A continuous spectrum

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Case vignette

A 41-year-old previously healthy man was referred to our hospital due to increasingly unsteady gait, intermittent diplopia, slurred speech, difficulties with swallowing, and prickling of the hands and legs for a few days. In addition, the patient reported suffering from a minor cold with a non-productive cough without a fever for one week. On admission, a neurological examination revealed slight dysphagia and dysarthria, upbeat nystagmus and bilateral horizontal gaze-evoked nystagmus, mild bradydiadochokinesia, possibly elevated spastic muscle tone and brisk tendon reflexes of the legs with negative Babinski's sign and without limb weakness, slightly reduced vibration sense over both ankles, moderately dysmetric finger-to-nose and heel-to-knee tests, slight gait ataxia, and undirected imbalance on Romberg's test despite normal position sense. The remaining physical examinations as well as the vital signs were normal. Routine laboratory results were unremarkable except for a slightly elevated CRP level. The cerebrospinal fluid (CSF) was completely normal (cell count, gram-staining, protein, glucose, and lactate), and furthermore no local production of antibodies or oligoclonal bands were detected. ECG and chest X-ray were normal. CT of the brain with angiography of the intra- and extra-cranial vessels and neurovascular ultrasound was also normal.

During the course of one day, the patient's state deteriorated: The patient was somnolent, bulbar palsy increased with progressive dysphagia, requiring placement of a nasogastric tube, and severe symmetric external ophthalmoparesis developed. The patient showed slight tetraparesis with increased muscle tone. MRI of the brain including diffusion-weighted (DWI) and gadolinium-enhanced T1-weighted images and EEG were normal. The patient's condition deteriorated further, cough and gag reflexes were diminished and respiratory failure developed on day three. Therefore, the patient was sedated, intubated and mechanically ventilated.

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Question 1

Our patient was most likely affected by:
A Bickerstaff's brainstem encephalitis
B Listeria rhombencephalitis
C Miller-Fisher syndrome
D Primary angiitis of the central nervous system
E Wernicke's encephalopathy

Question 2

Therapy in our patient primarily included:
A Antibiotic treatment
B Intravenous cyclophosphamide pulse therapy
C Intravenous immunoglobulin
D Thiamine substitution
E None of the above

Course of disease

Bickerstaff's brainstem encephalitis (BBE) was assumed. IgG-antiganglioside antibodies to GQ1b on day two showed a high serum level of 25 000% (<50). Serologic studies showed acute mycoplasma pneumonia infection.

Nerve conduction studies were performed on day four and showed reduced motor amplitudes in one of four nerves and reduced sensory amplitudes in three of three nerves, the remaining stimulation parameters were normal, rendering an axonal lesion more likely than a demyelinating process. Somatosensory evoked potentials (SEP) of the median nerve showed normal N9 and N13, but absent N20 on the left and prolonged N20 on the right side on day eight, pointing to a central lesion. Brainstem auditory-evoked potentials (BAEP) were normal on day four and eight. MRI of the brain and CSF were still normal on day ten.

The patient received intravenous immunoglobulin daily from day two to six, treatment with intravenous doxycycline was started on day seven. A tracheostomy tube was inserted on day eight and removed on day 38; percutaneous endoscopic gastrostomy was performed on day 30 and kept until day 58. On day eleven, the patient started to recover. Transfer to a rehabilitation facility was performed on day 18. On day 97, only slight ophthalmoparesis remained and the patient was discharged fully independent in performing activities of daily living. At follow-up on day 105, beside mild fatigue, the patient had recovered completely.

Question 3

The term anti-GQ1b antibody syndrome does not include:
A Acute ataxic neuropathy
B Acute motor axonal neuropathy
C Acute ophthalmoplegia
D Bickerstaff's brainstem encephalitis
E Miller-Fisher syndrome

Question 4

Auto-antibodies to GM1 are strongly associated with:
A Acute inflammatory demyelinating polyneuropathy
B Acute motor axonal neuropathy
C Chronic inflammatory demyelinating polyneuropathy
D Pharyngeal-cervical-brachial weakness
E None of the above

Question 5

Typical clinical features of Bickerstaff's brainstem encephalitis mainly include:
A Ataxia
B Ophthalmoplegia
C Pyramidal signs
D Coma
E All of the above

Overview of the literature

BBE is a rare monophasic immunological disease with signs of central and peripheral nervous system involvement [1]. Acute ophthalmoplegia, ataxia, and disturbance of consciousness, or limb weakness with normal or brisk muscle tendon reflexes and Babinski's sign develop over a course of days or weeks [2]. Along with this, facial weakness, bulbar palsy, sensory disturbance, and also flaccid limb weakness with diminished or absent muscle tendon reflexes are seen in some patients [2]. The course of the disease may be fulminant with severely decreased level of consciousness, absent cough and gag reflexes and respiratory failure, requiring intubation and mechanical ventilation [3]. Despite this, the outcome is usually good even without immunotherapy, and patients often recover more or less completely after days or weeks [2].

