RAP

Mini-review

Celiac disease and ADHD: mini-review and critique

Michele Fornaro[1]
Domenico De Berardis[2]
Rocco Pollice[3]
Venkataramanujan Srinivasan[4]
Concetta De Pasquale[1]

[1] Department of Education Sciences, University of Catania, Catania, Italy
[2] National Health Service, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4, Teramo, Italy
[3] Service for Monitoring and early Intervention against psychoLogical and mEntal suffering in young people" (SMILE), L'Aquila University, L'Aquila, Italy
[4] Sri Sathya Sai Medical Educational and Research Foundation, Medical Sciences Research Study Center, "Prasanthi Nilayam", Tamilnadu, India

Address for correspondence :
Michele Fornaro
Dipartimento di Scienze dell'Educazione
Università di Catania
via Teatro Greco 84
95125 Catania, Italy
E-mail: dott.fornaro@gmail.com

Summary

Celiac disease (CD) is debilitating autoimmune disease affecting individuals of both genders worldwide, usually from middle infancy onward. CD often includes a number of different clinical pictures, possibly including comorbid Attention Deficit Hyperactive Disorder (ADHD)-like symptoms too. Yet, despite the clinical relevance of such comorbidity and its major implications on pharmacological treatment strategies, prevalence data are still inconclusive or apparently discordant. This selective mini-review critically assessed the available data on both prevalence rates and potential clinical and treatment implications for CD/ADHD comorbidity. While methodological issues (especially diagnostic inconsistency among different studies) and heterogeneity of included samples ("apple and orange" bias), recall bias, and publication bias, lack of age and gender stratification, significantly hamper the reliability of presented results, the comorbidity of CD and ADHD may have major clinical resonance nonetheless, as critically discussed in this essay along with potential psychopharmacological treatment implications.

KEY WORDS: celiac disease, Attention Deficit Hyperactivity Disorder (ADHD), Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5).

Introduction

Celiac disease (CD) is an autoimmune condition of the mucosa of upper small intestine resulting from gluten ingestion in genetically predisposed individuals of all ages, from middle infancy onward. The term coeliac derives from the Ancient Greek "κοιλιακός/ koiliakós" ("abdominal"), referring to the occurrence of intractable stomach pain, atrophy, failure to thrive (in children), paleness and feebleness associated to diarrhea manifesting with steatorrhoea and/or anemia, often liable to periodic return (1). The pediatrician Samuel Gee gave the first modern-day description. He perceptively stated, "*If the patient can be cured at all, it must be by means of diet*" (2). Nowadays, the diagnosis of CD is essentially based on the demonstration of villus atrophy in jejunal biopsy (3), with the only therapy available being represented by a gluten-free diet or, to a lesser extent, B1, B12, D or K vitamin supplements, to prevent the body from attacking the gut when gluten is present (4). The diet can be cumbersome while failure to comply with the diet may cause relapse. Moreover, evidence suggests that CD may be still underdiagnosed, especially in primary school children worldwide, with prevalence rates varying a lot depending on the method used for the determination of serum immunoglobulin (Ig) G or A antigliadin antibodies (5), and general population average rates of 0.71-1.01% in the United States (6). Within the past years, increasing attention has been placed toward the assessment of point-prevalence rates of CD in specific populations including, among others, people with irritable bowel syndrome, diabetes, juvenile chronic arthritis, dyspepsia, Crohn's disease, autoimmune thyroiditis, helicobacter pylori infection, headache, cardiomyopathy and psoriasis. CD is relatively common in course of neuropsychiatric dysfunctions (7, 8), including the following: (occipital) epilepsy (9), psychosis (10), autism (11), ataxia (12), (recurrent) (13, 14) and Attention Deficit Hyperactivity

Disorder (ADHD) (15, 16). Also, though the actual prevalence of severe mental and behavioral disorders in untreated CD remains virtually unexplored, a history of psychiatric treatment before CD diagnosis was documented in up to 21% CD adults *vs* 5% age-matched medical controls by tiny-sampled preliminary studies carried in the 1980s (17, 18). This is a crucial issue, especially considering that many patients affected by a more or less overt CD show ADHD-like symptoms, especially before initiating a gluten-free diet, and that the available prevalence data on the matter basically rely just on a preliminary investigation carried on 132 CD patients (age range: 3-57 years) (15). Therefore, the aim of the present essay is to synthesize available data on the topic, critically focusing on the reported prevalence rates and providing a dissertation on the potential implications of future methodologically proof studies in the understanding of the eventual role of the psychopharmacological management of ADHD symptoms in course of CD, if ever needed.

