Celiac Disease: Background

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Celiac disease (CD) is known since ancient times. It was given its name by Aretaeus the Cappadocian in the first or second century A.D (Fig. 1) [1]. It was not until 1887, Samuel Gee described the disease in children [2] (Fig. 2). Later, in 1950, Willem Karel Dicke presented his thesis (Celiac Disease: investigation of harmful effects of certain types of cereal on patients with celiac disease) and the role of gluten was discovered [3].

The development of devices to obtain jejunal biopsies in children (Fig. 3) and interpreting the histology [4], the identification of serological markers [5, 6] and the association between CD and the HLA complex [7, 8] are only some of the milestones that have allowed the progress in the knowledge of pathogenesis, diagnosis and treatment of CD. Later, endoscopy replaced the use of biopsy capsules, providing the additional value of observing the macroscopic aspect of the mucosa and allowing for multiple biopsies from different locations.

CD is an autoimmune disorder characterized by enteropathy in response to intestinal exposure to gluten in genetically predisposed individuals. Just a few decades ago, it was thought to be an uncommon disease of childhood affecting predominantly European populations. It has since been shown to be present universally and can develop at any age in individuals consuming gluten-containing foods [9–11]. Furthermore, it is also now clear that CD may have variable presentation patterns ranging from no symptoms to a wide range of gastrointestinal or extra-digestive signs and symptoms. CD affects $\sim$ 1% of the global population but, despite its rising prevalence, the majority of patients remain undiagnosed [11]. Currently, most patients with suspected CD are screened serologically for antibody

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J. Amil-Dias and I. Polanco (eds.), *Advances in Celiac Disease*,
https://doi.org/10.1007/978-3-030-82401-3_1

Fig. 1 Aretaeus of Cappadocia

Fig. 2 Special edition of envelope and stamps on the occasion of the Samuel Gee symposium (London, 1988, organized by John Walker-Smith)

positivity, in particular for IgA antibodies to tissue transglutaminase 2 (tTG) and antiendomysial (EMA) IgA antibodies [9]. As these serological markers are not 100% specific for detecting intestinal lesions compatible with CD, positive celiac serology is confirmed by duodenal biopsies demonstrating the hallmark pathological changes of mucosal remodelling, such as villous atrophy, crypt hyperplasia and intraepitelial lymphocytosis [12].

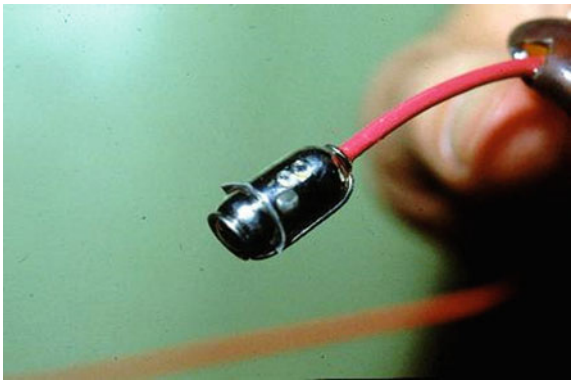

Fig. 3 Paediatric Crosby capsule with tube passed through a pacifier for infants

In 1969 in Interlaken, during the annual meeting of the then called ESPGAN (European Society for Paediatric Gastroenterology and Nutrition), strict diagnostic criteria for the diagnosis of celiac disease in the paediatric population were established for the first time. These were called the "Interlaken criteria (1969)", also known as the "three-biopsy rule" [13]. In fact, these criteria established that it was mandatory to demonstrate a typical intestinal lesion (hyperplasic jejunal villous atrophy) while the patient was on a gluten-containing diet, followed by complete histological recovery after removing gluten from the diet and subsequent histologic damage upon gluten re-exposure (challenge test). The demand for the three biopsies aimed at differentiating CD from other frequent causes of enteropathy and to demonstrate the permanent nature of the intolerance to gluten.

