COELIAC DISEASE: AN UNDER-RECOGNISED DISORDER

Lia Goltstein[1] and David Bandell[2]

[1] Master Student Medicine, Radboud university medical center, Nijmegen, the Netherlands.
[2] Medical graduate from Radboud university medical centre, Nijmegen, the Netherlands.

Perspectives

Patient A, a 56-year-old man, was admitted to the Department of Neurology because he had trouble walking in a straight line and was talking with slurred speech. He was diagnosed with cerebellar ataxia (poorly coordinated movements) of which the cause remained unknown after standard diagnostic workup [1]. During the time patient A was being evaluated, patient B, a 32-year-old woman, was admitted to the Department of Gynaecology because of a miscarriage. It was her third miscarriage that year and the cause could not be found [2]. While both patients were still in the dark about the cause of their symptoms, patient C, a four-year-old child, was seen by a paediatrician. Her mother was awfully worried because her daughter was suffering from chronic diarrhoea for the past year and was severely malnourished [3]. Although these three patients initially seem to have nothing in common, they actually share a lifelong illness. In the end, they were all diagnosed with coeliac disease [1, 2, 3].

Introduction

When the diet of humans changed from fruits, nuts and the occasional piece of meat to cultivated crops and various animals, new diseases arose. Novel antigens were introduced to mankind, which led to food intolerances. This new diet included antigens of cow milk protein, potatoes and gluten. This last protein is associated with coeliac disease (CD) [3]. Aretaeus of Cappadocia, a Greek physician of the first century AD, came up with the name. It is based on the Greek word "*koelia*" which means abdomen. Aretaeus called all individuals whose stomachs were unable to properly absorb food, coeliacs. In other words, coeliacs were all individuals who suffered from diarrhoea and malnutrition [4]. At the end of the 19th century, paediatricians Samuel Gee and Sidney Haas were able to link these symptoms to a specific diet. They published articles in which patients who suffered from CD were cured by a strict diet of Dutch mussels or bananas [5]. Although both were close to finding the culprit of this disease, the Dutch paediatrician Willem Dicke was the one who eventually figured out it was gluten in the year 1953. The discovery was made when professor Dicke found a paradoxical improvement in a subset of malnourished children in times of bread shortages during World War II. These children experienced a clinical decline and return of symptoms when Allied planes later dropped bread into the Netherlands [6]. His research is still considered revolutionary. Every five years, the golden Dicke-medallion is handed to gastrointestinal doctors with fundamental projects in the Netherlands [7].

In recent years, gluten intolerance has become a hype as many self-diagnosed individuals have embraced a gluten-free lifestyle. These individuals are not all "coeliacs" as the ancient Greeks would say [4]. They suffer from various symptoms ranging from fatigue to having a few extra pounds [8]. In the United States of America, one in five adults completely avoid gluten. For millennials, this percentage is even higher. Only one in twenty of these gluten-avoiders are actually suffering from CD [8]. Considering these statistics, one would assume CD has been overhyped in recent years. Conflicting enough, up to 90% of individuals who suffer from CD are still undiagnosed, making it a tremendously under-recognised disorder [9]. Since this disease can have many minor and severe consequences, it is a serious issue [9]. The widespread clinical presentation and the limited knowledge of healthcare providers may be the cause of underdiagnosis [10]. In this article, an extensive outline of CD is given with the aim to expand the readers' knowledge of this complicated disease.

Pathophysiology and aetiology of CD

Contrary to what most believe, CD is not an allergy, but an autoimmune disease with a very clear environmental trigger. Allergies are caused by the hypersensitivity of the immune system to harmless substances in the environment, whereas an autoimmune disease is an immune response to the body's own tissue [11, 12]. The environmental trigger for CD is gluten. Gluten is the main storage protein of wheat grains and consists of a mixture of hundreds of related but distinct proteins [13].

