CASE REPORT

Guillain-Barré syndrome with exaggerated pleocytosis and anti-GM1 ganglioside antibodies

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SUMMARY

An 81-year-old man presented with fever, confusion and rapidly-progressive flaccid tetraparesis. Clinical presentation and neurophysiology were consistent with a severe axonal polyneuropathy. Anti-GM1 and *Campylobacter* serology were both positive, consistent with postinfectious axonal-variant Guillain-Barré syndrome (GBS). GBS is characterised by albuminocytological dissociation, where an elevated protein and acellular cerebrospinal fluid are typical. However, in this case, CSF analysis revealed an exaggerated pleocytosis (72 white blood cells (WBC)/mm³). No source of central nervous system infection or inflammation was identified despite thorough investigation. The patient was treated with intravenous immunoglobulin and intensive rehabilitation. Albuminocytological dissociation classically distinguishes GBS from infective causes of flaccid weakness (eg, enteroviruses, flaviviruses and HIV). Diagnostic criteria frequently cite a pleocytosis of <50 WBC/mm³ as required in the diagnosis of GBS. However, this case demonstrates that pleocytosis exceeding this level can occur in the presence of convincing evidence of GBS and without demonstrable neurotropic infection.

BACKGROUND

Diagnostic criteria for Guillain-Barré syndrome (GBS) frequently require a pleocytosis of <50 white cell count (WBC)/mm³. However, this case demonstrates that an exaggerated pleocytosis can occur in the context of an acute flaccid tetraparesis with positive serological evidence of recent *Campylobacter* infection and anti-GM1 ganglioside attack. While albuminocytological dissociation remains helpful, the sensitivity and specificity of the universally-applied 50 WBC/mm³ cut-off will vary depending on the population to which it is applied. GBS should be considered a differential diagnosis in similar cases, particularly in populations where infectious causes of tetraparesis are uncommon, because treatment with intravenous immunoglobulin can improve recovery and reduce the duration of disability.

Case presentation

An 81-year-old, previously independent man of Punjabi origin attended the Accident and Emergency Department with confusion, fever, mild headache and photophobia of 1-day origin. He reported a brief illness with diarrhoea and vomiting 2 weeks before, a fall with transient loss of consciousness

1 week previously and intercurrent dysuria. There was no recent travel history. There was a medical history of hypertension only. He was disorientated and feverish (38.4°C). There was no overt limb or facial weakness on admission. Inflammatory markers were raised and the patient had a mildly raised creatinine (see [table 1](#)). Clinical examination, urinalysis and chest radiograph did not demonstrate a systemic cause for the fever. The patient was given one dose of gentamicin for a presumed urinary tract infection, after which management was changed to fluid resuscitation for dehydration secondary to a presumed viral illness. After the initial fever, the patient was consistently afebrile. On day 3, he appeared more confused with newly apparent symmetrical limb weakness without sensory deficits. Deep tendon reflexes were absent and plantar responses flexor. Ceftriaxone and aciclovir were started for suspected meningoencephalitis. Over the subsequent 2 days, his weakness progressed and GBS was added to the working diagnosis. [Table 2](#) summarises the clinical findings, investigations and treatments.

INVESTIGATIONS

CSF showed an elevated protein level as well as lymphocytosis when first sampled on day 4 of admission, as shown in [table 3](#). This conflated the usual findings of each original diagnosis: isolated mild lymphocytosis is seen in viral meningoencephalitis with normal or near-normal glucose and protein concentrations; isolated high protein with normal or near-normal WBC is typical of GBS. MRI head and whole spine (without contrast) did not show any significant abnormalities. Blood was sent for serology prior to starting intravenous immunoglobulin (Ig). *Campylobacter* IgA, IgG and IgM, *Mycoplasma pneumoniae* serology and anti-GM1 ganglioside antibodies (IgG) were all positive. Serum was negative for hepatitis A, hepatitis B surface antigen, hepatitis C, HIV, varicella zoster virus (VZV), enterovirus, parechovirus, herpes simplex virus (HSV), treponema and *Borrelia* as well as antinuclear antibody, extractable nuclear antigen, double-stranded DNA and antineutrophil cytoplasmic antibodies. Neurophysiology 6 days after presentation showed absent sensory responses from the lower limbs and significantly small sensory responses in amplitude in the upper limbs and absent or either small motor responses in both upper and lower limbs in keeping with severe sensorimotor (more motor) large fibre