Method

We searched the MedLine, Scopus, PsychINFO, Embase and Cochrane databases for the following terms or their combinations: “celiac disease”, “coeliac disease”, “celiac sprue”, “nontropical sprue”, “endemic sprue”, “gluten enteropathy, “celiac antibodies”, “gluten sensitivity”, “maladaptive absorbement syndrome”, “ADHD”, “neurological symptoms”, “psychiatric symptoms”, “diet” AND/OR “comorbidity”. The afore mentioned databases were inquired on March 7, 2014 by three independent authors, who reach a consensus for their eventual inclusion in this selective mini-review based on validity and reliability issues.

Results

Twenty-two original contributes were extracted. Of those latter, nine cross-sectional prevalence studies of ADHD in course of CD received the highest rank for inclusion in this review and have been synthesized in table 1. Additional contributes, including primary or secondary research papers (where available) or most comprehensive recent reviews were also accounted for inclusion. Redundant contributes were excluded (e.g. secondary research data dated 2000 or early) while papers with methodological constraints were presented in this report but critically evaluated into the discussion section of the present manuscript.

Even upon careful data collection, prevalence rates studies on CD-ADHD comorbidity were lacking. Moreover, wherever available, inconsistent rates have been documented, essentially depending on the investigated sample and the adopted diagnostic biomarkers, psychiatric criteria or rating tools. Specifically, to date the most rigorous study investigating the prevalence of ADHD symptoms in people with CD has been carried on 132 “highly motivated” participants, both genders, aged between 3 to 57 years old (mean=19.3 years), assessed using the Conners Rating Scale/”hypescheme” (19) and the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) criteria (20) for the ADHD diagnosis, before and 6-months after their prescription of a gluten-free diet (15). The authors found that ADHD-like symptoms were markedly overrepresented among untreated CD patients, and that a gluten-free diet may improve symptoms significantly within a short period of time, therefore suggesting the inclusion of CD in the list of diseases associated with ADHD-like symptomatology (15), a recommendation which the recent Fifth Edition of the DSM (DSM-V) actually neglected possibly due to the very preliminary nature of available evidence (21). A 2008 study by Ruggieri et al. (22), assessing the prevalence of neurological and psychiatric symptoms manifestations in children with gluten sensitivity found a low prevalence of febrile seizures, epilepsy, headache, mental retardation, neuropathy and bipolar disorder and no cases of ataxia or cerebellar disturbances. Yet, while many of the explored conditions may be associated to ADHD, the study did not assess the actual prevalence of ADHD-symptoms themselves. Therefore, despite its methodological accuracy about the immune diagnostic procedures and its homogeneous (children only) and large sample size (n=835), the results reported in this study could not be directly compared to the ones provided by other authors.

Inconsistency issues and poor comparability of results with the pivotal study by Niederhofer and Pittschieler (2006) (15) also regard the data recently reported by Gungor et al., (2013) who investigated the prevalence of CD in ADHD samples (n=363; ages 5-15 years) rather than the opposite (“ADHD prevalence in CD”), failing to show any significant difference of CD prevalence in ADHD *vs* age-matched psychiatrically healthy controls (n=390), concluding that no empirical recommendation of gluten-free diet seems necessary in ADHD children (23). An interesting finding from Gungor et al., (2013) was the higher portion of the patients of positive tTg or IgA (part of the diagnostic criteria adopted for the CD diagnosis in their study) having a history of seizures compared to seronegative ones (50 *vs* 7.8%; p=.032), concluding that more attention should be placed for the pharmacological management of seizures in case of ADHD-CD presentations (23). Concerning the prevalence of celiac antibodies in children with neurologic and psychiatric disorders (including ADHD with or without hyperactivity history; n=39 out of 167 subjects included in the study, aged 1-16 years, both genders), Lahat et al., (2000) found a different trend compared to the one historically documented in adults (24), failing to demonstrate any relationship between common neurologic disorders without a specific diagnosis during childhood and CD, thus discouraging a systematic screening for CD in the routinely diagnostic evaluation of children with such disorders (25). This discrepancy on prevalence rates of comorbid CD and ADHD,

