

Prikaz bolesnika | Case report

## Cyclic Vomiting: a late complication of COVID-19

### Cikličko povraćanje: kasna komplikacija bolesti COVID-19

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#### Summary

The novel coronavirus disease (COVID-19) has caused a great pandemic since the end of 2019. A variety of symptoms have been identified for this disease. In this case series we report 5 patients in different age groups who presented with cyclic vomiting as a late complication of COVID-19. All patients have gone through complete diagnostic process for cyclic vomiting syndrome (CVS) including endoscopy. However, they all showed normal findings. The diagnosis of cyclic vomiting syndrome was made based on the symptoms and normal endoscopic and laboratory findings. We treated all of the patients applying the guideline we previously published regarding treatment of CVS patients. According to the results of the present study, CVS might be a late complication of COVID-19 infection. So, it is necessary for physicians to consider it as a differential diagnosis in patients with recent COVID-19 infection and to be aware of its management in each phase.

#### Sažetak

Novi koronavirus izazvao je pandemiju bolesti COVID-19 od konca 2019. Identificiran je niz simptoma povezanih s ovom bolesti. U seriji slučajeva izvještavamo o pet bolesnika različitih dobni skupina u kojih se cikličko povraćanje pojavljuje kao kasna komplikacija COVID-19. Svi pacijenti su obavili kompletan dijagnostički postupak za sindrom cikličkog povraćanja (SCP) uključujući endoskopiju. Međutim, nalazi su bili u granicama normale. Dijagnoza sindroma cikličkog povraćanja postavljena je na temelju simptoma i normalnih endoskopskih i laboratorijskih nalaza. Svi su bolesnici liječeni prema prethodno publiciranim smjernicama za liječenje bolesnika sa SCP-om. Rezultati ovog istraživanja ukazuju da bi se SCP mogao smatrati kasnom komplikacijom infekcije COVID-19. Stoga je potrebno razmotriti ovaj sindrom kao diferencijalnu dijagnozu kod bolesnika koji su nedavno preboljeli infekciju COVID-19 i primijeniti odgovarajuće liječenje u svakoj njegovoj fazi.

## Introduction

The novel coronavirus disease (COVID-19) has caused a great pandemic since the end of 2019. A variety of symptoms of this disease have been identified. However, the most common presentation among COVID-19 patients is respiratory disease. Gastrointestinal manifestations such as nausea, vomiting, abdominal pain and diarrhoea are also common COVID-19 symptoms. In addition, studies indicated detection of SARS-CoV-2 RNA in rectal swabs and faeces of these patients even after upper respiratory clearance<sup>[1, 2]</sup>. In the present case-series we present cyclic vomiting syndrome (CVS) as a late complication of COVID-19 in 5 patients. CVS was described as episodes of severe nausea and vomiting lasting for hours to days, which are accompanied by asymptomatic periods in between, lasting weeks to months<sup>[3-5]</sup>. There are four phases of this disorder, including the prodrome (when the patient starts to feel nausea, however is still able to toler-

ate oral medicine), the emetic phase (persistent severe nausea and vomiting), the recovery phase (starts with decreased feeling of nausea and continues to regain the hunger and oral tolerance) and the inter-episodic phase (the period between emetic phases in which the patient is asymptomatic)<sup>[6,7]</sup>. The attacks were estimated to happen 6-12 times per year. Although this disorder is more prevalent in paediatric patients, there are several studies indicating that this disease can develop in adults as well. However, the clinical presentation can relatively differ by age<sup>[8]</sup>. CVS was recently added to the functional gastrointestinal disorders which are gut-brain disorders affecting various parts of gastrointestinal tract and cause symptoms that cannot be attributed to organic aetiologies<sup>[9]</sup>. In this case series we report 5 patients of different age groups who presented with cyclic vomiting as a late complication of COVID-19.

### Case 1

Our first case was a 40-year old male who was previously admitted with fever, dyspnoea, dry cough and a positive sputum PCR test for COVID-19. His past medical history was unremarkable. He was hospitalized for 4 days and after his vital signs were stabilized, he was discharged. His follow up PCR test was negative after 28 days and the patient became completely symptom-free. Meanwhile, a month after the patient's complete recovery, he was referred to our gastroenterology clinic presenting with heavy vomiting episodes associated with headache which started with sudden feeling of nausea and vomiting and recurred for 10 times during the last month. He mentioned no medical history and familial history of migraine. We performed the required neurologic and gastroenterological examinations (ultrasound, endoscopy and neurological consultation). However, no pathologic results were found. The vomiting crisis were stopped after five days, and were followed by a 3-week asymptomatic period. These crises recurred with more severity and the patient has undergone endoscopy which was completely normal. Although the patient did not meet all of the required criteria (NASPHAGN)<sup>[7]</sup> for cyclic vomiting, as the patient was resistant to other medications, such as anti-acid and anti-emetic. We started the cyclic vomiting treatment to which the patient responded well. The diagnosis of cyclic vomiting syndrome was made based on the patient's presentation and positive response to treatment<sup>[4]</sup>. We treated all of the patients applying the guideline we previously published regarding treatment of CVS patients<sup>[3]</sup>.

### Case 2

The second case was a 10-year-old boy firstly admitted with diarrhoea and a positive PCR test for COVID-19. No specific family medical history was reported. No radiologic signs of pathology were found in his chest CT-scan. He was not admitted to hospital. The follow-up PCR test became negative after two weeks. 20 days after his clinical recovery his first episode of vomiting occurred and lasted for two days. Despite receiving anti-acid and anti-emetic treatment his vomiting episodes kept happening every two weeks, each lasting one or two days, for a total of 5 episodes before referral. The patient underwent endoscopy because of persistent vomiting. However, the endoscopic results were completely normal. Other laboratory and imaging studies were negative as well (complete blood count, glucose, electrolytes, metabolic testing, abdominal ultrasound). Based on normal endoscopic results and laboratory tests, the diagnosis of CVS was suspect-

ed and he was treated according to the guideline which resulted in complete recovery and resolution of symptoms.