The wide application of these criteria by paediatric gastroenterologists in the subsequent years allowed to accumulate large experience. The additional result from relevant multicentre studies and the identification of a biological parameter—antigliadin antibodies (AGA)—as a marker for active CD led to a revision of these criteria 20 years later [14]. According to these, a single biopsy might be enough fora solid diagnosis of CD. Additional biopsies would only be needed in cases that were classified as CD without previous biopsy or the clinical response to gluten elimination was unclear.

The identification of more specific antibodies—anti-transglutaminase IgA (tTG IgA)—allowed further refinement in the diagnostic criteria. In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published new guidelines for the diagnosis of CD challenging the wide necessity for duodenal biopsies in paediatric patients [15]. It was then suggested that anti-tTG IgA antibody titre greater than 10 times the upper limit of normal (ULN), in combination with a positive EMA antibody test and compatible human leucocyte antigen (HLA) genotype, is sufficient to support the diagnosis of CD in symptomatic individuals. This eliminated the need for endoscopy and its associated costs/risks in selected paediatric patients.

The recent 2020 guidelines removed the requirement for the presence of symptoms and HLA testing in the diagnostic pathway [16]. This underscores the

specificity of a serology-based or 'no-biopsy' approach for the diagnosis of paediatric CD.

Studies have evaluated whether this strategy can be applied in symptomatic adult patients [17–27]. These studies have suggested that tTG levels of $\geq$ 10 $\times$ ULN could be predictive of CD in adults, and the recently published Finnish national guidelines for the diagnosis of CD have incorporated this diagnostic pathway into their practice (Working group appointed by the Finnish Medical Society Duodecim and the Finnish Gastroenterology Society, Celiac disease. Current care guidelines, 2018. Available at https://www.kaypahoito.fi/en/ccs00086). However, this approach has not been widely adopted into adult clinical practice or guidelines [28].

The clinical spectrum of celiac disease is wide, including cases with either classical intestinal (e.g. chronic diarrhoea, weight loss) or extraintestinal (e.g. anaemia, osteoporosis, neurological disturbances) features, as well as silent forms that are occasionally discovered because of serological screening [29, 30].

Clinical features of CD differ considerably depending on the age at presentation. Intestinal symptoms and failure to thrive are common in children diagnosed within the first years of life. Presentation of the disease later in childhood is characterized by the prevalence of extraintestinal signs, among which are short stature, delayed puberty, anaemia, enamel hypoplasia, osteopenia or bilateral occipital calcifications, related to the presence of gluten in the diet. In adults, all the above signs and symptoms may occur as well as osteoporosis and infertility [31, 32]. The broad spectrum of symptoms contributes to the large proportion of undiagnosed cases found in screening-studies.

Celiac disease is the only known treatable autoimmune disease, provided that a correct diagnosis is achieved and a strict, lifelong gluten-free diet is implemented, as this has become the cornerstone of the management of CD patients and must be recommended for life in both, symptomatic and asymptomatic individuals [33].

Implementation of a GFD should be monitored by a dietician, in order to ensure nutritional adequacy and prevent potential risks including micronutrient deficiencies, high fat, sugar and salt intake [34–37].

Family members of CD patients or those suffering from another immune-mediated disease are at higher risk of developing CD. Unrecognized and therefore untreated CD patients have a greater risk of developing associated complications or other immune-mediated diseases (e.g. type 1 diabetes, autoimmune hepatitis or thyroid disease) [38]. The antibodies used as markers for CD have a relatively high sensitivity and specificity, but those with mild lesions, partial villous atrophy, or children younger than 2 years may be missed by these tests [39, 40], so careful clinical judgement by a paediatric gastroenterologist is needed to evaluate all possible patients.

There is ongoing investigation in all fields of aetiology, pathogenesis, genetics and additional therapeutic options in this fascinating unique example of controllable auto-immune disease. This book aims at providing the reader with an updated overview of current status and future prospects in Celiac Disease.

Conflicts of Interest: The authors declare no conflict of interest.

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