Gliadin (a digestive product of gluten) is thought to be directly and indirectly toxic to the cells of patients with CD [12, 13]. The human body forms both antibodies against gliadin and antibodies against the patient's own antigens, mainly tissue transglutaminase [12]. The forming of antibodies against the body's own antigens is the definition of an autoimmune disorder and the main pathway of disease in CD [11, 12]. The different pathways lead to an inflammation cascade which results in apoptosis (regulated cell death) and atrophy (loss of cells) of the intestinal wall of the patient [12]. In the small intestines, this means that villous atrophy occurs. The intestinal villi are small, finger-like projections that increase the internal surface area of the intestinal walls, resulting in a greater surface area available for absorption [12]. Therefore, loss of surface area causes malabsorption [12].

Classical and non-classical CD

The original CD population, as described by Dicke, mainly consisted of children with both symptoms of maldigestion and diarrhoea [6]. Maldigestion often leads to malnutrition, which causes insufficient weight gain in children or inappropriate weight loss, known as failure to thrive. Diarrhoea in patients with CD is often foul-smelling and greasy due to an excess of fat. This fatty diarrhoea is called steatorrhoea [14]. These symptoms are caused by the inability of the small intestines to break down and take up nutrition, including fat, due to the villous atrophy [12].

In the past few decades we have learned that CD is most often not as classic as once thought. Only six percent of all individuals with CD resemble the original paediatric patients [15]. The World Gastroenterology Organisation therefore distinguishes two forms of

CD: The 'classical' and 'non-classical' CD. As suggested by the name, the 94% of CD patients in the latter group have extremely heterogeneous symptoms, including less specific gastrointestinal (GI) symptoms, such as abdominal pain and altered bowel habits, and extraintestinal symptoms, which will be discussed in the next paragraph [15]. Unlike 'classical' CD, which presents at young age, patients with 'non-classical' CD most often develop symptoms in their fourth or fifth decade. It is therefore also described as adult CD [15]. The discovery of these non-classical CD patients made it a relatively common disease, affecting one percent of the population [17].

Extraintestinal symptoms of CD

As mentioned in the last paragraph, patients with non-classical CD have heterogeneous symptoms which are not limited to the gastrointestinal tract. This is because CD is actually a multisystemic disease, to which more than a hundred different symptoms are linked from various organ systems. [16].

About 50% of CD patients present with extraintestinal symptoms that can be divided into neuropsychiatric symptoms and other extraintestinal symptoms [18]. The most characteristic example of extraintestinal CD is dermatitis herpetiformis (DH). This blistering skin disease is characterised by an intense itching and burning rash on the extremities. This disease is exclusively caused by a gluten-sensitive enteropathy, even though DH patients often do not have GI symptoms [19].

The most frequent extraintestinal presentation of CD is anaemia. This appears to be mainly due to iron deficiency, since iron is absorbed in the proximal duodenum. The prevalence of CD in patients with iron deficiency anaemia is believed to be six percent for individuals without gastrointestinal symptoms and up to fifteen percent for patients who do have these symptoms [20]. Therefore, anaemia guidelines recommend to screen for CD, but there are still many individuals who are treated in vain with iron tablets [21]. Other deficiency syndromes, such as fat-soluble vitamin deficiencies, can also be the first and only symptom of CD [22].

Extraintestinal presentations of CD also includes disorders in fertility and pregnancy. Untreated CD is linked to significantly delayed puberty in both genders, earlier menopause and an increased prevalence of secondary amenorrhea (no menstruation for at least three months) [23]. Females with CD can also have an increased risk of miscarriage [23]. In males with CD the sperm quality may be reduced [23].

Another important category of symptoms associated with CD are neuropsychiatric disorders [24, 25]. Over 50% of patients with CD are affected by or develop peripheral neuropathy [24]. Other associated neurological symptoms are: ataxia, seizure disorder, migraine and dementia [24]. Depression and anxiety are examples of psychiatric disorders often linked to CD, as an appropriate treatment of the underlying CD can resolve these symptoms [25]. In Figure 1 the different categories of CD patients are displayed.

