Down’s syndrome and inflammatory bowel disease: Is there a real link?

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ABSTRACT

Down’s syndrome (DS) is a genetic disease that has been associated with several immune and autoimmune diseases, including digestive and liver diseases, like celiac disease, autoimmune chronic hepatitis and sclerosing cholangitis.

Despite in inflammatory bowel disease (IBD) pathogenesis, genetics and immune mechanism play an important role, the association among DS and IBD has been poorly studied. Data about IBD diagnosis in DS patients is very scarce with only some individual case-reports. We report three cases of DS patients diagnosed of IBD and we discuss the possible association of these two entities.

Key words: Down’s syndrome. Inflammatory bowel disease. Immunity.

INTRODUCTION

Down syndrome (DS) is the most common genetic disease and presents with cognitive impairment, cardiac and gastrointestinal abnormalities, in addition to other miscellaneous clinical conditions. DS has been associated with several immune and autoimmune diseases. The abnormalities of the immune system associated with DS include: Mild to moderate T and B cell lymphopenia, impaired mitogen-induced T cell proliferation, reduced specific antibody responses to immunizations and defects of neutrophil chemotaxis (1).

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) characterized by a complex molecular pathogenesis resulting in an exaggerated immune response and mucosal destruction. Recent insights in the interaction of various susceptibility genes with intestinal bacteria have substantially helped to unravel the pathogenesis of IBD (2).

Despite all these, data about IBD diagnosis in DS patients is very scarce with only some case-reports (3,4), but without any case-series published. We report three cases of DS patients diagnosed of IBD and we discuss the possible association of these two entities.

CASE REPORT 1

Our first patient is a 34 year-old woman with DS diagnosed with UC at the age of 24. For medical history, she has a septal communication with left to right shunt. The patient was attended in the clinic because of occasional rectal bleeding. A colonoscopy was performed and revealed ulceration, erithema suggesting IBD from the anus up to 20 cm. The pathological examination confirmed UC so she received oral and topical aminosalicylates not having any problems until two years after the initial diagnosis when she had a new flare. She received systemic steroids but she presented intolerance of them. A colonoscopy was performed and showed inflammation from the anus up to hepatic flexure and an inflammatory stenosis in sigma. The patient partially improved with oral beclometasone.

Four years after the IBD diagnosis, she was admitted to intensive care with abdominal sepsis and hemodynamic instability which meant needing to administer her vasoactive drugs. The analysis was concordant with a septic state.
with 18,628 leucocytes, a metabolic acidosis (pH 7.21, bicarbonate 14, and lactic acid 13.7 mEq/L). She also presented severe anemia (haemoglobin 7 g/dl) and thrombocytosis with 800,000 platelets/dl.

An abdominal computerized tomography revealed a toxic megacolon and an abdominal collection in the lower-right region. Consequently, she received antibiotics and urgent surgery (subtotal colectomy with terminal ileostomy) was performed. After a torpid postsurgical period with a respiratory insufficiency which prolonged her stay in hospital, she was able to be discharged with a normal oral intake and normal bowel movements through the stoma.

Currently, the patient is asymptomatic without IBD drugs and is checked periodically in the clinic.

**CASE REPORT 2**

A 27 year-old man with DS was taken to the Gastroenterology Department to undergo a colonoscopy due to rectal bleeding. The patient did not present abdominal pain or diarrhea and the laboratory examination was also normal. The endoscopy revealed mucosal inflammation from the anus to 60 cm ascending from it with a discontinuous pattern, exudation and geographic ulcers (Fig. 1). Both the macroscopic and the pathological examination of the ileum were normal. Biopsies showed IBD suggesting CD. Small bowel affection was excluded. With the diagnosis of CD of the colon (L2), the patient received topical and oral aminosalicylates with absence of bleeding during the follow-up.

**CASE REPORT 3**

Our third DS patient is a 34 year-old man who was admitted to hospital for the first time in 2010 with vomiting, diarrhea and abdominal pain. His medical history had shown peptic esophagitis, lung tuberculosis in his childhood and a mild mitral prolapse without clinical relevance.

During his stay in hospital, the laboratory findings were normal. He had a haemoglobin level of 14.3 g/dL, leucocytes 11,410 per dl (84 % neutrophils) and the reactive C protein was also normal. The serological test for celiac disease was negative. A stool culture was performed and the result was negative. An abdominal ultrasound did not reveal any abnormalities and the radiological study with bario was normal. The clinical evolution was optimal with conventional medical treatment for support. The diarrhea disappeared in a few days and was discharged with the diagnostic hypothesis of acute gastroenteritis.

