

Acquired long QT syndrome due to antiemetics, COVID-19 and *Blastocystis hominis* induced exacerbation of congenital chloride losing diarrhoea

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SUMMARY

Congenital chloride losing diarrhoea (CCLD) is a rare disease caused by mutations in an intestinal chloride/bicarbonate ion exchange channel. Few reports describe CCLD in adults and none has described the impact of a parasitic infection on CCLD. Severe diarrhoea may result in hypokalaemia with QT interval prolongation. Treatment with antiemetics may further increase the QT interval. To raise awareness of this preventable complication, we describe the course of a woman in her 20s with CCLD who developed COVID-19 and a *Blastocystis hominis* infestation. Treatment with antiemetics and hypokalaemia resulted in prolongation of the QT interval to 640 ms. While, the QT interval normalised with discontinuation of antiemetics and electrolyte replacement, patients with CCLD must take precautions to prevent gastrointestinal infections. Regardless, whenever patients with CCLD present to hospital, the authors recommend monitoring the QT interval and avoiding medications that predispose to torsade de pointes.

BACKGROUND

Congenital chloride losing diarrhoea (CCLD) is caused by a rare mutation in the Solute Carrier Family 26 member 3 (SLC26A3) gene.^{1 2} This encodes an intestinal chloride/bicarbonate ion exchange channel.¹² When this ion channel is absent or dysfunctional, faecal chloride loss leads to the excretion of large volumes of watery diarrhoea.¹² If untreated, this results in hypochloraemia, hypokalaemia and hyponatraemia.¹²

There are few reports describing CCLD in adults and none has described the impact of a parasitic infection on CCLD. Severe diarrhoea may result in hypokalaemia with prolongation of the QT interval. To raise the awareness of CCLD and this preventable and treatable complication, we describe the course of a woman in her 20s with CCLD who developed COVID-19 followed by gastroenteritis and was found to have a *Blastocystis hominis* infestation. Treatment with antiemetics and hypokalaemia induced by vomiting and worsening diarrhoea resulted in prolongation of the QT interval to 640 ms.

CASE PRESENTATION

A woman in her 20s (height 156 cm; weight 47 kg; body mass index 19.31 kg/m²) with CCLD usually passed watery diarrhoea two times per day. Oral potassium chloride (16 mmol two times per day)

was required to maintain her electrolyte balance. She and several relatives were diagnosed with COVID-19. Although she denied respiratory symptoms, the SARS-CoV-2 infection had caused fatigue, general malaise and increased frequency of watery diarrhoea (four to five times per day). The diarrhoea improved over 72 hours, but she remained fatigued for several days.

Thirteen days after being diagnosed with COVID-19, she presented to the emergency department (ED) with a 24-hour history of nausea, vomiting, generalised abdominal discomfort and worsening diarrhoea. She had not eaten anything unusual and had only eaten home-cooked food. However, several cohabiting family members had also experienced similar symptoms.

She was initially treated with intravenous fluids and metoclopramide (5 mg intravenous). The vomiting settled and so the patient was discharged home from the ED with domperidone 10 mg three times per day as required, omeprazole and potassium supplements. A few hours later, she returned with persistent vomiting and diarrhoea. Granisetron (1 mg intravenous) was then administered.

On both presentations to the ED, vital signs were unremarkable (table 1). Physical examination revealed only dry mucous membranes and mild generalised abdominal tenderness without guarding or rebound tenderness. Bowel sounds were hyperactive.

INVESTIGATIONS

Ten years prior to this presentation, genetic testing had identified the presence of a homozygous nonsense mutation (p.G187X) in the patient's SLC26A3 gene. This is known to cause CCLD.

Table 1 correlates the patients' vital signs, investigations and treatment over the course of her illness. Although the COVID-19 PCR test was positive when taken on admission to hospital, a COVID-19 PCR test performed 14 days prior to this had also been positive. The chest X-ray was unremarkable.