As opposed to GI-symptoms, the aetiology of these extraintestinal symptoms remains unclear in most cases. Some CD-associated symptoms share an immune-mediated aetiology. DH is for example known to be an autoimmune disease, thought to be caused by the same autoantigen as CD, called tissue transglutaminase. Certain neuropsychiatric symptoms are also thought to be caused by this autoantigen, as mouse models have shown that tissue transglutaminase antibodies cause ataxia-like deficits [26]. Other CD-associated symptoms are caused by micronutrient malabsorption, such as anaemia. However, it is likely that other elements are also involved [19, 27].

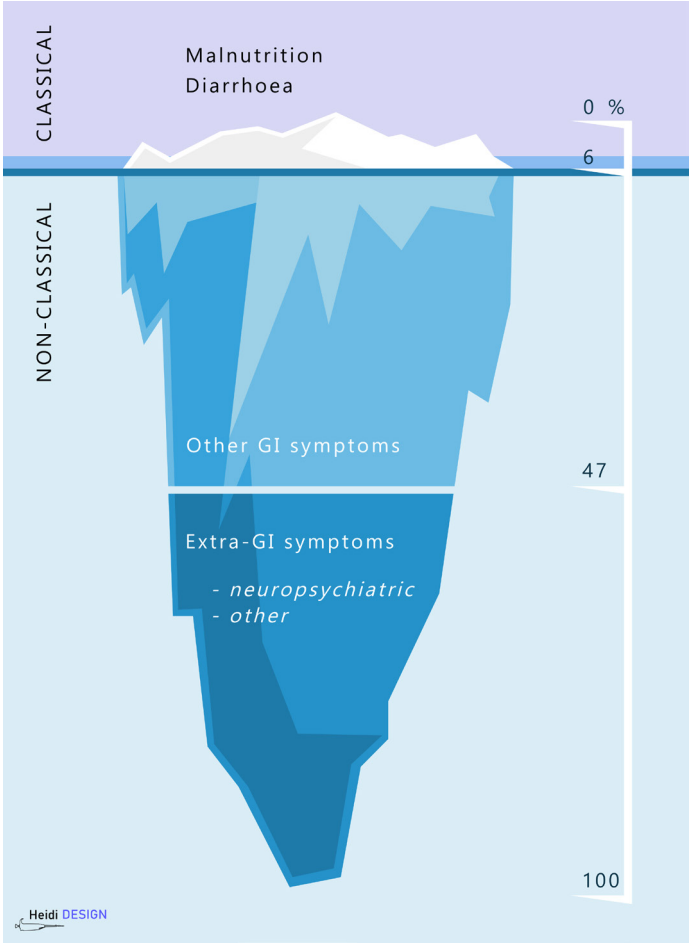

Figure 1: Presenting symptoms of coeliac disease (CD).
This figure illustrates that only six percent of individuals with CD present with the classic symptoms linked to this disease, which are malnutrition and diarrhoea. The other 94% of individuals with CD present with other symptoms, of which 50% is also gastrointestinal. The other 50% consists of extraintestinal symptoms, which can be divided into neuropsychiatric symptoms and various other symptoms.

Diagnosis

As mentioned before, up to 90% of individuals with CD remain undiagnosed [18]. Diagnosing CD is a challenging process that differs in local guidelines [29, 30]. When it comes to diagnosis of CD there are two main groups of patients, those with clinical symptoms of CD and those without symptoms, but a positive family history [18, 29]. Firstly, the patients are screened using serological or genetical testing (see Box 1) [29]. Secondly, the diagnosis is affirmed, by analysing endoscopically retrieved biopsies matching CD under a microscope. This is invasive for patients [29]. Screening is advised by the Coeliac Disease Foundation for all individuals older than three with symptoms of CD, first-degree relatives of patients with CD and any individual with an associated autoimmune disorder. The options regarding screening consist of multiple serological and genetic tests.

Because of shortcomings of both serological and genetic testing, a biopsy of the small intestine is the only way to confirm the diagnosis, even though this does require invasive diagnostic testing. Samples are collected from the duodenal wall for pathological testing using gastroduodenal endoscopy [29] .

