Diagnostic strategies in children with chronic gastrointestinal symptoms in primary care
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CHAPTER 1

GENERAL INTRODUCTION
Chronic or recurrent gastrointestinal symptoms are common presentations among children in primary care, where they account for approximately 2% to 5% of all childhood consultations. In most cases, these symptoms are attributed to functional gastrointestinal disorders, which are characterized by recurrent or continuous abdominal pain without signs of any inflammatory, anatomic, metabolic, or neoplastic pathology. To avoid delay in diagnosis and treatment of possible organic disease, a thorough assessment of the differential diagnosis is necessary in these children. At the same time, it is important to avoid unnecessary referrals and extensive testing of children with functional gastrointestinal disorders, because this may progress to chronic abdominal pain without reassurance for either children or parents. Indeed, failure to identify functional gastrointestinal disorders can have a major impact on both healthcare systems and the wellbeing of children. Early recognition of, and appropriate coping strategies for, functional abdominal symptoms can enable faster recovery and prevent associated familial, psychological, and co-morbid conditions. Because symptoms of functional gastrointestinal disorders may be indistinguishable from organic disease, it is a diagnostic challenge for physicians to differentiate between them accurately.

INFLAMMATORY BOWEL DISEASE

The differential diagnosis of chronic abdominal pain is broad and includes constipation, functional gastrointestinal disorders, gastroenteritis by parasites or colonic pathogens, celiac disease, and inflammatory bowel disease (IBD). Of these, IBD is an organic disease, comprising Crohn's disease, ulcerative colitis, and IBD unclassified, for which general practitioners should be vigilant. Although the incidence of IBD is increasing among children aged younger than 18 years, the overall incidence remains low at 5.2/100,000 new cases per year in the Netherlands. The clinical presentation of IBD can be very diverse and atypical. While the combination of rectal bleeding and diarrhoea is the most common presentation of ulcerative colitis, Crohn's disease may present with abdominal pain, diarrhoea, anaemia, unexplained weight loss, or growth failure. In children with suspected IBD, diagnosis should be made by endoscopy (ileo-colonoscopy and oesophagastroduodenoscopy) with biopsies. However, these are invasive and expensive tests that are limited to specialist care facilities, requiring general anaesthesia or deep sedation in children. It is also essential that appropriate therapy be started for IBD to reduce the inflammation (induction therapy), maintain remission (maintenance therapy), and improve the nutritional status and quality of life of the child. Any delay in diagnosis and appropriate treatment for IBD may lead to complications such as anaemia, irreversible growth failure, and delayed sexual maturation. In addition, children with IBD may experience social or emotional problems related to unrecognized IBD. Each of these problems can negatively influence the quality of life of children with IBD. Therefore, early recognition and timely treatment is essential, and any assessment of chronic gastrointestinal symptoms would ideally be able to differentiate IBD from other potential causes of the symptoms.

SYMPTOMS, SIGNS, AND DIAGNOSTIC TESTS

In the diagnostic process of children with chronic gastrointestinal symptoms, symptoms and signs should be able to help clinicians safely exclude IBD in children with chronic...
gastrointestinal symptoms, and help them select children who need further diagnostic assessment. However, common “alarm symptoms” (i.e., involuntary weight loss, rectal blood loss, family history of IBD, growth failure, extra-intestinal symptoms, and peri-anal lesions) assessed by history and physical examination, discriminate poorly between functional gastrointestinal disorders and IBD. This diagnostic uncertainty, coupled with the difficult trade-off between avoiding unnecessary referral for invasive testing and not missing a severe case of chronic disease, means that a simple, readily available, and accurate test is needed. According to national and international guidelines, the general practitioner should refer children with chronic diarrhoea and/or recurrent abdominal pain for further diagnostic assessment when alarm symptoms or deviant blood marker results (i.e., c-reactive protein, erythrocyte sedimentation rate, haemoglobin, and platelet count) are present. However, these commonly available blood markers are not specific for intestinal inflammation. Moreover, the recommendations are based on test characteristics assessed in highly selected populations, and these test characteristics may vary across different settings. To date, the added value of blood markers on alarm symptoms is unknown in symptomatic children.

