Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain–Barré syndrome

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Summary
Bickerstaff reported eight patients who, in addition to acute ophthalmoplegia and ataxia, showed drowsiness, extensor plantar responses or hemisensory loss. This condition has been named Bickerstaff's brainstem encephalitis (BBE). One patient had gross flaccid weakness in the four limbs. Presumably because of the rarity of this disorder, there has been no reported study on a large number of patients with BBE. To clarify its clinical features, we reviewed detailed clinical profiles and laboratory findings for 62 cases of BBE diagnosed by the strict criteria of progressive, relatively symmetrical external ophthalmoplegia and ataxia by 4 weeks, and disturbance of consciousness or hyperreflexia. Ninety-two per cent of the patients involved had had an antecedent illness. Besides ophthalmoplegia and ataxia, disturbance of consciousness was frequent (74%), and facial diplegia (45%), Babinski's sign (40%) and pupillary abnormality and bulbar palsy (34%) were present. Almost all the patients had a monophasic remitting course and generally a good outcome. Serum anti-GQ1b IgG antibody was positive in 66%, and MRI showed brain abnormality in 30% of the patients. Another striking feature was the association with flaccid symmetrical tetraparesis, seen in 60% of the patients. An autopsy study of a BBE patient clearly showed the presence of definite inflammatory changes in the brainstem: there was perivascular lymphocytic infiltration with oedema and glial nodules. Electrodiagnostic study results suggested peripheal motor axonal degeneration. Limb weakness in the BBE cases studied was considered the result of overlap with the axonal subtype of Guillain–Barré syndrome. These findings confirm that BBE constitutes a clinical entity and provide additional clinical and laboratory feaures of BBE. A considerable number of BBE patients have associated axonal Guillain–Barré syndrome, indicative that the two disorders are closely related and form a continuous spectrum.

Introduction
In 1951, Bickerstaff and Cloake (1951) reported three cases of drowsiness, ophthalmoplegia and ataxia, which they designated 'mesencephalitis and rhombencephalitis', and proposed that the lesion responsible for these clinical signs was in the midbrain. Five years later, Fisher (1956) described three cases of ophthalmoplegia, ataxia and areflexia. He postulated that this disorder is a variant of Guillain–Barré syndrome (GBS) because of the presence of areflexia and CSF albuminocytological dissociation. The condition was named Fisher syndrome (FS). The following year, Bickerstaff (1957) added five more cases to the original study, and as a definitive syndrome, named the condition 'brain-stem encephalitis'. Table 1 shows that almost all the patients had symmetrical ophthalmoplegia, ataxia and disturbance of

Table 1 *Clinical features of cases reported by Fisher, Bickerstaff and Al-Din et al.*

Authors and Case Nos	Antecedent illness	Neurological signs						CSF albumino-cytological dissociation	Our diagnosis
		Consciousness disturbance	Ophthalmo-plegia	Limb weakness	Tendon reflex	Babinski's sign	Ataxia		
Fisher (1956)									
1	Sore throat, malaise, headache	–	+	Mild	Absent	–	+	+	FS with overlapping GBS
2	Malaise, fever, cough	Drowsiness	+	–	Absent	–	+	–	BBE
3	Cough, headache	–	+	–	Absent	–	+	–	FS
Bickerstaff (1957)									
1*	Headache, muscular pains	Drowsiness	+			+	+	–	BBE
2*	Malaise, headache	Drowsiness	+		Decreased		+	+	BBE
3*	Headache	Drowsiness	+				+	–	BBE
4	Vertigo, vomiting	Drowsiness	+	Gross flaccid		+	+	–	BBE with overlapping GBS
5	Headache, malaise	Drowsiness	+	–	Absent	Equivocal	+	–	BBE
6	Malaise, fever, vomiting	Drowsiness	–				+	–	Brainstem encephalitis
7	Headache, malaise, vomiting	Drowsiness	+		Absent	+	+	–	BBE
8	Muscular pain, malaise	Drowsiness	+		Decreased		+	+	BBE
Al-Din et al. (1982)									
1	Headache	Drowsiness	+		Brisk	+	+	–	BBE
2	Headache	Drowsiness	+		Brisk		+	–	BBE
3			+		Absent		+	–	FS
4		Drowsiness	+		Normal	+	+	–	BBE
5			+		Absent		+	–	FS
6		Drowsiness	+	Slight	Absent		+	–	BBE with overlapping GBS
7		Drowsiness	+	Flaccid	Brisk	+	+	–	BBE with overlapping GBS
8			+	+	Brisk		+	–	BBE with overlapping GBS
9	Flu-like illness	Drowsiness	+		Absent		+	–	BBE
10	Headache, giddiness with vomiting	Drowsiness	+		Normal		+	–	BBE
11	Cough, headache	Drowsiness	+		Absent		+	–	BBE
12	Malaise	Comatose	+		Normal		+	–	BBE
13	Pharyngitis, diarrhoea, headache	Drowsiness	+	Mild	Absent		+	+	BBE with overlapping GBS
14	Headache	Drowsiness	+		Absent		+	–	BBE
15	Malaise		+		Absent		+		FS
16	Sore throat		+		Absent		+	–	FS
17	Upper respiratory tract infection	Drowsiness	+		Absent	+	+	+	BBE
18	Sore throat		+	Mild	Absent		+	+	FS with overlapping GBS

BBE = Bickerstaff's brainstem encephalitis; FS = Fisher syndrome; GBS = Guillain–Barré syndrome. *Three cases described by Bickerstaff and Cloake in 1951. Blank: information not available.