The ECG performed on the second presentation to the ED (figure 1) revealed marked prolongation of the QT interval (637 ms). An ECG performed after treatment (figure 2) demonstrated that the QT interval had shortened (440 ms).

The PCR test for *Clostridium difficile* was negative. Although stool culture was negative, stool microscopy for ova, cysts and parasites revealed many *B. hominis*.



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Table 1 Timeline correlating the patient's QT interval with select investigations and treatment

Day	0	1	1	1	1	1	1	2	2	2
Time*	20:00	01:00	04:00	10:30	11:30	12:20	21:00	06:20	09:30	16:00
Event	Presentation to ED	Metoclopramide 5 mg intravenous	Discharged home	Return to ED	Granisetron 1 mg intravenous	COVID-19 PCR positive			<i>Blastocystis hominis</i> detected	Discharged home
O ₂ saturation	100% RA			98% RA	99% RA	99% RA	99% RA	99% RA	99% RA	97% RA
RR (breaths per minute)	20			18	18	19	19	20	20	20
HR (beats per minute)	101			95	81	87	76	74	82	78
BP mm Hg	101/68			93/78	110/75	96/75	102/47	105/58	114/58	106/59
Temperature (°C)	36.5			36.7	36.8	36.9	36.9	36.7	36.7	36.8
QTc (ms)						640			440	
Potassium (mmol/L)	3.4					2.7	2.4	3.2		3.5
Magnesium (mmol/L)	0.83					0.78		0.84		
Calcium (mmol/L)	2.44					2.31		2.28		
Sodium (mmol/L)	137					136	140	141		142
Chloride (mmol/L)	92					87	101	104		108
Creatinine (μmol/L)	84					81	66	62		59
Urea (mmol/L)	6.2					9.5	5.3	3.7		3.2
Hb (g/L; mmol/L)	167					159		137		123
	10.4					9.9		8.5		7.6
WBC (×10 ¹² /L)	11.2					9.24		6.57		7.59
Platelets (×10 ⁹ /L)	362					317		255		248
ESR (mm/hour)						5				6
Procalcitonin (μg/L)							0.19			0.13

Timeline correlating arterial blood gases and respiratory support with select investigations and treatment.

*Calcium adjusted for serum albumin.

BP, blood pressure; ED, emergency department; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HR, heart rate; QTc, rate corrected QT interval; RA, room air; RR, respiratory rate; WBC, white blood cells.

DIFFERENTIAL DIAGNOSIS

The patient's diarrhoea was worsened by infection with SARS-CoV-2. However, this improved within 3 days. The COVID-19 PCR test remained positive on admission to hospital, 13 days after the initial diagnosis of COVID-19. However, this is likely

to represent persistent viral shedding rather than ongoing acute SARS-CoV-2 infection.

Although *B. hominis* is an enteric pathogen, asymptomatic carriage is common. The case was therefore discussed with a specialist in infectious diseases. It was agreed that the presence of many *B. hominis* in the patient's stool and the outbreak of similar symptoms among cohabiting relatives suggested that the

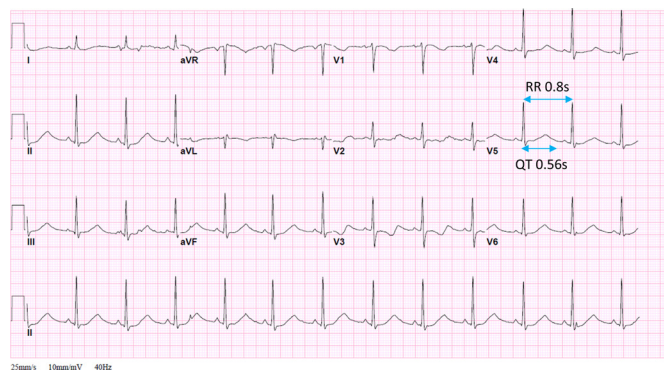


Figure 1 ECG performed after the patient returned to the emergency department shows sinus rhythm at a rate of 75 per minute. The QRS axis is +60°. The QT interval is 560 ms in lead V5. The RR interval is 0.8 s. The heart rate corrected QT interval (QTc) is 622 ms (using Bazett's formula). This is similar to the QTc interval calculated by the ECG machine (637 ms).

