

## *Campylobacter jejuni* bacteremia and *Helicobacter pylori* in a patient with X-linked agammaglobulinemia

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**Abstract** We describe a 15-year-old patient with X-linked agammaglobulinemia who developed malabsorption and bacteremia due to infection of *Helicobacter pylori* and *Campylobacter jejuni*. The *Campylobacter* bacteremia was only recognized after subculturing of blood culture bottles that failed to signal in the automated system. After 2 weeks of treatment with meropenem and erythromycin for 4 weeks, the patient developed a relapse of bacteremia 10 months later with a high level erythromycin resistant *C. jejuni*. Sequencing revealed an A2058C mutation in the 23 S rRNA gene associated with this resistance. Treatment with doxycycline for 4 weeks finally resulted in complete eradication. This case report illustrates the importance for physicians to use adapted culture methods and adequate prolonged therapy in patients with an immunodeficiency. A summary of published case reports and series of patients with hypogammaglobulinemia or agammaglobulinemia with *Campylobacter* or *Helicobacter* bacteremia is given.

### Introduction

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by a mutation in the Bruton Tyrosine Kinase (*BTK*)-gene [1]. This defect leads to abnormal development of B-lymphocytes and hypogammaglobulinemia. Patients with XLA usually present with recurrent bacterial infections, mainly of the respiratory and gastrointestinal tract. Other bacterial infections, like cellulitis, arthritis, meningitis and sepsis have also been described, but are less common. Various case reports mention a specific association of XLA patients and patients with acquired hypogammaglobulinemia with bacteremia caused by *Helicobacter* and *Campylobacter* species (Table 1) [2, 3].

Recently, we treated a boy with XLA who developed fever, loss of appetite and failure to thrive caused by a combination of *H. pylori* gastritis and recurrent *C. jejuni* bacteremia.

### Case report

A 5-year-old Iranian boy with a history of recurrent infections and an absence of peripheral blood B-lymphocytes was diagnosed with XLA. The boy was living in The Netherlands since his fifth year. DNA analysis revealed a frame shift mutation (1614delT) in exon 16 of the *BTK*-gene [4]. He was treated with prophylactic cotrimoxazole and intravenous immunoglobulin (IVIG) substitution therapy every 4 weeks. During the last 3 years, IgG levels varied from 5.0 to 8.7 g/L (normal range for IgG is 5.2–15.0 g/L). To reach a trough level of around 8 g/L he required a high dosage of IVIG of 1.2 g/kg [5]. He had no detectable IgA and IgM. At the age of 10 years he

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**Table 1** Summary of published case reports<sup>a</sup> and series of patients with hypogammaglobulinemia or XLA with *Campylobacter* or *Helicobacter* bacteremia

