Gluten free diet

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The aim of this entry was to assess the effects of a gluten free diet (GFD) in the management of epilepsy in people with coeliac disease (CD) or gluten sensitivity (GS). A systematic approach was used to undertake a literature review. Five electronic databases (PubMed; Scopus; Google Scholar; Cochrane Epilepsy Group specialised register; Cochrane Register of Controlled Trails (CENTRAL) via the Cochrane Register of Online Trials) were searched using predetermined relevant search terms. In total, 668 articles were identified. Duplicates were removed and predefined inclusion and exclusion criteria were applied, and a PRISMA flow chart was produced. Data was extracted using Covidence software. Twelve studies on Epilepsy and CD involving a total of 70 participants were selected for analysis; narrative synthesis was used owing to the small sample sizes in the selected studies. None of the 12 studies meeting inclusion criteria investigated gluten sensitivity and epilepsy. All the included studies support a link between epilepsy and CD. GFD was effective in 44 out of 70 participants across the studies in terms of a reduction of seizures, reduction of antiepileptic drugs (AEDs) or normalisation of EEG pattern. A total of 44 participants showed a reduction in seizures (across eight studies) and complete cessation of seizures was reported in 22 participants. In general, the earlier the GFD is implemented after the onset of seizures, the better the likelihood of the GFD being successful in supporting control of seizures. Mechanisms linking gluten with epilepsy are not fully understood; possible hypotheses include gluten mediated toxicity, immune-induced cortical damage and malabsorption. Evidence suggests the effectiveness of a GFD in supporting the management of epilepsy in patients with CD, although the quality of evidence is low. There appears to be a growing number of neurologists who are prepared to advocate the use of a GFD. A multidisciplinary approaches and further research are recommended. It could be argued that when balancing potential treatments such as AEDs or surgery, a GFD has a low likelihood of harm.

Keywords: epilepsy ; seizures ; ketogenic diet ; gluten free diet ; coeliac disease ; non-coeliac gluten sensitivity ; gluten ataxia

1. Epilepsy

Epilepsy is a neurological disorder that affects around 70 million people worldwide [1]. It can have a significant effect on the quality of life of those affected and their families [2]. Seizures are usually sudden, acute and unpredictable. People with epilepsy and their cohabiting relatives report higher levels of anxiety, depression and social anxiety disorders compared with the general population [3]. Epilepsy is not one disorder, but a term used to describe several conditions that share seizures as a common element [4]. There are over 40 different types of seizure[5] and the seizure type and appearance vary depending on which area of the brain is affected. Some people may lose consciousness, collapse and jerk or twitch (tonic-clonic seizure). Other seizures result in a brief loss of consciousness with stiffness, or a complete loss of muscle tone (tonic, atonic, or drop attacks). Absence seizures can cause a person to appear blank and unresponsive for a few seconds. Seizures are classified into two main categories: generalised seizures which affect large areas on both sides of the brain (tonic-clonic, absence or atonic) and focal seizures that affect a specific region of the brain [6].

In some people the cause is known; brain injury accounts for almost 5% of all seizures [7], but they can also be caused by brain tumour, electrolyte imbalance [8], hormone imbalance or genetic factors [4]. However, in 60% of cases the aetiology is unknown [9]and referred to as ‘idiopathic epilepsy’ [4]. Lack of sleep [10], stress and anxiety [11], hyperventilation [12] and high caffeine intake can increase seizure susceptibility (although long term low intake can protect from seizures [13]). Epilepsy is primarily controlled pharmacologically, through prescription AEDs, just over half of those taking medication will become seizure free. A further 20–30% will have a reduction in seizures. However, approximately 20% of people continue to suffer seizures despite taking one or more AEDs and this is termed refractory or intractable epilepsy [6].

2. Ketogenic Diet in Management of Epilepsy

The ketogenic diet (KD) might improve outcomes in people with epilepsy [14]. The KD has been used for around 100 years in the treatment of refractory epilepsy [15]. The KD is a high-fat, low carbohydrate, adequate protein diet [16]. Mechanisms by which the KD results in improved seizure control are not fully understood. It is thought that the high-fat, restricted carbohydrate intake, results in the production of ketones due to fat metabolism. The anticonvulsant effect of ketones is thought to be due to an upregulation of gene expression involved in energy metabolism in the brain [17]. In the UK, dietary intervention to support epilepsy management is not considered until AEDs have failed to control seizures. In refractory epilepsy, The National Institute for Health and Care Excellence (NICE) guidelines recommend all children, young people and adults be referred to tertiary services offering non-pharmacological interventions and this should involve a multidisciplinary team and include psychological interventions (relaxation, cognitive behaviour therapy, biofeedback); medical intervention (vagus nerve stimulation) or brain surgery [18]. NICE recommends children and young people (but not adults) whose seizures are not controlled by appropriate AEDs should be referred to a paediatric epilepsy specialist for consideration for the use of the KD [18].

