Chronic abdominal pain, fatigue and inflammatory bowel disease in children

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This dissertation addresses two particular knowledge gaps out of the many that exist in paediatric inflammatory bowel disease (IBD).

In the first part of this thesis, we evaluated diagnostic strategies to assess whether gastrointestinal complaints are due to IBD, for appropriate triage for endoscopic evaluation. In the second part, we quantified and characterised fatigue in IBD.

PART I - Triage for endoscopy

In our effort to develop an appropriate strategy whether or not endoscopy is indicated to evaluate IBD in a child with abdominal complaints, we first evaluated faecal calprotectin (FC) as an isolated triage test. First, we described a cohort of 117 children with chronic diarrhoea and nonspecific abdominal pain. The treating physicians had to base their decision whether or not to perform endoscopy on the standard practice at that time: a combination of signs, symptoms and blood results. Without the knowledge of the FC result, 62% of the patients that were selected for endoscopy were diagnosed with IBD. If they would have based the selection for endoscopy on the combination of raised FC levels (i.e. >50 µg/g) and negative stool cultures, the yield of ileocolonoscopy towards diagnosing IBD would have improved to 78%, without missing any IBD patient. At the same time, FC levels below this cut-off point would have prevented a considerable proportion of patients being subjected to an endoscopic procedure that would not have led to the diagnosis of IBD, and, arguably, could then even have been labelled 'futile'. Even though adding FC results to the decision strategy improved the diagnostic yield compared to the standard diagnostic strategy of that time, still 22% of the patients would have been subjected to an IBD-negative ileocolonoscopy.

Secondly, we evaluated whether another faecal biomarker for mucosal inflammation, calgranulin-C, is better than FC in predicting IBD in children and teenagers. When predefined test thresholds were used (50 µg/g for FC and 0.75 µg/g for calgranulin-C), the diagnostic accuracy of calgranulin-C indeed appeared to be better. However, when receiver-operator characteristic (ROC) curves were used to identify the optimal test threshold for each test separately, what appeared to be 400 µg/g for FC and 0.75 µg/g for calgranulin-C, the superiority of calgranulin-C relative to FC disappeared. We therefore concluded that the diagnostic accuracy of the calgranulin-C test was not superior to the FC test.

The cohort we evaluated included patients with rectal blood loss and perianal disease. These red flag symptoms provide sufficient reasons for immediate endoscopic evaluation to obviate the need for additional diagnostic testing. Inclusion of these patients increases the pre-test probability and causes an overestimation of the discriminating power of FC relative to the practical situation, where a test seems particularly useful to discriminate between those with IBD and those with functional abdominal pain. Children and teenagers presenting with *non-bloody* diarrhoea and abdominal pain, in other words without red flag symptoms, are a spectrum of patients more commonly seen in general paediatric practice. These patients constitute the most challenging group to discriminate IBD from Irritable Bowel Syndrome (IBS) because the pre-test probability for IBD is low. Previously published meta-analyses pooled studies which included patients with red flag symptoms and may have exaggerated the diagnostic accuracy of FC to diagnose IBD.

We therefore set out to determine the optimal test strategy in patients without red flag symptoms. This time we used a FC threshold of 250 µg/g, which was, according to new insights, considered to be the optimal cut-off point to discriminate IBD from functional abdominal disorders (1).

We compared four diagnostic strategies to predict the need of endoscopy based on (A) symptoms alone, (B) symptoms + blood markers, (C) symptoms + faecal calprotectin, and (D) symptoms + blood markers + faecal calprotectin. Triaging with strategy C resulted in 20 of 100 patients undergoing endoscopy, and triaging with strategy D further limited this number to 14 of 100 patients. Eleven out of 14 had IBD and three did not have IBD. No IBD-affected child was missed.

