



OPEN ACCESS

# Bickerstaff's brainstem encephalitis mimicking herpetic encephalomyelitis in a liver transplant patient with anti-GQ1b antibodies

Sehajdev Singh Bhatia ,<sup>1</sup> Carlo Canepa,<sup>2</sup> Asha Notarianni <sup>3</sup>

<sup>1</sup>Emergency Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

<sup>2</sup>Stroke and Neurology, James Paget University Hospitals NHS Foundation Trust, Great Yarmouth, UK

<sup>3</sup>General Surgery, Jersey General Hospital, Saint Helier, Jersey

## Correspondence to

Dr Seahajdev Singh Bhatia; sehajdev@hotmail.com

Accepted 1 December 2022

## SUMMARY

A woman in her late 70s with a history of liver transplant presented with ophthalmoplegia, ataxia, areflexia, positive Babinski's sign and reduced consciousness. This followed an antecedent illness in the form of a herpes zoster infection. MRI of the brain/spinal cord, cerebrospinal fluid analysis with viral PCR and routine blood tests were normal, and tacrolimus neurotoxicity was ruled out. Serum anti-GQ1b antibodies were positive. A diagnosis of Bickerstaff's brainstem encephalitis was made, forming part of the continuum that involves Miller-Fisher syndrome, entitled the 'anti-GQ1b syndrome'. Complete recovery ensued without intravenous immunoglobulins or plasma exchange. The role of monitoring anti-ganglioside pattern change to predict or confirm disease recurrence and disease severity is further discussed.

## BACKGROUND

Bickerstaff's brainstem encephalitis (BBE) is rare, with an estimated annual incidence of 0.078 per 100 000.<sup>1</sup> It forms part of the 'anti-GQ1b syndrome' which constitutes a common serological profile underpinning both Miller-Fisher syndrome (MFS) and BBE. To our knowledge, this is the first case report describing BBE in a liver transplant patient with a history of primary biliary cirrhosis (PBC) and positive anti-GQ1b antibodies. Despite its clinical rarity, the prognosis is excellent with potential treatment modalities extrapolated from those of Guillain-Barré syndrome (GBS). Serial anti-ganglioside testing, including titres, may be the future in predicting both disease severity and a monophasic or polyphasic course, which is commonly seen in other autoantibody-mediated conditions.

## CASE PRESENTATION

A woman in her late 70s presented with a 2-week history of progressive bilateral leg weakness, unstable gait and fluctuating drowsiness with moments of confusion. This followed a 4-week history of a progressive bilateral lumbosacral herpes zoster (HZ) infection that spread down her right groin and right leg. Medical history included: two liver transplants due to PBC, immunosuppression with tacrolimus, post-transplant lymphoproliferative disorder (PTLD) in remission and chronic pancreatitis.

On presentation, she was drowsy yet able to maintain conversation and obey simple commands.

Once verbal stimulus was eliminated, she would fall asleep, displaying signs of hypersomnolence. Examination of the cranial nerves revealed a bilateral upward gaze palsy and horizontal nystagmus on smooth pursuit. There was deep tendon areflexia, bilateral extensor plantar reflexes and a 2/5 symmetrical flaccid paraparesis in the lower limbs, with preserved tone and power in the upper limbs. A persistent non-painful paraesthesia in a glove-and-stocking distribution remained but otherwise sensory perception was globally preserved. Finally, there was no history of foreign travel, nor evidence of insect bites that may have resulted in a tickborne encephalitis.

## INVESTIGATIONS

Full blood count, liver function, renal function and repeat blood cultures were all normal. Tacrolimus levels were low at 3.3 µg/L (reference range 5.0–15.0 µg/L) and SARS-CoV-2 RNA virus was not detected. Anti-mitochondrial antibody M2, anti-M2-3E and anti-Ro52 were strongly positive. This was consistent with her previous diagnosis of PBC.

MRI with and without contrast of the brain and spinal cord did not reveal signs of encephalitis or myelitis. There was no conus medullaris syndrome, cauda equina syndrome, demyelination, stenosis, infarction, haemorrhage or oedema. Cerebrospinal fluid (CSF) analysis did not reveal protein-cytological dissociation (protein 0.37 g/L, glucose 3.2 mmol/L and white cell count of 0.0 × 10<sup>9</sup>/L). Importantly, viral PCR of the CSF did not detect herpes virus type 1, type 2, varicella zoster, enterovirus or adenovirus DNA.