independently on the age of investigated subjects, appears further puzzling considering that a 2011 report by Helmut Niederhofer on 67 (age 7-42 years; mean age=11.4 years; both genders) ADHD patients found 10 of them being positive for CD (7 male or 13.5% and 3 female or 20%) (26).

Table 1 - **Essential synthesis of the main studies accounted in the present mini-review: inconsistency of methodological procedures hamper the validity of comparisons across different studies, which appear to lead to inconsistent finding and recommendations too in the absence of further, well-designed, replication studies.**

Author, date	Sample & Method	Limits	Results & major clinical implications
Niederhofer et al., 2006	132 CD patients (including pediatric and adult cases). Behavioral and rating scales.	Berkson's bias.	ADHD-like symptoms were markedly overrepresented among unmediated CD patients. A gluten-free diet may lead also to a (short-term?) improvement of ADHD-like symptoms whenever associated (due?) to CD.
Ruggieri et al., 2008	835 children with GS (based on positive titers for serum anti-gliadin antibody [AGA], anti-endomysial antibody [EMA], and anti-tissue transglutamine [tTG] antibody and a positive gut biopsy), were recruited, prospectively followed up, and screened for neurologic and psychiatric disturbances.	No assessment of the actual prevalence of ADHD-symptoms themselves.	The prevalence of neurologic/ psychiatric manifestations in this group of children with GS was low but slightly higher than that in the controls (P = .041). Children with known (P = .772) and cryptogenic (P = 1.0) neurologic disorders did not exhibit a higher prevalence of GS.
Gungor, 2013	Pediatric ADHD patients (n=363; ages 5-15 years) were assess to explore the prevalence of eventual comorbid CD.	Some psychiatric diagnoses, including lifetime ADHD, may have been prone to recall bias and were based on the information gained by the parents/ care givers.	No statistically significant difference in terms of CD prevalence was observed between ADHD and age-matched psychiatric controls (n=390), concluding that no empirical need for a gluten-free diet is needed in course of pediatric ADHD. Interestingly, a higher proportion of ADHD patients having a history of positive tTg or IgA (part of the diagnostic criteria adopted for the CD diagnosis in their study) had also a history of seizures compared to seronegative ones (50 *vs* 7.8%; p=.032), concluding that more attention should be placed for the pharmacological management of seizures in case of ADHD-CD presentations.
Lahat, 2000	Pediatric sample (including ADHD with or without hyperactivity history; n=39 out of 167 subjects). Cross-prevalence study.	Relatively small sample size.	No relationship between common neurologic disorders without a specific diagnosis during childhood and CD was found, thus discouraging a systematic screening for CD in the routinely diagnostic evaluation of children with such disorders.

Legend: CD=Celiac disease; ADHD=Attention Deficit Hyperactivity Disorder; GS=gluten sensitivity.

Discussion

CD is tightly associated to hyperkinesia, dyslexia (27), sensory deficits and other neuropsychiatric manifestations (16), whereas a gastrointestinal maladaptive disorder may trigger an eating disorder such as anorexia nervosa (28). While the mechanisms involved in the etiology and pathogenesis of psychiatric symptoms in course of CD remain elusive, impaired availability of tryptophan at the central nervous system predisposes to disturbances in central serotonergic transmission, which is classically accounted as a crucial pathway in the genesis of either depressive and aggressive dysregulation (29) and to the cognitive, impulsive and aggressive ADHD dimensions (30).