Research into understanding the anti-seizure mechanisms of the KD has led some to postulate that the grain free, and therefore the gluten-free nature of the KD, may be a component in its success.

3. Gluten and Coeliac Disease

Gluten is the term used to describe the storage proteins found in wheat, barley and rye [19]. CD is a complex, systemic autoimmune disease triggered by the ingestion of gluten, in genetically susceptible individuals [20]. Worldwide, CD affects approximately 1% of the population [21]. Symptoms associated with CD include diarrhoea, constipation, weight loss and malabsorption [22]. Greater understanding of the pathogenesis of CD in the last few decades has established it can affect any part of the body [23].

CD diagnosis must be confirmed by duodenal biopsy [24]. Carrying HLA-DQ2/HLA-DQ8 genes are a key, but not sufficient, component of genetic susceptibility to developing CD [22]. Treatment is lifelong adherence to a strict GFD and although oats are generally considered safe for most people with CD [25], it appears to cause sensitivity for some people [26] most likely due to contamination with wheat, barley or rye during the production chain [27]. For the majority of individuals with CD after GFD symptoms subside and villi recover [28]. However, despite strict GFD some people with CD experience persistent gastrointestinal (GI) and extraintestinal (EI) symptoms [29].

4. Non Coeliac Gluten Sensitivity

Non coeliac gluten sensitivity (NCGS) is a controversial condition [30] and the pathophysiology remains unclear. However, NCGS has been legitimised and three international conferences [31][32][33] have provided consensus on the definition of NCGS and the criteria for diagnosis [33]. NCGS appears more common than CD [34][35] with an estimated prevalence in the general population of 13% [31][36]. Although GI symptoms are similar to CD there is little or no mucosal damage [37] and the serological markers that are effective in diagnosing CD are not detectable in NCGS [37]. As with CD, removing gluten from the diet results in improvement of symptoms and reintroduction leads to relapse [33].

Neurological dysfunction associated with GS was originally thought to be due to malabsorption, but further research has discovered inflammatory cells in histopathological results of individuals with gluten sensitivity and neurological manifestation and the theory of an innate immune mechanism has emerged [31][38]. In contrast, CD involves both innate and adaptive immune responses .

5. Association between Epilepsy and Coeliac Disease

A meta-analysis on epilepsy and systemic autoimmune disorders suggests that people with epilepsy have a 2.6-fold increased risk for CD [39]. In contrast, a large study of people with CD reported a 1.4-fold increased risk of epilepsy [40][41][43][44]. However, this number could be higher given that many people with CD do not have gastrointestinal symptoms [42]. Some studies suggest epilepsy is the most frequent disorder associated with CD [43][44].

Developments in the understanding of the role of gluten and the gut–brain axis [42] has provided a basis for exploring the possibility of supporting epilepsy management through the GFD. GFD has resulted in a reduction in seizures in some cases [45][46], particularly those with temporal lobe epilepsy and hippocampal sclerosis [47]. Other case studies have shown complete remission of intestinal and central nervous system manifestations (including electroencephalogram

abnormalities associated with seizures) after a GFD, that reappeared after gluten reintroduction [48]. Hence the aim of this review was to assess the effects of a GFD in the management of epilepsy in people with CD or GS. Strict, lifelong GFD is the cornerstone of treatment for CD.