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Table 1 Initial blood investigations

	Value	Normal range
Leucocytes ($\times 10^9/L$)	19.4	3.8–11
Lymphocytes ($\times 10^9/L$)	5.9	1.5–4
Neutrophils ($\times 10^9/L$)	11.9	2–7.5
CRP (mg/L)	41	<5
Creatinine ($\mu\text{mol/L}$)	127	74–110

CRP, C reactive protein.

predominantly axonal polyneuropathy affecting more so the lower limbs.

Differential diagnosis

This patient's initial symptoms of fever, confusion with headache and neck stiffness are suggestive of an acute meningoen- cephalitis. However, the patient did not develop seizures, other neurological dysfunction and the isolated confusion resolved within 48 hours of admission. The MRI head did not demon- strate parenchymal changes as well, collectively favouring a predominantly or exclusively meningitic process. Viral causes are common, specifically HSV, VZV, enterovirus and parechovirus, however CSF PCR for all these were negative. Neurotropic viruses can lead to an acute flaccid tetraparesis by destruction of the anterior horn cells and/or lower motor neurones, for example, enteroviruses (eg, polio), flaviviruses (eg, West Nile virus) and HIV seroconversion. However, none of these were detected on repeat serological testing or CSF PCR. Acute bacte- rial meningitis was not clinically suspected and the CSF glucose and lymphocyte predominance were also against this. Atypical bacterial infections including neuroborreliosis and syphilis were considered, however serology was negative for both and the patient had no risk factors for either infection. Inflammatory causes such as sarcoidosis and Behç et's can cause aseptic menin- gitis, but systemic features were absent.

TREATMENT

This patient was treated with 2 g/kg intravenous Immunoglob- ulin, given three times at 4-week intervals. The patient received careful neurological nursing, best supportive care and intensive physiotherapy and occupational therapy input in the neurosci- ences unit.

OUTCOME AND FOLLOW-UP

The patient's condition plateaued and he did not require ventila- tory support. During admission, he developed profound asymp- tomatic treatment-refractory hypotension, despite a history of hypertension (systolic 80–90 mm Hg; diastolic 40–50 mm

Table 2 Progression of symptoms

Day 1	Disorientated, feverish. Normal limb strength <i>Investigations: CT head (normal)</i> <i>Treatment: gentamicin and intravenous fluids</i>
Day 2	More confused, apyrexial. Moderate symmetrical flaccid tetraparesis with areflexia <i>Investigations: venous blood gas (normal)</i> <i>Treatment: ceftriaxone and aciclovir</i>
Days 4–5	Severe flaccid tetraparesis <i>Investigations: CSF, serology, MRI of head and whole spine</i> <i>Treatment: ceftriaxone and aciclovir (2-week duration), intravenous Ig (2 g/kg over 5 days)</i>

CSF, cerebrospinal fluid; Ig, immunoglobulin.

Table 3 CSF analysis results

	LP day 4	LP day 8	Normal range
CSF glucose (mmol/L)	3.1	3.4	>50% serum
Serum glucose (mmol/L)	5.9	6.4	4–11
Protein (g/L)	1	0.72	0.15–0.45
WBC (/mm ³)	72	14	<5
Lymphocytes (%)	97	71	0–100
RBC (/mm ³)	8	20	0
Oligoclonal bands (CSF)	Not done	Negative	Negative
Oligoclonal bands (serum)	Not done	Negative	Negative
Viral PCR (HSV 1 & 2, VZV, enterovirus)	Negative		Negative

CSF, cerebrospinal fluid; HSV, herpes simplex virus; LP, lymphocytosis; RBC, red blood cell; VZV, varicella zoster virus; WBC, white cell count.

