Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences
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Summary, general discussion and future perspectives
Inflammatory bowel disease (IBD) is a lifelong disease, characterized by chronic relapsing inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are two main phenotypes of IBD. In this thesis, several aspects of pediatric IBD are evaluated, including pathogenesis, diagnostics, treatment and psychosocial consequences.

Part I: Pathogenesis & Diagnostics of pediatric IBD
IBD results from an aberrant mucosal immune response to intestinal bacteria. Genetic susceptibility and environmental triggers, including Western lifestyle, are regarded as crucial contributors to the IBD pathogenesis. Most of the genes, linked to IBD, are crucial for epithelial barrier function, the innate immune regulation, autophagy and regulation of adaptive immunity. Previous studies have shown that human Peyer's patches of the terminal ileum contain black granular pigment deposits. These pigment deposits consist of titanium dioxide and aluminosilicate, derived from ingested materials such as food additives, pharmaceuticals and toothpaste. In chapter 1 we aimed to map the distribution of this exogenous pigment throughout the gastrointestinal tract of children suspected for IBD. Additionally the correlation between age and the presence and amount of exogenous pigment and its relation with pediatric IBD was investigated. We found in 42% of children deposits of black pigment, only located in Peyer’s patches in the terminal ileum. A significant correlation was found between increasing age and the amount of pigment in the Peyer’s patches. Furthermore, pigment deposits were found significantly less in CD patients compared to UC and non-IBD patients. Absence of pigment in Peyer’s patches in a higher number of CD patients suggests that microparticles might have become involved in the inflammatory process, possibly due to disrupted autophagy.

For making the diagnosis of IBD no single diagnostic test or ‘gold standard’ is available. The work up of a child with suspected IBD involves history taking, physical examination, endoscopy with biopsies and small bowel imaging. The value of upper gastrointestinal tract (UGT) endoscopy is still a topic of debate. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) IBD Working Group has recommended routine UGT endoscopy at initial presentation in every child suspected of IBD, whereas the working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the Crohn’s and Colitis Foundation of America (CCFA) refrained from recommending routine diagnostic use of endoscopy of the UGT. Furthermore, there is still no uniformity on the diagnostic criteria of IBD of the UGT. Pathological changes can be found in the UGT in both CD and UC. Therefore, in chapter 2, we investigated the role of UGT involvement in the diagnostic assessment of suspected IBD in children and surveyed histopathological changes in the
UGT mucosa which can distinguish CD from non-CD (UC and non-IBD). We found that 11% of the children with CD, had granulomatous inflammation in the UGT, without the other characteristics of CD. These children would have been misdiagnosed if endoscopy of the UGT had not been performed and the diagnosis would have been based on (ileo) colonoscopy alone. Furthermore, focal cryptitis of the duodenum and focally enhanced gastritis were found significantly more frequent in children with CD compared to children with UC and non-IBD. Of these inflammatory changes focal cryptitis of the duodenum showed a good specificity and positive predictive value of 99% and 93% respectively, whereas the specificity and positive predictive value of focally enhanced gastritis in CD, respectively 87.1% and 78.6%, were less convincing. We concluded that clinicians should perform UGT endoscopy in the diagnostic assessment of all children suspected for IBD.

In chapter 3 we compared the diagnostic accuracy of ultrasound and dynamic contrast-enhanced (DCE-)MR entero- and colonography with upper and lower tract endoscopy in children suspected for IBD. Additionally we assessed if ultrasound and MR entero- and colonography can differentiate between CD and UC. This study showed that ultrasound and DCE-MR entero- and colonography can be used to diagnose IBD in a pediatric population, but not to exclude IBD. Sensitivity and specificity were 55% and 100% for ultrasound, and 57% and 75-100% for MR entero- and colonography, respectively. By combining MR entero- and colonography and ultrasound, the sensitivity for detecting IBD increased up to 70-74%, with a specificity of 80-100%. Cases of IBD that were false negative were either mild disease cases or patients with rectal disease. When adding a DCE-sequence sensitivity increased to 83-87% and specificity to 80-100%. Ultrasound and MRI could only distinguish between CD and UC when terminal ileum lesions were found. Based on these results we can conclude that in the diagnostic assessment of children with suspected IBD endoscopy cannot be replaced by these techniques.

Part II: Treatment of pediatric IBD
In pediatric IBD, a ‘step-up’ approach of adding therapies if first-line or less-toxic approaches are unsuccessful within an appropriate period, is commonly used. In children with moderate-severe CD who are refractory to or intolerant of conventional therapy anti-tumor necrosis factor (TNF) agents, such as infliximab (IFX), has proven to be efficacious in inducing and maintaining remission. In chapter 4 the long term efficacy of IFX in the treatment of pediatric CD is discussed. Between October 1992 and November 2009, 152 pediatric CD patients in the Netherlands were treated with IFX, with a median number of 10.5 IFX infusions during a median follow-up of 25 months. We found that the cumulative probability of losing response to IFX in patients who needed repeated infusions, was 13%, 40% and 50% after 1, 3 and 5 years, respectively. Dose adjustments (dose increase to 10 mg/kg and/or shortening of the interval between two infusions) were needed in 49% of
patients, with a median time to any adjustment of 6 months. These findings emphasize the need for effective long-term strategies in pediatric CD, as well as the need for predictors of response to infliximab treatment to select the most suitable patients for this treatment.

