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Research Article

Celiac Disease and Attention Deficit Hyperactivity Disorder: A Systematic Review of the Literature

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- Attention Deficit Disorder with Hyperactivity
- Glutens

Abstract

Objective: To conduct a systematic review investigating the association between attention deficit hyperactivity disorder (ADHD) and celiac disease.

Method: Relevant articles were identified through EMBASE and MEDLINE using MeSH headings such as: 'celiac disease,' 'gluten free,' and 'glutenin.' These terms were combined with additional terms such as 'attention deficit disorder,' 'ADHD,' and 'ADD.' Articles published in a peer-reviewed journal, in English, with an appropriate study design (i.e. case control or experimental trial) were included.

Results: Five of six observational studies that met the inclusion criteria found no association between celiac disease and ADHD. Only one study found that a higher percentage of patients with celiac disease had evidence of learning disability/ADHD compared with controls.

Conclusions: Several studies were limited by sample size, reporting and detection bias. However, based on the available evidence, this systematic review provides support for suggesting that clinicians should not be routinely screening ADHD patients for celiac disease in the absence of additional symptoms.

ABBREVIATIONS

ADHD: Attention Deficit Disorder with Hyperactivity; ADD: Attention Deficit Disorder

INTRODUCTION

Since the original description of celiac disease in 1888, it has become increasingly recognized that its manifestations extend beyond the proximal gastrointestinal tract [1]. The well-recognized extra-intestinal manifestations include dermatitis herpetiformis, osteoporosis, arthritis, fatigue, and liver function abnormalities [1]. The list of potential extra intestinal manifestations, however, continues to expand, and may now also include neurological and psychiatric conditions such as peripheral neuropathy, cerebellar ataxia, depression, and attention deficit hyperactivity disorder (ADHD) [2,3]. The pathogenesis of these manifestations remains unknown; however, it is hypothesized to be multifactorial. Given that the disease is associated with malabsorption, the various neurological and psychiatric manifestations may be related to several concomitant vitamin deficiencies (e.g. Vitamin B12, E, and D). Humoral mechanisms involving immunoglobulin G antibodies may also be involved, particularly in the pathogenesis of peripheral neuropathy and cerebellar ataxia [3].

ADHD is defined as a persistent pattern of inattention and/or hyperactivity-impulsivity that adversely impacts social, academic, and occupational functioning [4]. The diagnosis is based on several inattentive and/or hyperactive-impulsive symptoms that are present before the age of 12, and occur in two or more settings (e.g. at home, school, or work) [4]. The dominant theory regarding the pathogenesis of ADHD is that it results from catecholaminergic dysregulations within the cerebral cortex [5]. Evidence from genetic molecular studies, animal models, imaging studies, and the frequent positive clinical response to stimulant medications are all in keeping with this [5]. There may also be an association with several environmental factors such as periobstetrical complications, idiosynctratic reactions to certain foods, and prenatal exposure to alcohol and nicotine [5].

The prevalence of ADHD has been on the rise in both the United States and Canada [6,7]. The prevalence of celiac disease has also been increasing, with global prevalence rates now doubling approximately every 20 years independent of increased diagnostic rates [1].

It is not surprising then, that several researchers have begun exploring the association between celiac disease and ADHD [8-15]. To our knowledge, no systematic review has been completed investigating this association. As such, the objectiveof this study was to provide a systematic review and critical appraisal of the current literature to explore what, if any, are the associations between celiac disease and ADHD. This study has the potential to increase the knowledge of healthcare providers and evidence for screening and/or treatment interventions.

MATERIALS AND METHODS

Two databases (Medline and EMBASE) were used to search for both observational and experimental studies, as well systematic reviews and meta-analyses. A classic Boolean search was performed using a combination of keywords and Medical Subject Headings (MeSH). These included terms such as: 'glutens,' 'celiac disease,' 'gluten free diet,' 'coeliac,' 'gliadin,' 'glutenin,' and 'celiac sprue.' These terms were then combined with additional search terms such as 'attention deficit hyperactivity disorder,' 'attention deficit disorder,' 'ADHD,' and 'ADD.' This search strategy yielded 10 and 60 results in Medline and EMBASE respectively (see Figure 1) [16].