Limitations of available studies and inconsistency of results

A number of limitations may obstruct a more accurate investigation on the matter (Fig. 1). In fact, a strong "publication bias", "selection by indication bias" (essentially the inclusion of subjects with different immune and psychopathological features) and "measurement bias" (namely the inconsistency of the CD and ADHD diagnoses across different studies) may hamper the reliability and validity of the limited results available to date. Moreover, a Berkson's bias may have occurred in tiny-sampled clinical-population studies due to the exclusion of more severe cases (e.g. those ones with multiple co-morbidities or more severe symptoms), who usually seek for clinical care rather than participating in epidemiological studies. One additional factors may account for the inconsistency of prevalence rates reported by different studies, including discrepancy between those studies having their primary focus on CD in ADHD cases rather than the opposite (ADHD prevalence in CD cases); along with the unrepresentative sizes of the investigated samples, this issue reduces the chances of reliable comparisons across multiple sources. In addition, the ADHD criteria outlined by the DSM-V urge additional clinical confirmation, with a special emphasis to the "341.01 (F90.2)" ("combined presentation"), "314.00 (F90.0)" ("predominantly inattentive presentation), "314.01 (F90.1)" ("predominantly hyperactive/impulsive presentation) specifiers, which may lead to an "apple and oranges" bias in the comparison of data merged from different sources. Similarly, the inclusion in the DSM-V criteria for ADHD of the "remission" and "severity" specifiers, neglected by the few studies carried to date on CD-ADHD comorbidity, may nonetheless provide more insights on the matter if accounted by future investigations. Moreover, most of the ADHD diagnoses made in CD samples (as well as in other subsets of patients), may be influenced by a recall bias due to the retrospective collection of data, especially in case of patients prone to cognitive or attentional deficits. Finally, as acknowledged by the DSM-V (page 61 of the 2013 American paperback edition) (21), current tests for ADHD are not sufficiently sensitive or specific to serve as diagnostic indexes, as properly disclosed by Niederhofer and Pittschieler (2006), but not by Lahat et al., (2000) concerning the diagnostic procedure for ADHD in their respective samples (15, 25).

Additional clinical considerations may regard the most likely longitudinal course of the co-occurrence of ADHD-like and other neuropsychiatric symptoms in not gluten-free diet CD patients. Specifically, while to the best of our knowledge no long-term follow studies have been carried out on the matter to date, and the clinical practice suggests that ADHD symptoms seen in a significant proportion of CD cases may follow a periodic course and the "willingness to follow the prescribed diet and/or medications", which may underscore the chances for an adequate treatment adherence, especially in non-adult samples characterized by significant impulsivity and/or distractibility. This clinical wisdom is also in line with the notion of a liability to periodic return of gastrointestinal symptoms already documented by Aretaeus of Cappadocia in "*ante-litteram*" CD patients (1), whereas a consistent proportion of ADHD patients, especially those with co-comorbid bipolar disorders (31, 32) and/or epilepsy and/or autism (33) may also be characterized by a periodic course of neuropsychiatric symptoms, independently on the CD co-occurrence, most likely due to a (common?) immune-pathological background, possibly influenced by diet as well (34). Therefore, future studies should also systematically assess the role of personality traits (35), bipolar hints and epilepsy in samples of CD patients with ADHD symptoms. Finally, while CD is a female predominant condition, the re-

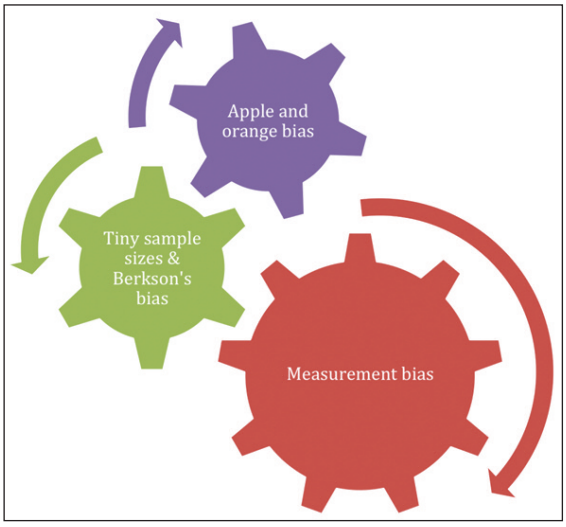

Figure 1 - Pictorial exemplification of the major biases hampering the generalizability of results of prevalence studies on CD-ADHD comorbidity. "Tuning the gearwheels" of future studies to overcome these issues may allow reliable conclusions on the actual impact of a gluten-free diet on "pseudo"-ADHD symptoms in course of CD or even allow for a more conscious psychopharmacological management of ADHD-like symptoms wherever aimed.

ported DSM-V ratios for M:F ADHD is 2:1 in childhood vs. 1.6:1 in adults, whereas females may be more likely to present primary inattentive features compared to males (36). Thus, more accurate age and gender stratifications should likewise accounted by future studies aiming at shedding further light on the understanding of the actual prevalence rates.