consciousness, and some also had Babinski's sign and hemisensory loss, suggestive of central involvement. The aetiology of this syndrome was speculated to be similar to that of GBS because of evidence of prodromal upper

respiratory infection, areflexia and CSF albuminocytological dissociation. Bickerstaff (1978) reviewed the syndrome for the *Handbook of Clinical Neurology* under the title 'Brain stem encephalitis (Bickerstaff's encephalitis)', but did not cite Fisher's 1956 paper. Since then, such a condition has been called Bickerstaff's brainstem encephalitis (BBE). A subsequent publication from a group of researchers, which included Bickerstaff (Al-Din *et al.*, 1982), reported 18 other patients with 'brainstem encephalitis and the syndrome of Miller Fisher' and argued a central origin. All 18 patients had ophthalmoplegia and ataxia. Eleven of them showed drowsiness, and one was comatosed. Tendon reflexes were absent in 11, normal in three and brisk in four. Four had Babinski's sign and two had long-tract sensory disturbance (Table 1). On the basis of radiological (three patients) and pathological (one patient) changes in the brainstem and abnormal EEG findings (12 patients), they insisted that the condition represents a clinical entity distinct from GBS. The next year, Ropper (1983) criticized their report. He considered that six of the 18 cases were typical FS, and the other 12 represented obscure brainstem lesions without peripheral polyneuropathy. From this historical perspective, BBE should be the diagnosis for patients who have acute onset of disturbance of consciousness, brisk tendon reflexes or long-tract sensory impairment in addition to ophthalmoplegia and ataxia.

The nosological relationship of BBE to FS or GBS remains controversial, and it is not clear whether BBE is a distinct disease entity or a variant of FS or GBS. Presumably, because of its rarity, there has been no study of a large number of BBE patients. Studies published in the 1990s showed that serum anti-GQ1b IgG antibody levels are frequently elevated in patients with FS (Chiba *et al.*, 1992; Willison *et al.*, 1993) and in those with BBE (Yuki *et al.*, 1993). The immunological profile common to BBE and FS lends supports to a common pathogenesis, but it does not provide the answer to the question of whether these syndromes are separate entities. Our study was undertaken to clarify the clinical, electrophysiological, neuroimaging and immunological features of a large number of patients with BBE. In addition, we present pathological findings for a patient with BBE.

Patients and methods
Diagnostic criteria for BBE
On the basis of the findings of Bickerstaff (1957) and Al-Din *et al.* (1982), 'progressive, relatively symmetric external ophthalmoplegia and ataxia by 4 weeks' and 'disturbance of consciousness or hyperreflexia' are required as clinical features for the diagnosis of BBE. With these strict criteria, BBE, not FS, was diagnosed for patients with drowsiness, although in Case 2 in the original report by Fisher (1956) there was mild drowsiness. For a diagnosis of BBE, the following diseases must be excludable: vascular disease involving the brainstem; Wernicke's encephalopathy; botulism, myasthenia gravis; brainstem tumour; pituitary

apoplexy; acute disseminated encephalomyelitis (disorders described in the papers of Bickerstaff and Cloake, 1951; Bickerstaff, 1957; Fisher, 1956; Al-Din *et al.*, 1982); multiple sclerosis; neuro-Behçet disease; vasculitis; and lymphoma (our addition). One patient among Bickerstaff's original cases had flaccid limb weakness, and BBE cases were divided into 'BBE without limb weakness' and 'BBE with limb weakness'.

Patients and clinical data
One of the present authors (M.O.) reviewed the medical records of 98 patients who had BBE (*n* = 48), brainstem encephalitis (*n* = 25), FS with CNS involvement (*n* = 14) or GBS associated with disturbance of consciousness (*n* = 11), as diagnosed by the primary physicians. Four of the patients had been admitted to our hospital and the others were referred to our neuroimmunological laboratory for serum antiganglioside antibody testing from hospitals throughout Japan between December 1994 and February 2000. On the basis of the preceding criteria, BBE was the rediagnosis for 62 of these 98 patients.

Information on the following was obtained from each primary physician: antecedent illness; initial symptoms; neurological signs during the illness; the clinical course; CSF, MRI, and neurophysiological (EEG, motor nerve conduction study, and needle electromyography) findings; treatment provided; and outcome. The neurological signs were assessed as disturbance of consciousness (drowsiness, stupor, semicoma or coma); blepharoptosis, external and internal ophthalmoplegia; nystagmus; facial weakness; bulbar palsy; limb weakness of 4 or ≤3 on the Medical Research Council (MRC) scale (two or more muscle groups); deep tendon reflexes (brisk, normal, absent or decreased); Babinski's sign; truncal or limb ataxia; and deep or superficial sense impairment.

CSF samples were tested at the various hospitals. CSF albuminocytological dissociation was defined as high protein (≥45 mg/dl) with normal cellularity (≤5 cells/µl). Serum IgM and IgG antibodies to GM2, GM1, GD1a, GalNAc-GD1a, GD1b, GT1b and GQ1b were measured by an enzyme-linked immunosorbent assay (ELISA), as described elsewhere (Odaka *et al.*, 1998). Serum was considered positive when the antibody titre was ≥500. Evidence of recent *Campylobacter jejuni* infection was tested serologically, as reported elsewhere (Koga *et al.*, 1998). In the nerve conduction studies, when motor distal latency was prolonged (≥10% of the upper normal limit) or conduction velocity was slowed (≤90% of the lower normal limit) in two or more nerves, the motor nerves were classified as demyelinated (Ho *et al.*, 1995). When patients had a decrease in the amplitude of the distal compound muscle action potentials (CMAPs) (≤80% of the lower normal limit) and no evidence of demyelination as defined above, the condition of the motor nerves was regarded as axonal degeneration.

Statistical analysis

Statistical calculations were made with Statcel® software (OMS, Saitama, Japan). Comparisons between groups of clinical features were made by *post hoc*. Differences in percentages were tested with χ^2 or Fisher's exact test. *P* values of $\leqslant 0.05$ denoted statistical significance.

