Journal of Neuroimmune Pharmacology (2019) 14:367–368
https://doi.org/10.1007/s11481-019-09841-6

LETTER TO THE EDITOR

Can Our Guts Tell Us Anything About MS?

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Received: 30 January 2019 / Accepted: 4 February 2019 / Published online: 15 February 2019

Dear Editor,

I read with great interest the recent paper by González-Oria et al. (2019) published online in this journal on January 16, 2019. The authors carried out a study evaluating peripheral immune markers in people with Multiple Sclerosis (MS) and also evaluating the status of the intestinal barrier, using the biomarker Intestinal Fatty Acid Binding Protein (IFABP). Of course, various previous studies have revealed changes in peripheral immune markers of lymphocytes and monocytes and their response to diverse immunomodulatory interventions. However, this is one of the first published studies assessing a possible association with the intestinal barrier. From recent and ongoing work, our group has presented data suggesting that IFABP is found in serum more often in people with MS compared to healthy controls (Camara et al. 2018), although the analytical methods used differed significantly from the present study.

Studies have shown that people with MS have increased intestinal permeability (Buscarinu et al. 2017; Yacyshyn et al. 1996). However, in these studies, a "functional" test (lactulose/mannitol ratio) was used to assess permeability, and not all subjects (less than 40%) had an "altered" intestinal permeability. In one of these studies, increased intestinal permeability was also associated with changes in peripheral CD45RO+ B cells (Yacyshyn et al. 1996). An altered intestinal barrier could lead to various changes in the gut immune system, the microbiota-host interactions, and to translocation of bacteria and noxious molecules that could alter neuroimmune responses (Camara-Lemarroy et al. 2018). González-Oria et al.´s findings of no differences in IFABP concentrations are therefore somewhat unexpected. However, I believe there are reasons that might explain this negative result, and that this area should continue to be investigated.

In the present study, the baseline (untreated) population of people with MS was quite heterogeneous, composed of participants with Clinically Isolated Syndrome, Relapsing Remitting MS (RRMS) and Primary Progressive MS (PPMS). First of all, it is unlikely that these 3 populations share similar inflammatory and metabolic profiles that might be related to intestinal barrier function. Studies have shown significantly different metabolomic (Dickens et al. 2014) and microbiome (Branton et al. 2016) patterns in RRMS compared to Progressive MS. Some people with CIS never convert to MS, and data on their baseline risk (MRI metrics and/or Oligoclonal band status) is missing. The inclusion of a treated group of RRMS is helpful, but there is evidence that disease modifying therapies can alter the intestinal barrier itself (Camara-Lemarroy et al. 2018).

The intestinal barrier is a complex, multilayer structure, with many vital homeostatic functions. Non-invasive markers of intestinal barrier function like IFABP exist, but it is unlikely that using a single marker could tell a complete story. IFABP is a small (14–15 kDa) protein, exclusively present in enterocytes, that is released into the circulation upon enterocyte membrane integrity (Grootjans et al. 2010). Elevations of IFABP can be seen after severe structural injury of the gut (ischemia, surgery, sepsis) (Grootjans et al. 2010), and may not be a sensitive marker of subtle intestinal barrier alterations. It has a half-life of a few minutes and enterocytes in intestinal epithelia are in constant turnover over a few days, so a single point measurement might be inexact. IFABP may also change with conditions such as exercise or presence of irritable bowel syndrome (Kartaram et al. 2018), factors that might not have been taken into consideration in the selection of participants.

The intestinal barrier might also be altered, even with stable IFABP levels. The barrier could be hyper-permeable due to paracellular changes in tight junctions not associated with enterocyte loss. There are functional markers of bacterial

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translocation such as D-Lactate and Lipopolysaccharide-Binding Protein that indicate gut barrier disruption that have been shown to be elevated in people with MS (Escribano et al. 2017). Other epithelial markers like Ileal Bile Acid Binding Protein and Citrulline could also be differentially altered or more specific (Grootjans et al. 2010). The microbiome is one of the main regulators of intestinal barrier function (Camara-Lemarroy et al. 2018), and this factor could be an important confounder in any study looking at the gut-brain axis in MS.

Despite the negative results concerning IFABP shown by González-Oria et al., there are still biologically plausible mechanisms that might link the intestinal barrier and MS pathophysiology. This area warrants further research and could lead to novel mechanistic insights and therapeutic avenues.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

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