He was seen periodically in the clinic and he was doing well for about a year until he had an isolated episode of rectal bleeding and occasional abdominal pain. He was undergone an ileocolonoscopy which reported a cicatricial macroscopic appearance of the right colon and ileocecal valve desestructuring. The result of the biopsies showed an unspecific IBD without dysplasia.

At that moment, the patient received oral and rectal aminosalicylates. Six months later, at the same time as an abdominal pain increase, the biological inflammation markers experienced an upload so we prescribed oral budesonide (6 mg) for two months with substantial improvement. At this moment, the patient is receiving aminosalicylates as a maintenance therapy, with a satisfactory evolution.

**DISCUSSION**

Some authors have postulated that among individuals with DS the frequency of gastrointestinal malformations or disorders, presented mainly in children, is estimated to be around 8 % which would indicate the need to be cautious about dealing with these patients in order to diagnose them adequately (5).

Based on this, Persic (3) reported that gastrointestinal pathologies affecting patients with trisomy 21 are related to developmental abnormalities of the gastrointestinal tract or intestinal pathologies with a similar genetic basis such as gluten gastroenteropathy. By contrast, our clinical impression is that diseases with an immune mechanism like IBD, especially ulcerative colitis, are quite infrequent in DS patients in our clinical practice. In our IBD clinic where about 1,200 patients are attended to, only three (0.2 % of prevalence) have DS which shown a good correlation with the DS prevalence in Spain known to be 0.1 %. This fact support that our findings can be explain “by chance” without any pathophysiology binding mechanism between both entities.

There are controversial data about the association between DS and IBD, for example, Hampe et al. concluded
that genetic factors (like trisomy 21) could be important determinants of susceptibility in IBD in the same way that an association between Ullrich-Turner syndrome (whose genetic alteration is located in the X chromosome) and IBD could be made (6).

Unlike our three patients, in some cases reported by Persic or Yamamoto (4), the IBD was diagnosed during their childhood and they had been published in paediatric journals.

Down’s syndrome has been associated with several immune and autoimmune diseases, including digestive and liver diseases, like celiac disease (7), autoimmune chronic hepatitis (8) and sclerosing cholangitis (9). Several observational epidemiological studies have observed that the incidence and prevalence of autoimmune diseases among DS individuals was higher than in the rest of the population (10), the most frequent lesions being atopic dermatitis (prevalence 35%). Concerning IBD, one in 120 patients in the Wallace’s series had ulcerative colitis (5).

Concerning the immune disorders in DS, Vajro (11) published a case of a DS child with CD and primary sclerosing cholangitis, an atypical association in subjects with a normal karyotype. It is also worth mentioning remarking the conjunction of two entities with an immune or autoimmune component in a DS subject like what Kaushik et al. (12) explained regarding a 33 year-old woman with hypothyroidism who was later diagnosed with autoimmune hepatitis.

The mechanism of the higher prevalence of autoimmune disorders in DS with respect to health controls is not well-established. Ugazio et al. postulated (13) that many abnormalities of the antibody responses are probably conditioned by defective T-cell control mechanisms rather than by intrinsic dysfunctions of B-cells. In addition to this, in DS subjects, a reduced expansion of T-cell precursors in the thymus had been observed, which would probably lead to an incomplete cell repertoire playing a role in the derangement of cellular immune response in DS. Other phenomena related to T-cells had been described, such as the higher representation of immature NK cells with lower intrinsic activity, reduced IL-2 expression, defective phagocyte chemotaxis and oxygen radical production. Besides that, some genes which transcribe proteins directly implicated in the immune response are on chromosome 21, such as interferon receptor, CD 18 or the gene AIRE (14), an autoimmune regulatory gene. We do not know if it is just a coincidental association or if a physiological explanation could be found. On the other hand, we have some observational data supporting the autoimmune exacerbation in DS. These patients had increased IgG and IgA activities to gluten proteins, casein and ovalbumin compared with an age- and sex-matched group of other patients with mental illness in the same hospital (10).

To summarize, in contrast to the clinical impression that IBD is rare among DS subjects, there are some links (immunity factors mainly) between these two entities which could determine the incidence of CD or UC in individuals carrying trisomy. Nevertheless, pathophysiology relationship is unclear and the data came from series of cases… At this point, the affirmation of DS is a predisposing factor to develop IBD cannot be made. Perhaps the more knowledge we obtain about IBD biology, with its immune and genetic component, the more we will understand about the association between IBD and some genetic diseases like DS.

REFERENCES