Nerve conduction studies at 8 weeks post-symptom onset were unremarkable, with no discernible demyelinating or axonal features, nor large fibre peripheral neuropathy noted. This would not have necessarily excluded a previous inflammatory event, which may have resolved.

Lastly, serum anti-ganglioside testing revealed positive anti-GQ1b IgM antibodies while both anti-GM1 and anti-GD1b subtypes were negative. CSF testing revealed negative anti-GM1; however, there was insufficient sample to complete analysis for anti-GQ1b. We plan to repeat serum anti-ganglioside testing on a 6-month basis for this patient.

## DIFFERENTIAL DIAGNOSIS

The initial presumptive diagnosis was an acute infectious herpetic encephalomyelitis, owing to the



© BMJ Publishing Group Limited 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Bhatia SS, Canepa C, Notarianni A. *BMJ Case Rep* 2022;**15**:e251784. doi:10.1136/bcr-2022-251784

## Case report

recent HZ infection. Acellular CSF with negative viral PCR and a normal MRI of the brain and spinal cord made this unlikely. The patient was taking long-term tacrolimus but its neurotoxic effects were ruled out by a normal MRI and by low serum levels. Additionally, despite the history of PBC and subsequent liver transplants, there was no gross concurrent hepatic dysfunction portrayed on the blood results that may have impeded the clearance of tacrolimus.

Another differential was an acute inflammatory demyelinating polyneuropathy such as GBS and its variants, acute motor axonal neuropathy (AMAN) and acute sensorimotor axonal neuropathy. Nerve conduction studies, however, did not show evidence of demyelination or axonal pathology, and this case had other positive and negative features that are not seen in the aforementioned syndromes. Acute disseminated encephalomyelitis (ADEM) was ruled out by a normal MRI of the brain and spinal cord. A final diagnosis of BBE, as part of the anti-GQ1b syndrome, was made, based on the clinical features, as a diagnosis of exclusion.

### TREATMENT

Ten days of intravenous acyclovir 800mg four times a day formed the primary treatment for the initially presumed herpetic encephalitis. Tacrolimus was withheld during the first 3 days of admission, until tacrolimus levels were confirmed to be low, after which it was reintroduced. She remained as an inpatient for 7 days, receiving physiotherapy to aid her strength and balance.

### OUTCOME AND FOLLOW-UP

By day 3 of her hospital stay, her consciousness level had improved significantly. At clinic, 4 weeks post-discharge, she had almost completely recovered. She was lucid in all domains of cognition, without dysarthria, memory loss or behavioural changes. Strength was intact in all four limbs; however, there was moderate limitation for bilateral lower limb flexion, mainly due to gluteal and quadriceps pain following her prolonged course of HZ infection. She was able to walk slowly and could stand on both feet without loss of balance. Her eye movements were completely normal, showing resolution of her upward gaze palsy and horizontal nystagmus. At her 6-month clinic follow-up, she was doing well, with no further symptom recurrence.

### DISCUSSION

MFS represents ophthalmoplegia, ataxia and areflexia. MFS associated with central nervous signs including pyramidal features and/or reduced level of consciousness (drowsiness) represents BBE.<sup>2</sup> Diagnosis of BBE is made in the context of these clinical features and antecedent infective illness.

Before the landmark discovery of anti-GQ1b antibody presence in patients with MFS in 1992, MFS and BBE had been considered separate clinical entities.<sup>3</sup> The term 'anti-GQ1b antibody syndrome' adequately represents the common serological profile that is now known to underpin the clinical spectrum of both MFS and BBE.<sup>4</sup>

Our patient presented primarily with a progressive ataxia, upward gaze palsy and global areflexia. She displayed additional features of extensor plantar reflexes, confusion and hypersomnolence, indicative of central nervous system (CNS) involvement. In the context of positive anti-GQ1b antibodies and by ruling out more common pathologies, a clinical diagnosis of BBE was made.

