

# Parechovirus infection preceding Guillain–Barré syndrome

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## Introduction

Since the near global eradication of poliomyelitis, Guillain-Barré syndrome (GBS) has become the most common cause of acute neuromuscular paralysis. In GBS, an autoimmune response is directed towards the Schwann-cell surface membrane, myelin, or axons of peripheral nerves. Recent *Campylobacter jejuni* infection is discovered in 30 % of GBS patients (Poropatich et al. 2010). Other infections preceding GBS include cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* (Hughes et al. 1999).

In this case report, we describe a 36-year-old male Finnish patient with GBS, who had a parechovirus infection preceding the neurological illness. Parechoviruses have not previously been described in context with polyradiculitis.

## Materials and methods

### Ethics statement

A written and signed patients' informed consent was obtained.

### The patient

A 36-year-old previously healthy man presented with a 5-day history of symmetric pain, tingling, and weakness in his

legs. One week earlier, he had a sore throat for a few days. At presentation, he could not walk on heels or toes. Deep tendon reflexes were absent in lower limbs. Cerebrospinal fluid (CSF) findings were consistent with GBS (Table 1). C-reactive protein was <1 ml/L. Ganglioside GM1 antibodies in the serum were marginally elevated to 1,700 units (reference range <800 units). Serum GQ1b IgG and GQ1b IgM antibodies were negative. The hematology analyses were done at the Turku University Hospital Central Laboratory and the ganglioside antibodies at the Helsinki University Hospital Laboratory.

On the second day in the hospital, the patient could walk only with bilateral assistance. Bladder and bowel dysfunction and a bilateral facial paresis developed. After a week, he could not walk even with bilateral assistance, and intravenous immunoglobulin (IVIG) 0.4 g/kg for 5 days was given. Two weeks after the onset of the symptoms, electroneuromyography was consistent with demyelinating GBS showing generally decreased motor nerve conduction velocities and absent tibial nerve F-responses. After the IVIG therapy, the patient started to recover. He was discharged from hospital after 10 weeks and made a complete recovery in 6 months.

### Microbiological analyses

Microbiological analyses were done at the Departments of Medical Microbiology and Virology, University of Turku. CSF analyses are shown in Table 1 and serum, nasal swab, and stool analyses in Table 2. A low titer (400–700 U) of IgG but no IgM or IgA antibodies against *C. jejuni* were detected using an ELISA test (cut-off value for positive AbG indicating a recent *Campylobacter* infection 1,250 U). HIV, *Borrelia burgdorferi*, and *M. pneumoniae* were negative. Picornavirus PCR was positive from a stool sample taken on the day following hospitalization. Bacterial culture from the stool was not done because the patient did not have diarrhea. A

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**Table 1** Etiological laboratory findings in the CSF

	Result	Normal values
Protein concentration	1,250 mg/L	150–450 mg/L
Leukocyte count	$17 \times 10^6/L$	$0-5 \times 10^6/L$
Lactate	2.5 mmol/L	0.6–2.7 mmol/L
Bacterial staining	Negative	
Bacterial and viral cultures	Negative	
HIV Ab	Negative	
Borrelia IgG, IgM, flagella Ab	Negative	
Picornavirus PCR	Negative	

CSF was taken at 5 days from the onset of the neurological symptoms (12 days from the onset of the respiratory symptoms)

CSF cerebrospinal fluid, Ab antibody

further PCR analysis revealed a parechovirus. Parechovirus RT-PCR test was performed from 5'UTR region of the genome (Benschop et al. 2008) with the following conditions: 10 min at 95°C, 45 cycles each consisting of 20 s at 95°C and 1 min at 60°C. For sequencing the amplicon, a parechovirus RT-PCR from the VP 3/1 region was performed (Harvala et al. 2008) with the inner primer pair. The 299-nt long sequence were run in the BLAST search confirming the sequence as parechovirus 1 from the VP1 region. Repeated picornavirus PCR from a control stool sample taken 11 days after the first positive stool sample was negative. Picornavirus PCR as well as a multiplex PCR test (Seplex, Seegene) for 12 respiratory viruses from nasal swabs taken at 6 and 17 days after the neurological symptom onset were negative.

