Early diagnosis and management of celiac disease in childhood

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General discussion and conclusions

Celiac disease (CD) is an immune-mediated disorder, in which the HLA immunogenetic background (DQ2 and DQ8 heterodimers) and environmental trigger (gluten) are well established. Both factors are necessary- but not sufficient- to develop CD.

CD is a common disease with a broad spectrum of intestinal and extraintestinal symptoms and potential complications like osteoporosis, autoimmunity and rare but severe malignancies. The prevalence of CD is increasing, which has been mainly attributed to the greater availability of sensitive and specific screening tests, the growing awareness of CD among health-professionals and identification of those at risk of CD which have led to a significant raise in diagnoses worldwide (1).

Despite the fact that knowledge about the pathophysiology, diagnosis, treatment and possible therapeutic options is gradually increasing, it remains unclear who develops CD and who does not. Timely diagnosis and adequate treatment and follow-up are important questions at this time and reason for the studies included in this thesis.

Since 2012 guidelines of the European society of Gastroenterology, Hepatology and Nutrition (ESPGHAN) allow for diagnosis of CD without performing small bowel biopsies in children with symptoms and levels of antibodies against tissue transglutaminase (TGA)≥ 10 x upper limit of normal (ULN), confirmed by detection of anti-endomysial antibodies (EMA) and positivity for HLA-DQ2/DQ8 (2). Prospective validation study of this approach showed positive prediction values ranged from 99.63 (95% CI, 98.67-99.96) to 100.00 (95% CI, 99.23-100.00) (3). In 2020, the Evidence based guidelines for the diagnosis of CD have been updated and published (4). In **chapter 2** of this thesis, our national prospective data show that in the Netherlands, the year after the publication of the 'non-biopsy' approach, the diagnosis was correctly established according to it in more than 75% of the children. In order to improve this, it is important that the general doctors and pediatricians who play an essential role in suspecting the diagnosis and ordering the initial serological tests, should be taken into account the recommendations made by the ESPGHAN guideline that the diagnosis always be established by a pediatric-gastroenterologists or pediatrician with sufficient experience and knowledge of CD to avoid both overdiagnosis and underdiagnosis and their consequences. In addition, due to the continuous changing clinical presentation as reported in our study, the age at time of diagnosis is significantly increasing, which makes it difficult to diagnose all children timely (5). Nevertheless, a rising incidence of childhood CD has been reported in many countries, including in the Netherlands likely caused by a combination of several factors, as the growing awareness of CD among healthcare professionals and increased screening of high-risk groups and the availability of reliable CD antibody tests (5, 6). However, also a true rise in the incidence of CD is also being considered (7), since similar increase

has been reported in other autoimmune diseases and allergic conditions in children, such as type 1 diabetes mellitus, asthma and allergic rhinitis (8-11). Understanding how tolerance to gluten is lost in CD is a fundamental question that needs more study, currently environmental factors have been linked to the rise in incidence of the disease, including viral infections during childhood or changes in gut microbiota (composition or metabolite production) (12). In **chapter 3** a review on the current knowledge of the preventive strategies of CD is presented. Advances in the pathophysiology of CD could also enable primary preventive strategies in individuals genetically predisposed to the disease, but till now, primary prevention of CD is not (yet) possible. Early infant feeding practices have been prospectively studied in this respect and it has been shown that neither the timing of gluten introduction nor the duration or maintenance of breastfeeding influence the risk of CD (13-17) Recent studies from birth cohorts of children from CD families suggest that the quantity of gluten consumed early in life, may be a (preventable) risk factor for CD development (18-20), but before 'prevention' recommendations on this aspect might be given, this topic should be studied in randomized controlled intervention trials. At this moment the definite microbial signature and the exact role of dysbiosis in CD pathogenesis is not recognized, but an association between alterations in the gut microbiota and the development of CD has been demonstrated. Results of the CDGEMM study (Celiac Disease Genomic, Environmental, Microbiome, and Metabolomic) are expected and could help to understand the role that the gut microbiome show in the early steps involved in the pathogenesis of CD (21). Knowledge of the role of intestinal bacteria in the development of CD opens new possibilities for its treatment through probiotic administration, even though further studies are needed to better clarify whether probiotics can help treat or prevent the disease and to define which probiotics to use, at what dose and for how long (22-26). As long as primary prevention of CD is not possible, diagnosing the disease in its earliest stage – secondary prevention – seems the best option. Despite the increasing numbers of diagnosed CD, a substantial number of people with CD remain undiagnosed (11), the possibility and feasibility of screening strategies to identify undetected CD patients should be explored. Major questions have emerged about who to test for CD and when. Early diagnosis may be achieved both by case finding or by mass screening, albeit both methods are still controversial because of their ethical implications (27-29). In **chapter 4** of this thesis our national project on early diagnosis of CD, GLUTENSCREEN, in children from the general population who have CD-related symptoms is presented. This concerns the first case-finding project in the Netherlands on early detection of CD, to show that it is feasible, efficient, cost-effective and well accepted by the population. In GLUTENSCREEN the parents of all the children 1-4 years old who visit the Preventive Youth Health Care Centres (YHCCs) in the region of Kennemerland for a regular consultation were asked for CD-related symptoms from a standardised list. If one or more symptoms were present, a point of care test (POCT)