Many patients have evidence of upper respiratory or gastrointestinal infection a few weeks before the onset of neurological symptoms [4]. Serologic studies may confirm recent infection with *Campylobacter jejuni*, *Mycoplasma pneumonia*, or *Haemophilus influenza* pointing to an autoimmune origin, secondary to molecular mimicry between infectious organisms and host gangliosides [1]. IgG antiganglioside antibodies to GQ1b are frequently detected in the serum with a peak in the first week, whereas albuminocytological dissociation in the CSF often appears later [1, 5]. MRI of the brain is normal or may show at least temporarily infratentorial hyperintense signal changes on T2-weighted sequences [2]. Gadolinium enhancement on T1-weighted images or hyperintensive signal changes on DWI and bright lesions on ADC maps may point to vasogenic oedema [6]. Electrophysiological studies may show motor or sensory axonal neuropathy, but also demyelination and conduction block on electroneurography [1–2, 5], abnormal SEP that point to lesions of the dorsal column-lemniscal system [1], and abnormal EEG with diffuse slow activity [1].

Other diseases may mimic symptoms and signs of BBE: acute disseminated encephalomyelitis and multiple sclerosis, vasculitis, bacterial and viral meningo-encephalitis, neoplastic meningitis, myasthenia gravis and other paraneoplastic syndromes, brainstem tumours, mitochondrial disorders, botulism, and Wernicke's encephalopathy.

In the last two decades, serum antibodies to different gangliosides have been identified in some Guillain-Barré subtypes and variants [7]. Gangliosides are a subclass of glycosphingolipides, contain one or more sialic acid residues, and regulate cell signal processing [7]. GM1, GD1a, GT1a, and GQ1b differ with regard to the number and position of their sialic acids [7]. GQ1b is strongly expressed at the neuromuscular junctions within the extraocular muscles and muscle spindles, and probably reticular formation in the brainstem [8–9]. GM1 and GD1a are strongly expressed at the nodes of Ranvier on motor nerve axons [9].

Antibodies to GQ1b, which cross-react with GT1a, are strongly associated with BBE, Miller-Fisher syndrome and its incomplete forms, acute ophthalmoparesis (without ataxia) and acute ataxic neuropathy (without ophthalmoparesis) [7]. The eponym Fisher-Bickerstaff syndrome and the term anti-GQ1b antibody syndrome were proposed in order to recognise the continuous spectrum between these illnesses [1, 10]. Furthermore, there is an overlap between Fisher-Bickerstaff syndrome and the motor axonal neuropathy variant of Guillain-Barré syndrome [7]. However, in this disease antiganglioside antibodies against GM1 and GD1a, but usually not against GQ1b, may be found [7]. There is no association between these antiganglioside antibodies and acute inflammatory demyelinating polyneuropathy [7].

Owing to the lack of randomised controlled trials, treatments used for Guillain-Barré syndrome, intravenous immunoglobulin and plasma exchange are usually applied [7]. Immuno-adsorption may be an alternative option [11]. Oral steroids and intravenous methylprednisolone alone were not beneficial in the treatment of Guillain-Barré syndrome, so they are considered to be ineffective for the treatment of Bickerstaff's encephalitis [7]. Moreover, antibiotics such as doxycyclin, macrolides, and fluorochinolones may be appropriate in case of verified acute bacterial infection. However, recovery has been described in patients with or without antibiotic therapy [12].

Answers:

1: A
2: C
3: B
4: B
5: E

References

1 Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum. J Neurol. 2008;255(5):674–82.
2 Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. Brain. 2003;126(10):2279–90.
3 Hunter G, Young GB, Ang LC. Bickerstaff's encephalitis presenting to the ICU. Neurocrit Care. 2012;17(1):102–6.
4 Koga M, Kusunoki S, Kaida K, Uehara R, Nakamura Y, Kohriyama T, et al. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. J Neurol Neurosurg Psychiatry. 2012;83(12):1210–5.
5 Aranyi Z, Kovacs T, Sipos I, Bereczki D. Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings. Eur J Neurol. 2012;19(1):15–20.
6 Weidauer S, Ziemann U, Thomalske C, Gaa J, Lanfermann H, Zanella FE. Vasogenic edema in Bickerstaff's brainstem encephalitis. Neurology. 2003;61(6):836–8.
7 Yuki N, Hartung HP. Guillain-Barré syndrome. N Engl J Med. 2012;366(24):2294–304.
8 Shahrizaila N, Yuki N. Bickerstaff's brainstem encephalitis and Fisher syndrome: anti GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry. 2012; Sep 15 [Epub ahead of print].
9 Yuki N. Fisher syndrome and Bickerstaff brainstem encephalitis (Fisher Bickerstaff syndrome). J Neuroimmunol. 2009;215(1–2):1–9.
10 Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. J Neurol Neurosurg Psychiatry. 2001;70(1):50–5.
11 Yuki N. Tryptophan-immobilized column adsorbs immunoglobulin G anti-GQ1b antibody from Fisher's syndrome: a new approach to treatment. Neurology. 1996;46(6):1644–51.
12 Tsoridas S, Kelesidis I, Kelesidis T, Stamboulis E, Giamarellou H. Central nervous system manifestations of mycoplasma pneumonia infections. J Infect. 2005;51(5):343–54.