ANNALS OF GASTROENTEROLOGY 2004, 17(2):138-139

Editorial

Calprotectin: A sensitive marker of intestinal inflammation

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Whether inflammatory or neoplastic, the cause of elevated calprotectin MUST be ascertained by endoscopy or radiography. If these evaluations do not yield signs of overt disease, other tests may be considered to uncover causes of chronic bowel inflammation. The upcoming studies that are underway should provide answer to the question of whether if fecal calprotectin is going to become a standard test for early detection and treatment/ activity monitoring in IBD.

Crohn's disease and ulcerative colitis are related conditions characterized by periods of remission marked by episodes of clinical relapse. The landmark of a clinical relapse, namely an increase in symptoms, is usually due to acute intestinal inflammation. Treatment is primarily aimed at reducing inflammation during relapse and secondarily at prolonging the time spent in remission. Conventionally, both of these aims are governed by consideration of clinical symptoms, rather than objective evidence of inflammatory activity. Symptoms of inflammatory bowel disease (IBD) often appear to be the direct consequence of the inflammatory process itself, and frequently vary, depending on the location of the inflammation. Most patients with quiescent IBD have low-grade inflammation and it is possible that symptomatic relapse occurs only when the inflammatory process reaches critical intensity. Furthermore, because inflammation is a continuous process, direct assessment of the level of inflammatory activity may provide a quantitative pre-symptomatic measure of impending disease relapse. The clinical implications of this knowledge, if substantiated, are considerable. It may allow targeted treatment at an earlier stage (with fewer side effects) to avoid the relapse, as well as assessment of new therapeutic strategies for maintenance of symptomatic remission

Recently there has been an increased interest in calprotectin as a marker of inflammation in IBD[1-4]. Nycomed Pharma AS, a Norwegian company, has had a fecal calprotectin ELISA test from 1994. and a review of this topic has been written by their Diagnostics Research Manager[1].

Calprotectin is a calcium binding protein with antimicrobial activity derived predominantly from neutrophils and monocytes. Since 1980, when it was first described and named L1, it has been found to have clinical relevance in cystic fibrosis, rheumatoid arthritis, IBD, colorectal cancer, HIV and other inflammatory diseases. Its level has been measured in serum/plasma, oral, cerebrospinal and synovial fluids, in urine and feces. Apparent advantages of fecal calprotectin in GI disorders were recognized early on: stable for 3-7 days at room temperature enabling possible sample shipping through regular mail, correlated to fecal alpha 1-antitrypsin in patients with Crohn's disease, and elevated in the great majority of patients with gastrointestinal carcinomas and IBD[2]. Comparing this marker is standard fecal occult blood screening in colorectal cancer, a group from Mayo Clinic suggested that the mechanism of luminal calprotectin entry appears to be both different from and less erratic than bleeding[3]. It was found that fecal calprotectin correlates well with endoscopic and histological gradings of disease activity in ulcerative colitis[4], and with fecal excretion of indium-111-labelled neutrophilic granulocytes, which has been suggested as the gold standard of disease activity in IBD[5].

Current reports show that clinical indices of disease activity in IBD do not adequately reflect the degree of inflammation in remission or prior to diagnosis. Elevated levels of calprotectin in these patients are, according to researchers, a much better predictor of relapse than standard inflammatory markers (ESR, CRP, Hb, small intestinal permeability). At a cut-off level of 50 mg/l the

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sensitivity of calprotectin for predicting relapse was 90% with a specificity of 83%[6].

Fecal calprotectin has several characteristics of an ideal test: simple, non-invasive, and low cost. These features allow for serial monitoring of the disease activity and treatment success, especially in evaluation of new and empirical drugs. Most recently this test was shown to be able to disclose treatment failure, allowing for these patients to avoid prolonged, useless courses of steroids[7].

A delay from the onset of symptoms to diagnosis has been recognized in IBD, with Crohn's disease having a longer delay than ulcerative colitis. A recent study has found that this delay stems from the prolonged prodromal period (symptom duration with negative investigation)[8], rather than from delay to consult and be referred to a medical specialist, as previously reported. During the prodromal period, 1/4 of the patients were given a wrong diagnosis of IBS. An important indication for fecal calprotectin test would be to distinguish between inflammatory (IBD) and functional chronic GI disorder (IBS), allowing for earlier diagnosis when the treatment has more potential to change the natural history of the disease.

A hint of diagnostic indication for this test was a finding that fecal calprotectin, although significantly increased in children with UC and Crohn's, did not differ from controls in children with indeterminate colitis[9]. In another study, this test (at 200 ug/g value) was able to distinguish the inflammatory process in patients with diarrhea with sensitivity of 78%, specificity 87%, PPV 67% and NPV 92%[10].

IN CONCLUSION

Calprotectin is a sensitive, stable marker that is unaffected by medication, dietary supplements, or enzymatic degradation. This neutrophil-derived protein:

- Reflects the flux of leukocytes into the intestinal lumen.
- Can be conveniently assessed in small samples sent by mail.
- Correlates strongly with 111-indium-labeled leukocyte excretion (the "gold standard") as well as histologic and endoscopic grading of disease activity in ulcerative colitis.
- Helps differentiate between Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD).
- Predicts relapse in patients with IBD, and serves as an objective marker to assist in deciding when to treat.
- Assists in selecting patients for endoscopy and in monitoring response to treatment, especially in children who may require general anesthesia to undergo more invasive analyses.

Simple, reliable, and noninvasive, calprotectin can be assessed often:

- To assist in selecting patients with abdominal symptoms who may require further diagnostic procedures.
- To distinguish between IBD, IBS, and gastrointestinal neoplasm.
- To select children for endoscopy.
- To determine disease activity and risk of relapse in IBD.
- To monitor IBD treatment response and to determine when a clinical remission has been achieved
- To evaluate efficacy in trials of new treatments for IBD.

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