There is no comprehensive overview, in either primary or specialist care, of readily available tests for the triage of children who may need further diagnostic assessment for IBD. Triage instruments are simple and inexpensive tests that can be used to determine which patients should receive the more invasive and expensive existing test. The triage tests may be less accurate that the existing tests and do not need to replace them. An overview of triage tests could assist in suggesting which tests can exclude IBD safely, and which tests can best identify children who need further investigation. This information could improve the clinical decision making of doctors who encounter children with chronic gastrointestinal symptoms.

**Faecal Calprotectin**

Inflammation of the mucosal layer of the colon increases the excretion of neutrophil granulocytes into the bowel lumen. Calprotectin, first described in 1980, is a calcium-binding protein released from activated granulocytes, particularly neutrophils in plasma, tissue, and faeces. Calprotectin resists enzymatic degradation and is stable in stool samples for up to seven days at room temperature, so faecal calprotectin levels can be used as a non-invasive diagnostic test for intestinal inflammation. Thus, a method was developed in 1992 to measure faecal calprotectin, and this was later improved in 2000. The improved method only required 50–200 mg of faeces instead of the 5 g required by the original test, and allowed for stool samples to be collect at home and send to laboratories. Although this conventional testing of faecal calprotectin required laboratory facilities for enzyme-linked immunosorbent assay, point-of-care tests have now become available that allow the patient to bring a stool sample to the clinic and get a test result within 15 minutes.

There are other salient factors to consider with faecal calprotectin. Several studies have shown that calprotectin concentrations are increased in the faeces of adults with IBD, colon cancer, and colonic pathogens, but not in patients with functional gastrointestinal disorders or coeliac disease. Importantly, the calprotectin level has also been shown to be increased in children with IBD, while results for coeliac and other organic diseases are limited in this population. Children with functional gastrointestinal disorders had normal or slightly elevated calprotectin levels. Finally, although the recognized threshold is >50 μg/g faeces for intestinal inflammation, this threshold is not applicable to children younger than 4 years, because young healthy children also have high calprotectin concentrations in their faeces.

**Evidence of Faecal Calprotectin in Children**

Several meta-analyses have shown that faecal calprotectin has a very high sensitivity (0.92–0.98) and modest specificity (0.68–0.76) for IBD in referred children. Therefore, this is an excellent test for excluding IBD when the result is normal, and can prevent unnecessary invasive endoscopies. Although these meta-analyses included studies performed in children with symptoms suggestive of IBD, all of the included studies were performed in children who had a high pre-test probability of disease. Indeed, the referred populations in these studies had a IBD prevalence of approximately 60%. Prevalence may reflect other mechanisms that influence the sensitivity and specificity, such as patient spectrum, referral filter, and reader expectations. These mechanisms may cause that sensitivity and specificity vary in different clinical populations. The prevalence of IBD is much lower among non-referred children presenting in primary care, so it is reasonable to assume that this might influence the sensitivity and specificity of the tests in those settings. The results of the meta-analyses may, therefore, not be generalizable to children presenting in primary care. Before testing with faecal calprotectin can be recommended for children with gastrointestinal symptoms in primary care, more information is needed about the diagnostic accuracy of faecal calprotectin in this population.