Reference	Number of patients (age in years)	Disease	Micro-organisms, sites other than blood	Resistance	Symptoms	Treatment, duration (number of relapses of bacteremia)
Le Bar et al. (1985)	2 (24, 36)	Hypo	<i>C. jejuni</i> , Stool	NA	Fever, pneumonia, cellulitis	MC, AMG, 8 months (4), 6 months (1)
Spelman et al. (1986)	2 (25, 29)	XLA	<i>C. jejuni</i>	NA	Cellulitis, fever, ureter colics	MC, AMG, 6 months (2)
van der Meer et al. (1986)	1 (24)	XLA	<i>C. jejuni</i> , Stool	NA	Fever	NA, >1 year (NA)
Chusid et al. (1987)	1 (11)	XLA	<i>C. jejuni</i> , Stool	NA	Malaise	PEN, AMG, 1 week (0)
Kerstens et al. (1992)	3 (26, 20, 24)	XLA, Hypo	<i>C. jejuni</i> , Stool, skin	FQ	Cellulitis, fever, osteomyelitis	CA, MC, 1 ;month (1), 1 year (2), 1 year (2)
Borleffs et al. (1993)	2 (23, 25)	Hypo	<i>C. jejuni</i> , Stool	NA	Cellulitis, fever	CA, FQ, i.v. IgM, 6 months (2), 6 months (3)
Simon et al. (1995)	1 (70)	Hypo	<i>C. jejuni</i>	NA	Arthritis, diarrhea	NA, Patient died
Autenrieth et al. (1996)	1 (7)	XLA	<i>C. jejuni</i>	NA	Cellulitis	FQ, maternal plasma, >2 years (NA)
Moore et al. (2001)	1 (NA)	Hypo	<i>C. jejuni</i> , Stool	NA	Diarrhea	NA, 2 year (5)
Rafi and Matz (2002)	1 (32)	XLA	<i>C. jejuni</i> , Stool, colon, pericardial fluid	NA	Pericardial tamponade, pneumonia	MC, FQ, NA
Tokuda et al. (2004)	1 (16)	XLA	<i>C. coli</i>	NA	Cellulitis	CA, AMG, 6 months (1)
Arai et al. (2007)	1 (35)	XLA	<i>C. coli</i> , Stool	MC	Arthritis, fever	TET, CA, 1 year and 7 months (3)
Okada et al. (2008)	1 (33)	XLA	<i>C. coli</i> , Intestinal biopsy	NA	Endocarditis, osteomyelitis	CA, FQ, TET, AMG, 8 months (4)
Chusid et al. (1990)	1 (16)	Hypo	<i>C. upsaliens</i>	NA	Fever	Ceph, 6 months (1)
Neuzil et al. (1994)	1 (50)	Hypo	<i>C. fetus</i>	NA	Osteomyelitis, cellulitis	CA, MC, 10 months (2)
Jirapongsananuruk et al. (2006)	1 (15)	XLA	<i>C. lari</i>	Ceph, FQ	Sinusitis, fever	AMC, MC, 9 months (3)
Weir et al. (1999)	1 (36)	XLA	<i>Flexispira rappini</i>	PEN, MC, Ceph, FQ	Cellulitis	AMG, CA, 3 years (NA)
Cuccherini et al. (2000)	2 (36, 21)	XLA	<i>Helicobacter, flexispira</i> -like organism	Metr	Cellulitis, synovitis, fever, gastritis	AMG, CA, 1 year (NA)
Gerrard et al. (2001)	1 (27)	XLA	<i>H. canis, Flexispira rappini</i>	NA	Cellulitis, fever	TET, Metr, 2 months (1)
Simons et al. (2004)	1 (54)	XLA	<i>H. cinaedi</i>	NA	Cellulitis	AMG, CA, 3 months (2)
van den Bruele, this paper	1 (15)	XLA	<i>C. jejuni, H. pylori</i> , stool	MC	Fever, anorexia	CA, MC, TET, 10 months (1)

XLA X-linked agammaglobulinemia, Hypo hypogammaglobulinemia, NA not available, i.v. IgM intravenous immunoglobulin M, AMC amoxicillin/clavulanic acid, AMG aminoglycoside, CA carbapenem, Ceph cephalosporin, FQ fluoroquinolone, MC macrolide, Metr metronidazole, PEN penicillin, TET tetracycline

<sup>a</sup> For the references of Table 1 refer to the supplemental material

developed epilepsy caused by left occipital lesions, presumably acquired by infections in the past.

