HISTORY OF MEDICINE

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Historical development of the understanding of coeliac disease

Istorijski razvoj saznanja o celijačnoj bolesti

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Introduction

Celiac disease (CD), also known as the malabsorption syndrome or gluten-sensitive enteropathy, is an immune-mediated disorder that occurs in individuals with a genetic predisposition as a result of gluten consumption. Gluten is found in wheat, rye, barley, and oats [1]. CD occurs in about 1% of the total population. The prevalence of CD varies from country to country (0.3% in Germany, 0.7% in Italy, 0.8% in Sweden, 2.4% in Finland, and 0.7%–0.8% in the USA). It is a lifelong disease that is associated with reduced quality of life and high-risk comorbidity and death [2, 3]. Differences in the incidence of the disease depend not only on genetic factors and diet but also on the availability of modern diagnostic technology. The disease occurs in children and adults, but its typical form is more frequent in early life, between the 7th and 24th month [4]. The diagnosis is based on small intestinal biopsy, tissue transglutaminase (tTG) antigen test, and human leukocyte antigen markers (HLA DQ2 and HLA DQ8) [5]. The mainstay of treatment is a gluten-free diet (GFD) [5–7]. Appropriately diagnosed and treated patients have a reasonable chance of living a normal life. However, about 85% of people with CD are asymptomatic, although serological parameters and histopathological findings in the small bowel mucosa might reveal increased intraepithelial lymphocyte infiltration [8, 9].

Earliest descriptions

CD has been known since the ancient times. For years, it was exclusively considered a disease of the Old Continent because it was found that it primarily occurred in the white population, especially in certain groups, while it occurred less frequently in people of other races [10]. Today, it is known that CD is present in different groups of people, and it is widespread throughout the world [11]. A long time ago, humans lived in hunter-gatherer groups, and their diet consisted of fruits, drupes, roots, and occasional meat [10]. In the New Stone Age (Neolithic), humans first started to domesticate animals, cultivate the land, and grow crops for human consumption. The way of life and their former diet had been replaced during the period of the agricultural revolution. Hunting and gathering fruits were replaced by growing crops and animals, which challenged the human gastrointestinal tract to adapt to a new diet and a new, previously unknown, antigenic stimulation [10, 12, 13].

The ancient Greek physician Aretaeus of Cappadocia gave the first known description of the disease in the first century, anno domini (AD). Aretaeus worked as a physician during the reign of Nero. He most probably studied in Alexandria and lived and worked in Alexandria and Rome [13]. He described a disease encompassing the disturbance of “pepsis” and “anadosis”, which could be loosely translated into modern terms as digestion and absorption [14]. He suggested that it was a chronic disease in adults, manifested

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by general debility, dehydration, generalized wasting, the passage of undigested food, and malodorous white clay-like stools. The disease was not transmitted and was prone to recur. Aretaeus believed that the problem was a lack of heat in the stomach that was essential for digestion. He also believed that this was a disease of older people, more common in women, and that it never occurred in children. He believed that the disease was not chronic and even thought that the "consumption of large amounts of cold water after a strong thirst" might be a possible cause. He also emphasized the importance of a modified diet but did not give any details of the diet composition [14]. In his work, Aretaeus also described a single patient who was pale, thin, weak, incapable of working, and had abdominal pain. Diarrheal stools were whitish, malodorous, and followed by flatulence.

CD in the XIX century

After Aretaeus, no tangible progress had been made in understanding CD until the modern era. Here, Francis Adams ought to be credited for keeping the scientific society aware of Aretaeus's work in his lecture given at the Sydenham Society in London in 1856 [14]. The first detailed description of CD dates back to 1887 and is associated with the English paediatrician Samuel Gee.

Samuel Gee [15] (1839–1911) gained a sufficient reading skill in ancient Greek. He gave a modern description of the condition in a lecture at St. Bartholomew's Hospital and Hospital for Sick Children, Great Ormond Street, London. A year later, the lecture was published in the reports of his hospital. It represents the first modern clinical description of CD, along with the theory that highlights the importance of the diet in patients with CD. This work is considered the first comprehensive description of the condition and is usually referred to in all subsequent publications [16]. Gee [15] further investigated the disease in his research and acknowledged the previously existing term coined after the Greek word *coeliacus*, loosely translated as the abdominal cavity. Thus, it was emphasized that a large stomach, along with very thin arms and legs, dominated the condition, and disorder in digestion was established as a basic problem. Gee [15] described patients' stools as heavy, greasy, and extremely malodorous, i.e. severe steatorrhea and cachexia were present due to poor appetite in persons of all ages. Contrary to Aretaeus, Gee included children, mainly those aged 1 to 5 years. Unfortunately, most of these children died soon due to severe cachexia. After their death, Gee examined their intestines, but, as the wall of the small intestine rapidly decays after death, he failed to find the cause of CD [10].