Results

Case reports

Illustrative case of typical BBE
Patient 1

A 29-year-old man experienced coughing and nasal discharge, which resolved in 7 days. Ten days after resolution, he suffered numbness of the arms and legs, diplopia, dysarthria, drowsiness and unsteady gait (day 1). On day 7, he was drowsy but easily aroused by stimulation. Neurological examination revealed mild bilateral blepharoptosis, limitation of horizontal gaze and incomplete convergence. There was upbeating nystagmus on upward gaze, and bilateral horizontal gaze-evoked nystagmus. His pupils were dilated and light reflexes were absent. Bell's phenomenon and oculocephalic reflexes were preserved. Slurred speech was present, but there was no facial or oropharyngeal palsy. There was no weakness. Finger-to-nose and heel-to-knee tests were ataxic. Deep tendon reflexes were diminished in the upper limbs and absent in the lower ones. Pathological reflexes were lacking. He could hold himself erect with a wide-based stance, but could not walk without support. Hypoaesthesiae of the glove-and-stocking type were present, but vibration sense was intact.

High-resolution MRI with and without gadolinium enhancement detected no plaques in the brainstem and brain. The serum anti-GQ1b IgG antibody titre was high (51 200), and between days 13 and 22 the patient underwent seven sessions of immunoadsorption with a tryptophan-conjugated column (TR-350®; Asahi Medical, Tokyo, Japan), which highly adsorbs this autoantibody (Yuki, 1996). He became fully conscious on day 14, and the next day could walk around the room with a wide-based gait, holding onto the furniture. There was slight movement of the eyeballs in downward gaze. CSF protein was 149 mg/dl, with normal cellularity. On day 20 he could walk >5 m without support, although unsteadily. Motor and sensory nerve conduction velocities were normal. On day 29 there was no extraocular muscles paresis, except for limitation of abduction. Ataxic gait disappeared, and on day 35 he could stand on one foot. On day 60 his range of eye movements was complete, and he was discharged. By day 73, nystagmus had disappeared.

Illustrative cases of BBE with overlapping GBS
Patient 2

A 37-year-old man had chills and a cough. On the morning after the sixth day (day 1) he had dysaesthesiae, dysarthria
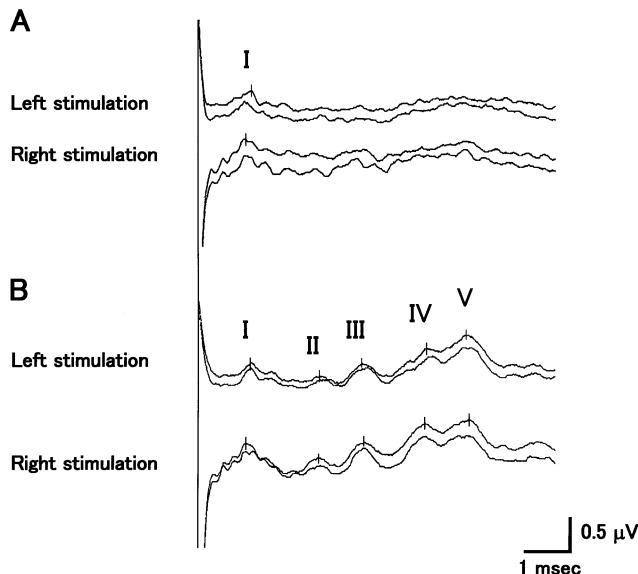
Fig. 1 (**A**) Auditory evoked brainstem responses showing the absence of II–V waves on both sides on day 7. (**B**) On day 32, the patient's auditory evoked brainstem responses were normal.

and ataxic gait, but he was alert. Limitation of ocular movement was detected in the lateral gaze of both eyes. Limb strength in the arms and legs was 4 on the MRC scale. All tendon jerks were absent. Plantar responses were indifferent. Formal tests of limb coordination showed decomposition and dysmetria. Paraesthesiae and hypoaesthesiae of the glove-and-stocking type were present. Vibration and position senses were intact. GBS was diagnosed. By the evening he could not swallow. He was intubated and placed on a respirator as respiration was apneustic breathing and he was comatosed. At that time, he was considered to have overlapping GBS and BBE.

CSF protein was 59 mg/dl associated with pleocytosis (57 cells/µl). He underwent four sessions of immunoadsorption, on days 2, 5, 7 and 12. On day 7, auditory evoked brainstem responses showed the absence of waves II–V on both sides (Fig. 1A). MRI on days 6 and 21, with and without enhancement, detected no abnormalities in the brainstem and brain. Because coma continued, he was given 0.4 g/kg of human immunoglobulin daily for 5 days, starting on day 13. Electrophysiological examination on day 9 showed reduced amplitudes of CMAPs with normal motor conduction velocities in the median, ulnar and tibial nerves, indicative of primary axonal degeneration (Table 2). On day 18 the distal and proximal CMAP amplitudes had further decreased, but the motor conduction velocity continued to be normal. ELISA confirmed that serum obtained on day 2 had high IgG antibody titres to GM1 (4000), GD1a (4000), GD1b (2000), GalNAc-GD1a (4000) and GQ1b (500). He began to recover from respiratory failure on day 15, but a tracheostomy was performed because his coma continued. Recovery from coma began on day 23, and he was fully alert on day 33. Limb weakness lessened, and on day 32 his auditory evoked

Table 2 *Motor nerve conduction study results for Patients 2 and 3*

	Patient 2			Patient 3			Normal limit		
	Median nerve	Ulnar nerve	Tibial nerve	Median nerve	Ulnar nerve	Tibial nerve	Median nerve	Ulnar nerve	Tibial nerve
Distal latency (ms)	4.1	2.3	4.6	4.2	2.5	6.0	<4.5	<3.5	<5.6
Motor nerve conduction velocity (m/s)	60.2	60.8	44.1	52.2	50.7	37.9	>48	>48	>38
Distal CMAP amplitude (mV)	4.3	5.3	4.0	2.1	1.6	1.9	>4.4	>4.6	>5.8
Proximal CMAP amplitude (mV)	4.2	5.1	3.9	2.4	1.2	0.9	>4.2	>4.2	>5.8

CMAP = compound muscle action potential.

brainstem responses were normal (Fig. 1B). He was taken off the mechanical respirator. However, he suddenly died of suffocation due to obstruction with sputum on day 45.

