Department of Women´s and Children´s Health
Pediatric Endocrinology Unit

Coeliac disease in children and adolescents with type 1 diabetes
– Screening, diagnosis and prevalence

Mara Cerqueiro Bybrant

This Ph.D. thesis for doctoral degree will be publicly defended on Friday the 18th December 2020, at 09:00 am CET. Conference room Charles, Wideströmska Huset, Tomtebodavägen 18, Campus Solna, Karolinska Institutet, Stockholm, Sweden.

Zoom link https://ki-se.zoom.us/j/69323106691

Principal Supervisor:
Adjunct Professor Annelie Carlsson
Lund University
Faculty of Medicine
Department of Clinical Sciences
Lund

Co-supervisor(s):
Ph. D. Eva Örtqvist
Karolinska Institutet
Department of Women's and Children's Health
Paediatric Endocrinology Unit
Stockholm

Associate Professor Hans Hildebrand
Stockholm

Opponent:
Professor Steffen Husby
University of Southern Denmark
Faculty of Health Sciences
Department of Clinical Research
Odense

Examination Board:
Associate Professor Sofia Carlsson
Karolinska Institutet
Institute of Environmental Medicine
Epidemiology
Stockholm

Associate Professor Klas Sjöberg
Lund University
Faculty of Medicine
Department of Clinical Sciences
Malmö

Associate Professor Jannet Svensson
University of Copenhagen
Faculty of Health and Medical Sciences
Department of Clinical Medicine
Copenhagen

ABSTRACT

Background

Coeliac disease (CD) is more common in children and adolescents with type 1 diabetes (T1D). Both diseases share the same high-risk genes: human leukocyte antigen (HLA) DQ2 and DQ8. Other factors than gluten intake and high-risk genes are necessary to develop CD. In Sweden, there was a dramatic increase in CD in young, otherwise healthy, children between 1984 and 1996 and this has been called the "Swedish epidemic of coeliac disease", hereinafter referred as the Swedish CD epidemic. Over the last decade, the diagnostic guidelines for CD in children and adolescents have changed, but children with T1D are still not included in protocols to determine CD diagnosis without a biopsy, due to a lack of data.

Aims

The overall purpose of this dissertation was to expand current knowledge about CD in children and adolescents with T1D, with regard to the screening, diagnosis and prevalence of CD. One aim was to investigate the prevalence of CD in Swedish children and adolescents with T1D and compare the prevalence in individuals born before, during and after the Swedish CD epidemic. Another aim was to explore how CD screening in children and adolescents with T1D may be improved.

Research strategy

In Study I, we examined the medical records of 1,151 paediatric patients at a diabetes clinic in Stockholm to determine the prevalence of CD in children and adolescents with T1D, as well as the prevalence of CD in three subgroups. These were children born before, during and after the Swedish CD epidemic. In Study II, we investigated the prevalence of CD in patients with T1D at a Swedish national level, using several databases. We identified 1,642 children with T1D born during the Swedish CD epidemic (1992–1993) and 1,380 born after the epidemic (1997–1998). The total number of individuals born during these years was 430,374. In Studies III and IV, we used national cohort data from the Swedish prospective study Better Diabetes Diagnosis (BDD). In Study III, we analysed blood samples from 2,705 children and adolescents when they were diagnosed with T1D, to determine the links between HLA-DQ2 and HLA-DQ8, CD biomarker tissue transglutaminase (tTG) and diabetes autoantibodies. In Study IV, we analysed information from 2,035 children and adolescents with T1D, combined with data from the medical records kept by their diabetes clinics, to evaluate if high levels of tTG could predict CD. All the studies were approved by the Swedish Ethical Review Authority.

Results

Every tenth child and adolescent with T1D in Sweden also had CD. No difference in CD prevalence was found in children with T1D born before, during or after the Swedish CD epidemic. Many children were diagnosed with both diseases almost at the same time and the majority were diagnosed with CD within two years of being diagnosed with T1D. The CD biomarker tTG was related to the HLA high-risk genes DQ2 and DQ8, but not to diabetes autoantibodies. These risk-genes were absent in approximately 8% of the children with T1D. When the CD biomarker tTG was 10 times above the upper limit of normal, it was accurate in predicting CD in children and adolescents with T1D.

Conclusion

The prevalence of CD in children and adolescents with T1D in Sweden was shown to be one of the highest in the world. Children with T1D were not affected by different gluten intake recommendations in infancy, unlike the general population during the Swedish CD epidemic. This finding can be taken into account when planning both long-term observational studies and interventional studies about how to prevent CD. HLA was only useful in identifying the T1D population that was not at-risk of developing CD. We recommend repeated CD screening in children with T1D and HLA DQ2 and/or DQ8, and suggest that the first two years after their T1D diagnosis is the most important time. It is also suggested that guidelines for diagnosing CD in screened children should also apply to children with T1D, with regard to when biopsies can be avoided.