## Discussion

Our patient had a mild clinical parechovirus infection preceding GBS. The most common infections preceding GBS are *C. jejuni* and cytomegalovirus. Cytomegalovirus triggers

more severe sensory symptoms than other infections, whereas *C. jejuni* is associated with motor axonal forms of GBS (Hughes et al. 1999; Poropatich et al. 2010). *C. jejuni* strains isolated from GBS patients have a lipo-oligosaccharide (LOS) with a GM1-like structure. Molecular mimicry between LOS and the peripheral nerves has been demonstrated in animal models of human GBS (Israeli et al. 2010). The criteria for a *C. jejuni* infection preceding GBS include serological evidence of *C. jejuni* infection (*C. jejuni* IgG antibody titer  $\geq 1:2,000$  by ELISA test) and a definite history of diarrhea within the previous 3 weeks of GBS onset (Kuwabara et al. 2004). Our patient had neither diarrhea nor serological evidence of a recent *C. jejuni* infection.

Human parechoviruses (HPeV) are a recently recognized genus in the *Picornavirus* family. The disease entities resemble those caused by human enteroviruses, which belong to Picornaviruses as well. The clinical HPeV symptoms vary from mild respiratory and gastrointestinal infections to more severe central nervous infections and sepsis-like syndromes in infants. HPeV 1 and 2 infections, previous echovirus 22 and 23 in the genus Enteroviruses, are common in early childhood (Joki-Korpela and Hyypiä 2001). During recent years, new parechovirus genotypes have been found by PCR techniques. To date, 16 genotypes are known. HPeV 1 and 6 usually cause respiratory infections and HPeV3 systemic infections and infections of central nervous system (CNS) in neonates (Harvala et al. 2008; Piñeiro et al. 2010; Harvala et al. 2011).

HPeV has been described as a cause of uveitis in adults (de Groot-Mijnes et al. 2010), transient paralysis in a child (Ito et al. 2004), and meningoencephalitis in neonates (Verboon-Macielek et al. 2008). In these cases, the viruses replicate in the CNS. In GBS, the nerve damage is mediated by immunological mechanisms and the triggering pathogen is undetectable in the CSF. Molecular mimicry between enteroviruses and myocardial and islet cell antigens has been shown, but possible mechanisms of autoimmune

**Table 2** Bacterial and viral analyses from the serum, nasal swab, and stool samples

Microbial agent	Test	From where sample was taken	Result
<i>Campylobacter jejuni</i>	AbA, AbM, AbG, ELISA	Serum	AbM, AbA negative, AbG low positive
<i>Mycoplasma pneumoniae</i>	AbM, AbG, ELISA	Serum	AbM negative, AbG low positive
<i>Borrelia burgdorferi</i>	AbM, AbG, ELISA	Serum	Negative
HIV	AgAb	Serum	Negative
12 respiratory viruses <sup>a</sup>	Seplex®, multiplex PCR	Nasal swab	Negative
Picornavirus	PCR	Nasal swab	Negative
Picornavirus	PCR	Stool	Positive
Parechovirus	RT-PCR sequencing	Stool	Parechovirus 1 VP1 region

<sup>a</sup> Parainfluenza viruses 1, 2, and 3, human metapneumovirus, human coronavirus. 229E/NL63 and OC43, adenovirus, influenza viruses A and B, human respiratory syncytial viruses A and B, and human rhinovirus A/B

nervous system damage after parechovirus infection remains elusive. It remains unproven whether HPeV had any causative role in triggering autoimmunity in our patient, but no other acute or recent microbial infections were detected.

Parechoviruses are emerging viruses, and their exact prevalence, epidemiology and clinical manifestations are not fully known. PCR is a fast and easy method to diagnose picornaviruses (Vuorinen et al. 2003). Examination of stool samples is recommended when suspecting picornavirus, such as HPeV infection (Kupila et al. 2005), since Picornaviruses are secreted into stool for many days, even weeks, after symptom onset.

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**Conflict of interest** Saara Linden, Tytti Vuorinen, and Riikka Österback declare that they have no conflicts of interest. Merja Soilu-Hänninen has attended conferences at the cost of pharmaceutical companies and got lecture, consulting, and investigator fees from pharmaceutical companies (Astra-Tech, Bayer, Biogen-Idec, Eisai, GSK, Lundbeck, Merck, Novartis, Orion, Sanofi-Aventis, UCB)

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