An autopsy was performed. The brain weighed 1530 g. Histological examination results for the cerebrum were normal. The cerebellum showed occasional grumose degeneration in the dentate nucleus. The brainstem had perivascular lymphocytic infiltration with perivascular oedema (Fig. 2A) and glial nodules (Fig. 2B). The trigeminal motor nucleus showed marked central chromatolysis of the neurons (Fig. 2C), and chromatolytic changes in the neuronal cytoplasm were frequent in the spinal anterior horn. Focal lymphocytic infiltration was seen in the dorsal root ganglia. Bronchial mucosal lymphocytic infiltration was detected in the lungs, indicative of systemic infective processes. No pulmonary embolism and coronary artery occlusion were present.

Patient 3
A 54-year-old man suffered coughing with sputum and diarrhoea, which all abated after a few days. Several days after their resolution, he experienced diplopia in the morning (day 1). The next day there was worsened diplopia and ataxic gait. On day 3 he remained alert. In addition to complete ophthalmoplegia, there were mild bifacial palsy, severe oropharyngeal palsy and slightly explosive speech. Light reflexes were prompt. There was proximal upper limb weakness, of 4 on the MRC scale. Deep tendon reflexes were absent, but extensor plantar responses were present. Finger-to-nose and heel-to-knee tests showed ataxia. Paraesthesiae of the glove-and-stocking type were present. Vibration sense was mildly decreased in the lower limbs.

CSF protein was 31 mg/dl, with normal cellularity. MRI detected no abnormalities in the brainstem. Motor nerve conduction velocities were not reduced in the median, ulnar and tibial nerves, whereas CMAP amplitudes were decreased markedly (Table 2). ELISA confirmed that serum obtained on day 3 had high IgG antibody titres to GD1a (500), GD1b (500), GT1b (2000) and GQ1b (64 000). On day 4 he had become disorientated and his limb weakness had worsened. Deltoid and triceps muscle weakness registered 3 on the MRC scale. Laboratory studies of the identifiable causes of disorientation (analysis of blood gas, blood sugar, sodium, creatinine, thiamin, renin activity and ammonia) were all normal. Hypoxia and metabolic diseases, such as diabetes mellitus, hyponatraemia, uraemia, Wernicke's encephalopathy, Addison's disease, hepatic encephalopathy and alcoholism, were excluded on the basis of physical and laboratory findings. On days 4, 5, 8, 9, 10, 11 and 12, he underwent seven sessions of immunoadsorption. Recovery began on day 24. His neurological signs disappeared in the order of ophthalmoplegia, ataxia, limb weakness and dysaesthesia. Two months later, he could climb stairs without support.

Clinical features of 62 patients with BBE
According to our BBE diagnostic criteria, the condition was diagnosed for 62 of the 98 patients. Table 3 shows the clinical profiles of the 62 patients, 37 of whom were men and 25 women, aged 3–91 years (median, 39 years). Fifty-seven (92%) patients had had antecedent illnesses (66% upper respiratory infectious symptoms only, 9% fever only, 6% fever and headache, 5% diarrhoea only, and 5% both upper respiratory infectious symptoms and diarrhoea).

The most common initial symptoms were diplopia (52% of the patients) and gait disturbance (35%), and 14 (23%) developed both on the same day. Twelve patients (19%) had dysaesthesiae of the upper and/or lower limbs, eight (13%) disturbance of consciousness, and seven (11%) dysarthria or limb weakness. Other initial symptoms were blepharoptosis and photophobia (<5%).

According to the BBE diagnostic criteria, all the patients had external ophthalmoplegia and ataxia (both truncal and limb, 71%; truncal only, 18%; limb only, 11%). During the illness, consciousness was disturbed in 74% (drowsiness, 45%; stupor, semicoma or coma, 29%). All those without disturbance of consciousness had hyper-reflexia. Limb weakness was appreciable in 60%. Deep tendon reflexes were absent or decreased in 58%, normal in 8%, and brisk in 34%. Babinski's sign was present in 40%. All the patients had ataxia, but only 16% had deep sense impairment. Facial weakness (45%), internal ophthalmoplegia and bulbar palsy (34%), superficial sense impairment (31%), blepharoptosis (29%) and nystagmus (27%) were relatively frequent.
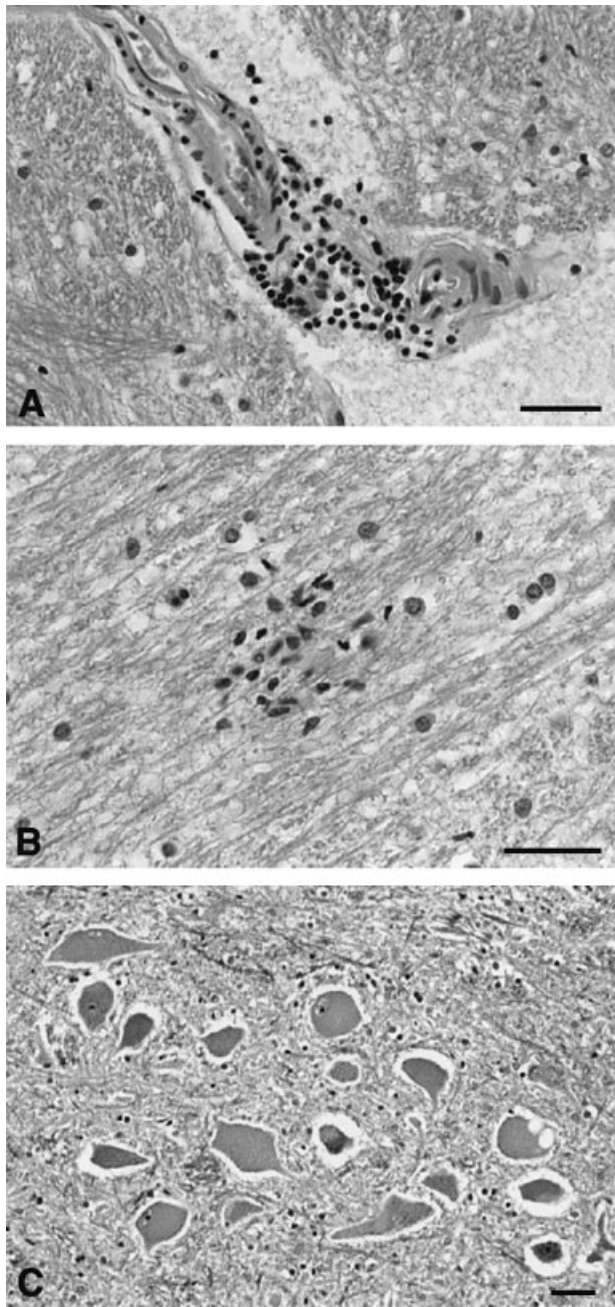
Fig. 2 Photomicrographs of the central and peripheral nervous systems of Patient 2, who had BBE and limb weakness. Paraffin sections stained with haematoxylin and eosin. (**A**) Perivascular lymphocytic infiltration with surrounding oedema in the medulla oblongata. (**B**) A glial nodule composed of microglia in the medulla oblongata. (**C**) Trigeminal motor nucleus showing central chromatolysis. Scale bars = 40 μm.