CD in the first half of the XX century

In the early 20th century, the diagnosis of CD was based on clinical features, distinctive appearance of stools, and typical age at which the disease occurred [16–18]. It was not until the beginning of the XX century that it became clear that the cause of CD was a disorder of absorption in the small intestine [11]. Gee [15] believed that children suffering from the disease could be cured by a dietary regime, so he recommended avoiding starch-rich foods. He forbade the intake of milk, rice, fruit, and vegetables. He particularly recommended the intake of shellfish, but almost no child could bear this type of diet for a longer period of time [11].

Christian Archibald Herter, an American physician, introduced a new name for this disease in 1908 – intestinal infantilism – considering that an intestinal disorder was the cause of the disease [16]. In 1908, Herter [17] wrote a book on children with CD titled "Intestinal Infantilism". The author noted that the growth of these children was slow and they had better fat tolerance compared with carbohydrates, while the disease was described as severe insufficiency of digestion. In 1924, Haas and Haas [18] promoted the positive effect of a banana diet for treating CD. During their career, they treated over 600 patients with CD. In 1951, their son, Dr. Merrill P. Haas, joined them and published the medical textbook – "The Management of Coeliac Disease". Until 1940, the phosphorylation of fats and insufficient secretion of digestive juices and enzymes (particularly pancreatic) were thought to be the possible causes of CD disturbances. On the other hand, it was also thought that the disease might be a result of a variety of conditions, therefore, celiac syndrome was mentioned [19]. During this period, the disease was treated by trying various diets. In England, Leonard Parsons [20] advised the exclusion of fats from the diet, while carbohydrates were excluded on the recommendation of John Howland [21] in the USA.

CD in the second half of the XX century

In his dissertation published in 1950, the Dutch paediatrician Dr. Willem Dicke [22] observed the exclusion of wheat from children's diet. He concluded that it led to dramatic improvement, while the disease was getting worse once the wheat was included again. This observation was the result of a natural experiment conducted during wartime when wheat was scarce. This was later confirmed under laboratory conditions by a paediatrician Charlotte Anderson who discovered that wheat gluten caused severe symptoms. The medical team from Birmingham, Anderson et al. [23], concluded in 1952 that gluten was a necessary factor for the development of damage to the mucous membrane of the small intestine in patients with CD.

During the 1950s, the diagnosis was based on the characteristics of malabsorption and clinical observations. In the mid-50s, Shiner [24], in England, and Royer [25], in Argentina, independently of one another, constructed the instruments for peroral small intestine mucosal biopsy. The application of these devices allowed Margot Shiner [26] in 1957 to discover that children with CD had villous atrophy in the small intestine. Intestinal biopsy has become the gold standard for CD ever since.

It was not until the 50s that the individual works of Wim Dicke [26] and those made in collaboration – Dicke et al. [27] – announced the discovery of gluten and led to major progress in the knowledge and treatment of the disease. Their

work, however, did not win much understanding and acceptance by the general medical community of the time and was published with a delay of several years.

The implementation of peroral aspiration biopsy of the small intestinal mucosa using a capsule developed by Crosby and Kugler [28] enabled subsequent progress in the histopathological examinations since it made the procedure easier and more comfortable for the patients. In their statement published in 1990, The European Society for Paediatric Gastroenterology and Nutrition (ESPGHAN) working group recommended using the biopsy capsule rather than the endoscopic biopsy in order to ensure diagnostically adequate specimens [5]. This procedure has become more and more popular and is still being further developed [29, 30].

+Paulley [31] provided the description of typical morphological changes in the small intestinal mucosa in adults in 1954, while Sakula and Shiner [32] proved these changes in children in 1957. Throughout the 1960s, other characteristics of CD were being described, while the importance of the hereditary factor in the emergence of this disease was established in 1965 [33].

Numerous methods of laboratory tests of metabolism and absorption of nutrients were developed simultaneously. The European Society for Paediatric Gastroenterology (and Nutrition – as added later – ESPGHAN) was founded in 1968 in Paris with 14 members, with Dolf Weijers as the first president because of the better cooperation, more precise classification and definition of malabsorption, and diagnosis and treatment of CD. According to the first ESPGHAN diagnostic criteria adopted in Interlaken (Switzerland) in 1969, besides the initial intestinal biopsy, it was necessary to obtain at least two additional biopsy specimens, one after 2–4 years of GFD and the other one during the 3–6 months period of reintroduction of gluten [34]. An important contribution to diagnosis was the use of a stereomicroscope which allows three-dimensional visualization and ideal preparation of the sample drawn from the small bowel mucosa for histopathological analysis. Due to the experience gained and further advances in the use of stereomicroscope, as well as the introduction of serological indicators specific to CD, the 1970 criteria were substantially supplemented and corrected at the ESPGHAN meeting in Budapest in 1989 [5].