References

1. Singh, A.; Trevick, S. The Epidemiology of Global Epilepsy. Neurol. Clin. 2016, 34, 837–847.
2. Jones, C.; Reilly, C. Parental anxiety in childhood epilepsy: A systematic review. Epilepsia 2016, 57, 529–537.
3. Altintas, E.; Yerdelen, D.; Taskintuna, N. Social anxiety level in adult patients with epilepsy and their first-degree cohabiting relatives. J. Neuropsychiatry Clin. Neurosci. 2015, 27, 339–344.
4. What Is Epilepsy? Available online:http://www.epilepsysociety.org.uk (Accessed 18 March 2019).
5. Berg, A.; Berkovic, S.; Brodie, M.; Buchhalter, J.; Cross, J.; Van Emde Boas, W.; Engel, J.; French, J.; Glauser, T.; Mathern, G.; et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010, 51, 676–685.
6. What Is Epilepsy?; Epilepsy Research UK: London, UK, 2018.
7. Diaz-Arrastia, R.; Agostini, M.A.; Madden, C.J.; Van Ness, P.C. Posttraumatic epilepsy: The endophenotypes of a human model of epileptogenesis. Epilepsia 2009, 50, 14–20.
8. Castilla-Guerra, L.; del Carmen Fernandez-Moreno, M.; Lopez-Chozas, M.; Fernandez-Bolanos, R. Electrolytes disturbances and seizures. Epilepsia 2006, 47, 1990–1998.
9. Fiest, K.; Sauro, K.; Wiebe, S.; Patten, S.; Kwon, C.; Dykeman, J.; Pringsheim, T.; Lorenzetti, D.; Jette, N. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017, 88, 296–303.
10. Ferlisi, M.; Shorvon, S. Seizure precipitants (triggering factors) in patients with epilepsy. Epilepsy Behav. 2014, 33, 101–105.
11. McKee, H.; Privitera, M.D. Stress as a seizure precipitant: Identification, associated factors and treatment options. Seizure 2017, 44, 21–26.
12. Chater, S.; Simpson, K. Effect of passive hyperventilation on seizure duration in patients undergoing ECT. Br. J. Anaesth. 1988, 60, 70–73.
13. van Koert, R.R.; Bauer, P.R.; Schuitema, I.; Sander, J.W.; Visser, G.H. Caffeine and seizures: Asystematic review and quantitative analysis. Epilepsy Behav. 2018, 80, 37–47.
14. Martin, K.; Jackson, C.F.; Levy, R.G.; Cooper, P.N. Ketogenic diet and other dietary treaments for epilepsy. Cochrane Database Syst. Rev. 2016, 2, CD001903.
15. Neal, E.; Chaffe, H.; Schwartz, R.; Lawson, M.; Edwards, N.; Fitzsimmons, G.; Whitney, A.; Cross, J. The ketogenic diet for the treatment of childhood epilepsy: A randomised controlled trial. Lancet Neurol. 2008, 7, 500–506.
16. Zhang, Y.; Xu, J.; Zhang, K.; Yang, W.; Li, B. The anticonvulsant effects of ketogenic diet on epileptic seizures and potential mechanisms. Curr. Neuropharmacol. 2018, 16, 66–70.
17. Bough, K.; Wetherington, J.; Hassel, B.; Pare, J.; Gawryluk, J.; Greene, J.; Shaw, R.; Smith, Y.; Geiger, J.; Dingledine, R. Mitochondrial Biogenesis in the Anticonvulsant Mechanism of the Ketogenic Diet. Ann. Neurol. 2006, 60, 223–235.
18. Epilepsies: Diagnosis and Management. Clinical Guideline [CG137]: NICE; NICE National Institute for Health and Care Excellence: London, UK, 2012.
19. Biesiekierski, J.R. What is gluten? J. Gastroenterol. Hepatol. 2017, 32, 78–81.
20. Husby, S.; Koletzko, S.; Korponay-Szabo, I.; Mearin, M.; Phillips, A.; Shamir, R. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnoss of coeliac disease. J. Pediatric Gastroenterol. Nutr. 2012, 54, 136–160.
21. Catassi, C.; Gatti, S.; Fasano, A. The new epidemiology of celiac disease. J. Pediatric Gastroenterol. Nutr. 2014, 59, 7–9.
22. Sollid, L.M. Coeliac disease: Dissecting a complex inflammatory disorder. Nat. Rev. 2002, 2, 647–655.
23. Fasano, A.; Catassi, C. Clinical Practice. Celiac disease. N. Engl. J. Med. 2012, 367, 2419–2426.
24. Ludvigsson, J.F.; Leffler, D.A.; Bai, J.C.; Biai, F.; Fasano, A.; Green, P.; Hadjivassilliou, M.; Kaukinen, K.; Kelly, C.; Leonard, J.N.; et al. The Oslo definitions for coeliac disease and related terms. Gut 2013, 62, 43–52.

25. Garsed, K.; Scott, B.B. Can oats be taken in a gluten-free diet? A systematic review. Scand. J. Gastroenterol. 2007, 42, 171–178.

26. Silano, M.; Dessi, M.; De Vincenzi, M.; Cornell, H. In vitro tests indicate that certain varieties of oats may be harmful to patients with coeliac disease. J. Gastroenterol. Hepatol. 2007, 22, 528–531.

27. Rostami, K.; Bold, J.; Parr, A.; Johnson, M. Gluten-free diet indications, safety, quality, labels and challenges. Nutrients 2017, 9, 846.

28. Di Sabatino, A.; Corazza, G.R. Clinical Practice. Celiac disease. Lancet 2009, 373, 1480–1493.

29. Abdulkarim, A.S.; Burgart, L.J.; See, J.; Murray, J.A. Eitiology of nonresponsive celiac disease: Results of a systematic approach. Am. J. Gastroenterol. 2002, 97, 2016–2021.

30. Spence, D. Bad medicine: Food intolerance. Br. Med. J. (Online) 2013, 346, doi:10.1136/bmj.f1529.

31. Catassi, C.; Bai, J.; Bonaz, B.; Bouma, G.; Calabro, A.; Carroccio, A.; Castillejo, G.; Ciacci, C.; Cristofori, F.; Dolinsek, J.; et al. Non-celiac gluten sensitivity: The new frontier of gluten related disorders. Nutrients 2013, 5, 3839–3853.

