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Original article

The importance of calprotectin for differentiating organic inflammatory disease and avoiding unnecessary procedures in paediatrics

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ABSTRACT

Background and objective: The objective of the study was to determine the ability of faecal calprotectin to differentiate functional and organic intestinal diseases in paediatric patients, and to evaluate the correlation between inflammatory parameters and levels of faecal calprotectin.
Patients and methods: This retrospective study involved clinical data from 129 paediatric patients with symptoms of intestinal pathology. Faecal calprotectin was determined by quantitative immunoassay. Patients were classified into three groups: functional (32.8% of patients); organic non-inflammatory bowel disease (IBD, 53.9%); and organic IBD (13.3%).
Results: Calprotectin levels were significantly different among the three groups; between patients with IBD and the others, and also between patients with non-organic IBD and functional. Positive associations were found between high levels of calprotectin and higher erythrocyte sedimentation rate (rho = 0.497), C-reactive protein (rho = 0.460), and platelet count (rho = 0.232). Nevertheless, an inverse correlation was found between high levels of calprotectin and transferrin saturation (rho = −0.310), albumin (rho = −0.412), and haemoglobin levels (rho = −0.309).
Discussion: Determination of faecal calprotectin is a complementary tool in clinical practice for discriminating between functional and organic IBD, avoiding, according to the levels of calprotectin, unnecessary invasive procedures in paediatric patients.

Importancia de la calprotectina para la diferenciación de la enfermedad inflamatoria orgánica y la evitación de procedimientos innecesarios en pediatría

Palabras clave:
Calprotectina
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RESUMEN

Antecedentes y objetivo: El objetivo de este estudio fue determinar la capacidad de la calprotectina fecal para diferenciar las enfermedades funcionales y orgánicas en los pacientes pediátricos, y evaluar la correlación entre los parámetros inflamatorios y los niveles de calprotectina fecal.
Pacientes y métodos: Este estudio retrospectivo incluyó los datos clínicos de 129 pacientes pediátricos con síntomas de enfermedad intestinal. Se determinaron los valores de calprotectina fecal mediante inmunoensayo cuantitativo. Se clasificaron los pacientes en 3 grupos: funcionales (32,8% de pacientes), enfermedad intestinal inflamatoria no orgánica (EII, 53,9%) e EII orgánica (13,3%).
Resultados: Los niveles de calprotectina fueron significativamente diferentes entre los 3 grupos; entre los pacientes con EII y el resto, y también entre los pacientes con EII no orgánica e EII funcional. Se encontraron asociaciones positivas entre los niveles altos de calprotectina y la tasa de sedimentación eritrocítica alta (Rho = 0,497), proteína C reactiva (Rho = 0,460) y recuento plaquetario (Rho = 0,232). Sin embargo, se encontró una correlación inversa entre los niveles altos de calprotectina y la saturación de transferrina (Rho = −0,310), albúmina (Rho = −0,412) y niveles de hemoglobina (Rho = −0,309).

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Discusión: La determinación de la calprotectina fecal es una herramienta complementara en la práctica clínica para discriminar entre EII funcional y EII orgánica, y evitar con arreglo a los niveles de calprotectina, los procedimientos invasivos innecesarios en pacientes pediátricos.

Introduction

A frequent challenge that gastroenterologists face at the time of diagnosis is the differentiation between functional and organic intestinal disorders.[1] Intense abdominal pain, diarrhoea, and generalised malaise are symptoms frequently associated with functional gastrointestinal disorders, including functional abdominal pain, irritable bowel syndrome, functional dyspepsia, and abdominal migraine.[2] Nevertheless, patients with organic intestinal disorders (Crohn's disease and ulcerative colitis) also experience some of these symptoms.[3] Crohn's disease and ulcerative colitis are chronic disorders characterised by the inflammation of the gastrointestinal tract. Diagnosis and confirmation require invasive endoscopic or radiological procedures that have potential risks, especially in paediatrics.[4] In contrast, the diagnosis of irritable bowel syndrome is mainly based on symptoms.[5] Different acute-phase reactants such as ESR (erythrocyte sedimentation rate) and C-reactive protein (CRP) have been traditionally used as serological markers of inflammation. In the last few years, faecal calprotectin has become a biomarker for the diagnosis of IBD.[6–8] Calprotectin is a protein of the S100 family that is released mainly by neutrophils, monocytes and macrophages.[9,10] It constitutes the response generated by the innate immune system. Calprotectin also exerts antibacterial, pro-apoptotic, and chemotactic activity.[11–13] Calprotectin has been measured in serum, plasma, saliva, urine, cerebrospinal fluid, and synovial fluid. The highest concentration has been found in faeces.[14,15] Plasma calprotectin levels have been shown to increase about 5–40 fold under inflammatory and pathological conditions. Faecal levels are approximately 6 fold higher than plasma levels.[16] Calprotectin is stable in stools for >7 days due to its resistance to proteolytic degradation. Despite the number of studies characterising faecal calprotectin in recent years, data on paediatric populations are still incomplete.[17–20] The objective of the study was to determine the ability of faecal calprotectin for differentiating between functional and organic (intestinal bowel disease, IBD, and non-IBD) diseases in paediatric patients, and to evaluate the correlation between traditional inflammatory parameters and levels of faecal calprotectin.