In 1975, it was established that gluten peptides lead to a cell-mediated immune response in the small intestine [35]. HLA class II molecules present epitopes in their binding groove to CD4+ T-helper cells and activate the immune system against the gluten, resulting in a characteristic enteropathy with intraepithelial lymphocytosis, hyperplasia of the crypts, and villous destruction [36]. Later on, it was discovered that gluten-specific CD4+ T-cells could be isolated from the small intestine of CD patients but not in controls [37, 38]. Along with the cellular response, a strong B-cell response was also discovered in the form of auto-antibodies, defined as antireticulin, and then anti-endomysium to indicate a poorly defined reaction to an extracellular matrix component of the intestine [39]. In the late 1990s, it was discovered that enzyme tTG triggered these antibodies [40]. Subsequently, tTG was implicated in the deamidation of gliadin [41, 42]. In this reaction, the glutamine in gliadin is transformed into glutamic acid, thus making gluten antigen fit perfectly in the binding groove of HLA-DQ2.5 and HLA-DQ8 molecules, which results in a stronger immune response [43–45].

During this long period, CD was a common but often unrecognized disease. This is partly due to its variable clinical presentation and symptoms that range from malabsorption followed by chronic diarrhea, growth retardation in children, abdominal distention, and weight loss to nonspecific signs and symptoms such as fatigue, osteoporosis, iron deficiency, or anaemia. Serological indicators of the disease, although highly sensitive and specific, had no absolute diagnostic value. Serological tests have been generally recommended as the first step when CD is suspected in order to identify patients who should undergo intestinal biopsy [5].

CD nowadays

The diagnostic criteria for CD were proposed by ESPGHAN and published in 1990. The criteria have not been renewed for more than 20 years. During this time, the perception of CD has changed from a rather uncommon enteropathy to a common multiorgan disease with a strong genetic predisposition associated mainly with human leukocyte antigen HLA-DQ2 and HLA-DQ8. The studies of monozygotic twins found a multitude of genetic factors responsible for CD susceptibility [46]. Recently, genome-wide association studies have identified 39 non-HLA loci that also predispose CD [47]. The diagnosis of CD has also changed as a result of the availability of CD-specific antibody tests, based mainly on tTG type 2 antibodies [48]. Environmental factors have been found to play a role in the emergence of the disease at least to some extent. Infection with rotavirus has been investigated, and the results demonstrate an increased risk of CD autoimmunity in children [49]. Early feeding habits, such as the milk feeding type and breastfeeding duration, can influence the intestinal microenvironment [50], which is characterized by an increased number of intestinal Gram-negative bacteria and a lower level of Bifidobacteria in CD patients [51].

CD is now considered to be a systemic immune-mediated disorder [52–54]. Activated CD4+ T-lymphocytes produce high levels of either a T-helper 1 or a T-helper 2 pattern of pro-inflammatory cytokines, which causes a clonal expansion of plasma-cells secreting anti-gliadin and anti-tTG antibodies [55]. An increased density of CD8+ intraepithelial cells is considered a hallmark of CD [56], and tTG also enhances the gliadin-specific T-cell responses [57].

ESPGHAN summarized the scientific progress to publish the latest guidelines for the diagnosis of CD in 2012 [58]. The guidelines underline the gluten-dependent symptoms, CD-specific antibody levels, HLA markers, and specific small intestinal biopsy findings as a ground for diagnosing CD. It was also suggested that if a high antibody level is present, then performing the biopsy is not necessary. Moreover, the decline of antibody levels can be used to

confirm the diagnosis and follow the response to GFD. However, the 2012 guidelines reserve the small intestinal biopsy and gluten challenge for all uncertain cases [58]. These current guidelines are due to be comprehensively scrutinized and reevaluated.

Currently, adherence to a strict lifelong gluten-free diet is the only available treatment for CD [58]. Research performed since the beginning of the 21st century aims to explore the possibilities for developing effective therapies that could reduce the burden of GFD. Such are dietary modulation with enzyme-treated coeliac-safe wheat [59], wheat gene modulation, and bacterial fermentation [61]. Oral exogenous enzyme intake has been considered in order to reduce gluten toxicity by decreasing the immunogenicity of peptide sequences before ingestion or in the gut [62–65]. Modulation of intestinal permeability for gluten has also been investigated [66, 67]. Experimental therapies attempting to reduce immunogenicity or suppress inflammation include the restoration of oral tolerance by administering gluten peptides pretreated with enzymes secreted by Lactococcus [68], immunomodulation by helminths [69], tTG inhibitors [70, 71], HLA-DQ groove antagonists [72], and inhibitors of adhesion molecules [69]. Clinical trials have been conducted to evaluate the efficacy of a vaccine based on a set of gluten peptides [73]. However, the potential risks of immune system activation, clinical effectiveness, safety, and affordability require further investigations of the vaccine.

Conclusions and future directions

The understanding of CD has greatly improved since the first description in 1887. Intensive studying has changed many attitudes about the disease, opened a number of questions, and, thus, imposed the necessity of additional research and decision-making. Unfortunately, CD is increasingly becoming a public health problem. CD is now more widely discussed, and symptomatic patients are more easily recognized. It is very important that the environment in which the patient lives is aware of the problem and alleviates their suffering.

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