Titles and/or abstracts were reviewed in detail, and all studies that did not specifically address ADHD and celiac disease were excluded. As such, studies that focused on 'non-celiac gluten sensitivity' as opposed to celiac disease were excluded. Individual case reports, expert commentaries, and all studies not published in English were also excluded. No publication date or publication status restrictions were imposed. The literature search is current as of January 10th, 2015.

Studies were reviewed and critically appraised primarily for internal validity (e.g. study design, sample size, selection bias, detection bias, recall bias, and reporting bias) using the Critical Appraisal Skills Programme (CASP) checklist for Case Control and Diagnostic studies [17]. Nine out of the eleven questions from the CASP checklist can be answered with a simple 'yes,' 'no,' or 'can't tell.' As such, the max attainable score for any observational study was nine out of nine. The authors agreed that any score less than seven has a high risk of poor internal validity.

RESULTS AND DISCUSSION

Overall, eight studies were deemed relevant and met the inclusion/exclusion criteria. This included six observational studies and two experimental studies [8-15]. Table 1 presents the data sources, study population, data collection methodology, study results, and CASP checklist score.

The observational studies were all case-control studies with case sample sizes that ranged from 39 to 8201 participants. The demographics of the case population also varied considerably with some studies restricting the sample population to just children [10,11,13], while others placed no age restrictions [8,9,12]. Each of these studies had a slightly different methodology, therefore prohibiting a useful meta-analysis. For example, in some studies, the case population included patients with ADHD, and they were screened for celiac disease. In other studies, the case population included patients with celiac disease, and they were evaluated for ADHD [12]. Two of the six observational studies were based purely on a retrospective chart review looking for a concurrent diagnosis of celiac disease and ADHD [8,9].

Overall, five out of the six observational studies found no association between celiac disease and ADHD [8-11,13]. Only the study by Zelnick *et al.,* (n=111) found that 20.7% of patients of

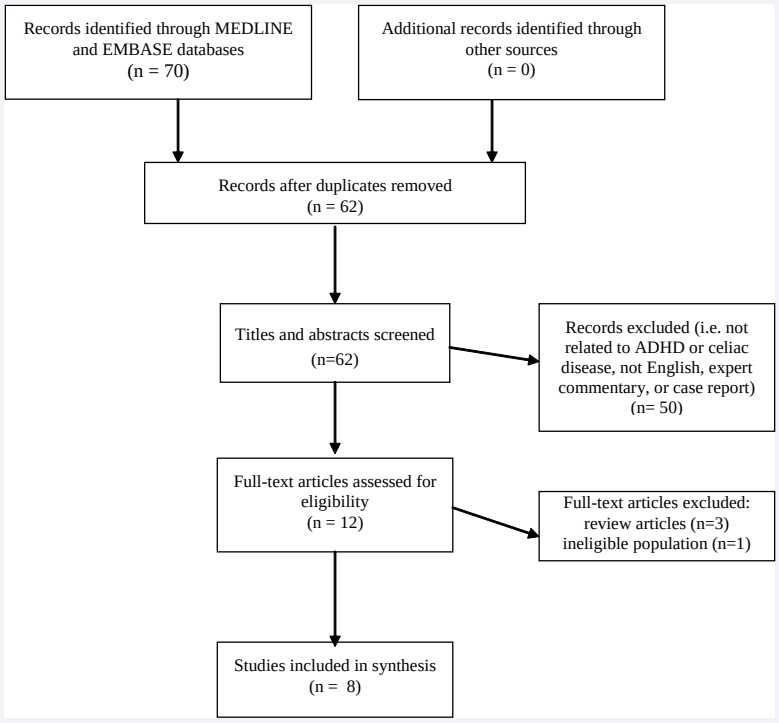

Figure 1 Results of literature search.

Table 1: Summary of study populations, methods and results including critical appraisal.

