Gastrointestinal Involvement in Extra-Digestive Disease

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Calprotectin (CP) is a dimer composed of S100A8 and S100A9, which are calcium and zinc binding proteins. CP is found mainly in neutrophils, where under constitutive conditions, it represents about 45% of the total cytosolic protein. Moreover, calprotectin is constitutively expressed by monocytes, macrophages, dendritic cells oral keratocytes and squamous mucosal epithelium. In inflammation, the expression of calprotectin is increased. CP is released by neutrophils, monocytes, and macrophages during inflammation due to its antimicrobial properties. CP can be detected in serum, urine, cerebrospinal, synovial, and pleural fluids in proportion to the degree of any existing inflammation, but the most useful and widely used form is in stool as a reliable marker of intestinal tissue inflammation. Moreover, CP concentration in feces is approximately six times higher than in plasma.

fecal calprotectin psoriasis behcet's disease atopic dermatitis

1. Fecal Calprotectin and Rheumatologic Diseases

1.1. Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic rheumatic disease characterized by inflammation and ankylosis of the joints (e.g., sacroiliac joints), spine, peripheral joints and entheses but it also affects the eyes, urinary tract, gut and heart. There is a close relationship between spondyloarthropathy (SpA) and IBD. In both diseases the immune system dysregulation, the gut dysbiosis, and genetic factors (HLA B27) play an important role in the development and pathogenesis [1]. Moreover, IBD may be associated with sacroiliitis, arthritis and uveitis. Approximately 50% of patients with SpA have microscopic bowel lesions on colonoscopy and this gut inflammation is associated with more severe axial disease. An interesting hypothesis is that the presence of bowel inflammation with HLS B12 positivity allows the contact between bacterial antigen and the immune system leading to a possible cross mimicry reaction between joints, bone, cartilage and bacteria that contribute to AS-development. Many studies have found an association between FC and SpA. One of the first studies showed that in more than 200 patients, 70% of enrolled subjects with AS had elevated levels of FC greater than 50 mg/kg and 30% showed levels higher than 200 mg/kg. Moreover, the levels of FC were significantly related to the number of tender joints affected, increasing age of patients, and disease duration. On the other hand, all patients had low or normal levels of serum calprotectin [2]. Kang et al. [3] performed a study on 190 patients with axSpA and found that the levels of FC were related to the activity of the disease. Specifically, high FC levels were more closely related to peripheral joint inflammation than to axial joint inflammation [3]. Furthermore, Gazim et al. [4] measured the levels of FC in a series of patients with

anterior uveitis and AS, AS alone, and uveitis of other etiologies to determine whether anterior uveitis with AS had higher levels compared with other groups. In this cross-sectional study performed on 28 patients subjects with AS and both AS and uveitis were found to have elevated levels of FC compared with patients with uveitis, leading them to conclude that the dosage of FC may be useful in distinguishing uveitis associated with spondylarthritis from uveitis of other etiologies. This confirms the close link between AS and colitis.

1.2. Behcet Diseases

Behçet's disease (BD) is a systemic inflammatory vasculitis of unknown etiology. It is characterized by recurrent oral and genital ulcers, skin lesions, and ocular inflammation. In some patients has been observed the involvement of the vascular, neurologic, and gastrointestinal (GI) systems. In their work, Özşeker et al. [5] estimated the usefulness of FC in the detecting intestinal involvement in patients with BD. Their study included 30 subjects affected by BD and 25 healthy volunteers as a control group. FC was the only statistically significantly increased marker of inflammation in patients with BD compared to the control group. No statistically significant differences were found in other inflammatory markers such as C reactive protein (CRP). Subjects with intestinal involvement as ileitis and ulcers in the terminal ileum showed a significantly increase level of FC compared to the group with negative intestinal involvement [5]. Another study confirms these results and suggest FC as a useful tool for diagnosis gastrointestinal involvement in patients with BD. Fecal and serum calprotectin, CRP levels, and colonoscopy were performed in 39 patients with BD. FC, but not serum calprotectin seemed to be a useful noninvasive tool to evaluate disease activity. Moreover, in a multivariate analysis, the FC test was the only significant predictor of remission in patients with [6].