Before stepping up therapy of a child with refractory disease, adherence to medication should be reviewed first. Chapter 5 is a systematic review of the current literature concerning medication adherence in adolescents with IBD. The documented rates of medication non-adherence in adolescents with IBD are widespread depending on the method of assessment used. Rates of medication non-adherence ranged from 3 to 73%. There is no gold standard for the measurement of non-adherence and no uniform definition of medication adherence exists. Each method of adherence assessment has its limitations and strengths. The use of a multimethod approach to assessment that incorporates both subjective (e.g. self-reported questionnaires) and objective (e.g. pill count or bioassays) methods is recommended. The most frequent barriers reported by adolescents and their parents are ‘just forgot’, ‘wasn’t home’ and ‘interferes with activity’. Difficulties in family and social interactions, as well as psychosocial dysfunction can influence medication adherence and therefore jeopardize IBD treatment outcome.

Part III: Psychosocial consequences of pediatric IBD

Pediatric IBD can affect many areas of psychosocial functioning. Little is known about the effect on the developmental trajectory of adolescents growing up with IBD. Chapter 6 described the autonomy, psycho-sexual and social development (“course of life”) and socio-demographic outcomes in adolescents with IBD in comparison with peers from the general population. This study showed that the psychosocial developmental trajectory of adolescents growing up with IBD is delayed compared to peers from the general population. Patients with IBD achieved fewer milestones on the domains of autonomy, psychosexual and social development. They went less frequently on holidays without adults, had fewer jobs during secondary school, were less frequently going out to a bar/disco during secondary school and were older when falling in love for the first time. After secondary school, IBD patients were more often unemployed. Health care physicians should be attentive to these consequences of IBD and provide additional support if necessary.

Adolescents with IBD are at increased risk for poor health related quality of life (HRQoL). Several domains of risk factors for impaired HRQoL have been investigated, including disease-related, psychosocial, and relationship factors. Relationship factors such as social support or family functioning rarely have been explored as influencing HRQoL in pediatric IBD. In chapter 7 we aimed to assess the perceived relational support from parents and from best friends and the HRQoL in adolescents with IBD. Additionally, the association between perceived relational support from parents and friends and HRQoL was
investigated. Adolescents with IBD reported high scores of perceived relational support from parents, as well as from best friends. No significant differences were measured between perceived support from parents and from best friends. In comparison with peers, the HRQoL of adolescents with IBD was impaired on domains of social functioning, role limitations due to physical health and vitality. Furthermore, a positive relationship between relational support from parents and friends and HRQoL was found, with higher levels of perceived parental and friend support correlating with better HRQoL. We stressed that clinicians should be aware of these associations and identify patients at risk of difficulties in relationships with parents and friends. Especially adolescents with limited ability to participate in social activities with friends, high absenteeism from school and patients with family dysfunction need attention.
DISCUSSION AND FUTURE PERSPECTIVES

Pathogenesis & Diagnostics of pediatric IBD

Inflammatory bowel disease (IBD) is most likely the result of a complex interplay of both genetic and environmental factors. Although a similar pathogenesis has been suggested in pediatric and adult populations with IBD, compared with adults with IBD, the exposure time to environmental risk factors is relative short in pediatric-onset IBD. The evidence for specific environmental factors contributing to pediatric onset is limited and inconsistent. Most of the studies are case-control studies with exposure established using questionnaires, which are limited by potential recall bias and reverse causality (1). In this thesis we hypothesize that microparticles of titanium dioxide and aluminosilicate, derived from ingested materials such as food additives, pharmaceuticals and toothpaste, might play a role in the inflammatory process in Crohn’s disease (CD). Our observation that pigment is found significantly less in the lysosomes of Crohn’s disease patient raises the question whether this observation is associated with autophagy related disease variants and prompts future research in this direction.

Therefore, the next step should be assessing the interaction between these microparticles and NOD2 and ATG16L1 mutations in children with CD. Furthermore, future studies should focus on gene-environmental interactions to get a clearer understanding of the underlying mechanisms of IBD which might provide insight for improved prevention and treatment.

Pediatric IBD has a different phenotypic appearance compared to IBD in adults, with regard to disease location and disease behavior. In pediatric-onset ulcerative colitis (UC) pancolitis or extensive colitis (up to the hepatic flexure) can be found in up to 90% of all cases, which is twice as often as in adults (2-5). Therefore differentiation between CD and UC can be difficult in children. The use of upper gastrointestinal tract (UGT) endoscopy can help to distinguish CD from UC by finding granulomas solely confined to the UGT. We showed that focal cryptitis of the duodenum and focally enhanced gastritis is of assistance in differentiating CD from UC. However, focal enhanced gastritis is not exclusively found in CD, and does not reliably differentiate between CD, UC and non-IBD patients. The European Society of Pathology (ESP) and the European Crohn’s and Colitis Organisation (ECCO) has recently reached European consensus on criteria for the histopathology diagnosis of inflammatory bowel disease (6). Usage of these criteria will facilitate comparison of research data and stimulate collaboration in this field.