for TGA was performed. If the POCT was positive, the child was referred to the Leiden University Medical Centre for diagnosis according to the guideline. The results of GLUTENSCREEN are beyond expectations: CD was confirmed in 1.8% of the tested children, more than expected on the basis of the current literature, which is approximately 1% (30). In addition, this case-finding method for early CD-diagnosis is well-accepted by the parents of young children in the Netherlands. Also, the majority of the healthcare professionals support this case-finding at the (YHCCs) (31). However, it is well known that the predictive value of symptoms to identify CD is limited, since symptoms associated with CD are as prevalent in individuals with and without the disease (32). In the database of GLUTENSCREEN, we will first examine whether some symptoms better distinguish the presence of CD or what the optimal set of symptoms is as an indication for (early) initiation of CD testing. The primary limitation of case-finding for early detection of CD, even when well implemented, is that subclinical cases will be missed (33). An alternative is a general screening program to identify all CD cases, but this was opposed in 2017 by the Medical Ethical Committee Leiden-Den Haag-Delft (METC-LDD) and The Dutch Central Committee on Research Involving Human Subjects (CCMO). On the contrary, a CD-mass-screening programme was reported as acceptable by 70% of the parents from the Dutch general population (31). Since the development of CD requires genetic susceptibility (HLA-DQ2 and/or DQ8), adding the HLA-genotype to the case finding strategy for CD could optimize the targeted population to develop CD. Currently, HLA typing is not part of GLUTENSCREEN because the existing technique requiring DNA extraction has significant drawbacks in settings without the availability of a laboratory, such as the consultation offices. However, this approach will also not solve the problem of the asymptomatic children.

But, the asymptomatic children remain undiagnosed using this strategy and will only be diagnosed with CD by mass screening. Results from the 'Generation R'-study among 6-year-old children from the general population showed in 1.3% undiagnosed CD (57/4442 screened children was positive for TG2A) and was associated with important health problems, such as a reduced bone mineral density and a delayed growth in weight (33). In addition, children of women with undiagnosed and thus untreated coeliac disease had a reduced fetal growth and a lower birth weight (34). Together with literature that mass screening for CD is cost-effective, it will be time to re-open the discussion about mass screening for CD (35-37). After many years a possible mass screening for CD is still a matter of debate. The controversy over whether the general population would accept mass screening seems to be answered by the preliminary results of GLUTENSCREEN that the majority of the general population (approximately 70%) find mass-screening for CD acceptable. Also, the results from PreventCD, a prospective, European, dietary-intervention study among infants from families with high risk of CD,

have provided valuable information about the natural course of CD. Both in children from CD families and in the general population, the development of CD is very high in the first four years of life. With the gaining of these new insights, it seems time to re-open the discussion 'is it time for mass screening' since all the ten criteria for mass-screening made by Wilson and Jungner, have finally been answered (38). Expanding CD testing in asymptomatic children will provide insight into the actual prevalence of CD and allow timely diagnosis for all children with CD. It will be a good step in the right direction for preventive care in the Netherlands.

Early CD diagnosis through target serological screening of high-risk groups, such as first-degree relatives (FDR) of CD patients and patients with autoimmune diseases, is already recommended both by the Dutch and most international guidelines (2, 39, 40). Nevertheless, little information is available about the improvement of symptoms after early diagnosis and treatment in these children. About half of these children have complaints at the time of diagnosis. In our multicenter PreventCD study children have been prospectively assessed for the development of CD by using a standardized questionnaire on their health status (reported by the parents) and CD antibodies, these data have been analysed to prospectively assess whether children from coeliac families benefit from screening, early diagnosis and treatment. These data show that symptomatic children from CD families do benefit from early detection, diagnosis and treatment. Most of the symptoms significantly improved after treatment with a GFD (manuscript in preparation).

That children from CD families have a higher risk of developing the disease, is generally known, but **in chapter 5**, our prospectively obtained data of the PREVENTCD cohort shows a significantly higher risk for the disease during the first years of life than previously assumed (1, 41). Until recently, the lifetime risk of CD for FDR of CD patients was considered to be 5%-10%. Our data show that at the age of eight years, the probability of CD is as high as 17%, stressing even more, the importance of early screening and diagnosis. However, evidence on the frequency of and at what age to perform screening, is lacking. Based on the natural course of CD, our data show that different factors influence the risk. CD develops very young age (mean age 4.3 years), significantly more often in girls ($p=0.005$) and in HLA-DQ2 homozygous individuals ($p<0.001$). Based on these factors, and the current age, prediction models for CD development were created for individualized screening advice in children with affected FDR as presented in **chapter 5**. From the findings of PREVENTCD and GLUTENSCREEN, we know now that the natural history of CD includes a very early development in life. However, whether the prediction models and resulting screening advice are also applicable in children from the general population, should be separately evaluated.

