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EDITORIAL

The enteric nervous system: another forgotten autonomic target in viral infections?

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Tick-borne encephalitis (TBE) is an arboviral infection caused by the TBE virus (TBEV), a flavivirus transmitted via the bite of an infected tick (*Ixodes sp*), found in forested areas in Central and East Europe and Asia. TBE is considered a zoonotic infection, and small rodents are natural hosts, whereas large mammals, such as deer and humans, are infected only accidentally. Rate outbreaks of TBE have been reported following the consumption of dairy products and unpasteurised milk from viraemic ruminants, such as the goat. The incidence of TBEV infection is rising worldwide, and endemic areas are expanding; climate changes may play an influential role in these developments.

TBEV infection usually has a biphasic course. Flu-like features (fever, headache, muscle and joint pain) are common at onset, with non-specific gastrointestinal symptoms and abdominal pain possibly also present during the acute phase. Following a symptom-free interval, neurological signs of the infection appear, with symptoms ranging from mild meningitis to severe meningoencephalomyelitis. The most common clinical manifestations are meningitis (50%), meningoencephalitis (40%) and meningoencephalomyelitis. Encephalomyeloradiculitis causes a severe flaccid paresis of the extremities and is associated with long-term disability [1]. Autonomic dysfunction has been occasionally described in patients infected with the TBEV, including a decreased heart rate variability, reduced bowel mobility and constipation [2].

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In this issue of *Clinical Autonomic Research* Versace et al. describe an elderly patient who suffered severe gastrointestinal autonomic dysfunction following encephalomyeloradiculitis due to infection with TBEV [3]. The patient presented with flaccid tetraparesis and ataxia. A scan of the brain and spine did not detect any significant abnormality. Three weeks after symptom onset, the patient had recurrent episodes of vomiting, abdominal pain and chronic constipation, which persisted during the following months, causing irreversible ileus. The authors hypothesised that the TBEV had caused a myenteric plexus infection, although no pathological confirmation of viral particles in myenteric cells was performed.

This hypothesis is attractive. Indeed, a study using a TBEV murine experimental model showed that the infected rodents had small bowel distension secondary to infection of the myenteric plexus, paresis and death [4]. TBEV was isolated from the infected mice, and TBEV antigens were detected in the gastric myenteric and celiac plexus by means of immunohistochemical techniques. The authors concluded that TBEV invaded the central nervous system via the autonomic nerves running from the plexus. These findings support the notion that TBE pathogenesis depends on the neuroinvasion route after viraemia and could also explain the cases of TBEV infection following oral ingestion of contaminated dairy products.

Viral infections may affect not only the gastrointestinal system but also the enteric nervous system. There is a growing body of evidence, based on case series and case reports, showing that herpes family virus [varicella zoster virus (VZV), cytomegalovirus, Epstein–Barr virus (EBV)] and JC virus infections may be associated with some cases of chronic intestinal idiopathic pseudo-obstruction (CIIPO) [5]. CIIPO is a chronic and progressive condition characterised by severe impairment of gastrointestinal motility.

Clinical features of CIIPO include recurrent episodes of nausea and vomiting associated with abdominal pain and distension in the absence of mechanical obstruction. It is a life-threatening disorder that often leads to severe weight loss and malnutrition. It is believed that viral infections, among other causes, including metabolic and paraneoplastic syndromes, can affect the neuromuscular layer of the gut and cause this syndrome. Cases of VZV infection associated to acute colonic pseudo-obstruction (Ogilvie's syndrome), severe abdominal pain preceding fatal varicella, autonomic dysfunction and intestinal pseudobstruction symptoms following glandular fever secondary to EBV infection have been published [5]. VZV has also been reported to infect and establish latency in ganglia of the enteric nervous system [6]. Myenteric ganglionitis characterised by inflammatory infiltrates within the myenteric plexuses has been described in EBV infection, and EBV, cytomegalovirus and VZV viral inclusions have been found in the myenteric plexus [5]. JC virus has also been shown to actively infect the enteric glia of the myoenteric plexus in some patients with CIIPO. The localisation of JC virus in enteroglial cells has been suggested to play a possible pathological role in enteric neuropathy [5].

Nevertheless, there is a gap in our knowledge on the pathogenic mechanisms and potential impact of viral infections affecting the autonomic and myenteric system. Some patients who develop significant inflammatory damage of the spinal cord may present with severe bladder and bowel dysfunction. However, there are also patients with arboviral (such as TBEV) and other viral infections that present as polio-like syndromes, in which the primary damage to the enteric system may have been overlooked. Objective measures of autonomic and enteric nervous system function are needed, and these tests should be performed in the context of acute viral encephalomyelitis and other idiopathic infectious or para-infectious conditions affecting the bowel function.

Autonomic dysfunction of the bowel and the enteric nervous system and the link between such dysfunction and viral infections remain a great challenge to physicians and researchers. Some viruses may be responsible for chronic conditions such as CIIPO and also for acute ileus in the context of systemic and central nervous system infections. Further studies are needed to evaluate the impact of TBEV on the enteric nervous system.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interests.

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