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CLINICAL COMMENTARY

The subtle link between myenteric ganglionitis and inflammatory bowel disease

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Chronic intestinal pseudo-obstruction (CIPO) is a syndrome associated with chronic or recurrent obstructive symptoms, but without an organic obstruction of the digestive tract.

The first case of CIPO described in a horse dates back to the 90s when myenteric ganglionitis (MG) of unknown origin was diagnosed in a 4-year-old mare. Subsequently, a growing number of cases have been reported, including the one described by Magalhães et al. (2024) in this issue. As anticipated by the authors of this case report, we are facing the eternal question of what came first, intestinal inflammation or enteric neuritis. Possibly there is no right answer as in single cases different mechanisms may lead to the same result. Partial thickness rectal or duodenal biopsies have an important limitation as they do not permit the evaluation of the myenteric plexus. Although a reasonable step in the work-up of a case, in patients nonresponsive to classical management and with recurrent episodes of intestinal obstruction, we should not delay a full-thickness biopsy to reach a more complete diagnosis and better define the prognosis.

Chronic intestinal pseudo-obstruction (CIPO) is a syndrome associated with chronic or recurrent obstructive symptoms, but without an organic obstruction of the digestive tract (Billiauws et al., 2022). Disruption in smooth muscle cells (visceral myopathy), intrinsic intestinal innervation and/or extrinsic autonomic innervation (visceral neuropathy), interstitial cell of Cajal (mesenchymopathy) act alone or together to cause severe dysmotility and related signs of CIPO (Billiauws et al., 2022; Downes et al., 2018). In humans, neuropathy is considered the most common cause of CIPO, which can be further subdivided into inflammatory or degenerative (Downes et al., 2018). A variety of conditions may result in inflammatory neuropathy, including autoimmune diseases, paraneoplastic syndromes, neurological diseases and infections, whereby extensive cell infiltration in the neuromuscular compartment results in ganglionitis, disrupting signalling within the enteric nervous system (ENS). Degenerative neuropathy may be caused by endogenous and/or exogenous insult to the ENS mediated by a noninflammatory response (Downes et al., 2018).

The first case of CIPO described in a horse dates back to the 90s when myenteric ganglionitis (MG) of unknown origin was diagnosed in a 4-year-old mare (Burns et al., 1990). Since then, an increasing number of cases have been reported (Barros et al., 2022; Blake et al., 2012; Chénier et al., 2011; Ortolani et al., 2021; Pavone et al., 2013), including the one described in this issue by Magalhães et al. (2024). Neurotropic viruses, such as equine herpesvirus, were suspected in most cases and confirmed in some of them (Barros et al., 2022; Magalhães et al., 2024; Pavone et al., 2013). Latent infection of EHV-1, indeed, has been demonstrated not only in the most common locations such as trigeminal ganglion and retropharyngeal lymph nodes, but also in abdominal neuronal and lymphoid tissues (Giessler et al., 2020). However, healthy subjects rarely harbour detectable viral DNA in the myenteric plexuses, thus the presence of herpesvirus associated with MG might suggest that the virus could be related with the disease (De Giorgio et al., 2002; Magalhães et al., 2024).

Interestingly, MG has also been reported in association with *Anoplocephala perfoliata* (Pavone et al., 2011). The damage to the ENS observed by these authors may explain the altered motility and recurrent colic commonly linked to this parasite. In this case, the enteric neuropathy is considered secondary to the diffuse gut inflammation or a result of a molecular mimicry mechanism, responsible for an immune cross-reactivity between the parasite and the enteric neuronal cells (Ortolani et al., 2021; Pavone et al., 2011). Motility disturbances and recurrent colic are also common complaints in inflammatory bowel disease (IBD) cases. Similarly, the inflammatory process of the intestine can have a detrimental effect on the myenteric ganglion and the interstitial cells of Cajal causing a subsequent form of visceral neuropathy or mesenchymopathy, as reported by others (Asakawa et al., 2022; Fintl et al., 2020).

Thus, as anticipated by the authors of the last case report (Magalhães et al., 2024), we are facing the eternal question of what came first, intestinal inflammation or enteric neuritis. Possibly there is no definitive answer as in single cases different mechanisms may lead to the same result.

While some authors (Blake et al., 2012; Chénier et al., 2011) put forward the hypothesis of primary ganglionitis with subsequent intestinal dysfunction supported by the fact that in some cases a decreased neuronal density was found in the absence of concurrent inflammatory process (Schusser et al., 2000), others believe that ganglionopathy could be secondary to diffuse severe gut inflammation (Ortolani et al., 2021).

Herpesviruses have received significant attention on this aspect due to their demonstrated enteric neurotropism (De Giorgio et al., 2002; Giessler et al., 2020). If we add that the predominant cells found around the myenteric plexus are lymphocytes, it is reasonable to suspect a viral origin of the disease, even in the cases in which it was not confirmed by PCR (Burns et al., 1990; Chénier et al., 2011). On the other hand, if we consider the myenteric ganglionitis associated with *A. perfoliata* it becomes evident that, in this case, it is the severe local inflammation triggered by the parasite that causes a secondary neuronal degeneration (Pavone et al., 2011).

However, in many cases, the reasoning cannot be so obvious, especially if time has passed from the initial insult and the neuronal degeneration.

Inflammatory infiltrates in the gut mucosa are a nonspecific pattern of hyper-reactivity thus, it is often challenging to find out the exact cause. The immunohistochemical examination could add relevant information, as T cells are the predominant component of an immune-mediated mechanism but might still not clarify the exact underlying cause of such a mechanism.

It is time to consider IBD diagnosed with the classical diagnostic work-up (Vitale, 2022) as a clinical manifestation rather than a definitive diagnosis, as it can assemble different forms, degrees and causes of intestinal dysfunction. In particular, the mucosal infiltrates found on noninvasive biopsies may or may not be the cause or the consequence of neuronal dysfunction.

The authors of the recent clinical report (Magalhães et al., 2024) highlight the limitations of partial thickness rectal or duodenal biopsies as they do not permit the evaluation of the myenteric plexus. Although a reasonable step in the work-up of a case, in patients nonresponsive to classical management and with recurrent episodes of intestinal obstruction, we should not delay a full-thickness biopsy to reach a comprehensive diagnosis and better define the prognosis. From a research perspective, elucidating which microorganisms or immune-mediated reactions contribute to these forms of enteric neuropathies would be extremely interesting. However, in practice, understanding the pathophysiological mechanism at the basis of the intestinal inflammation/dysfunction is more important than identifying a specific pathogen or antigen. Extensive neuronal damage is irreversible, leading to a poor long-term outcome (Chénier et al., 2011) and opening the way to alternative treatments that may help to regulate neuronal survival, development and function (Magalhães et al., 2024).

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ETHICS STATEMENT

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