### Case 3

The patient was a 28-year-old female who complained of a decreased sense of smelling and had positive PCR test for COVID-19. No respiratory signs and symptoms were present and her CT-scan was normal. She mentioned no medical history and no family history of migraine. The patient was managed as an outpatient since no life-threatening signs or symptoms were present. Meanwhile, she was referred to our clinic a month after her recovery and negative PCR test with stereotypical episodes of vomiting each lasting for one day. She had experienced 5 episodes until then. Her complete evaluation including laboratory tests and endoscopy were normal. After exclusion of other differential diagnoses, the diagnosis of CVS was made and the patient was treated based on this diagnosis.

### Case 4

The fourth patient was a 3-year-old girl hospitalized with fever, nausea, vomiting, diarrhoea, lymphocytopenia and a positive PCR test for COVID-19. The patient had no respiratory signs or symptoms. She was hospitalized and received medical and supportive treatment until she was symptom-free and her follow-up PCR test became negative after two weeks. Two months after her complete recovery she experienced 4 episodes of severe vomiting each lasting for two days with 15-day symptom-free periods in between. Although anti-emetic and anti-acid treatment was started, her episodes of crisis did not stop. In addition, endoscopic evaluation did not reveal any pathology. The patient was diagnosed with CVS and received proper treatment.

### Case 5

Our last case was a 40-year-old male who came to the hospital with the chief complaint of abdominal pain and diarrhoea. He also had a positive PCR test indicative of COVID-19 disease. The patient was hospitalized and received supportive treatment. He was discharged 3 days later and his PCR test became negative after two weeks. 25 days after complete recovery from COVID-19, he was referred to the gastroenterology clinic because of intermittent vomiting lasting for 3 weeks. The patient has experienced 6 episodes of vomiting during this time each lasting for about 7 hours. He had consumed all types of antiemetic and anti-acid drugs. However, there was no change in his

attacks. The patient underwent endoscopy which was negative. Considering the resistance to treatment and negative endoscopic findings, the diagnosis of CVS was suspected and he received proper treatment to which he showed a positive response.

### Discussion

In general, patients with COVID-19 infection present with respiratory symptoms and fever, but numerous systemic reviews and meta-analyses have confirmed the involvement of the gastrointestinal system in COVID-19 infection<sup>[2, 10]</sup>. Some studies have also suggested that isolated gastrointestinal symptoms such as abdominal pain, nausea, and vomiting are associated with increased severity of COVID-19 infection<sup>[11]</sup>. SARS-CoV-2 virus enters host cells through functional receptors on the angiotensin-converting enzyme (ACE-II). ACE-II is expressed in type II alveolar cells in the lungs, but evidence suggests that it is expressed in the gastrointestinal tract, as well, especially in the small intestine and colon<sup>[1]</sup>. We reported 5 patients with COVID-19 infection aged 3 to 40 years who experienced recurrent episodes of severe nausea and vomiting 3 weeks to 2 months after complete recovery from COVID-19 infection. After ruling out other possible diagnoses, CVS was considered as the final diagnosis. The aetiology of CVS is not entirely clear. However, studies have shown that there is a link between CVS and other neurological diseases, including seizures, migraine, and even irritable bowel syndrome, so that they may share a common pathophysiology<sup>[12, 13]</sup>. In addition, evidence suggests that neurological disorders might be a complication of COVID-19 infection, as is case with other viral infections such as influenza<sup>[14, 15]</sup>. Also, since SARS-CoV-2 enters intestinal cells through ACE-II receptors, it leads to condition of inflammation, intestinal dysfunction, and altered gut microbiota, resulting in changes in intestinal bacteria, all of which cause intestinal motility disorders. It is suggested that this process might explain repeated vomiting in these patients<sup>[16, 17]</sup>. In addition, headache is one of the most common neurological symptoms of COVID-19 followed by dizziness, hypogeusia, and hyposmia<sup>[18]</sup>. On the other hand, as CVS is a brain-gut disorder, it must be considered that all kinds of physical and psychological stress can stimulate the beginning of CVS or increase the severity of its episodes which can partly explain the patient's unresponsiveness to antiemetics. COVID-19 is not only involved in patients' physical health but also has an alarming impact on their mental health. There are several studies reporting anxiety and depression in COVID-19

survivors<sup>[18-20]</sup>. All of these may partly explain CVS as a complication of COVID-19 infection. Meanwhile, there have been no reports of CVS in patients with COVID-19 infection, and this is the first study to introduce CVS as a possible late complication of COVID-19 infection. In this study, the vomiting episodes were successfully controlled with the treatment we reported earlier. As previously reported in our guidelines, we consider 4 phases for the treatment of CVS; in the phase 1, our goal was to prevent episodes by applying lifestyle modifications (including sleep and diet). In the second phase, infusions of 10% dextrose combined with antiemetic and sedative medications were suggested in order to decrease the neurologic and gut stimulation. Our goal in the third phase was to terminate the episode promptly using a combination of lorazepam, ondansetron, chlorpromazine and diphenhydramine and finally for the patients in phase four who still experience some episodes, we recommended propranolol 1mg/kg for a period of 9 months for prophylaxis.

### Conclusion

According to the results of the present study, CVS might be a late complication of COVID-19 infection. So, it is necessary for physicians to consider it as a differential diagnosis in patients with recent COVID-19 infection and to be aware of its management in each phase.

**Informed consent:** All patients filled a written consent form regarding the usage of their information in this manuscript.

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