At the age of 15 years he was admitted to our hospital with progressive loss of appetite, initially ascribed to his anti-epileptic medication. He was severely malnourished (weight/length ratio  $-3$  Dutch standard deviation score, comparable to Iranian growth charts). Stool antigen test for *H. pylori* was positive. Endoscopy and biopsies of the gastric antrum, corpus and duodenum showed chronic active inflammation with atrophy and intestinal metaplasia. Cultures of the antrum and corpus were positive for *H. pylori* as well as for *C. jejuni*. Biopsies of antrum and corpus were inoculated on non-selective blood agar media and onto specific *H. pylori* media (Pylori agar, Biomérieux, France) in a micro-aerophilic environment for 7 days. Identification was performed by conventional biochemical reactions according to standard operation procedures [6]. During hospitalization the patient had periods of fever. Laboratory tests showed an elevated C-reactive protein (up to 94 U/L; normal  $<5$  U/L). His leukocyte and neutrophil counts were always normal. Blood cultures revealed *C. jejuni*, sensitive for ciprofloxacin (MIC 0.032 mg/L), erythromycin (MIC 0.75 mg/L) and meropenem (MIC 0.012 mg/L) as determined by *E*-testing (AB Biomérieux, Solna, Sweden). An identical strain was isolated from the patient's feces. Other pathogens were never detected from stool, throat, urine or spinal fluid; cultures or PCR tests were negative for enteric parasites, viruses including enteroviruses and pathogenic bacteria. The patient was treated with intravenous meropenem for 2 weeks, followed by oral erythromycin for another 4 weeks. Repeated blood cultures after 10 days were negative. For eradication of *H. pylori* he additionally received triple therapy with amoxicillin, clarithromycin and omeprazol for one week. *H. pylori* was sensitive to erythromycin (MIC 0.38 mg/L), clarithromycin (MIC 0.19 mg/L) and meropenem (MIC 0.002 mg/L).

During follow-up he improved clinically and with tube feeding his weight increased to  $-1$  standard deviation score. Endoscopy was repeated 8 months later and showed much less inflammation of the gastric mucosa and absence of *H. pylori* in microscopy and culture of biopsies. However, from a fecal specimen a *C. jejuni* strain was isolated with secondary resistance to erythromycin (MIC  $\geq 256$  mg/L) but persistent sensitivity to ciprofloxacin (MIC 0.125 mg/L) and meropenem (MIC 0.008 mg/L). Ten months later, he again developed a *C. jejuni* bacteremia. The strain had a similar pattern as the stool isolate, with high level resistance to erythromycin by *E*-testing (MIC  $\geq 256$  mg/L), but the strain was sensitive to tetracycline. Sequence analysis of part of the 23S rRNA gene revealed an A2058C mutation (position of nucleotide reported as the *Escherichia coli* equivalent), known to be associated with erythromycin resistance [7, 8]. The strain isolated 8 weeks earlier from

the feces did not have this mutation. No other pathogens were isolated. He again had complaints of loss of appetite, no diarrhea or skin lesions and some weight loss. Cotrimoxazole prophylactic therapy was switched to azithromycin (for 2 weeks) and later to doxycycline (for 4 weeks), which resulted in clinical improvement and negative stool and blood cultures at follow-up after 6 months.

## Discussion

In the primary antibody deficiency disorders such as XLA, enteropathogenic *Helicobacter* species and the closely related species *Flexispira* and *Campylobacter* can cause persistent gastrointestinal infections and bacteremia, as well as skin and bone infections [2, 3, 9, 10]. In immunocompetent individuals bacteria are eliminated from the blood by antibody- and complement-mediated lysis. Patients with XLA form no or inadequate specific antibodies [1, 11]. Despite immunoglobulin substitution therapy with normal IgG levels (IgA and IgM antibodies remained absent), severe infections with *Campylobacter* and *Helicobacter* can emerge [11]. Higher IgG through levels during immunoglobulin supplementation may lead to better protection [5].

In the Netherlands the incidence of *Campylobacter* infections is 39 per 100,000 people per year (children and adults) [12]. *C. jejuni* is the most frequently isolated pathogen of the *Campylobacter* species; *C. coli*, *C. lari* and *C. upsaliensis* are less frequently encountered pathogens. Transmission of *C. jejuni* occurs by ingestion of contaminated food (i.e. chicken and pork), water and unpasteurized milk. *Helicobacter* infections in children are acquired early in life, mainly via oral–fecal contact. In the Netherlands, the prevalence of *H. pylori* in children is very low (1.2%); most infected children are offspring of non-Dutch parents like our patient [13]. Our patient had a double infection, which may be coincidental but could also be based on his Iranian background. In Iran, the prevalence of *H. pylori* was reported to be 58% in healthy 15-year-old children [14].

