation linked to CD. Patients with epilepsy of unknown aetiology should have their serum screened for AGA, anti tTG and

EMA. This is especially important in patients suffering with AED resistant occipital lobe seizures. It is likely that there are many patients who are being treated with AED polytherapy who can be managed with a GFD alone or with GFD and reduced AED. There is a need to study the prevalence of TG6 antibodies in patients with epilepsy to identify whether anti-TG6 could be used to identify individuals at risk of epilepsy due to their gluten sensitivity.

It is important that epilepsy is more broadly recognised within the spectrum of gluten-related disorders as these patients can be managed effectively if identified. However, clinicians must approach these cases with caution so as to not incorrectly diagnose epilepsy in those with gluten intolerance who have epilepsy mimics such as syncope, psychogenic non-epileptic seizures or migraine, amongst others. Clinicians must also recognise the limitations to the specificity of the GS/CD serum markers and take into account the full clinical picture when proceeding with diagnosis.

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