Table 4 shows abnormal MRI and neurophysiological findings. Detailed information was available for 54 patients for MRI, 33 for EEG and 34 for motor nerve conduction studies. Sixteen (30%) had high-intensity abnormalities on T_2-weighted images of the brainstem, thalamus, cerebellum or white matter of the cerebrum. Twenty-four (73%) showed

θ or δ activity at rest. Fifteen (44%) had abnormal motor nerve conduction study findings, the predominant process being axonal degeneration in 13 (38%) and demyelination in two (6%). Needle electromyography was performed in six patients. Active denervation potentials (positive sharp waves or fibrillation potentials) were present in three, with limb weakness on days 21–53. Data on CSF were obtained 1–3 times (median, 1) in 54 patients, all within 4 weeks after the neurological onset (median, 6 days; range, 1–26 days). Table 5 shows CSF findings during the first week, the second week, and the third and fourth weeks. The CSF cell count ranged from 0 to 142/μl (median, 2 cells/μl) and protein concentration from 10 to 678 mg/dl (median, 47 mg/dl). The CSF protein concentration was increased in 32 (59%) patients during the first 4 weeks after the onset. Cell count was >5 cells/μl in 20 (37%), none of whom had human immunodeficiency virus infection. The median CSF protein concentration after the second week was higher than that during the first week. CSF albuminocytological dissociation was found in 19 patients (35%) during the first 4 weeks, and the frequency increased from 19% in the first week to 57% in the third and fourth weeks. Of the 62 patients with BBE, anti-GQ1b IgG antibody was present in 41 (66%) and anti-GM1, anti-GD1a or anti-GalNAc-GD1a IgG antibody in 11 (18%) (Table 6). Serological evidence of recent *C. jejuni* infection was found in 14 (23%) of 60 patients; sera from the other two patients were not available.

Treatment of the 62 patients was as follows: combinations of steroids and plasmapheresis (plasma exchange, double-filtration plasmapheresis or immunoadsorption therapy) were given to 16 (26%) patients, plasmapheresis only to 14 (23%), steroids only to 13 (21%), combinations of steroids and intravenous immunoglobulin (IVIg) to five (8%), combinations of steroids and plasmapheresis followed by IVIg to three (5%), plasmapheresis followed by IVIg and IVIg only to two (3%), and no specific immunotherapy to seven (11%). Assisted ventilation was required for 10 (16%) of the 62 BBE patients during the acute phase. By 6 months after disease onset, 37 (66%) of the 56 patients for whom outcome data were available showed complete remission with no residual symptoms. Dysaesthesiae or limb weakness persisted in eight (14%) and diplopia or gait disturbance in five (9%). Three patients had residual symptoms; one each had psychic change, dementia and dysphagia. In addition to Patient 2 described in the case reports, two patients died, one of sudden cardiopulmonary arrest and the other of haemorrhagic infarction, a complication in the right cerebrum caused by candida meningitis.

Clinical features of BBE with overlapping GBS

In the 37 patients who had BBE with limb weakness, muscle weakness was symmetrical and flaccid. The clinical diagnosis was therefore BBE with overlapping GBS. Twenty-five had GBS with limb weakness of 4 on the MRC scale, and the other 12 had scores of ≤3. There was no significant

Table 3 *Clinical profiles of patients with BBE and BBE with limb weakness*

	Total	BBE without limb weakness	BBE with limb weakness
Number of patients	62	25	37
Sex (male/female)	37/25	17/8	20/17
Age (years): median (range)	39 (3–91)	48 (3–91)	37 (13–80)
Antecedent illness: *n* (%)			
Upper respiratory infection	45 (73)	16 (64)	29 (78)
Diarrhoea	7 (11)	3 (12)	4 (11)
Other	9 (15)	5 (20)	4 (11)
Initial symptoms: *n* (%)			
Diplopia	32 (52)	13 (52)	19 (51)
Gait disturbance	22 (35)	7 (28)	15 (41)
Dysaesthesia	12 (19)	2 (8)	10 (27)
Consciousness disturbance	8 (13)	6 (24)	2 (5)
Dysarthria	7 (11)	1 (4)	6 (16)
Limb weakness	7 (11)	0	7 (19)
Blepharoptosis	3 (5)	2 (8)	1 (3)
Photophobia	2 (3)	1 (4)	1 (3)
Neurological signs during the course of the illness			
Consciousness disturbance			
Drowsiness	28 (45)	12 (48)	16 (43)
Stupor, semicoma or coma	18 (29)	4 (16)	14 (38)
Blepharoptosis	18 (29)	8 (32)	10 (27)
External ophthalmoplegia	62 (100)	25 (100)	37 (100)
Internal ophthalmoplegia	21 (34)	7 (28)	14 (38)
Nystagmus	17 (27)	11 (44)	6 (16)
Facial weakness	28 (45)	7 (28)	21 (57)
Bulbar palsy	21 (34)	5 (20)	16 (43)
Limb weakness	37 (60)	0	25 (68)*, 12 (32)**
Tendon reflex			
Brisk	21 (34)	10 (40)	11 (30)
Normal	5 (8)	4 (16)	1 (3)
Absent or decreased	36 (58)	11 (44)	25 (67)
Babinski's sign	25 (40)	7 (28)	18 (49)
Ataxia	62 (100)	25 (100)	37 (100)
Deep sense impairment	10 (16)	2 (8)	8 (22)
Superficial sense impairment	19 (31)	3 (12)	16 (43)

*4 on the MRC scale; **≤3 on the MRC scale.