Hg). This was attributed to autonomic nerve involvement, a recognised component of GBS. He was discharged for ongoing specialist rehabilitation. Three months after admission, he was able to stand with the assistance of two and use a stationary bicycle. He had flickers of finger movement (MRC 1), but required full assistance with eating, drinking and personal care.

DISCUSSION

The acute motor-sensory axonal neuropathy variant of GBS is a variant of the demyelinating form originally described by Guillain *et al.*¹ A hallmark of GBS is albuminocytological disso- ciation: the presence of elevated protein in an otherwise acel- lular CSF.^{1,2} In the original study by Guillain *et al*, the cohort of patients with acute areflexive paralysis was notable precisely because of the albuminocytological dissociation in CSF, estab- lishing a new disease phenotype.¹ Albuminocytological dissocia- tion remains a core feature of the three current major diagnostic criteria for the GBS^{3–5} and a cut-off of 50 WBC/mm³ is frequently cited.^{2–4,6,7} Worldwide, infections such as polio and other entero- viruses, flaviviruses and HIV are the major differential diagnostic category for acute flaccid paralysis, as distinguished by pleocy- tosis.⁴ However, this patient had no personal travel history or relevant contact history and investigations for specific viruses were entirely negative.

We are not the first to identify a case of GBS with a significant pleocytosis. We searched PubMed using the search term: '(Guil- lain Barré Syndrome albuminocytologic dissociation) OR Guil- lain Barré Syndrome cerebrospinal pleocytosis' and this returned 119 results. By reviewing titles and abstracts, we created a short- list of case reviews and cohort studies addressing this issue. In addition to a recent paper detailing the characteristics of lumbar puncture among patients with GBS in East Asian countries, which found 8 out of 507 patients had CSF with >50 WBC/mm³,⁸ we found four articles detailing five case studies describing GBS with pleocytosis of >50 WBC/mm³.^{9–12} These are summarised in table 4. In each case, the diagnosis was essentially made after excluding infectious, inflammatory or metabolic causes to a vari- able extent. Only Berciano *et al* detected *Campylobacter*,⁹ and none of these cases reported positive ganglioside antibodies. Our case provides a more compelling case for a postinfectious anti- GM1 antibody-mediated aetiology provoked by recent, symp- tomatic *Campylobacter* infection.

While albuminocytological dissociation remains helpful, the sensitivity and specificity of the universally applied 50 WBC/ mm³ cut-off will vary depending on the population to which it is applied. In environments with a high burden of infectious disease causing paralysis, CSF pleocytosis will have a high negative

