The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease.

Paul Henderson, MBChB, MRPCH, Aoife Casey, MBChB, Sally J. Lawrence, MBChB, MRCPH, Nicholas A. Kennedy, MBBS, Kathleen Kingstone, BDc, MSc, MPhil, Pam Rogers, RGN, RSCN, Peter M. Gillet, MBChB, FRCP, FRCPH and David C. Wilson, MD, FRCP, FRCPH.

Am J Gastroenterol advance online publication, 28 february 2012

ELS VAN DE VIJVER
Pediatric gastro-enterology, hepatology and nutrition Department
Antwerp University Hospital,

Els Van de Vijver
is currently working as a pediatric gastroenterologist at the Antwerp University Hospital. She has a broad interest in IBD, more specific in fecal calprotectin and anemia in IBD.

Introduction

Diagnosis of IBD is still made by endoscopic assessment and histology. Due to long waiting lists for endoscopy, a procedure considered invasive and uncomfortable, and the rising incidence of IBD in children, a good screening tool is necessary.

Calprotectin is a calcium-binding protein and is found in neutrophil granulocytes. Measured in stool samples, it is a stable marker of mucosal inflammation.

Similar to the development of new drugs, diagnostic test development goes through several phases.1 In phase I of the development of a calprotectin test, researchers showed that patients with IBD have different test results from healthy individuals. In Phase II studies researchers compare fecal calprotectin levels between preselected groups of healthy individuals and of individuals with severe IBD and show that the test can discriminate under ideal circumstances. Phase III studies evaluate whether fecal calprotectin can discriminate in routine pediatric practice. In this type of studies, patients in whom it is clinically reasonable to suspect IBD are consecutively enrolled. All patients are included, regardless of lost results or indeterminate diagnosis. In Phase II studies, the same reference standard is used for patients with and without IBD. Phase III studies more often use different standards for patients with and without the disease.

What this paper is about/ what are the key findings?

This paper is a retrospective case-control study that evaluates the diagnostic accuracy of fecal calprotectin (FC) in suspected IBD compared to six commonly used blood parameters and endoscopy as the reference tests. The study patients, who had FC measured as part of their initial diagnostic work-up, were identified from a departmental database from all incident cases of pediatric IBD (PIBD) diagnosed by the PORTO criteria since August 1997. This search resulted in 91 patients with IBD and 99 non-IBD (control) patients during the 6-year period of FC data from 2005 to 2010.

The following key findings were found in this article: (1) children with IBD have significantly elevated FC at diagnosis compared with controls undergoing endoscopy. The authors calculated the diagnostic accuracy for different cutoff levels. As mentioned in other articles, using the manufacturer's cutoff of >50 µg/g results in high sensitivity (0.98) but low specificity (0.44) for IBD. (2) FC levels in children with IBD are not influenced by sex, age, IBD type or disease location. In the examined IBD patients there was no difference in the median FC levels between those with upper intestinal CD location and those without. CD patients with isolated colonic or ileo-colonic disease had a similar median FC level compared with those with UC and IBD-U combined. (3) FC performs better than commonly used blood parameters as a diagnostic biomarker during the evaluation of children with suspected IBD. The area under the curve was greater than all six blood parameters at 0.93 (95% CI 0.89-0.97) and significantly higher than ESR (P= 0.011), CRP (P=0.006), total white cell count (P<0.001), hemoglobin (P<0.001), and platelet count (P<0.001), but was not significantly greater than albumin (P=0.374).

Critical Remarks

This evaluation of the diagnostic accuracy of FC is a Phase II study. There was no inclusion of consecutive patients in whom it was clinically justified to suspect IBD. The authors selected retrospectively all patients who had FC and upper and lower endoscopy, not those who fulfilled the criteria for suspicion of gut inflammation. So they could not formulate the answer to the hypothesis stated in the introduction: "We therefore hypothesized that the diagnostic accuracy of FC in suspected PIBD would be equivalent to endoscopy and superior to six commonly used blood parameters."

The authors cannot conclude whether diagnostic accuracy is equivalent to endoscopy because they did not take into account the number of patients, who had an elevated calprotectin without endoscopic evaluation. Hence, the measures of diagnostic accuracy of fecal calprotectin are overestimated. The authors mentioned a long waiting time for endoscopic evaluation. One can therefore assume that only those patients with high clinical suspicion for IBD went on to have endoscopic evaluation. This can lead to selection bias.
Time period between index test (FC) and reference standard (endoscopy) could be up to six months. This is a rather long period considering IBD as a disease with exacerbations and spontaneous remissions. The same remark applies to the blood results evaluated in six months within the endoscopy. These could over- or underestimate the diagnostic accuracy of FC.

A valid reference test was used but the index test and reference test were not independently judged. The authors mentioned this in the discussion but although none of the endoscopies were annulated, some patients with high FC and low clinical suspicion were not endoscopically evaluated and could have a delay in diagnosis with a possible overestimation of the sensitivity.

It is not clear from the article if the decision for the reference test was independent of the results of the index test for all patients.

Conclusion

This study is confirming in a large pediatric study population that FC discriminates under ideal circumstances. What this study adds is that fecal calprotectin at diagnosis of IBD is not influenced by age, sex, PIBD type, or disease location.

The diagnostic accuracy of the commonly measured blood parameters (ESR, CRP, total white cell count, hemoglobin and platelet count) is low in a study population of children with a high clinical suspicion of IBD

References

1. Knottnerus JA, Buntinx F, The evidence base of clinical diagnosis, theory and methods of diagnostic research. Second edition. Table 2.3 p29