Table 4 *Abnormal MRI and neurophysiological study findings for patients with BBE and BBE with limb weakness*

Abnormal findings of	BBE, total (*n* = 62)		BBE without limb weakness (*n* = 25)		BBE with limb weakness (*n* = 37)	
	Available data	*n* (%)	Available data	*n* (%)	Available data	*n* (%)
MRI	54	16 (30)	23	9 (39)	31	7 (23)
EEG	33	24 (73)	13	10 (77)	20	14 (70)
Motor nerve conduction study	34	15 (44)	10	1 (10)	24	14 (58)
Axonal degeneration		13 (38)		1 (10)		12 (50)
Demyelination		2 (6)		0		2 (8)
Needle electromyography	6	3 (50)	2	0	4	3 (75)

difference in the clinical profiles of the two subgroups. Upper respiratory infection was the most frequent preceding symptom, diplopia (51%) or gait disturbance (41%) again being the most frequent initial neurological symptom. Dysaesthesiae was present in 27%, limb weakness in 19% and dysarthria in 16% (Table 3).

Table 5 *CSF findings during the first, second, and third and fourth weeks for patients with BBE and BBE with limb weakness*

	BBE, total (n = 62)			BBE without limb weakness (*n* = 25)			BBE with limb weakness (*n* = 37)		
Available data of patients (%)	54 (87)			20 (80)			34 (92)		
Day of sampling from onset: median (range)	6 (1–26)			6 (1–19)			5 (1–26)		
	1st week	2nd week	3rd and 4th weeks	1st week	2nd week	3rd and 4th weeks	1st week	2nd week	3rd and 4th weeks
Number of samples (%)	42 (68)	14 (23)	14 (23)	15 (60)	7 (28)	3 (12)	27 (73)	7 (19)	11 (30)
Cell count (cells/µl): median (range)	3 (0–71)	2 (0–142)	1 (0–21)	4 (0–60)	1 (0–63)	1 (0–5)	3 (0–71)	2 (1–142)	1 (0–21)
Pleocytosis (%)	15 (36)	6 (43)	3 (21)	6 (40)	3 (43)	1 (33)	9 (33)	3 (43)	2 (18)
Protein concentration (mg/dl): median (range)	42 (10–292)	89 (24–295)	89 (24–678)	42 (10–81)	81 (24–121)	46 (24–149)	34 (16–292)	106 (25–295)	89 (25–678)
Elevated protein concentration (%)	16 (38)	11 (79)	9 (64)	7 (47)	6 (86)	2 (67)	9 (33)	5 (71)	8 (73)
CSF albuminocytological dissociation (%)	8 (19)	6 (43)	8 (57)	4 (27)	4 (57)	2 (67)	4 (15)	2 (29)	6 (55)

Table 6 *Anti-ganglioside IgG antibodies for patients with BBE and BBE with limb weakness*

IgG antibody to	BBE, total (*n* = 62)	BBE without limb weakness (*n* = 25)	BBE with limb weakness (*n* = 37)
GM2	2 (3)	0	2 (5)
GM1	6 (10)	2 (8)	4 (11)
GD1a	8 (13)	1 (4)	7 (19)
GalNAc-GD1a	1 (2)	0	1 (3)
GD1b	11 (18)	2 (8)	9 (24)
GT1b	3 (5)	0	3 (8)
GQ1b	41 (66)	15 (60)	26 (70)
GM1, GD1a or GalNAc-GD1a	11 (18)	2 (8)	9 (24)

Data are *n* (%).

Consciousness was disturbed in 81% (drowsiness, 43%; stupor or coma, 38%). All those without disturbance of consciousness had hyper-reflexia. Deep tendon reflexes were absent or decreased in 67%, normal in 3% and brisk in 30%. Babinski's sign was present in 49%. All the patients had ataxia, but only 22% had deep sense impairment. Facial weakness (57%), bulbar palsy and superficial sense impairment (43%), internal ophthalmoplegia (38%), blepharoptosis (27%) and nystagmus (16%) were again relatively common. As shown in Table 3, except for limb weakness, there was no significant difference in the clinical profiles of the subgroups of BBE without weakness and BBE with overlapping GBS.

Abnormal MRI findings were detected in 23% (seven of 31) and abnormal EEG in 70% (14 of 20) (Table 4). Abnormal motor nerve conduction study findings were obtained for 58% (14 of 24 patients; axonal degeneration 50%, demyelination 8%), suggestive of predominant axonal involvement. Needle electromyography showed positive sharp waves or fibrillation potentials in three patients on days 21–53. The CSF protein concentration was increased in 19 (56%) of the 34 patients during the first 4 weeks. CSF albuminocytological dissociation was present in 10 (29%), and the frequencies were increased from 15% in the first week to 55% in the third and fourth weeks (Table 5). Anti-GQ1b IgG antibody was present in 70%, and anti-GM1, anti-GD1a or anti-GalNAc-GD1a IgG antibody in 24% of the 37 patients with BBE and overlapping GBS (Table 6) and in 50% of the 12 patients with a score of ≤3 or less. Serological evidence of recent *C. jejuni* infection was found in eight (22%) of 36 patients, and *C. jejuni* was isolated from one patient. There was no significant difference in frequency of positive *C. jejuni* serology between BBE and BBE with overlapping GBS.

