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EDITORIAL

Abnormal immune regulation in children with irritable bowel syndrome☆,☆☆

Regulación inmune anormal en niños con síndrome de intestino irritable

Irritable bowel syndrome (IBS) is regarded as a multifactorial disorder, but there has been evidence over the last few years leading to the proposal of the presence of abnormal immune regulation due to a decrease in anti-inflammatory cytokines and an increase in the proinflammatory ones.[1] For example, a systematic review suggested the presence of low levels of IL-10 in blood with increased levels of proinflammatory cytokines, even though the results were inconsistent.[2] In a recent meta-analysis by Bashashati et al. that analyzed IL-10 and TNF-α levels, no differences were found in IL-10 between subjects with IBS and controls. However, upon analyzing differences in relation to sex, IL-10 levels were lower in men with IBS vs men in the control group.[3] Furthermore, TNF-α levels tended to be higher in the IBS subjects, compared with the controls.[3] In IBS, increased proinflammatory cytokines derived from peripheral blood mononuclear cells (PBMC) have also been shown in both the baseline period, as well as after bacterial lipopolysaccharide (LPS) stimulation.[4] In addition, lower IL-10 mRNA expression in the colonic mucosa has been reported in patients with IBS vs healthy controls.[5] Nevertheless, all these data are from studies carried out on adults.

In this issue of the *Revista de Gastroenterología de México*, Vázquez-Frias et al. published what is perhaps the first study on the pediatric population that analyzes the free plasma levels of anti-inflammatory and proinflammatory cytokines in Mexican patients with IBS based on the Rome III criteria, compared with healthy controls.[6] They emphasize four findings: *1)* lower anti-inflammatory cytokine IL-10 levels in IBS; *2)* higher proinflammatory IL-12 levels in IBS; *3)* higher levels of TGF-β, and *4)* increased levels of proinflammatory TNF-α in both IBS patients and controls, with no differences between them.[6]

1. In relation to the low levels of IL-10 in IBS reported in the present study, this finding coincides with an analysis from Taiwan, the only other study conducted on children with IBS vs controls.[7] However, unlike the study by Vázquez-Frias et al.,[6] Hua et al. analyzed IL-10 in the supernatant of PBMC cultures stimulated by *Escherichia coli* LPS.[7] Lower IL-10 levels in IBS is in agreement with studies which suggest a protective role for high producer IL-10 gene polymorphisms in this functional disorder,[8,9] although in Mexican patients there was a greater frequency of the low producer IL-10 just in patients with diarrhea-predominant IBS (IBS-D).[10] In addition, the reduced levels of IL-10 in plasma in Mexican children with IBS vs controls also concurs with a previous study carried out on adults in Mexico that found lower levels of IL-10 in volunteers with IBS vs controls.[11] In that study, IBS and female sex were independent predictors of low IL-10 levels, and women with diarrhea-predominant IBS (IBS-D) presented with lower levels of that cytokine.[11] Vázquez-Frias et al. did not make comparisons based on sex and did not provide information on the race and ethnicity of the children in each group. Although one may speculate that the children were mestizo as the majority of the Mexican population, an analysis of the genomic diversity has provided evidence of genetic differences between Mexican subpopulations[12] that should be considered in the design and analysis of association studies of complex diseases such as IBS. Further, the results of the meta-analysis that suggested that the IL-10 rs1800872 (-592A/C) polymorphisms were associated with an increased risk of IBS in Asian ethnicity[8]

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underscores the importance of providing demographic information of the subjects of the study.

2. The higher levels of the proinflammatory cytokine, IL-12, in the present study are controversial. On the one hand, Kindt et al. found lower IL-12 expression in LPS-stimulated monocytes in adults with IBS vs controls in a Belgian study on adults.[13] Moreover, in China, Fu et al. found no differences in IL-12 peripheral blood levels or in its expression in the colonic mucosa in IBS vs controls,[14] and no relation was found between the IL-12 (-1188 C/A) polymorphism and IBS either, all of which makes the association of this cytokine with IBS uncertain.[15]
3. The higher levels of TGF-β in children with IBS, is a novel finding. The role that TGF-β plays in IBS is still unknown, but it could be related to the production of IL-10 from Th1 cells.[16] Also, TGFβ1 is a multifunctional cytokine that may be associated with gastrointestinal and extraintestinal processes. Moreover, in a post-infectious IBS (PI-IBS) murine model, TGF-β1 mRNA expression, together with that of other cytokines, incremented in the longitudinal muscle of the jejunum during acute infection with *Trichinella spiralis*.[17] Later, in the PI-IBS phase, TGF-β1 remained elevated, whereas the Th2 cytokines returned to their normal values. Likewise, the incubation of muscle tissue with IL-4, IL-13 increased the level of TGF-β1. Similarly, the incubation of tissue with Th2 cytokines induced muscle hypercontractility due to TGF-β1 expression and an over-regulation of COX-2 and PGE 2 at the smooth muscle cell level.[17] Therefore, TGF-β1 may be related to smooth muscle hyperactivity which may potentially increase bowel motility in IBS.
4. The absence of differences in TNF-α in children with IBS vs controls contrasted with the study on adults in Mexico, in which higher levels of this cytokine were found in subjects with IBS vs controls.[11] One possibility is that a pathologic stimulus is required, raising the levels of TNF-α throughout a person's lifetime and exacerbating IBS; a follow-up of this cohort would be necessary in order to determine what occurs in later years of age. In fact, in Mexico, it appears that TNF-α in IBS is not genetically determined, given that no differences, at least not in the -308G/A polymorphism, were found.[10] However, an important finding of the present study is the high TNF-α levels in the children with IBS, as well as in the controls. This seems to be related to the kit utilized in the analysis[6] and should be taken into consideration when making comparisons with different studies.

In conclusion, the study by Vázquez-Frias et al. shows that children with IBS, like adults, present with an alteration in immune regulation. Low plasma levels of IL-10 could become an IBS biomarker in Mexico. In addition, further studies are required to determine the role of TGF-β in IBS. Longitudinal studies comparing cytokine levels in children with IBS with active symptoms and asymptomatic children with a history of IBS could help clarify their role in the pathophysiology of IBS. Moreover, it is important to analyze circulating cytokine levels as well as cytokine secretion based on IBS subtypes and the presence of PI-IBS and the need for comparative studies on different populations, utilizing not only the same diagnostic criteria, but also the same laboratory methods.

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Conflict of interest

The authors declare no conflict of interest in relation to the present article.

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