Patients' resistance to gastroduodenal endoscopy, age or difficulty screening due to gluten-free diet requires the physicians to be flexible

Serology [18, 29-31]
The tissue transglutaminase IgA antibody and IgA antibody test (tTG-IgA test) is the first step in testing for CD for those who are eating a gluten-containing diet. The tTG-IgA test has a sensitivity of 98% and a specificity of 95%. Total IgA antibodies are tested to rule out that a patient is IgA-deficient, rendering the tTG-IgA test unreliable.

Other serological tests include IgA and IgE endomysial antibody and deamidated gliadin peptide (IgA and IgG). While these are being used for testing individuals with low IgA antibody levels and to double-check for potential false positives or false negatives. They do not offer much in making final diagnoses as sensitivity and specificity are low, and due to this double false negative or double false positive testing is still possible. Furthermore, a single negative serological screening is not enough to rule out CD later in life, as the disease can develop after prolonged exposure to gluten.

Genetics [18, 29, 30]
Genetic testing is based on testing for the *HLA DQ2* and *DQ8* genes. Testing negative for both these genes excludes the possibility of having or developing CD. This is irrespective of gluten-containing diet and age. The genetic testing cannot be used to diagnose CD because if you carry *HLA DQ2* and/or *DQ8*, your risk of developing CD is still "only" three percent. Up to 30% of the population tests positive for these genes. However, with a negative test for the *HLA DQ2* and *DQ8* genes, CD can be excluded, making the test a viable option for screening patients with family members with CD.

Box 1: In-depth information about serology and genetics in CD.

with diagnosing CD. It sometimes results in using an improvement due to a gluten-free diet (GFD) as a diagnostic tool. However, this introduces false positive diagnosis due to the placebo effect [29]. Recent evidence suggests that endoscopy is not obliged if clinical presentation and serological testing align, making the diagnosis very likely [30, 32].

Treatment

Currently, the only treatment of CD is the lifelong adherence to a GFD [33]. However, over half of patients with CD do not achieve an excellent or good level of adherence. Patients explain that the diet is psychologically and practically challenging, as many foods contain gluten and gluten free food is more expensive [34]. A recent study found that the of burden of following a GFD is comparable to that of dialysis in end-stage renal disease [35].

Around 30 to 50% of patients do not respond well to this treatment, often due to diet mistakes [36]. There is also a small group of patients who do not respond to treatment, even when the GFD is precisely followed. This is called non-responsive CD or refractory CD and it is defined as persisting symptoms of CD, elevated CD antibodies or small intestinal damage (seen during endoscopy) after following a strict GFD for 6 to 12 months. It is important to properly check the diets of non-responsive patients and to exclude alternative diagnoses that could have caused the symptoms to be falsely linked to CD [29, 36].

Since a GFD is hard to follow for various reasons and not all patients respond well to it, newer therapeutic modalities are being studied in clinical trials. An example is an antibody fragment that blocks the invading gluten molecule without triggering the immune system [37]. However, this is still in an experimental stage, therefore, at this moment CD patients still have to follow a GFD.

Conclusion

CD is a common disorder, since it affects one percent of the population. The classical presentation of this disease is maldigestion and diarrhoea, which starts at a young age. However, over 90% of patients present with different symptoms and at various ages. These symptoms consist of less specific gastrointestinal symptoms, such as abdominal pain. In addition, they consist of more than a 100 extraintestinal symptoms, such as DH, anaemia, fertility problems and certain neuropsychiatric disorders. This heterogeneity in presentation explains why up to 96% of individuals with CD remain undiagnosed, making it a tremendously under-recognised disorder. Since CD has a major impact on the quality of life, it is important that doctors become more aware of the fact that CD is a multisystemic disease with a broad variety in presentation and of the diagnostic and treatment options of this disorder as outlined in this article.