Clinical Implications

Our search for the optimal diagnostic approach to triage paediatric patients with gastrointestinal complaints and absence of red flags for endoscopy culminated in a combination of meticulous history taking with measuring C-reactive protein in blood and calprotectin in stool. This strategy provides an easy and effective way to correctly selecting those who appeared to have IBD. Clinical practitioners can be reassured that in patients with a low CRP (≤10 mg/L), normal haemoglobin and low FC (<250 µg/g), endoscopy can safely be avoided without missing a case of IBD. Effective therapeutic interventions in children with a negligible risk for IBD, e.g. gut-directed hypnotherapy, can be initiated without losing time on further diagnostics. Simultaneously, children with increased FC in combination with increased CRP, low haemoglobin, or both, who have a high risk for IBD, can have an endoscopic confirmation of this diagnosis sooner and consequently have an earlier start of appropriate treatment.

Omitting the diagnostic strategy that comprises the combination of CRP, haemoglobin and calprotectin in children with *non-bloody* diarrhoea and abdominal pain may cause considerable harm, such as linear growth impairment and progressive bowel damage requiring surgery early after diagnosis (2, 3-5).

Tips for reliable faecal calprotectin results

The reliability of the diagnostic strategy strongly depends on biological, pre–analytical and analytical factors influencing the FC test. Stool samples are relatively easy to obtain, but there are several obstacles in the trajectory from stool collection to analysis that can affect the test result. First, it is advisable to use the first bowel movement of the day to catch the highest possible concentration of calprotectin (6). The faeces sample must not come into contact with toilet water as it may contain bleaches and disinfectants that may degrade calprotectin. Secondly, medication that is commonly prescribed in patients with abdominal pain, including non-steroidal anti-inflammatory drugs (e.g. aspirin or

ibuprofen) and proton pump inhibitors, can increase FC (7, 8). Ideally, these medications should be discontinued a week before stool collection. Thirdly, recent publications have shown that the protein calprotectin may be less stable at room temperature than previously thought (6, 9, 10). Protein degradation can be delayed when the filled stool container is refrigerated until delivery at the laboratory. Unrefrigerated stool samples of children with vague gastrointestinal complaints that arrive with a delay exceeding 48 hours and with a FC result between 50 and 250 *µg*/g, may falsely reassure doctors and patients because of degradation of initially increased FC levels and therefore require analysis of another fresh faecal sample.

Comparison of FC test accuracy per manufacturer

At present, most clinical practitioners have access to one or more faecal calprotectin tests, but these tests are neither standardized nor harmonized. We nevertheless feel that our findings can be extrapolated to settings with calprotectin tests from different manufacturers, as they fairly agree in the lower range (below 250 µg/g) (11). Above this cut-off point however, inter-assay variability is considerable. On the other hand, tests with a limited measuring range (say 50 to 300 µg/g) are considered unsuitable for triaging for endoscopy. In the absence of assay standardisation, more assay-specific cut-offs are needed.

Applicability in the primary care setting

Our test-strategy was evaluated in second- and third-line care settings, but not in primary care. In primary care, where IBD prevalence is low, an isolated positive FC result is rarely indicative of IBD, but an FC result below 50 µg/g on the other hand, does rule out IBD (13). The decision to refer children for endoscopy should therefore not be made at the general practitioner's level, but at the level of the paediatrician.

For this part of the thesis we conclude that the inclusion of the FC test in the triage for endoscopy allows to accurately select individuals with a high risk for IBD from a cohort of children with non-specific chronic intestinal complaints. Even in settings with high pre-test probability for IBD (i.e. prevalence > 70%), the optimal decision strategy based on symptoms, blood markers and faecal calprotectin continues to be beneficial. Paediatricians working at either secondary or tertiary care level can be reassured that this is a highly accurate and non-invasive approach to determine the likelihood of IBD.

PART II - Quality of life beyond clinical remission: fatigue in paediatric IBD

Children with IBD often experience fatigue and consider it one of the most burdensome symptoms. Fatigue is common at times of active inflammation, but a considerable proportion of the children also experiences fatigue when their IBD is in remission. The rates of fatigue in paediatric IBD are comparable to rates observed in paediatric oncology patients (50-75%) (14). IBD-related fatigue negatively impacts the quality-of-life and daily activities, including school attendance and sports participation. Despite its frequent occurrence, fatigue has been addressed in paediatric IBD literature only scarcely and not in considerable detail.