A timely diagnosis of this chronic disease is beneficial in (a)symptomatic children but to monitor the results of its treatment after diagnosis is, however, equally important. The only treatment for CD is a life-long strict gluten-free diet (GFD), which is difficult to maintain because of gluten being present in most processed foods, and dietary restrictions affect Quality of Life (QoL). In addition, gluten-free food is not widely available, it is more expensive, with lower palatability, resulting in low compliance. Many trials are underway to explore non-dietary treatment as possible options for tertiary prevention (42).

Good adherence to the GFD reduces the complications of CD and may be considered as a tertiary preventive measurement (43). Determination of TGA, which usually disappear approximately 12 months after starting a GFD, is mostly performed during the follow up and are widely used as a biomarker for mucosal healing in CD children, but the results do not correlate well with diet compliance (44). Despite the absence of a gold standard to assess dietary compliance, a dietary evaluation by a trained dietitian is considered the best method, but this is time-consuming and requires expert personnel which is not always available. Short dietary questionnaires and TGA determinations in serum fail to detect dietary transgressions in children and adolescents with CD, showing poor sensitivity to identify all patients who consume gluten (45). To assess the dietary compliance in children and adolescents with CD, a dietary questionnaire has been developed and validated (46). Other methods, as measurement of gliadin immunogenic peptides (GIP) in urine and/or in faeces have emerged as more sensitive tools to detect gluten ingestion (47), but they are not yet used in the standard clinical care. In **chapter 6,** the results of our clinical study report, that the combination of the dietary questionnaire and urinary GIP test is the most effective method in detecting (un)intentional gluten transgressions. However, both test as well as the TGA determination, have their limitations to monitor dietary compliance. Because GIP test detects gluten which is ingested only a few days prior to testing, gluten consumption before this time may remain undetected. As presented in our study, GIP determination might be helpful in specific clinical settings to rule out (un)intentional gluten intake, for example in children 1. with recently diagnosed with CD as they familiarize themselves with the GFD, 2. reporting symptoms with normal tTGA and no errors in the dietary questionary, 3. with (persistent) elevated or very slow normalisation of tTGA-levels despite no errors in the dietary questionnaire and, 4. with suspected intentional gluten intake. In contrast to the currently used biomarkers for screening and diagnosis, there is a need for a clinically useable biomarker which can assist in the monitoring of the disease over a longer period time.

Traditional medical care for CD 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 (4). Therefore, other possibilities outside the outpatient clinic should be considered. Self-management has shown beneficial effects on the healthcare of other chronic diseases (48). 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. In **chapter 7** the results are presented of a systematic review on the utilization and effectives of electronic-health technologies in the management of CD patients. The majority of the patient are satisfied with E-Health and the use may be effective in specific aspects of CD care; improved QoL, adherence rate, and knowledge on CD and GFD.

During the follow-up visits of children and adolescents with CD it is necessary to assess symptoms, nutritional status and growth, QoL and to prevent complications. Other general goals of coeliac follow-up are to ensure disease education and social support and to motivate the child and its family, reinforcing at each visit, the importance of dietary compliance. Currently, the follow-up of CD children is not standardized and based largely on expert opinions, resulting in substantial differences in follow up between countries and even regionally within countries applying the same health care system (49-50). So, there is a need for structured evidence based follow up guideline for CD. In the meanwhile, an international collaboration of experts in the field of CD has produced the ESPGHAN position paper for the management of CD. Based on available literature, recommendations have been formulated for a more structured follow-up of children with CD (51). Let's hope that these recommendations will be followed as quickly and efficiently as the ESPGHAN guideline for diagnosis of CD in children and adolescents.

FUTURE PERSPECTIVES

For now, as primary prevention of CD is a highly attractive, but as yet unrealized goal, the focus must be on driving expeditious diagnosis and treatment in (a)symptomatic children and adolescents. The preliminary results of GLUTENSCREEN show that case finding detects a significant part of the otherwise undetected children and shortens the time to diagnosis and provides us information about the cost-effectiveness and acceptability of early diagnosis in symptomatic children with CD. Based on these positive results, the YHCC's in the region of Kennemerland have decided to implement the early detection of CD in their regular care. Efforts are being made to expand the case finding approach to all other YHCCs in the Netherlands. To optimize the targeted population, funding has been requested to develop a novel test to perform HLA typing in dried blood

spots (as done at the neonatal heel-prick) obtained from an extra droplet of blood from the finger prick performed for the POCT for TGA at the YHCC. This approach will make the successful case finding more effective and reduce the burden in the HLA-DQ2/8 negative children.

In the meantime, we continue to explore opportunities for primary prevention.

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