Potential implications for future studies to explore the psychopharmacological management of ADHD in course of CD

While the above clinical speculations urge for confirmations by more methodologically accurate studies, major implications for the clinical practice of CD-ADHD cases may be postulated as well. In fact, if confirmed by reliable studies, the CD-ADHD comorbidity may eventually shift the research focus on a shared immune background, eventually discouraging the prescription of the some psychopharmacological agents already endorsed for non-CD cases of ADHD (37), to eventually promote the gluten-free dietary approach before exposing the patients to potentially unnecessary or even harmful psychotropic drugs. Nonetheless, even in the absence of any conclusive evidence on the matter and specific treatment guidelines for ADHD symptoms in course of CD, the eventual prescription of tryptophan supplements or even the off-label prescription of Selective Serotonergic Reuptake Inhibitors (SSRIs) may be evaluated for each given case. In fact, if ever directed, the serotonergic precursor tryptophan or antidepressants SSRIs should be co-administered with an anti-epileptic drug (ideally having also mood-stabilizer or anti-impulsive effects as valproate or carbamazepine), due to the chance of a lowered epileptic threshold induced by serotonergic stimulation.
Indeed, it must be remarked that the above provided clinical considerations should not be “a priori” translated into the clinical practice in the absence of any reliable and conclusive evidence in their support or discharge, rather, we submit them to serve as potential advices to be tested by further studies on CD-ADHD comorbidity, a clinical issues still almost completely neglected by the currently available preliminary and often outdated studies imbalanced by major methodological limitations, despite the notion that CD-ADHD comorbidity may be the source of considerable sufferance and socio-economic burden for the affected ones and their caregivers.

Acknowledgments

The authors have no conflict of interest, nor financial support to state for the present independent work. The authors wish to dedicate the present work to Prof. Rocco Pollice, MD, PhD, a gifted psychiatrist whose kind manners, bright scientific and clinical skills, inspired a number of us as colleagues, friends and/or trainees before his premature departure.

