As recently reported in this journal by Patel et al., diarrhea is the most frequent gastrointestinal symptoms in COVID-19 hospitalized patients, but its pathophysiology is obscure [1]. Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide member of the calcitonin family. CGRP is widely distributed in the human body and can induce multiple biological effects such as vasodilation or immunomodulation. CGRP has been shown to be the key molecule explaining the pathophysiology of migraine, a disease frequently accompanied by gastrointestinal symptoms. CGRP has two forms differing two amino acids from each other: CGRPα, encoded in CALC-I gene, whose expression is concentrated in sensory neurons within the central nervous system, and CGRPβ, encoded in CALC-II gene, which is specifically located in the enteric nervous system [2].

Interestingly, infusion of CGRP to human volunteers induces migraine-like headache together with diarrhea [3]. Also, the main adverse event of the novel CGRP monoclonal antibodies, highly efficacious in migraine prevention, is constipation [4]. While headache is clearly related to the release of CGRP by the sensory neurons in the trigemino-vascular system, it is tempting to propose a role for the CGRPβ and its enteric receptors in the pathophysiology of CGRP-induced diarrhea.

COVID-19 infection has a wide spectrum of clinical manifestations. Headache and diarrhea, two symptoms seen with CGRP infusion, are among the most common in COVID-19 patients and could perfectly be explained by a CGRP release [1, 4]. Angiotensin-converting enzyme 2 (ACE2) and the serine protease TMRPSS2, the two proteins required for COVID-19 infection, are highly coexpressed in gastrointestinal cells. There is little doubt that direct viral infection is the likely cause of gastrointestinal manifestations, including diarrhea, in COVID-19, but the specific mechanisms involved in diarrhea pathogenesis remain unclear [1]. Our aim was to analyze the levels of CGRPβ in a series of COVID-19 patients with diarrhea.

CGRPβ levels were assessed from morning fasting blood samples in 30 matched healthy controls (mean age = 61.3 ± 15.1 years, range 29–89 years; 66.6% females) and 26 COVID-19 inpatients experiencing diarrhea (mean age = 61.8 ± 15.7 years, range 31–91 years; 69.2% females). The study was approved by our institutional ethics committee. Twenty-two patients (85%) were receiving methylprednisolone (20–80 mg/24 h) and 25 were treated with analgesics. Samples were obtained from December 2020 to May 2021. The blood was collected from the antecubital vein and allowed to clot; afterward, serum was separated after centrifugation for 10 min at 3500 rpm. Aliquots were immediately stored at −80 °C until assayed. CGRPβ levels were determined using a commercial ELISA (CUSABIO; China) strictly following manufacturer’s instructions. The detection limit of the assay was 0.39 pg/mL. CGRPβ levels were significantly elevated in COVID-19 patients (6.3 ± 2.6 pg/mL) vs controls (4.2 ± 2.4 pg/mL) (+26.2%; p < 0.01) (Fig. 1).

We show for the first time a significant elevation in CGRPβ levels in serum of COVID-19 patients experiencing diarrhea as compared to healthy controls. This increase was clear even in the presence of drugs such as corticosteroids or analgesics, which could theoretically diminish CGRP release, supports a role for the β form of this ubiquitous peptide in the gastrointestinal manifestations of COVID-19, and suggests that CGRP, and its β isoform in particular in patients with diarrhea, could be one of the molecules released in the cytokine storm induced by COVID-19 infection. CGRP is known to enhance interleukin-6 production, the main biomarker of COVID-19 severity, which has brought the proposal that CGRP antagonists could be of help in COVID-19 infection [6]. This increase in CGRPβ levels
also supports a role of CGRPβ isoform both in the gastrointestinal manifestations of migraine and in the constipation induced by the novel monoclonal antibodies antagonizing CGRP used in migraine prevention.

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Declarations

Conflict of interest There are no conflicts of interest.

References

1. Patel HK, Kovacic R, Chandrasekar VT et al. Correlation of gastrointestinal symptoms at initial presentation with clinical outcomes in hospitalized COVID-19 patients. Results from a large health system in the southern USA. *Dig Dis Sci*. 2022. https://doi.org/10.1007/s10620-022-07384-0.
2. Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans M. Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. *Nature* 1992;298:240–244.
3. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev* 2014;94:1099–1142.
4. Falkenberg K, Bjerg HR, Olesen J. Two-hour CGRP infusion causes gastrointestinal hyperactivity: possible relevance for CGRP antibody treatment. *Headache* 2020;60:929–937.
5. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. *Lancet* 2019;394:1765–1774.
6. Robertson CE. Could CGRP antagonists be helpful in the fight against COVID-19? *Headache* 2020;60:1450–1452.

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