Early diagnosis and management of celiac disease in childhood

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated systemic disorder elicited by the ingestion of gluten containing cereals (among others wheat, rye and barley) from the normal diet in genetically susceptible individuals. CD is characterised by a variable combination of gluten-dependent clinical manifestations, CD specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy (1). CD may present with a large variety of nonspecific signs and symptoms. It is important to diagnose CD not only in children with obvious gastrointestinal symptoms but also in children with a less clear clinical picture (or without complaints) because the disease may have negative health consequences. However, one of the greatest challenges in childhood is to diagnose the disease timely and to manage it adequately.

Epidemiology

The genotypes HLA-DQ2 or HLA-DQ8 coded by chromosome 6, present in 40% of the general population, is necessary but not sufficient for CD to develop. The prevalence of CD has doubled in the past 50 years and currently affects about 1% of the world's population (2-7). Despite the increasing prevalence of CD, the rate of diagnosis has increased more slowly. The prevalence of undiagnosed CD remains substantial (5, 8-10). Because of the multitude of symptoms associated with CD, it is difficult to diagnose promptly and accurately. In addition, the clinical manifestation of CD has changed dramatically in the last decades from symptoms of malabsorption in childhood to milder manifestations or may even have no gastro-intestinal problems at all. Extra intestinal manifestations are more often presented at the time of diagnosis. Patients with atypical or nonspecific symptoms often report a delay in diagnosis of CD that may last for years (11) or even worse, CD remains unrecognized and, therefore, untreated (12-14). Untreated disease is associated with inflammation within the small intestine and villous atrophy leading to malabsorption, chronic anaemia, delayed puberty, neuropsychiatric disturbances, associated autoimmune disorders, infertility, small-for-date-births, osteoporosis and, rarely, malignancy and it can reduce the quality of life (QoL) (1, 15, 16).

Diagnosis

CD is characterized by the production of autoantibodies among others against transglutaminase type 2 (TG2A) and endomysium (EMA), during a period of gluten ingestion. Serological testing identifies most CD patients using CD-specific and -sensitive antibodies (17). Due to good accuracy of the serology-tests, ESPGHAN published in 2012 new guidelines for the diagnosis of CD in children and adolescents, including the novel so-called "non-biopsy approach" for selected cases (1).

However, TG2A measurement requires specialized laboratories, and the results are not immediately available. The call for point-of-care (POC) testing, defined as performing a diagnostic procedure outside the laboratory, has resulted in the commercial availability of several POC tests for TG2A. These tests obviate the need for purified or recombinant transglutaminase type 2 (TG2) or for serum separation because TG2 is also found in red blood cells (RBCs). Therefore, the patient's own TG2 can be used in TG2A detection by haemolysing a whole blood sample and liberating the self-TG2 from the RBCs. Tests can be performed at home or at the doctor's office and results become available within 10 minutes, which may save costs and prove to be more convenient for the patients. Several studies have investigated the accuracy of POC tests based on TG2A for CD screening, and sensitivities and specificities similar to those of determination of TG2A in serum were reported (70.1- 97% and 76-100% respectively) (18, 19).

Treatment

The only treatment available for CD is adhering to a gluten-free diet (GFD). Adherence to a GFD is widely accepted to be challenging; it can be influenced by many factors including, reduced QoL, symptoms on ingestion of gluten, knowledge of gluten free foods, understanding of food labels, cost and availability of gluten free foods including receiving GF foods on prescription, and membership of a celiac society. Adherence to a GFD ranges between 25-50% among children and adolescents with CD (20-22).

Treatment with a GFD restores small bowel histology, reduces the burden of morbidity and mortality associated with untreated CD and prevents complications on the long-term. Noncompliance can be intentional, but accidental gluten ingestion also happens because of contamination of non-toxic cereals such as oats or corn due to co-culture or spilling during food-processing either in factories or at home or during transport.

Follow up

General recommendations for follow up of CD patients differ substantially between countries and even regionally within countries applying the same healthcare system. Evidence on the frequency, who and what should be assessed during follow up is lacking. Clinical follow-up of children and adolescents with CD is necessary to assess the evolution of their symptoms as well as their growth and development and to monitor dietary compliance to the treatment with a GFD. Determination of TG2A, which usually disappear approximately 12 months after starting a GFD, is also performed during the follow up (23-26). The determinations are widely used during follow-up as a proxy for mucosal healing in CD children (27), but the results do not correlate well with diet compliance (22, 28, 29).

Despite the absence of a gold standard to assess dietary compliance, a dietary evaluation by a trained dietician is considered the best method, but this is time-consuming and requires expert personnel which is not always available. Short dietary questionnaires and TG2A determinations in serum fail to detect dietary transgressions in children and adolescents with CD, showing poor sensitivity to identify all patients who consume gluten (22, 30, 31). To assess the dietary compliance in children and adolescents with CD a dietary questionnaire has been developed and validated (22). Other methods, as measurement of gliadin immunogenic peptides (GIP) in urine and/or in faeces have been introduced to detect contaminating gluten into the GFD, but they are not used in the standard clinical care (32-34).