References

1. Dowd B, Walker-Smith J. Samuel Gee, Aretaeus, and the coeliac affection. Br Med J. 1974; 2(5909):45-47.
2. Losowsky MS. A history of coeliac disease. Dig Dis. 2008; 26(2):112-120.
3. Bahia M, et al. Serum antigliadin antibody levels as a screening criterion before jejunal biopsy indication for celiac disease in a developing country. Braz J Med Biol Res. 2001; 34(11): 1415-1420.
4. Gasbarrini GB, et al. Coeliac disease: an old or a new disease? History of a pathology. Intern Emerg Med. 2014.
5. Nenna R, et al. The celiac iceberg: characterization of the disease in primary schoolchildren. J Pediatr Gastroenterol Nutr. 2013; 56(4):416-421.
6. Rubio-Tapia A, et al. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012; 107(10):1538-1544; quiz 1537, 1545.
7. Addolorato G, et al. Affective and psychiatric disorders in celiac disease. Dig Dis. 2008; 26(2):140-148.
8. Hadjivassiliou M, et al. Does cryptic gluten sensitivity play a part in neurological illness? Lancet. 1996; 347(8998):369-371.
9. Giordano L, et al. Celiac disease-related antibodies in Italian children with epilepsy. Pediatr Neurol. 2009; 41(1):34-36.
10. Lozano Gutierrez F, et al. [Psychosis, epilepsy and celiac disease]. Med Clin. (Barc) 2000; 114(3):118.
11. Grzadzinski R, et al. Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? J Autism Dev Disord. 2011; 41(9):1178-1191.
12. Rashtak S, et al. Serology of celiac disease in gluten-sensitive ataxia or neuropathy: role of deamidated gliadin antibody. J Neuroimmunol. 2011; 230(1-2):130-134.
13. Smith DF, Gerdes LU. Meta-analysis on anxiety and depression in adult celiac disease. Acta Psychiatr Scand. 2012; 125(3):189-193.
14. Carta MG, et al. Recurrent brief depression in celiac disease. J Psychosom Res. 2003; 55(6):573-574.
15. Niederhofer H, Pittschieler K. A preliminary investigation of ADHD symptoms in persons with celiac disease. J Atten Disord. 2006; 10(2):200-204.
16. Nikpour S. Neurological manifestations, diagnosis, and treatment of celiac disease: A comprehensive review. Iran J Neurol. 2012; 11(2):59-64.
17. Hallert C, Astrom J. Psychic disturbances in adult coeliac disease. II. Psychological findings. Scand J Gastroenterol. 1982; 17(1):21-24.
18. Hallert C, Derefeldt T. Psychic disturbances in adult coeliac disease. I. Clinical observations. Scand J Gastroenterol. 1982; 17(1):17-19.
19. Curran S, et al. Hypescheme: an operational criteria checklist and minimum data set for molecular genetic studies of attention deficit and hyperactivity disorders. Am J Med Genet. 2000; 96(3):244-250.
20. APA ed. Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV). ed. A.P. Association. 1994; Washington DC, USA.
21. APA ed. Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-V). ed. A.P. Association. 2013; Washington DC, USA.
22. Ruggieri M, et al. Low prevalence of neurologic and psychiatric manifestations in children with gluten sensitivity. J Pediatr. 2008; 152(2):244-249.
23. Gungor S, et al. Frequency of celiac disease in attention-deficit/hyperactivity disorder. J Pediatr Gastroenterol Nutr. 2013; 56(2):211-214.
24. Albers JW, Nostrant TT, Riggs JE. Neurologic manifestations of gastrointestinal disease. Neurol Clin. 1989; 7(3):525-548.

25. Lahat E, et al. Prevalence of celiac antibodies in children with neurologic disorders. Pediatr Neurol. 2000; 22(5):393-396.
26. Niederhofer H. Association of attention-deficit/hyperactivity disorder and celiac disease: a brief report. Prim Care Companion CNS Disord. 2011; 13(3).
27. Guevara JP, Stein MT. Evidence based management of attention deficit hyperactivity disorder. BMJ. 2001; 323(7323): 1232-1235.
28. Basso MS, et al. Is the screening for celiac disease useful in anorexia nervosa? Eur J Pediatr. 2013; 172(2):261-263.
29. Van Praag HM. Anxiety and increased aggression as pacemakers of depression. Acta Psychiatr Scand Suppl. 1998; 393:81-88.
30. Oades RD, et al. The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/hyperactivity disorder (ADHD): Findings from a family-based association test (FBAT) analysis. Behav Brain Funct. 2008; 4:48.
31. Watkins CC, Sawa A, Pomper MG. Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. Transl Psychiatry. 2014; 4:e350.
32. Rege S, Hodgkinson SJ. Immune dysregulation and autoimmunity in bipolar disorder: Synthesis of the evidence and its clinical application. Aust N Z J Psychiatry. 2013; 47(12): 1136-1151.
33. Sharma A. Immune response also connects autism and epilepsy. Nat Med. 2011; 17(8):922.
34. Severance EG, et al. Immune activation by casein dietary antigens in bipolar disorder. Bipolar Disord. 2010; 12(8):834-842.
35. Di Nicola M, et al. Adult attention-deficit/hyperactivity disorder in major depressed and bipolar subjects: role of personality traits and clinical implications. Eur Arch Psychiatry Clin Neurosci. 2013.
36. APA ed. DSM-V: Diagnostic and Statistical Manual for Mental Disorders, Fifth edition. ed. A.P. Association. 2013; Washington DC.
37. O'Dowd C. ADHD guidelines - flaws in the literature and the need to scrutinise the evidence. Aust Fam Physician. 2012; 41(3):87-88.