The state and level of consciousness gave clues to the site of pathology. Level of consciousness is governed by the cortex,

disorders of which give rise to an awake-encephalopathic picture, for example, delirium. State of consciousness is controlled in a more binary fashion by the reticular activating system in the brainstem, for example, awake or asleep. The clinical finding of when engaged in conversation, the patient was able to remain awake, but as soon as this cognitive stimulus was removed, the patient would enter sleep, suggested a brainstem pathology.<sup>5</sup>

Odaka *et al* reported 62 cases of BBE and quantified the prevalence of individual symptoms: 100% involved external ophthalmoplegia, 92% an antecedent illness, 60% limb weakness, 58% absent/reduced reflexes, 45% consciousness disturbance, 40% Babinski's sign, 34% hyper-reflexia, 27% nystagmus and 8% normal reflexes, to isolate a few of the displayed symptoms.<sup>2</sup> Our patient developed all of the aforementioned symptoms over a 2-week course.

Solid organ transplantation can result in multiple neurological complications including post-transplant autoimmune encephalitis. The causes of which are diverse and include medication toxicity, posterior reversible encephalopathy syndrome, viral infections and PTLD.<sup>6</sup> Our patient's PTLD episode was in remission but has been reported to cause CNS manifestations that commonly have radiological abnormalities, which were absent in our patient.<sup>7,8</sup> A viral CNS infection was more plausible given our patient's preceding episode of shingles.

HZ encephalomyelitis (HZE) is rare and represents CNS involvement after acute dissemination of reactivated HZ (shingles), following childhood varicella (chicken pox).<sup>9-11</sup> Our patient had an unremarkable viral PCR and absence of lymphocytic pleocytosis, making HZE unlikely.<sup>12</sup> Even though an aseptic HZE subtype exists, it was the combination of clinical features, antecedent HZ infection, positive anti-ganglioside antibodies and negative viral screen, which pushed the diagnosis towards BBE rather than HZE.<sup>13</sup>

A broader set of differentials included other immune-mediated neuropathies (acute inflammatory demyelinating polyneuropathies, AMAN, acute sensorimotor neuropathy) encephalitis, encephalomyelitis, ADEM, cerebrovascular infarct/ischaemia, myasthenia gravis and Wernicke's encephalopathy.

A key investigation was CSF analysis, which was completely normal in our patient. In comparison with GBS, the frequency of protein-cytological dissociation has been shown to be lower than in MFS or BBE. Despite this, the extent of protein-cytological dissociation has been shown to develop over time, in isolated cases of BBE.<sup>2</sup> Interestingly, not only are anti-ganglioside antibodies present in the acute phase sera of MFS and BBE, but many cases report the presence of anti-GQ1b antibodies in the CSF itself, confirming that the antibodies can access the CNS. It is postulated that this occurs in areas where the blood-brain barrier is most deficient, such as the brainstem.<sup>14</sup>

MRI is important when ruling out alternative aetiologies of brainstem encephalitis.<sup>15,16</sup> Serial MRI studies have shown hyperintense signal changes on T2-weighted images in BBE, though MRI abnormality is still uncommon, reported in 11%–30% of BBE cases.<sup>2,4</sup> Our case report showed a completely normal MRI with and without contrast of the brain and spinal cord.

The pathophysiology of the underlying neuropathy is subject to ongoing debate, and electrophysiology studies have been used to differentiate GBS, MFS and BBE. The nerve conduction study of our patient at 6 weeks post-discharge and 8 weeks post-symptom onset was unremarkable. Alberti *et al* found that among 12 patients with overlapping Fisher-Bickerstaff syndrome, the day 10 nerve conduction studies revealed reduced sensory nerve action potential (SNAP) amplitude but no signs of demyelination or other motor neuropathies. At days 15 and

18, all showed improvement or resolution in SNAP, in line with a reversible sensory conduction block.<sup>17</sup> These findings have moved the anti-ganglioside-mediated neuropathies closer to the axonal forms of GBS, rather than the traditional demyelinating type. The node of Ranvier has also been found to be a site of dysfunction in BBE and has given rise to the term ‘nodoparanopathy’, which perhaps better describes the neuropathy in the anti-GQ1b syndrome.<sup>18</sup>