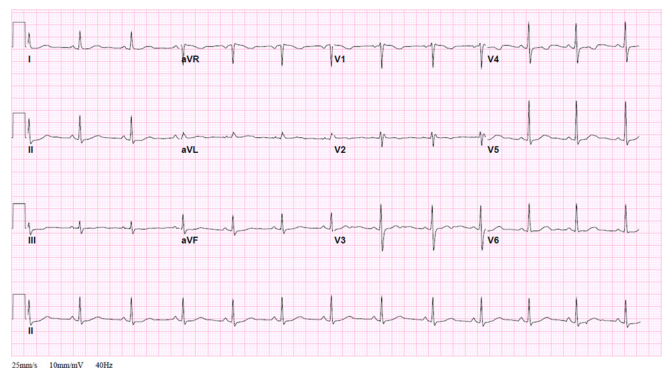


Figure 2 ECG performed after discontinuation of QT prolonging medications and electrolyte replacement shows sinus rhythm at a rate of 75 per minute. The QRS axis is +30°. The rate corrected QT interval is 440 ms and U waves are present in V3-V6.

gastroenteritis was induced by consumption of food or water contaminated with *B. hominis*.

Hypokalaemia developed as a result of increased losses from the gastrointestinal tract and decreased potassium intake due to vomiting induced by *B. hominis*. Electrolytes may also have been depleted during the preceding SARS-CoV-2 infection. However, there was no suggestion that medications, renal losses or the redistribution of potassium were relevant.

At the second presentation to the ED, the QT interval was markedly prolonged. Prolongation of the QT interval may be congenital or acquired. On direct questioning, the patient denied any family history of prolonged QT interval and unexpected sudden death. ECGs performed months to years prior to this presentation confirmed that the QT interval had previously been less than 460 ms. The patient had also received medications that can prolong the QT interval (metoclopramide, granisetron, domperidone) and had developed hypokalaemia. The patient denied any previous episodes of QT interval prolongation. Moreover, the QT interval shortened with discontinuation of these medications and potassium replacement. Indeed, based on the time interval between the patient's ECGs (table 1) the prolongation of the QT interval resolved within 21 hours. Thus, the long QT syndrome was almost certainly acquired after the initial presentation to hospital with vomiting and diarrhoea.

TREATMENT

Continuous cardiac monitoring was initiated. All QT prolonging medications were stopped. The patient was initially kept nil by mouth and intravenous esomeprazole 40 mg per day was administered. The patient was rehydrated with intravenous 0.9% saline and potassium chloride (40 mmol). However, in the setting of magnesium deficiency, hypokalaemia may be refractory to potassium replacement. Furthermore, the QT interval was significantly prolonged. Thus, although the serum magnesium was greater than 0.7 mmol/L, intravenous magnesium sulphate (8 mmol) was also administered.

The management of the symptomatic *B. hominis* infestation was discussed with a specialist in infectious diseases. They advocated supportive therapy and recommended that metronidazole should only be considered if the symptoms of gastroenteritis persisted more than 24 hours after correction of the QT interval.

OUTCOME AND FOLLOW-UP

Within 24 hours of admission to hospital, the patient's vomiting resolved completely, and the frequency of the diarrhoea reduced to the baseline of 2–3 bowel motions per day. As the gastroenteritis resolved spontaneously, no specific treatment was required for the *B. hominis* infestation. However, to prevent recurrent parasitic infection, the patient was advised on personal hygiene, food safety and nutrition. The patient was then discharged home with omeprazole and potassium supplements.