Radiologic evaluation of the small bowel is part of the complete diagnostic work-up in children with suspected IBD. It is used for assessing disease activity of the small bowel in patients with no definite diagnosis of UC based on endoscopy and histology (7). In the last years magnetic resonance imaging (MRI)-enterography has replaced small bowel
follow through, because this technique has no radiation exposure (8). In this thesis we investigated if MRI-enterography in combination with MRI-colonography and ultrasound can replace endoscopy in the diagnostic work-up. We added dynamic contrast enhanced (DCE)-MRI to conventional MRI sequences with the specific purpose to detect mild disease activity. We showed that ultrasound and DCE-MR entero- and colonography can be used to diagnose IBD in a pediatric population, but not to exclude IBD. However, the sensitivity of this new technique is still too low for replacing endoscopy in children with suspected IBD, especially in patients with mild disease and rectal disease. Further studies are needed to optimize imaging techniques to increase imaging adequacy. Undergoing an endoscopy can be burdensome for children. Endoscopies in children are performed under general anesthesia and they always need a bowel preparation, which often takes place in the hospital. Since the flavor of the irrigation fluid is salty (polyethylene glycol), many children are not able to drink the fluid themselves and thus need a nasogastric tube to ingest the fluid. Therefore, it will be a great benefit for children when endoscopy can be replaced by another less invasive procedure in the future.

Treatment of pediatric IBD
The management of pediatric IBD has changed considerably over the last two decades due to the introduction of biologicals. In line with previous studies (9-11), we showed that infliximab (IFX) is effective in inducing and maintaining remission in children with refractory CD. However, a substantial number of patients loses their initial response and requires dose adjustments to maintain clinical response or switch to other therapies. IFX and adalimumab (ADA) are currently the only anti-TNF drugs that have been registered for use in pediatric IBD patients, the latter only in CD patients. Multicenter trials are needed to determine the safety and efficacy of new biologicals in pediatric IBD, which already have been proven effective in inducing and maintaining remission in adult patients, such as certolizumab (12,13), and more recently vedolizumab (14,15). With the approaching expiration of the patent on infliximab, two biosimilar infliximabs have already been filed for approval by the European Medicines Agency (EMA) (16). Biosimilar products are not generic medical products, and therefore it might be possible that differences in the manufacturing process will lead to subtle differences with similar biological medicines (17). Until now, the efficacy of biosimilar drugs in IBD has not been investigated. Therefore, clinical trials are needed to assess efficacy and safety of biosimilars in adult and pediatric IBD patients. Uniform consensus is needed before introducing biologicals in pediatric IBD management. For future research it is important to get more insight in pediatric IBD phenotypes using combinations of serological, genetic and clinical markers, such as disease localization and behavior, and eventually predict disease course and response to medical therapy. This will lead to a more personalized, tailored therapy, whereby patients who are likely to have an aggressive course of disease might benefit from an early introduction of biological therapy.
Medication non-adherence is a significant health care problem in IBD. In this thesis we systematically reviewed the rates of non-adherence of conventional therapy in adolescents with inflammatory bowel disease and found that non-adherence is a significant health care problem. Interventions should be developed to enhance adherence to treatment regimens. Future studies are needed to determine the effect of non-adherence on patient clinical outcomes and on health care costs.

Psychosocial consequences of pediatric IBD
Decreasing physical symptoms is the main goal of medical treatment of patients with IBD. However, health care professionals should also guide the adolescent in the process of growing up with a chronic disease. We have shown that the psychosocial developmental trajectory of adolescents growing up with IBD is delayed compared to peers from the general population. Furthermore, in comparison with peers, adolescents with IBD reported a significantly lower health related quality of life (HRQoL). Several studies have investigated risk factors for impaired HRQoL and psychosocial functioning. We found a positive relationship between relational support from parents and friends and HRQoL. In accordance with our study, most studies have a cross-sectional design, which is limited by potential reverse causality. Therefore, longitudinal studies are needed to examine mechanisms by which risk factors, such as disease-related factors, relationship factors and personal traits influence HRQoL and psychosocial functioning. This will hopefully result in early identification of patients at high risk of developing psychosocial problems related to their chronic illness. Screening of psychosocial functioning and HRQoL should be a structural component of the comprehensive care of adolescents with IBD. In fact, a single center study has recently started, investigating the potential benefit of a digital tool (kwaliteit van leven in kaart, KLIK) measuring HRQoL of the adolescent with IBD. Adolescents at risk of impaired HRQoL and psychosocial functioning should be offered psychoeducational or skills-based programs (18,19). Future studies should analyze the precise effects of these interventions on psychological state and quality of life, but also on the course of IBD itself.
REFERENCES