Acknowledgements

RAMS would like to thank dr. F. Berden, from the Department of Gastroenterology and Hepatology of Radboud university medical center, Nijmegen, the Netherlands and of Jeroen Bosch medical center, Den Bosch, the Netherlands for providing the authors of this article with insight into the subject and providing feedback on this article.

References

1. Casella, G et al. Cerebellar Ataxia, Celiac Disease and Non-Celiac Gluten Sensitivity. Giovanni Casella. Archives of Neuroscience. 4(2): e44187 (2017)
2. Eliakim, R et al. Celiac disease: Fertility and pregnancy. Gynaecologic and Obstetric Investigation. 51:3-7 (2001)
3. Mocan, O et al. The broad spectrum of celiac disease and gluten sensitive enteropathy. Clujul Medical. 89(3): 335–342 (2016)
4. Gasbarrini, G et al. Wheat-related disorders: A broad spectrum of'evolving' diseases. United European Gastroenterology Journal. 2(4):254-62 (2014)
5. Losowsky, M et al. A history of coeliac disease. Digestive Diseases. 26(2):112-20 (2008)
6. Berge-Henegouwen, G et al. Pioneer in the gluten free diet: Willem-Karel Dicke 1905-1962, over 50 years of gluten free diet. Gut. 34(11): 1473–1475 (1993)
7. NVGE Nederlandse vereniging voor gastro-enterologie (2019). Dicke medaille en ereleden. Retrieved from: https://www.nvge.nl/organisatie/dicke-medaille-en-ereleden (Accessed: 05-07-2019).
8. Wu, K (2018, Apr 12). You Asked: What's the deal with gluten? Harvard University, the graduate School of Arts and Sciences, Blogs. Retrieved from: http://sitn.hms.harvard.edu/flash/2018/asked-whats-deal-gluten/ (Accessed: 06-07-2019)
9. Goddard, C et al. Complications of coeliac disease: are all patients at risk? Postgraduate Medical Journal. 82(973): 705–712 (2006)
10. Lanzarotto, F et al. Is under diagnosis of celiac disease compounded by mismanagement in the primary care setting? A survey in the Italian Province of Brescia. Minerva Gastroenterologica e Dietologica. 50(4):283-8 (2004)
11. McConnell, T. H. et al. The Nature of Disease: Pathology for the Health Professions. Baltimore, MD: Lippincott Williams & Wilkins. p. 159. ISBN 978-0-7817-5317-3. (2007)
12. Barker JM, Liu E. Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions. Adv Pediatr. 55:349–365 (2008)
13. Biesiekierski, J. R. What is gluten?. Journal of Gastroenterology and Hepatology, 32: 78– 81 (2017)
14. Davidson, L et al. Incidence of the sprue syndrome; with some observations on the natural history. The British Medical Journal. 1:1157-61 (1950)
15. Mooney, P et al. Coeliac disease. The British Medical Journal. 348:g1561