Traditional medical care for celiac patients consists of regular physician visits. The limited time allotted for outpatient follow-up also typically restricts comprehensive assessment of a patient's health-related quality of life (HRQoL) and dietary adherence (35). Self-management has shown beneficial effects on the healthcare of other chronic diseases. E-health can play an important role in supporting patients in their self-management, as internet and technology can reach users easily and rapidly, with a wide range of contents and attractive formats. E-health is defined as healthcare services and information delivered or enhanced electronically via the internet and related technologies. Work from our research group shows that online consultations for children and young adults with CD are cost saving, increase CD-specific QoL, and are satisfactory for the majority.

Prevention

Prevention is defined as any activity that reduces the burden of mortality or morbidity from disease, taking place at the primary (avoiding disease development), secondary (early detection and treatment) or tertiary level (avoiding complications by improved treatment) (36). The development of CD requires genetic susceptibility, present in 40% of the general population. However, only a minority of individuals genetically at risk of CD, 1%, develop the disease. So, environmental and/or lifestyle factors may play a causal role in the development of CD. Primary prevention strategies are not (yet) possible. Data from prospective studies of large cohorts evaluated the effect of the timing of gluten introduction on the risk of CD in at-risk children. Results have shown that neither the timing of gluten introduction nor the duration or maintenance of breastfeeding influence the risk of CD. Secondary prevention is possible through early diagnosis. Most international guidelines already recommend testing for CD in high-risk groups, such as first-degree relatives of CD patients (CD families) and patients with other autoimmune diseases. Case-finding and mass screening are still controversial because of the ethical implications. Active case finding refers to liberal diagnostic testing of patients with CD-

associated symptoms, while mass-screening refers to test the whole population for CD. However, since the clinical presentation of CD has changed dramatically in the last decades, patients with atypical or nonspecific symptoms often report a delay in diagnosis of CD that may last for years (11) or even worse, CD remains unrecognized and, therefore, untreated (12-14). Nowadays, regular follow up to ensure strict adherence to a GFD, is the only available, effective tertiary prevention option. Given that the GFD poses a major challenge and requires patient education, continuous motivation and follow-up, several trials are ongoing or underway to explore non-dietary treatment as possible options for tertiary prevention, but none of them have been tested in clinical trials yet.

OUTLINE OF THIS THESIS

The focus of this thesis is the improvement of diagnosis, early detection and treatment of CD in children. Increased knowledge, available guidelines and reliable diagnostics allow for timely diagnosis which can prevent complications and improve QoL, but the current healthcare approach is often unable to make the diagnosis in a timely manner. Moreover, despite timely diagnosis and effective therapy, there is a need to improve the follow up. **Chapter 2** describes the efficient implementation of the ESPGHAN guidelines for the diagnosis of childhood CD in the Netherlands and presents the difference in incidence and clinical presentation of CD in the Netherlands over the last 40 years. **Chapter 3** shows an overview of the current knowledge of the preventive strategies for CD. In the following two chapters, results of secondary prevention strategies are presented. **Chapter 4** shows the protocol of the case finding study GLUTENSCREEN: a prospective study to detect CD in young children attending the Preventive Youth Health Care Centers in the region Kennemerland for a regular visit. **Chapter 5** presents our developed and validated clinically useful prediction models for CD development among genetically predisposed children from celiac families and the application to provide individualized screening advice. The results are based on data from the long-term follow up of the PreventCD cohort. The PreventCD study evaluates the influence of infant feeding on the development of childhood CD and explored the possibility of inducing tolerance to gluten.

Clinical follow-up of children and adolescents with CD is necessary but evidence concerning the content of the follow up, as well as the frequency, is lacking. The next two chapters assess how to manage the follow up of CD in children and adolescents. Since the GFD is currently the only effective treatment of CD, assessment of dietary-adherence is important during the follow up of CD patients. A relatively new method for monitoring dietary compliance is the detection of GIP. **Chapter 6** presents the features

of GIP in urine during a consultation on the outpatient clinic. Children with CD visit the outpatient clinic for their follow up, but communication over the internet offers new opportunities. E-health has shown beneficial effects on the costs and quality of other chronic disease management, but the evidence of E-health in CD follow-up has not been systematically reviewed. Finally, **Chapter 7** shows the results of the systematic review of the current knowledge of E-health for the follow-up in CD patients. In **Chapter 8**, the main findings of this thesis are discussed in the light of the current literature, followed by the discussion and conclusion in Dutch in **Chapter 9**.

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