Bacteremia with *Campylobacter* and *Helicobacter* species is frequently found in XLA patients. Winkelstein et al. [2] found a prevalence of 10% in 21 septicemic patients from a series of 201 XLA patients. Recognition of bacteremia with *Helicobacter* and *Campylobacter* species is sometimes difficult, since *Helicobacter* and *Campylobacter* grow slowly in standard automatic blood culture systems. It is recommended to subculture blood culture bottles to solid media after one week of incubation when no signal of growth has appeared. In some microbiological laboratories this is a standard procedure for blood culture bottles from patients with endocarditis or from patients with hypogammaglobulinemia. In our patient the standard blood

cultures were negative; only subculturing resulted in recognition of *C. jejuni*.

Symptoms, antibiotic treatment, antibiotic resistance, and duration of bacteremia of published cases are summarized in Table 1. Twenty-six immunocompromised patients with bacteremia caused by *Campylobacter* or *Helicobacter* species have been described in the literature; only five of these cases were children (<18 years of age). Remarkably, diarrhea or other gastrointestinal complaints are not always present (33–37%) [9]. Erysipelas-like cellulitis was present in 11 of 26 patients (40%); it mostly disappears within several days after start of antibiotic therapy but is an important early clinical sign for *Helicobacter* or *Campylobacter* bacteremia. Five of 25 patients (20%) had septic arthritis or osteomyelitis, which is remarkably high; others described an incidence of, respectively, 7% and 3% in 201 patients with XLA [2].

Most patients needed prolonged antibiotic therapy to eradicate the microorganisms, with a mean duration of approximately 10 months (ranging from 1 week to 3 years). Our patient presented with fever, malaise and anorexia. He had a long lasting and recurrent bacteremia, which almost exclusively appears in immunocompromised patients.

In immunocompetent individuals, *H. pylori* remains a superficial chronic gastritis, with a small percentage of individuals progressing to duodenal or gastric ulcers and rarely to gastrointestinal malignancies. Common variable immunodeficiency patients have an almost 50-fold increased risk for gastric cancer and a 30-fold increased risk for lymphoma [11]. The patient we described did not develop a relapse or recurrent *H. pylori* infection.

Antibiotic resistance of *Campylobacter* species to fluoroquinolones and macrolides is increasing. In The Netherlands, resistance to fluoroquinolones and macrolides is up to 35% and 2.7% of the isolates, respectively [12]. However, the latter may be overestimated, since phenotypical routine susceptibility tests for erythromycin are difficult to interpret [15]. Most *Campylobacter* isolates are sensitive for amoxicillin-clavulanic acid (resistance rate 1–2%) [9]. The strain of our patient had high-level resistance to erythromycin (MIC  $\geq$  256 mg/L). Because of reported difficulties in the phenotypic recognition of erythromycin resistant isolates, the presence of the erythromycin resistant *C. jejuni* was confirmed by 23S rRNA gene sequence; analysis revealed an A2058C mutation [7, 15]. *Campylobacter* isolates displaying resistance to erythromycin usually have resistance-associated mutations at position 2058 and/or 2059 of the 23S rRNA gene. They lead to cross-resistance to macrolide and lincosamide antibiotics. No resistance has been described for carbapenem antibiotics, such as meropenem [9].

The mortality of inadequately treated bacteremia is estimated to be around 2.5–5.5% [9]. The mean duration

of treatment of bacteremia is 10 to 14 days in immunocompetent individuals. In immunocompromised patients longer treatment may be necessary. Also, in our patient the *Campylobacter* was hard to eradicate. He received 2 weeks intravenous treatment with meropenem, followed by 4 weeks erythromycin with apparently good effect. However, despite changes of antibiotic treatment *C. jejuni* remained detectable in his stool cultures, and later on he had a relapse of bacteremia. After a 4-week course of doxycycline, *C. jejuni* could be eradicated.

In conclusion, multiple infections can be encountered in patients with XLA that present with vague symptoms such as failure to thrive, weight loss or anorexia and fever. Bacteremia with the *Campylobacter* species is hard to detect and needs specific laboratory expertise. In patients with agammaglobulinemia, *Campylobacter* eradication can only be achieved with adequate antibiotic therapy and prolonged treatment; *H. pylori* seems easier to eliminate.

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