Assisted ventilation was required for nine (24%) of the 37 patients with BBE with limb weakness. Six months after onset, 18 (51%) of the 35 patients for whom outcome data were available showed complete remission with no residual symptoms. Limb weakness persisted in eight (23%).

Discussion

Nosological entity of BBE

Detailed clinical and laboratory features of BBE were documented in a large number of patients. The findings confirmed that BBE can be defined as a syndrome presenting acute ophthalmoplegia, ataxia and disturbance of consciousness as its major manifestations, in association with certain symptoms and signs indicative of central involvement, and that it constitutes a clinical entity. Furthermore, a considerable number of patients with BBE developed flaccid tetraparesis, which is presumed to be a sign of overlapping GBS.

Our diagnosis for the original cases reported by Fisher and Bickerstaff et al.

One of the three patients described by Fisher in 1956 showed mild drowsiness (Fisher, 1956). Although, according to his report, drowsiness may be accompanied by FS, all eight patients reported in Bickerstaff's paper (Bickerstaff, 1957) showed drowsiness. BBE, not FS, therefore was the diagnosis for those who showed drowsiness. Six (Nos 1, 2, 3, 5, 7 and 8) of the eight cases described by Bickerstaff (1957) fulfil our tentative criteria for BBE, whereas none satisfy the criteria for FS (Table 1). The patient of Case 4 showed gross flaccid weakness, and in our study the tentative diagnosis was BBE with overlapping GBS. Another patient (No. 6) who did not show ophthalmoplegia did not fulfil our strict criteria for FS or BBE. According to the criteria, BBE was the diagnosis in 9 (Nos 1, 2, 4, 9, 10, 11, 12, 14 and 17) of the 18 cases described by Al-Din *et al.* (1982), and FS in four (Nos 3, 5, 15 and 16). Because four patients (Nos 6, 7, 8 and 13) showed drowsiness and limb weakness, or hyper-reflexia and limb weakness, BBE with overlapping GBS was diagnosed. These diagnoses are consistent with those made by Ropper (1983), who considered the presence of drowsiness and Babinski's sign difficult for FS.

Clinical analysis of BBE

Our findings have added information about the clinical features of BBE. The male : female ratio for the 62 patients with BBE was about 3 : 2. The most frequent preceding symptom was upper respiratory infection, and the most frequent initial symptoms were diplopia and gait disturbance. By means of our diagnostic criteria, the clinical features of the patients with BBE were characterized as disturbance of consciousness, ophthalmoplegia, hyper-reflexia and ataxia. Pupillary abnormalities, facial weakness, bulbar palsy and Babinski's sign were frequent, occurring in one-third to one-half of the BBE patients. Half the patients had normo- or hyper-reflexia, the others hypo- or areflexia. Deep sensation was frequently unimpaired despite profound ataxia.

Abnormal lesions (high-intensity areas on T_2-weighted images of the brainstem, thalamus, cerebellum and cerebrum) on MRI findings were present in about one-third of the BBE patients. Normal MRIs have been reported for some BBE patients, whereas in others high-signal lesions, documented on T_2-weighted images of the upper mesencephalon, cerebellum, thalamus or brainstem, may move and regress with the clinical course of the illness (Yaqub *et al.*, 1990; Camarda *et al.*, 1992; Kikuchi *et al.*, 1997; Chataway *et al.*, 2001; Mondéjar *et al.*, 2002). The frequency of our patients who had slow-wave activity in the θ to δ range in EEG findings also indicated CNS involvement, consistent with disturbance of consciousness. Al-Din *et al.* (1982) reported the likelihood of abnormality within the brainstem itself on the basis of results of clinical, neurophysiological, radiological and pathological studies of BBE, and that areflexia is explained by the involvement of the mesencephalic and upper pontine reticular formations. In the nerve conduction studies, most patients with BBE without limb weakness were normal, whereas half of those who had BBE and overlapping GBS showed indications of motor nerve dysfunction, predominantly axonal dysfunction. Two of the eight patients described in the original paper of Bickerstaff (1957) had CSF albuminocytological dissociation and the other six had CSF pleocytosis (median, 26 cells/μl; range, 10–153 cells/μl). The CSF protein concentration was normal in about two-thirds of our BBE patients during the first week, but its frequency increased during subsequent weeks. CSF pleocytosis was present in about one-third during the first 4 weeks. In our previous study, CSF albuminocytological dissociation was detected in 62% of 120 patients with GBS during the first 3 weeks after the onset (47% during the first week, 60% during the second week, 74% during the third week) and in 59% of 123 with FS (35% during the first week and 75% during the second week) (Y.Nishimoto, N.Yuki, M.Okada, K.Itivata, unpublished data). The frequency of CSF albuminocytological dissociation tended to be lower in our BBE series than in GBS and FS series, because CSF pleocytosis was also present. Pleocytosis may reflect severe breakdown in the blood–CSF barrier or invasion of leucocytes into the CSF. CSF studies showed some degree of elevated protein concentration with and without pleocytosis in most patients with BBE during the first 4 weeks, but some patients were normal throughout the course of the illness.

From an immunological perspective, anti-GQ1b IgG antibody is frequently detected in sera from patients with BBE (Yuki *et al.*, 1993; Odaka *et al.*, 2001; Williams, 2001). Anti-GQ1b IgG antibody was present in two-thirds of our BBE patients. The fact that BBE and FS have an autoantibody in common suggests that the two disorders are closely related. BBE patients definitely have CNS involvement that is responsible for disturbance of consciousness, extensor plantar responses and hemisensory loss, but not all the features of BBE, including ophthalmoplegia and ataxia, are necessarily explained by central lesions. Chiba *et al.* (1993) showed the presence of a GQ1b epitope in the extramedullary regions of human ocular motor nerves, indicative of a role for anti-GQ1b antibody in the pathogenesis of ophthalmoplegia in FS.