Patients and methods

This retrospective study involved clinical data from 129 paediatric patients presenting to the Department of Paediatric Gastroenterology at Miguel Servet University Hospital with symptoms of intestinal pathology, including intense abdominal pain, diarrhoea, weight loss and rectal bleeding, between August 2013 and January 2015. The primary endpoint included a differential diagnosis between functional disorder, organic IBD, and organic non-IBD by using faecal calprotectin. The second endpoint involved the analysis of correlation between clinical parameters and levels of calprotectin. Before establishing the final diagnosis, all patients underwent a complete evaluation of serological parameters, including ESR (mm/h), CRP (mg/dl), transferrin saturation (%), serum ferritin (ng/ml), albumin (g/dl), haemoglobin levels (g/dl), and platelet count/l. Faecal calprotectin was also determined in all patients. A stool sample was collected from each patient and frozen at −70 °C until analysis. The quantitative determination of calprotectin levels in faeces was performed by Quantum Blue® immunoassay (Bühlmann Laboratories AG). Functional gastrointestinal disorders were diagnosed by following Rome II paediatric criteria.[21] Intestinal inflammation was evaluated in patients with cystic fibrosis as part of the annual nutritional and digestive monitoring. Procedures were performed in accordance with guidelines established by the hospital's Ethics Committee.

Statistical analysis

Categorical variables were expressed as absolute and relative (%) frequencies and continuous variables as median and interquartile range (IQR). Comparisons between diagnostic groups were performed by using Mann–Whitney *U* test and Bonferroni correction. The correlation between calprotectin levels and serological parameters was evaluated by performing a Spearman's rho test. The statistical significance was established for $p \leq 0.05$. All statistical procedures were performed with SPSS 15.0 software.

Results

Although the initial number of paediatric patients was 129, diagnostic information was not available for one of them and the total number of patients included in the analysis was therefore 128. The reasons for presenting to the specialist are shown in Table 1, the main ones being: abdominal pain (41 patients, 32.0%); cystic fibrosis (29, 22.7%); rectal bleeding (16, 12.5%); and diarrhoea (14 patients, 10.9%). According to the final diagnosis, patients were classified into three groups: functional (42 patients, 32.8%); organic non-IBD (69, 53.9%); and organic IBD (17, 13.3%) (Table 2). Of the 129 patients, 70 were male (54.3%) and 59 female (45.7%), with a mean age of 9.1 years (SD 4.5). Demographic and clinical characteristics of patients according to final diagnosis are shown in Table 3. Median values of parameters at baseline were: ESR 11.0 mm/h (IQR 4.0–26.0); CRP 0.11 mg/dl (IQR 0.03–0.31); transferrin saturation 20.7% (IQR 15.0–25.5); ferritin 44.2 ng/ml (IQR 23.5–77.5); albumin 4.4 g/dl (IQR 4.2–4.7); haemoglobin 13.1 g/dl (IQR 12.4–13.6); and platelet count 2.8×10^5/l (IQR $2.3–3.4 \times 10^5$). To establish the final diagnosis, specialists needed to perform an endoscopy in 52 patients (41.3%). Of these, 11 patients (26.8%) were

Table 1
Reasons for presenting to the specialist for the total number of paediatric patients.

Reasons for presenting to the specialist, *n* (%)	Total (*N* = 128)
Abdominal pain	41 (32.0)
Abdominal pain and weight loss	4 (3.1)
Cystic fibrosis	29 (22.7)
Diarrhoea	14 (10.9)
Diarrhoea and weight loss	2 (1.6)
Rectal bleeding	16 (12.5)
Rectal bleeding and diarrhoea	7 (5.5)
Rectal bleeding and constipation	1 (0.8)
Crohn's disease	2 (1.6)
Fistula	2 (1.6)
Hirschsprung's disease, colostomy	2 (1.6)
Underweight	2 (1.6)
Melaena	1 (0.8)
Pallor	1 (0.8)
Melaena and haematemesis	1 (0.8)
Raised markers for coeliac disease	1 (0.8)
Vitamin B12 deficiency	1 (0.8)
Iron-deficiency anaemia	1 (0.8)

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