(2014)
16. Kochhar, G et al. Celiac disease: Managing a multisystem disorder. Cleveland Clinical Journal of Medicine. 83(3):217-27 (2016)
17. Ludvigsson, J et al. Increasing incidence of celiac disease in a North American population. American Journal of Gastroenterology. 108:818-24 (2013)
18. Gujral, N et al. Celiac disease: Prevalence, diagnosis, pathogenesis and treatment. World Journal of Gastroenterology. 14; 18(42): 6036–6059 (2012)
19. Clarindo, M et al. Dermatitis herpetiformis: pathophysiology, clinical presentation, diagnosis and treatment. An Bras Dermatol. 89(6):865-75 (2014)
20. Freeman, H et al. Iron deficiency anemia in celiac disease. World Journal of Gastroenterology. 21(31):9233-8 (2015)
21. Goddard, A et al. Guidelines for the management of iron deficiency anaemia. Gut. 60(10):1309-16 (2011)
22. Wierdsma, N et al. Vitamin and Mineral Deficiencies Are Highly Prevalent in Newly Diagnosed Celiac Disease Patients. Nutrients. 5(10): 3975–3992 (2013)
23. Freeman, H et al. Reproductive changes associated with celiac disease. World J Gastroenterol. 16(46): 5810–5814 (2010)
24. Nikpour, S et al. Neurological manifestations, diagnosis, and treatment of celiac disease: A comprehensive review. Iran Journal of Neurology. 11(2): 59–64 (2012)
25. Jackson, J et al. Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity. Psychiatric Quarterly. 83(1):91-102 (2012)
26. Boscolo, S et al. Anti-transglutaminase antibodies cause ataxia in mice. PLoS One. 2010 Mar 15; 5(3):e9698.
27. Singh, P et al. Non-classical Celiac Disease: Often Missed. International Journal of Celiac Disease 2(3):76-85 (2014)
28. Lewis, Diana et al. Testing for coeliac disease. Australian prescriber vol. 40,3 (2017)
29. Richtlijn Coeliakie en Dermatitis Herpetiformis (Guideline Coeliac Disease and Dermatitis Herpetiformis). Nederlandse Vereniging Van Maag-, Darm-, en Leverziekten (Dutch Society of Gastroenterology); 2008.
30. Rubio-Tapia, A et al. ACG clinical guidelines: diagnosis and management of celiac disease. American Journal of Gastroenterology. 108(5):656-76 (2013)
31. Rostom, A et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology. :S38-46 (2005)
32. Shomaf, M et al. Is the Diagnosis of Celiac Disease Possible Without Intestinal Biopsy? Balkan Med J. 2017 Jul; 34(4): 313–317.
33. Oberhuber G. Histopathology of celiac disease. Biomedicine & Pharmacotherapy. 54(7):368-372 (2000)
34. Raipoot P, Sharma A et al. Adherence to gluten-free diet and barriers to adherence in patients with celiac disease. Indian J Gastroenterol. 2015 Sep;34(5):380-6.
35. Shah, S et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. American Journal of Gastroenterology. 109(9):1304-11 (2014)
36. Laurikka, P et al. Gastrointestinal Symptoms in Celiac Disease Patients on a Long-Term Gluten-Free Diet. Nutrients. 8(7). pii: E429 (2016)
37. Vienna University of Technology (2018, Sept 24). A new remedy for celiac disease. BMC Biotechnology. Retrieved from: https://medicalxpress.com/news/2018-09-remedy-celiac-disease.html (Accessed 07-07-2019)

CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
B. Kidneys

The dorsal side of the kidneys is adjacent to the dorsal abdominal wall. The anterior side has contact to several other organs. Together with the adrenal glands, the kidneys are separated from the other abdominal organs by the parietal peritoneum, the renal fascia and the adipose capsule.

For further reading:
Waschke, P. *Pelvis and Retroperitoneal Space* in Sobotta: Atlas of Human Anatomy, Vol. 15 (Elsevier GmbH, Germany, 2011)

During the exam, 68% of the participants answered this question correctly.

Answer question 2:
A. A first-degree family member who has prostate cancer

Risk factors for prostate cancer include advanced age, race and a family history. The first-degree relatives of men with prostate cancer have twice the risk compared to the general population. This is higher than in those diagnosed below the age of 60 years and 50% higher in monozygotic twins.

For further reading:
Yaqoob, M.M. *Kidney and urinary tract disease* in Kumar and Clark's Clinical Medicine, Vol. 9 (Elsevier Ltd, the Netherlands, 2017)

During the exam, 73% of the participants answered this question correctly.
The exam questions can be found back on page 6 in this journal.

Assembly of the clinical issues (KVS) exam

The KVS exam is assembled by the KVS-committee, where many medical specialties are represented. This committee gathers once every two weeks, and during these meetings, new questions (provided by all module coordinators) are evaluated in their appropriateness for the exam. After the exam is made by students, this committee looks extensively to the exam analysis and comments of the students. From this evaluation, it is decided what happens with these questions. Recently, the committee decided that a reaction to the student's commentary will be made available to read for all students. The final grading is then determined based on the Cohen-Schotanus formula, after which the final grades will be checked again and made public within 15 working days after the exam date.