Study	Type	Population	Methods	Results	CASP Score*
Chen *et al.,* (2013)	Case Control	N = 8201 patients with ADHD N = 30 000 controls	Chart review looked for concurrent diagnosis of several auto-immune conditions, including CD. Prevalence of these diseases among case population was compared with that of a control population	No statistically significant increased odds ratio of CD among ADHD cases compared with control population. No odds ratios, confidence interval, or P-value provided	4
Ruggieri M et al., (2008)	Case Control	N = 835 children with celiac disease N = 630 children with neurological disorders of unknown cause N = 300 children neurological disorders of known cause. N = 300 healthy children served as controls	One case population was screened for neurological and psychiatric disorders. Another case population of children with neurological disorders including ADHD was screened for CD using serology. Both case populations were then compared with a control population	No cases of ADHD identified among CD patients. Only 0.86% of neurological cases had positive CD serology compared with 0.66% of controls (no p-value given)	7
Gungor S et al., (2013)	Case Control	N = 362 children with ADHD N = 390 age-matched control patients	Children with ADHD were tested for CD using serology and intestinal biopsy, if required. The results were compared to aged-matched control patients tested in the same manner	No statistical difference in prevalence of positive IgA TTG antibodies between cases and controls (p=0.716)	8
Dazy K et al., (2013)	Case Control	N = 281 patients with serology and biopsy proven CD N = 301 controls	Chart review of patients with CD looked for concurrent diagnosis of ADHD and/or prescribed use of methylphenidate	2.49% of CD patients had concurrent diagnosis of ADHD vs. 2.66% of controls (p=0.63). 1.42% of CD patients had been prescribed methylphenidate vs. 1.99% of controls (no p-value given)	7
Zelnick N *et al.,* (2004)	Case Control	N = 111 patients with biopsy proven CD N = 211 age and gender-matched controls	Patients with CD were assessed for neurological symptoms as well as learning disabilities and ADHD. Results were compared to age and gender-matched controls	20.7% of CD patients had evidence of learning disability/ ADHD compared with only 10.5% of control patients (p<0.01)	5
Lahat E et al., (2000)	Case Control	N = 39 patients with previously established ADHD/ADD N = 34 controls	Patients with ADHD/ADD were screened for CD with serology. The control population underwent similar screening	Zero percent of ADHD patients were positive for IgA antibodies, as were zero percent of control patients.	5
Niederhofer H and Pittschieler K. (2006)	Experimental Trial	N= 78 patients with biopsy-proven CD	Patients with CD were assessed for ADHD using Hypescheme scoring system pre and post six month trial of gluten-free diet	Overall ADHD Hypescheme scores decreased from 22 to 16 (p=0.024) with gluten-free diet	n/a
Niederhofer H. (2011)	Experimental Trial	N = 67 patients with known ADHD	Patients with ADHD were screened for CD using serology. Then those with positive serology underwent trial of gluten-free diet. Hypescheme scores monitored before and after six month trial	Among 10 patients with ADHD and positive CD serology, Hypescheme scores decreased from 21.24 to 14.18 (p=0.023) with gluten-free diet	n/a

Note: CASP Score [17] = number of definitive YES answers for 9 possible questions. Max score = 9/9.
Abbreviations: CD: Celiac Disease; ADHD: Attention Deficit Hyperactivity Disorder

biopsy proven celiac disease had evidence of learning disability/ ADHD compared with only 10.5% of controls (p<0.01) [12].

Two experimental studies were found that attempted to assess whether a gluten-free diet could alleviate symptoms of hyperactivity and inattention [14,15]. Both studies were controlled trials wherein patients diagnosed with celiac disease and ADHD were subjected to a minimum of a six-month trial of a gluten-free diet. ADHD symptomatology was recorded before and after the trial using the Hypescheme scoring system (an operational criteria checklist for ADHD that incorporates criteria from both the DSM-IV and ICD-10). In both studies, there was a statistically significant decrease in mean symptoms of ADHD-like symptomology, as scored by the Hypescheme checklist, following a trial of gluten-free diet (p=0.023 and 0.024) [14,15]. In both studies, no patients were given pharmacological treatment for ADHD, therefore the authors concluded that it was the gluten-free

diet alone that was responsible for the improved Hypescheme scores.

Discussion

Many of the observational studies described above suffer from methodological weaknesses. For example, given that the prevalence of celiac disease in the general population is only one percent, two of the six studies had sample sizes that were likely underpowered to detect any association between ADHD and celiac disease [11,13]. It is therefore not surprising that the studies by Lahat *et al.,* (n=34) and Gungor *et al.,* (n=362) had negative findings.

Also, in several of the studies, we are provided little comparative demographic and/or health data for the case and control populations [8-10]. As such, there is no way to reliably assess the appropriateness of the control population in these studies.