We systematically reviewed existing literature to identify factors contributing to fatigue. In the absence of randomised controlled trials, we selected cross-sectional or case-control studies reporting on fatigue in paediatric patients with IBD. The selected studies varied in the methodology to quantify or measure fatigue. Several studies used self-reporting surveys or a combination of parent-proxy reports and self-reports; only one tried to measure decline in activity with a portable pedometer. While working on the literature review it became clear that fatigue should be regarded as a multidimensional phenomenon, characterised by biological, psychobehavioural and functional factors (**table 1**).

Consequently, we assessed the relationship between biological and functional factors and IBD-associated fatigue. We evaluated haemoglobin, iron status, calprotectin (as marker of intestinal inflammation), disease-specific quality-of-life (with the IMPACT-III questionnaire) and physical fitness (by 6 minute walking distance, 6MWD) in children with quiescent, mild or moderate IBD. Using the PedsQL™ multidimensional fatigue scale, participating children with IBD were classified as fatigued or non-fatigued. We found no differences between the fatigued or non-fatigued groups in terms of haemoglobin concentration, faecal calprotectin, and ferritin concentration. The mean 6MWD in the cohort of paediatric IBD patients was 1 standard deviation below age-related healthy controls, but the mean 6MWD in the fatigued and non-fatigued IBD patients was not significantly different. The quality-of-life score was inversely related to fatigue: the more fatigued, the lower the quality-of-life score.

Table 1: *Identification of factors contributing to IBD-associated fatigue. Adult studies printed in grey*

Predictors of fatigue	Effect on fatigue	
	Aggravation	**Alleviation**
Biological factors		
Disease activity	Compared to patients with quiescent disease, adolescents with active disease have impaired physical wellbeing and more trouble sleeping (15) IBD adolescents are more tired in case of active disease (16)	Effective induction and maintenance therapy
Medication	Use of corticosteroids, thiopurines, and anti-TNF agents are associated with more fatigue (17-19)	Anti-inflammatory management. (20, 21)
Haematological factors	Iron deficiency anaemia(22)	iron supplements or intravenous iron therapy
Psychobehavioural factors		
Family support	Family dysfunction (23)	Maternal positive affect (23)
Psychological factors	Depression and anxiety (24)	Mindfulness and relaxation (25) Cognitive behavioural therapy (25, 26)
Functional factors		
Physical activity	Impairment in motor functioning(27) Decreased physical exercise (28)	Physical training reduces fatigue in postoperative IBD patients (29)

Future perspectives

Despite the high impact of fatigue in paediatric IBD there has been very limited evidence on successful pharmacological or non-pharmacological interventions, neither in paediatric nor in adults studies (25). Future research needs to make use of validated measures of fatigue, and interventions should have a measurable effect on these fatigue scores.

Non-pharmacological treatments also warrant further investigation in the paediatric IBD population. Physical activity, mindfulness, cognitive and behavioural therapy are some of the treatments to be investigated, particularly in children and adolescents with cancer. Despite the scarce data in children, Robinson et al. underline the beneficial effect of physical activity interventions and relaxation or mindfulness exercise in the management of fatigue in children and adolescents with cancer (14). Future research can show whether these beneficial effects can also be obtained in children with IBD.

In conclusion, this dissertation addressed the diagnostic strategy that best selects, out of a group of children with gastrointestinal complaints, those that are most likely to have IBD. Secondly, it provides an attempt to quantify and characterise fatigue in children with IBD.

With regard to the former point, we are confident in the quality of the optimal diagnostic strategy (with CRP, haemoglobin and faecal calprotectin). In the field of IBD-associated fatigue, however, it has become apparent that there is a lack of good quality studies. Measuring the efficacy of both pharmacological and non-pharmacological interventions for fatigue should be a research priority to improve the quality-of-life of children with IBD.

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