2. Fecal Calprotectin and Dermatological Diseases

2.1. Psoriasis

Psoriasis is a common, chronic, and inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenesis. Skin lesions occur on the knees, elbows, trunk and scalp and are characterized by red, itchy, and scaly patches [7][8]. Inflammation is not limited to psoriatic skin but may involve various organ systems. Therefore, it has been postulated that psoriasis is a systemic entity rather than a simple dermatologic disease [9]. Patients with psoriasis have a leaky gut, which causes increased permeability with increased blood concentrations of metabolites derived from the gut microbiota. This is responsible for the systemic inflammation. The new therapeutic approach based on these mechanisms, attempts to modulate the intestinal barrier and reduce gut inflammation [10]. Few studies investigated the level of FC in patients with psoriasis.

2.2. Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory disorder that affects over 20% of children. Several factors are involved in the development of AD such as an imbalance of the gut microbiota, the dysfunction of the skin barrier, the dysregulation of the immune system, and other environmental factors. Dysbiosis and the resulting intestinal

inflammation seem to play a crucial role in the development of allergic diseases. For this reason, in the recent years, several authors have attempted to evaluate the role of FC as a marker of intestinal inflammation in children affected by AD. Seo et al. [11] studied 65 children with AD and a control group. In 32.3% of enrolled subjects FC was higher than 50 µg/g but they found no significant difference in age, sex, body mass index (BMI), and birth weight between the high or low FC groups. Interestingly, children with higher values of FC showed a more severe AD, a higher blood eosinophil and IgE levels [11]. Orivuori et al. [12] demonstrated in their study that children with a high value of FC at 2 months of age had an increased risk of developing AD later. This risk could be due to the imbalance of gut microbiota in the early childhood determining an increased intestinal inflammation which affects the immune system and promote to the development of AD.

3. Fecal Calprotectin and Neurological Diseases

3.1. Parkinson's Disease

Parkinson's disease (PD) and multiple system atrophy (MSA) are neurodegenerative disorders in which there is an accumulation of insoluble α-synuclein protein in the nervous system, in neurons (PD), or in the glial cells (MSA). Constipation is a very common gastrointestinal (GI) symptom in these patients, and the pathological α-synuclein has been found in the enteric nervous system in both diseases [13][14]. The so-called "gut-brain axis" seems to be involved in the pathogenesis of these disorders, especially in PD. A significant intestinal inflammation associated with increased expression of proinflammatory cytokines has been found in colonic biopsies from PD patients [14]. A causal relationship between the gut and PD has not been established but intestinal dysbiosis, with gut imbalance is common in PD. Moreover, the Resista-PD Trial [15] showed that in PD-patients with a prevalence of proinflammatory bacteria, elevated levels of FC were detected. In addition, epidemiological data suggest an association between IBD and PD. Hor et al. [16] published an interesting paper highlighting the increased levels of FC in patients with PD and MSA compared to controls. The levels are higher in MSA and in patients older than 65 years. These data support the presence of intestinal inflammation in these neurological disorders. At the same time, they found no correlations between FC and gender [16] or PD duration [16].

3.2. Alzheimer's Disease

Alzheimer's disease is a common neurodegenerative disorder, characterized by the accumulation of extracellular aggregates of amyloid-β (Aβ) plaques in the cortical and limbic brain areas of the human brain. The intestinal inflammation seen in Alzheimer's disease affected patients leads to an increase in calprotectin, which may contribute to the formation of amyloid fibril in both the gut and the central nervous system. Calprotectin is composed by two distinct subunits S100A8 and S100A9, which are capable of forming amyloid oligomers and fibrils very similar to α-syn and Aβ. Leblhuber et al. [17] determined the level of FC in a group of 22 patients with Alzheimer's disease and found that it correlated with the level of aromatic amino acids value. They observed that 73% of the patients had high level of FC and the concentrations correlated inversely with the serum levels of tryptophan, tyrosine, and phenylalanine ($p < 0.05$) [17]. Moreover, Horvath et al. [18] discovered a high level of S100A9 subunit in cerebrospinal fluid of patients with Alzheimer's disease. On the other hand, Stolzenberg et al.

[19] discovered a high expression of α-syn in the inflamed intestinal mucosa with a strong attraction to leukocytes (neutrophils and monocytes), which determine the immune response. A possible role of leaky gut in the pathogenesis of Alzheimer's disease was postulated by Kohler et al. [20][21]. The presence of dysbiosis may in some subjects determined a leaky gut with a translocation of bacteria, thus increasing inflammation and accumulation of Aβ. Recent study has also hypotized an implication of *H. pylori* infection in determining an alteration of gastric pH, thus influencing gut microbiota composition and promoting dysbiosis with an increase of proinflammatory bacteria such as *Proteobacteria* and *Enterobacteria* [21].

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