Additionally, in the studies where the case population was evaluated for ADHD, there is a high risk of bias that compromises the internal validity of the study [10,12]. For example, in the study by Zelnick *et al.,* there is a high risk of reporting bias; the case population (celiac disease patients) was potentially more likely to over-report any abnormal behavioural symptoms in comparison with the control population. In the same study, there is also a high risk of detection bias given that there is no mention of blinding among the observers who were assessing for ADHD [12]. The same risk of detection bias may be present in the study by Ruggieri *et al.,* wherein clinicians were non-blinded when celiac disease patients were assessed for ADHD [10].

With regard to the experimental studies by Niederhofer, they too suffer from considerable methodological flaws [14,15]. First, the sample sizes for these studies were relatively small. For example, in the 2011 study, despite enrolling 67 patients for the study, only 10 patients tested positive for celiac disease and went on to participate in the gluten-free trial [15]. Second, in the 2011 study, the diagnosis of celiac disease is based purely on serology, and not on endoscopic biopsy [15]. As such, one cannot know what percentage of the study participants even had true celiac disease at the outset of the gluten-free trial. Third, the baseline Hypescheme scores were based on retrospective reporting of symptoms. This is associated with a high risk of reporting bias, as patients can over state their symptoms prior to the trial thereby overestimating the treatment effect. Fourth, there is also a high risk of detection bias as neither the patients nor the observers were blinded pre and post gluten-free diet. Fifth, given that there was no placebo-controlled population, there is no way to determine what percentage of the positive treatment effect is explained purely by placebo. And finally, because there is no detailed information regarding the diet of the patients prior to initiation of the study, it is difficult to rule out confounding biases (i.e. was the improved Hypescheme scores a result of decreased gliadin protein ingestion, or was it actually related to decreased intake of carbohydrates and/or high sugar foods?).

Overall, based on the currently available low quality evidence, clinicians should not be routinely screening ADHD patients for celiac disease in the absence of additional symptoms (i.e. weight loss, diarrhea, bloating, arthralgias, dermatitis herpetiformis etc.). Additionally, a gluten-free diet should not be a routine recommendation for those patients diagnosed with ADHD, unless there is a concurrent biopsy-proven diagnosis of celiac disease.

For several parents, even if serological tests for celiac disease are negative, they may insist on trying their child on an empiric trial of a gluten-free diet. In the absence of objective findings of celiac disease or gluten sensitivity, clinicians should advise against such practices and inform parents of the potential harms of a gluten-free diet. First, a gluten-free diet can be a significant financial burden for a family. Gluten-free foods cost 76-518% more than non gluten-free equivalents ($p<0.001$) [18,19]. Second, starting a child on a gluten-free diet can potentially adversely impact a child's ability to participate in social activities such as school pizza lunches or birthday parties [20,21]. And third, a gluten-free diet that is started empirically without first consulting with a dietician carries the risk of long-term nutritional deficiencies [22].

CONCLUSIONS

With regards to the primary aim of this study, five out of six observational studies found no association between celiac disease and ADHD. The study by Zelnick *et al.,* was the only study to find a potential association, however, this study had a high risk of reporting bias and detection bias. Both of the controlled trials by Niederhofer found that consumption of a gluten-free diet resulted in a statistically significant decrease in Hypescheme scores. These studies, however, also suffered from very poor internal validity and small sample sizes. Overall, based on the currently available low quality evidence, clinicians should not be routinely screening ADHD patients for celiac disease in the absence of additional symptoms, or unless belonging to a high-risk group.

The knowledge-base surrounding celiac disease is expanding, and the list of extra-intestinal manifestations continues to grow. With regards to the potential association between celiac disease and ADHD, there remains a need for both larger and better quality studies. For example, there is a need for larger case-control studies wherein a case population of previously diagnosed ADHD patients is then tested for celiac disease. In the context of a trial, testing ADHD patients for celiac disease—using an objective blood test— is less vulnerable to detection bias as compared with testing celiac disease patients for ADHD. The only way to minimize this potential bias is to blind the observers. With regards to whether or not a gluten-free diet can help minimize symptoms of ADHD, there is a need for higher quality evidence that involves both blinding and a placebo controlled arm. The author acknowledges that in the case of diet interventions, this can be both logistically challenging and very costly.

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