32. Biesiekierski, J.R.; Iven, J. Non-coeliac gluten sensitivity: piecing the puzzle together. United Eur. Gastroenterol. J. 201 5, 3, 160–165.

33. Sapone, A.; Bai, J.C.; Dolinsek, J.; Green, P.H.; Hadjivassiliou, M.; Kaukinen, K.; Rostami, K.; Sanders, D.S.; Schuman n, M.; Ullrich, R.; et al. Spectrum of gluten-related disorders: Consensus on new nomeclature and classification. BMC Med. 2012, 10, 1–13.

34. Catassi, C.; Elli, L.; Bonaz, B.; Bouma, G.; Carroccio, A.; Cellier, C.; Cristofori, F.; de Magistris, L.; Dolinsek, J.; Dieteric h, W.; et al. Diagnosis of non-celiac gluten sensitivity (NCGS): The Salerno experts' criteria. Nutrients 2015, 7, 4966–49 77.

35. Volta, U.; Bardella, M.T.; Calabro, A.; Troncone, R.; Corazza, G.R. Study group for non-coeliac gluten sensitivity. BMC Med. 2014, 12, doi:10.1186/1741-7015-1112-1185.

36. Molina-Infante, J.; Santolaria, S.; Sanders, D.S.; Fernandez-Banares, F. Systematic review: Noncoeliac gluten sensitivit y. Aliment. Pharmacol. Ther. 2015, 41, 807–820.

37. Tonutti, E.; Bizzaro, N. Diagnosis and classification of celiac disease and gluten sensitivity. Autoimmun. Rev. 2014, 13, 472–476.

38. Sapone, A.; Lammers, K.M.; Mazzarella, G.; Mikhailenko, I.; Carten, M.; Casolaro, V.; Fasano, A. Differential mucosal I L-17 expression in two gliadin-induced disorders: Guten sensitivity and the autoimmune enteropathy celiac disease. In t. Arch. Allergy Immunol. 2010, 152, 75–80.

39. Lin, Z.; Si, Q.; Xiaoyi, Z. Association between epilepsy and systemic autoimmune diseases: A meta-analysis. Seizure 2 016, 41, 160–166.

40. Ludvigsson, J.F.; Zingone, F.; Tomson, T.; Ekbom, A.; Ciacci, C. Increased risk of epilepsy in biopsy-verified celiac dise ase: A population-based cohort study. Neurology 2012, 78, 1401–1407.

41. Rana, A.; Musto, A. The role of inflammation in the development of epilepsy. J. Neuroinflamm. 2018, 15, 144, doi:110.1 186/s12974-12018-11192-12977.

42. Hadjivassiliou, M.; Sanders, D.; Grunewald, R.; Woodroofe, N.; Boscolo, S.; Aeschlimann, D. Gluten sensitivity: From g ut to brain. Lancet Neurol. 2010, 9, 318–330.

43. Fois, A.; Vascotto, M.; Di Bartolo, R.M.; Di Marco, V. Celiac disease and epilepsy in pediatric patients. Childs Nerv. Sys t. 1994, 10, 450–454.

44. Zelnik, N.; Pacht, A.; Obeid, R.; Lerner, A. Range of neurologic disorders in patients with celiac disease. Pediatrics 200 4, 113, 1672–1676.

45. Canales, P.; Mery, V.P.; Larrondo, F.J.; Bravo, F.L.; Godoy, J. Epilepsy and celiac disease: Favourable outcome with a g luten-free diet in a patient refractory to antiepileptic drugs. Neurologist 2006, 12, 318–321.

46. Hadjivassiliou, M.; Dasappaiah, G.; Grunewald, R.; Aeschlimann, D.; Sarrigiannis, P.; Hoggard, N.; Aeschlimann, P.; Mo oney, P.; DAvid, S. Neurological dysfunction in coeliac disease and non-coeliac gluten sensitivity. Am. J. Gastroenterol. 2016, 9, 561–567.

47. Peltola, M.; Kaukinen, K.; Dastidar, P.; Haimila, K.; Partanen, J.; Haapala, A.; Maki, M.; Keranen, T.; Peltola, J. Hippoca mpal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity. J. Neurol. Neurosurg. Psychiatr y 2009, 80, 626–630.

48. Pratesi, R.; Modelli, I.C.; Martins, R.C.; Almeida, P.L.; Gandolfi, L. Celiac disease and epilepsy:favourable outcome in a child with difficult to control seizures. Acta Neurol. Scand. 2003, 108, 290–293. doi:10.1034/j.1600-040.