Further research is needed to clarify whether the mechanisms of ophthalmoplegia and ataxia in BBE and FS are identical.

Most patients with BBE were given immunotherapy, such as steroids, plasmapheresis and IVIg. Three of the 62 patients died during the course of illness, but the outcome for the BBE patients was generally good. Effective therapy for BBE has yet to be established. Several reports have suggested that plasmapheresis and IVIg have a beneficial effect in patients with BBE (Yuki *et al.*, 1993; Yuki, 1995; Kikuchi *et al.*, 1997; Shimokawa *et al.*, 1998; Fox *et al.*, 2000). In GBS, IVIg is as effective as plasma exchange (van der Meché and Schmitz, 1992; Plasma Exchange/Sandoglobulin Guillain–Barré Trial Group, 1997). Moreover, combined therapy of IVIg and high-dose methylprednisolone was a more efficacious therapy than IVIg alone in patients with GBS (van Koningsveld *et al.*, 2002). BBE and GBS are so closely related that combined therapy of IVIg and high-dose methylprednisolone should be used. Controlled clinical trials are needed to test this proposal.

Definitive inflammatory changes in the brainstem of a patient with BBE

Unlike the many clinical findings of apparent brainstem involvement in BBE, neuropathological findings in this disease are relatively few. In Bickerstaff's (1957) original report, the brainstem of an autopsy patient (Case 8) showed no apparent neuronal death, but there were oedematous changes with astrocytic proliferation. The cerebellum showed diffuse, slight loss of Purkinje cells, but some folia were completely lacking these cells. Lymphocytic cuffing was present around some blood vessels in the frontal lobe. Bickerstaff considered these changes to be caused by cerebral oedema secondary to viral infection or to be the result of hypersensitivity to infection. In the report by Al-Din *et al.* (1982), in one autopsy patient (Case 17) the numerous necrotic lesions in the brainstem were associated with activated microglia, astrocytic proliferation and small foci of round cell (lymphocyte) infiltration. There was also very marked perivascular round cell cuffing, sometimes with numerous macrophages. These changes were interpreted as evidence of encephalitis. Although the pathological process, as reported by Al-Din *et al.* (1982), was predominantly in the CNS, Ropper (1983) doubted the presence of BBE and considered that CNS involvement in GBS could be mimicked by peripheral nerve disease. The post-mortem examination of our Patient 2, however, clearly showed the presence of definite inflammatory changes in the brainstem: perivascular lymphocytic infiltration with perivascular oedema and glial nodules. Inflammatory conditions, which affected the brainstem, may have exerted a certain influence on dentate neurons. These inflammatory processes probably have a pivotal role in the development of the characteristic phenotypes of BBE.

Subgroup of BBE associated with GBS

Analysis of the clinical features of 62 patients with BBE, based on our proposed criteria, showed that 37 (60%) patients with BBE associated with GBS had coexisting limb weakness. The clinical features of these patients were disturbance of consciousness, ophthalmoplegia, hyper-reflexia, ataxia and limb weakness. Because, except for limb weakness, the clinical profiles of BBE and BBE with overlapping GBS did not differ significantly, the conditions may be closely associated. The frequency of disturbance of consciousness in patients with BBE with overlapping GBS was almost the same for drowsiness and for stupor, semicoma and coma. The frequencies of facial weakness, bulbar palsy, Babinski's sign and superficial sense impairment were about 1/2, those of internal ophthalmoplegia 1/3, and those of blepharoptosis and deep sense impairment 1/4. The ratio of patients with normo- or hyperreflexia and those with hypo- or areflexia was about 1 : 2. The outcomes for the patients were generally good, but one-quarter of those who scored ≤3 on the MRC scale had persistent limb weakness.

Our findings based on electrodiagnostic criteria suggest that motor nerve dysfunction is predominantly axonal and that the form of GBS that overlaps with BBE may be the axonal subtype, i.e. acute motor axonal neuropathy (AMAN) (Ho *et al.*, 1995). Needle electromyography results confirmed active denervation potentials in three patients studied 3–8 weeks after the onset. Patients with AMAN invariably have low distal CMAPs, which could be caused by either axonal degeneration or distal conduction block (Ogawara *et al.*, 2000), and once axonal degeneration develops recovery is slow and incomplete. Accumulated evidence supports the speculation that AMAN is caused by the IgG antibody against the gangliosides GM1, GD1a or GalNAc-GD1a (Yuki *et al.*, 1990, 2001; Kornberg *et al.*, 1994; Kusunoki *et al.*, 1994; Carpo *et al.*, 1999; Ho *et al.*, 1999; Ogawara *et al.*, 2000; Hadden *et al.*, 2001). Our previous study showed that anti-GM1 antibodies were present in 64% of 33 AMAN patients, anti-GD1a in 45% and anti-GalNAc-GD1a in 33%, and anti-*C. jejuni* antibody in 14 (42%) (Ogawara *et al.*, 2000). The BBE patients in the present study, with or without overlapping GBS, also had these antibodies, although the frequencies were lower than in the AMAN patients. This suggests that elements of the autoimmune mechanism are common to both, and that they are not distinct but are closely related conditions.

A number of reports described GBS patients experiencing coma with abolished oculocephalic reflex (Carroll and Mastaglia, 1979; Najim Al-Din *et al.*, 1987; Coad and Byrne, 1990; Hassan and Mumford, 1991; Martí-Massó *et al.*, 1993). These cases with severe brainstem involvement should be diagnosed as having BBE. Autopsy findings have been reported for a patient in whom BBE associated with GBS was diagnosed clinically (Yuki *et al.*, 1997), although the case was not included in this study: there was loss of large myelinated fibers in the nerve roots, including the cranial

nerves, but a normal midbrain, pons and medulla oblongata. The clinical, electrophysiological and immunological findings reported in our study support the original hypothesis of Bickerstaff and Cloake (1951), that BBE is closely related to GBS and that they form a continuous spectrum.

Acknowledgements

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