Ganglioside antibodies are abundant in neural tissue. When anti-ganglioside antibodies are produced via molecular mimicry due to antecedent pathogens, characteristic neurological phenotypes manifest.<sup>19</sup> GQ1b forms 5%–6% of the total gangliosides in human peripheral nervous tissue, but a greater 11%–13% in the cranial nerves.<sup>20</sup> The IgG anti-GQ1b has been shown to be present in 68% of BBE cases (n=53) and 83% of MFS cases (n=466), but typically the prevalence in patients with GBS is much lower.<sup>21</sup> Antibody-positive BBE has been shown to display distinctive clinical features, with preceding infection and sensory disturbance being more frequent. However, CSF cell counts and abnormal MRI of the brain findings are more rare.<sup>22</sup> The antibody titre has also been shown to closely follow the clinical course of GBS, MFS and BBE, rendering them pathogenic antibodies.<sup>20</sup>

Recurrence of disease is more common in the anti-GQ1b syndrome (MFS or BBE) than in GBS (14% and 4%, respectively).<sup>23</sup> Ito *et al* reported a case in 2018 with recurrent MFS–GBS overlap and subsequently BBE–GBS overlap who was initially seronegative for anti-GQ1b. This patient later became positive for other anti-ganglioside antibodies with each successive recurrence, while remaining negative for anti-GQ1b.<sup>24</sup> Conversely, Barbagallo *et al* reported a case where initially GQ1b-seronegative MFS–BBE overlap recurred 12 years later with positive anti-GQ1b antibodies.<sup>25</sup> Moreover, recurrence has been associated with increased clinical severity and anti-ganglioside antibody pattern change. The latter term implies individual antibodies among the numerous anti-ganglioside antibodies, for example, anti-GQ1b, anti-GT1a and anti-GM1 becoming positive or negative on serial testing. It is possible that clinical severity and anti-ganglioside antibody patterning are linked.

Cases of BBE may be self-limiting, require intravenous immunoglobulin or plasma exchange. In refractory cases, anti-CD20 monoclonal antibodies in the form of rituximab have been used.<sup>14</sup> A 2007 Cochrane review found no randomised data for the treatment of MFS and BBE but found it clinically logical to extrapolate the evidence in treatment of GBS to both MFS

and BBE.<sup>26</sup> Our patient completed her course of intravenous acyclovir for the initially presumed herpetic encephalomyelitis but did not receive any new immunotherapies during this episode and regardless, recovered fully.

Owing to its rarity, research into the mechanisms, efficacy of current treatments and role of antibody titres to prognosticate the course of illness is limited. This case was unique as BBE has behaved as a mimic of herpetic encephalomyelitis and has shone light on the future of predicting polyphasic disease and clinical severity.

**Contributors** SSB was the primary author and wrote the case report in line with CC’s concept. SSB performed all data acquisition, analysis, literature review and formulation of the final draft. AN was a secondary author with substantial contribution to the discussion section, alongside formulation of the final draft. CC was a secondary author and the neurology consultant in charge of the patient’s care. He formed the initial concept of the case and reviewed two of the local drafts prior to submission.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

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.