**Clinical Relevance**

A test is considered clinically relevant to primary care when it is useful, simple, and non-invasive, with good test characteristics; thus, a test should have a low false-negative rate (high sensitivity) and a low false-positive rate (high specificity). Whether false-negative and false-positive rates are acceptable for patients and for decision making are dependent on the pre-test probability and the trade-off between false negatives and false positives. In children presenting with chronic gastrointestinal symptoms, the probability of having IBD is very low. Therefore, although failure to diagnose IBD is serious in these children, the impact of false positives is much higher than that of false negatives. These false positives may have serious consequences, including excessive testing and decreased wellbeing for children with functional gastrointestinal disorders. A low false-positive rate is important for any test assessing IBD in children presenting with chronic gastrointestinal symptoms in primary care. In contrast, the pre-test probability of IBD is much higher in children presenting with chronic gastrointestinal symptoms and alarm symptoms, and in this population the impact of false negatives becomes higher because of the greater likelihood of IBD. Therefore, false negatives are less acceptable than false positives, and the risks of referral of false positives are reduced, because children might have other organic diseases (e.g., celiac disease).

If the test characteristics are suitable to the primary care setting, it is important to evaluate the added value of testing to symptoms and signs measured by history and physical examination, which are a routine part of daily practice. A key question is whether additional
testing for faecal calprotectin can improve the value of the diagnostic assessment beyond that are already available. If a test could be showed to have good test characteristics and added value to symptoms and signs, it may not only improving the clinical management of patients in primary care but also optimizing the referral of patients to specialist care.

**METHODOLOGICAL RELEVANCE**

The quality of the diagnostic process is essential for the quality of patient care. The number of diagnostic techniques is progressively increasing today. However, the diagnostic value of tests is often not properly evaluated before use in practice, because diagnostic accuracy studies are not a prerequisite for being allowed on the market according to the European CE approval system. To determine the diagnostic accuracy of a test is an essential step in the evaluation of tests. The diagnostic accuracy of a test is evaluated by comparing the results of the test under evaluation with the results of the reference standard in the same patients. Ideally, a cohort of consecutive patients suspected for the condition of interest is included in which both the test(s) under evaluation and the reference standard is performed in all patients.

In primary care, there are two main methodological challenges in diagnostic accuracy studies. Firstly, the prior probability of the disease in patients with symptoms is often low in primary care. Studies performed in patients with low prior disease probabilities have specific methodological challenges with patient selection, because the inclusion of a cohort with a proper number of patients with disease suspicion requires a large population to identify sufficient patients with the disease to calculate the sensitivity with adequate precision. Secondly, reference standards for disease detection are almost always performed in hospital settings and often require invasive tests. Therefore, the evaluation of triage tests in non-referred primary care populations can be difficult or unfeasible. It is important to address and analyse these methodological challenges appropriately to develop analytical and/or methodological solutions.

**OBJECTIVE OF THIS THESIS**

The main objective of this thesis was to study the diagnostic strategies for IBD in children with chronic gastrointestinal symptoms, focusing on the value of testing with faecal calprotectin in primary care.

**OUTLINE OF THIS THESIS**

In chapter 2, we give a systematic overview of the test characteristics for the symptoms, signs, laboratory tests, and combinations of these tests for IBD in children presenting with gastrointestinal symptoms. In chapter 3, we present research into the added value of blood markers and faecal calprotectin testing beyond disease-specific symptoms for IBD in referred children, using individual patient data meta-analysis.

The four subsequent chapters then concern the design and data analysis of the DOK study (DOK: *Darm Onderzoek bij Kinderen*; translated as *bowel research in children*), a prospective cohort study with a follow-up period of 12 months. In chapter 4, we describe the methodological challenges for diagnostic accuracy studies in primary care and present the design of the DOK study. In chapter 5, we determine the diagnostic accuracy of faecal calprotectin in diagnosing IBD in children aged 4 to 18 years and presenting with chronic gastrointestinal symptoms in primary care, by comparing test results with endoscopy or clinical follow-up results. In chapter 6, we compare the added diagnostic value of c-reactive protein and faecal calprotectin beyond alarm symptoms to determine the optimal diagnostic test strategy for referral for specialist care in children suspected of IBD. In chapter 7, the diagnostic accuracy of a point-of-care test for faecal calprotectin and lactoferrin in primary care is evaluated. Finally, in chapter 8, we discuss the implications of our findings for clinical practice, methodology and future studies.
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