Table 4 Summary of case reports of GBS with pleocytosis

Source	Clinical details	CSF findings			Nerve conduction studies	Imaging	How were alternative diagnoses excluded?	Comments
		WBC (mm ³)	Lymphocytes (%)	Protein (g/L)				
Present case	81 M, rapid onset ascending tetraparesis, recent gastrointestinal symptoms. Recovered use of all limbs and discharged to rehabilitation unit	72	97	1	Motor-predominant large-fibre neuropathy with axonal features	Grossly normal appearance		
Berciano <i>et al</i> ⁹	67 M, ascending symmetrical tetraparesis. Progressing to global paralysis. Died after 18 days	100	60	198	Serial electrophysiology suggested demyelination followed by Wallerian degeneration	—		
Rauschka <i>et al</i> ¹⁰	58 M, ascending tetraparesis, recent 'common cold'. Died after 4 days	197	10	2.8	— (Pathology suggests unclassifiable pattern of inflammation)	—	Negative findings for infectious and rheumatological work up	LP post-intravenous Ig but no symptoms of chemical meningitis. No anti-ganglioside antibodies detected
Rauschka <i>et al</i> ¹⁰	73 F, ascending tetraparesis with prominent sensory symptoms and cranial nerve involvement. Died after 100 days	74	—	1.03	— (Pathology suggests spinal root demyelination with relative axonal sparing)	(Pathology suggested anterior and posterior roots demyelinated equally)	Autopsy. Immunohistochemistry for HSV1, HSV2, CMV, EBV, VZV, enterovirus, tick born encephalitis; staining for spirochetes. Case prior to HIV pandemic	Case review with new staining of preserved CNS segments
Dy <i>et al</i> ¹¹	17 F, asymmetrical ascending tetraparesis, dysphagia, recent upper respiratory tract infection, previous demyelinating GBS, rapid response to intravenous Ig	46	74	0.74	Motor neuropathy, with more axonal than demyelinating features	Anterior nerve root enhancement of the cervical and lumbar spines	Autopsy. Immunohistochemistry for HSV1, HSV2, CMV, EBV, VZV, enterovirus, tick born encephalitis; staining for spirochetes. Case prior to HIV pandemic	Case review with new staining of preserved CNS segments
Padidam <i>et al</i> ¹²	60 M, insidious onset ascending tetraparesis, requiring intubation. Discharged to long-term acute care unit with no improvement	81	97	1.09	Motor neuropathy with both demyelinating and axonal features	Bilateral anterior and posterior nerve root enhancement along bilateral anterior and posterior nerve roots	Test for porphyria, tick born encephalitis and HIV	<i>C. jejuni</i> antibodies present. No anti-ganglioside antibodies present

C. jejuni, *Campylobacter jejuni*; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; GBS, Guillain-Barré syndrome; HSV, herpes simplex virus; Ig, immunoglobulin; LP, lymphocytosis; RBC, red blood cell; VZV, varicella zoster virus; WBC, white cell count.

predictive value (NPV) for GBS. In settings such as ours, with a low rate of such infectious disease, the NPV of CSF pleocytosis is much lower. While it should prompt a search for infectious causes, we recommend that GBS should still be considered in the differential diagnosis because treatment with intravenous Ig can improve recovery and reduce the duration of disability.

The aetiology of GBS remains a subject of research.^{2,6,13} Current evidence favours the model of molecular mimicry, in which immunological clearance of foreign antigens which resemble self-antigens leads to subsequent antibody-mediated damage against host cells. In the case of GBS, *C. jejuni* lipopolysaccharides resemble ganglioside moieties expressed on peripheral nerves at nodes of Ranvier, leading to antibody-mediated neuronal damage.^{2,6,13} Antibodies to both *Campylobacter* and ganglioside GM1 antigens were detected in this patient, and this process is particularly associated with the acute motor axonal neuropathy pattern identified on Electromyography (EMG).^{2,6,13} At present, anti-GM1 antibodies are not included in any of the current diagnostic criteria for GBS.^{3–5} However, ganglioside antibodies are widely available in developed countries which are also those countries in which an exaggerated pleocytosis has the lowest negative predictive value. It would be helpful to consider the usage of these two tests in an observational study of GBS in this population.

In summary, this is the first published case of a patient presented with an exaggerated CSF pleocytosis, with diagnosis made based on clinical features, preceding *Campylobacter* infection, anti-GM1 positivity and acute axonal neuropathy, despite the pleocytosis. This case highlights the value of testing ganglioside antibodies and using caution when applying an absolute CSF WBC cut-off to individual cases from different populations.

Learning points

- ▶ Albuminocytological dissociation is a feature of the three major current diagnostic criteria for the Guillain-Barré syndrome (GBS) where a cut-off of 50 white cell count/mm³ is frequently cited.
- ▶ This is the first case describing anti-GM1 antibodies and positive *Campylobacter* serology in the context of GBS with exaggerated pleocytosis, and provides a more compelling case for a postinfectious aetiology.
- ▶ In healthcare settings where there is a low prior probability of an infectious cause of flaccid paralysis, cerebrospinal fluid pleocytosis should not exclude a diagnosis of GBS and anti-ganglioside antibody testing can be particularly helpful.

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