#### ORCID iDs

Sehajdev Singh Bhatia <http://orcid.org/0000-0001-7004-4568>

Asha Notarianni <http://orcid.org/0000-0001-9409-8130>

#### REFERENCES

- Koga M, Kusunoki S, Kaida K, *et al*. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. *J Neurol Neurosurg Psychiatry* 2012;83:1210–5.
- Odaka M, Yuki N, Yamada M, *et al*. Bickerstaff’s brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain* 2003;126:2279–90.
- Chiba A, Kusunoki S, Shimizu T, *et al*. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Ann Neurol* 1992;31:677–9.
- Shahrazila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. *J Neurol Neurosurg Psychiatry* 2013;84:576–83.
- Parvizi J, Damasio A. Consciousness and the brainstem. *Cognition* 2001;79:135–60.
- Cohen DA, Lopez-Chiriboga AS, Pittock SJ, *et al*. Posttransplant autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e497.
- Kamdar KY, Rooney CM, Heslop HE. Posttransplant lymphoproliferative disease following liver transplantation. *Curr Opin Organ Transplant* 2011;16:274–80.
- Castellano-Sanchez AA, Li S, Qian J, *et al*. Primary central nervous system posttransplant lymphoproliferative disorders. *Am J Clin Pathol* 2004;121:246–53.
- McCormick WF, Rodnitzky RL, Schochet SS, Jr S, *et al*. Varicella-Zoster encephalomyelitis. A morphologic and virologic study. *Arch Neurol* 1969;21:559–70.
- Pergam SA, Forsberg CW, Boeckh MJ, *et al*. Herpes zoster incidence in a multicenter cohort of solid organ transplant recipients. *Transpl Infect Dis* 2011;13:15–23.
- Kang M, Aslam S. Varicella zoster virus encephalitis in solid organ transplant recipients: case series and review of literature. *Transpl Infect Dis* 2019;21:e13038.
- Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, *et al*. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000;342:635–45.
- Bennett JE. *Infectious diseases and their etiological agents. Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier/Saunders, 2015: 2157–87.
- Hardy TA, Barnett MH, Mohamed A, *et al*. Severe Bickerstaff’s encephalitis treated with rituximab: serum and CSF GQ1b antibodies. *J Neuroimmunol* 2012;251:107–9.
- Sotoudeh H, Razaeei A, Saadatpour Z, *et al*. Brainstem encephalitis. The role of imaging in diagnosis. *Curr Probl Diagn Radiol* 2021;50:946–60.

#### Learning points

- ▶ Suspect Bickerstaff’s brainstem encephalitis (BBE) when a syndrome of antecedent infection, ataxia, ophthalmoplegia and areflexia develop alongside pyramidal signs or altered consciousness.
- ▶ Guillain-Barré syndrome (GBS) and its variants, including BBE, may be mimicked by other conditions including encephalomyelitis, which must be ruled out.
- ▶ Anti-GQ1b antibody titres have been shown to follow the clinical course from onset to resolution of disease.
- ▶ Anti-ganglioside pattern change may be linked to both polyphasic BBE and disease severity.
- ▶ The majority of cases are self-limiting and current treatment options have been extrapolated from those of GBS.

- 16 Mondéjar RR, Santos JMG, Villalba EF. Mri findings in a remitting-relapsing case of Bickerstaff encephalitis. *Neuroradiology* 2002;44:411–4.
- 17 Alberti MA, Povedano M, Montero J, *et al.* Early electrophysiological findings in Fisher-Bickerstaff syndrome. *Neurologia* 2020;35:40–5.
- 18 Uncini A, Susuki K, Yuki N. Nodoparaneuropathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. *Clin Neurophysiol* 2013;124:1928–34.
- 19 Yuki N. Anti-Ganglioside antibody and neuropathy: review of our research. *J Peripher Nerv Syst* 1998;3:3–18.
- 20 Uchibori A. Anti-GQ1b antibody: recent topics. *Clinical & Exp Neuroim* 2021;12:158–64.
- 21 Ito M, Kuwabara S, Odaka M, *et al.* Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum. *J Neurol* 2008;255:674–82.
- 22 Yoshikawa K, Kuwahara M, Morikawa M, *et al.* Bickerstaff brainstem encephalitis with or without anti-GQ1b antibody. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e889.
- 23 Ishii J, Yuki N, Kawamoto M, *et al.* Recurrent Guillain-Barré syndrome, Miller Fisher syndrome and Bickerstaff brainstem encephalitis. *J Neurol Sci* 2016;364:59–64.
- 24 Ito H, Hatanaka Y, Fukami Y, *et al.* Anti-Ganglioside complex antibody profiles in a recurrent complicated case of GQ1b-seronegative Miller Fisher syndrome and Bickerstaff brainstem encephalitis: a case report. *BMC Neurol* 2018;18:72.
- 25 Barbagallo G, Caggiola M, Lupo A, *et al.* Recurrent Miller-Fisher syndrome overlapping Guillain-Barré syndrome and Bickerstaff brainstem encephalitis: a case report. *Clin Neurol Neurosurg* 2021;206:106691.
- 26 Overell JR, Hsieh ST, Odaka M, *et al.* Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. *Cochrane Database Syst Rev* 2007;2007:CD004761.

Copyright 2022 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>  
 BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

### Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at [support@bmj.com](mailto:support@bmj.com).

Visit [casereports.bmj.com](http://casereports.bmj.com) for more articles like this and to become a Fellow