DISCUSSION

B. hominis is a common, anaerobic, intestinal, protozoan parasite that infects humans.^{3–5} Transmission of *Blastocystis* between humans is oro-faecal (eg, via contaminated food and water).⁴

The prevalence of *Blastocystis* is high.⁴ *Blastocystis* infestation has a high rate of asymptomatic carriage, so its role in human health and disease remains unclear.^{3–6} Thus, treatment of *B. hominis* is only recommended if symptomatic patients have many cysts in their stool (>5 per high-power field).

Regardless, *B. hominis* can cause a diverse range of gastrointestinal symptoms (eg, nausea, abdominal pain and diarrhoea).^{7,8}

This can, therefore, exacerbate the osmotic diarrhoea that characterises CCLD. In patients with CCLD intestinal acidity impairs the absorption of sodium, worsening hyponatraemia.² Inadequate secretion of bicarbonate in the gastrointestinal tract and excessive renal losses of protons induce alkalosis.⁹ Compensatory mechanisms to maintain sodium balance induce hyperaldosteronism, worsening hypokalaemia.⁹

Although fatal if untreated, patients with CCLD usually learn how to manage their condition themselves by replacing the faecal losses of water, sodium, chloride and potassium.⁹ However, it is difficult to maintain homeostasis. The present case demonstrates that even relatively minor insults can rapidly disrupt this equilibrium and induce severe electrolyte imbalances.

It is well recognised that hypokalaemia and hypomagnesaemia can prolong the QT interval.¹⁰ Yet, somewhat surprisingly, there are no previous reports of QT interval prolongation in patients with symptomatic *B. hominis* infestation or CCLD. This suggests underdiagnosis of this potentially life-threatening phenomenon in these cohorts. It is also likely that the effect of hypokalaemia on the QT interval in the present case was exacerbated by the administration of antiemetics.

Several classes of antiemetics, including the antihistamines, dopamine antagonists (phenothiazines, butyrophenones, benzamides) and the serotonin receptor antagonists (ondansetron, granisetron) prolong the QT interval.^{10,11} Metoclopramide elimination is dose-dependent.¹² Graffner *et al*, reported that the mean elimination half-life after administration of metoclopramide 5 mg intravenous was 4.4 hours. After administration of metoclopramide 10 mg intravenous, the mean elimination half-life was longer (5.4 hours).¹² The elimination half-life of domperidone is around 7.5 hours.¹³ The mean half-life of granisetron varies from 4.1 to 6.3 hours and its mean residence time is in the range from 5.2 to 8.1 hours.¹⁴

Thus, based on the temporal relationship between their administration and the ECGs demonstrating prolongation and improvement of the QT interval, it is likely that metoclopramide, domperidone and granisetron exacerbated the effects of the patient's electrolyte deficiencies on her QT interval.

Alternative antiemetics that do not prolong the QT interval include stimulation of the Nei guan point at the wrist (acupuncture point PC6),¹⁵ benzodiazepines, cannabinoids, neurokinin receptor blockers and steroids.¹¹

If the QT interval is prolonged, the risk of arrhythmias (ie, torsades de pointes) increases.¹⁰ Thus, serum electrolytes and the QT interval must be monitored in patients with CCLD presenting to hospital. Medications that prolong the QT interval should be avoided. It is crucial for patients with CCLD to take precautions to avoid infections of the gastrointestinal tract.

Learning points

- Congenital chloride losing diarrhoea may cause sudden, severe hypokalaemia.
- Gastrointestinal pathogens can exacerbate congenital chloride losing diarrhoea.
- Medications which prolong the QT interval should be avoided in patients with congenital chloride losing diarrhoea.
- Serum electrolytes and the QT interval should be monitored regularly while patients with congenital chloride losing diarrhoea are in hospital.
- Patients with congenital chloride losing diarrhoea must be advised on how to reduce the risk of gastrointestinal disease.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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