SCIENTIFIC COMMENTARY
The other BSE

Brainstem encephalitis has long proved complex and cryptic, but the waters are beginning to clear. Six decades ago, Edwin Bickerstaff (1921–2008), writing from Birmingham with Professor Philip Cloake (1890–1969), described three cases of ‘mesencephalitis and rhombencephalitis’ (Bickerstaff and Cloak, 1951). Each individual presented with a brainstem oculomotor disturbance, other cranial neuropathies and ataxia (with variable other signs); two had a hypercellular cerebrospinal fluid. The patients recovered well; and though lamenting the lack of pathological characterization, the authors considered ‘their clinical features and course were so remarkably similar that it seemed highly probable that the same or a closely related pathological process was involved’. Six years later, Bickerstaff published eight cases of what he now designated ‘brainstem encephalitis’ (Bickerstaff, 1957); others later came to attach Bickerstaff’s name to the disorder.

The waters were, however, already becoming rather muddied: only one case had come to autopsy, and no brainstem inflammation was apparent (Bickerstaff, 1957). What is more, four of these eight cases of ophthalmoplegia and ataxia had areflexia (one also with extensor plantar responses); and 1 year earlier Charles Miller Fisher had described three cases of ‘an unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia)’ (Fisher, 1956), which of course also came to bear his name. There followed a long period of uncertainty as to whether Fisher and Bickerstaff syndromes were one and the same, and of central or peripheral origin; only in the last few years has (mainly) immunological characterization begun to resolve these matters.

This brief neuro-history offers a backdrop to last year’s fascinating description in Brain of a new brainstem inflammatory syndrome. Sean Pittcock, Jan Debruyn, Brian Weinsenker and Mark Keegan and colleagues, from the Mayo Clinic (USA) and from Ghent University Hospital (Belgium), beautifully and succinctly (if perhaps not euphoniously) described ‘CLIPPERS’ (Pittcock et al., 2010)—Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids—as a distinct form of idiopathic brainstem encephalitis centred on the pons.

All eight patients with CLIPPERS had a brainstem oculomotor disturbance and ataxia; but what was striking and may (speculatively) have inspired the initial identification of these cases was a remarkable pattern of MRI change, ‘symmetric curvilinear gadolinium enhancement peppering the pons’, changes extending in all cases to other parts of the brainstem, principally the medulla or the midbrain, and occasionally beyond to the cerebellum or spinal cord. One patient had a CSF pleocytosis, three had cyto-albumin dissociation, and three had oligoclonal bands specific to the cerebrospinal fluid. Importantly, four patients underwent brain biopsy, and the tissue again showed a similar picture—hindbrain lymphocytic infiltration, largely but not wholly perivascular in distribution, accompanied by a moderate number of histiocytes and activated microglia. No demyelination was seen; no vasculitic, granulomatous or lymphomatous changes; and no neuronal or astrocytic changes are mentioned. All patients improved after corticosteroid treatment, some proving steroid dependent.

Reports of similar cases have quickly followed—four are printed online as part of the current issue of Brain—and already have begun to extend the phenotype. Taeib et al. (2011) describe a patient with comparable imaging changes and steroid responsiveness, with childhood onset, and persisting over decades—with, notably, normal MRI for the first 9 years. Duprez and Sindic (2011) present a patient with little steroid response, and propose that new imaging criteria obviate the need for biopsy as spinal fluid results are reported and there is no neuropathology. In their reply, Keegan et al. (2011) demur here, consider the imaging picture dissimilar and suggest that the individual reported likely had an alternative disorder. List et al. (2011) report a single more typical case, with negative anti-ganglioside antibody testing; spinal fluid examination showed transient oligoclonal bands, but no cellular reaction. These authors also did not pursue biopsy, partly ‘given the typical clinical and radiological features of CLIPPERS’. Keegan et al. (2011) are alert to the risk that their description should encourage any reluctance to biopsy, notwithstanding the delicate site of the disorder. Making CLIPPERS a ‘disease,’ diagnosed only on imaging, will hardly advance our understanding of brainstem inflammatory disorders. Cerebral and brainstem biopsies are increasingly seen as safer than often previously considered, and informative (Rachinger et al., 2009; Rajshekhar and Moorthy, 2010; Rice et al., 2011). Moreover, as Jones et al. (2011) illustrate, these magnetic resonance findings are not pathognomonic: low-grade glioma may masquerade as CLIPPERS. Lastly, Kastrup et al. (2011) report three further cases. All had extra-pontine involvement clinically and radiologically. Interestingly, two exhibited a marked elevation of serum IgE. None had a cerebrospinal fluid pleocytosis or oligoclonal bands. All three patients had normal peripheral nerve conduction studies, and all had brain biopsies. These showed a similar pattern of mainly but not exclusively angiocentric infiltration by lymphocytes, with
few histiocytes and activated microglia. Some cell proliferation was reported; no eosinophils were present. One patient required intensified immunosuppression with cyclophosphamide, with near resolution of MRI lesions. These authors also caution against any recommendation not to biopsy, stressing the non-specific nature of the clinical presentation and the absence of any clear mechanistic understanding.

So how does this new syndrome fit in: a separate, new disorder; or could it be part of a ‘Bickerstaff spectrum’? To explore this requires an update on how Bickerstaff’s ‘mesencephalitis and rhombencephalitis’ has evolved. The Birmingham group maintained that Bickerstaff’s was exclusively a disorder of the CNS. They reported 18 cases in 1982 (Al-Din et al., 1982), one with autopsy-proven brainstem encephalitis. Eleven had areflexia, but the authors considered this feature to have originated within the mesencephalic and upper pontine reticular formation. In support of this interpretation, 2 of the 11 cases also had extensor plantar responses, and nerve conduction studies were normal in three, as indeed had been a number of other reported cases (Miller Fisher averred that the disorder he described was a peripheral disorder. As more cases of ophthalmoplegia and ataxia—without or without areflexia—were described and studied, however, and in particular when anti-ganglioside antibody assays and MRI scanning became available, a spectrum of anti-GQ1b antibody-associated disease emerged, encompassing Fisher syndrome and Bickerstaff’s brainstem encephalitis.

Odaka et al. (2003) described 62 cases of Bickerstaff’s brainstem encephalitis, proposing this to be ‘closely related to GBS and that they form a continuous spectrum’. Serum anti-GQ1b antibodies were detected in 66% of tested patients; while 44% of 34 patients tested had abnormal peripheral neurophysiology; and 30% of the 54 imaged patients had brainstem magnetic resonance abnormalities. The same group went on to describe a remarkable 681 cases in 2008, finding nothing to alter their earlier conclusion that ‘Bickerstaff’s brainstem encephalitis and Fisher syndrome form a continuous spectrum with variable CNS and PNS involvement’ (Ito et al., 2008). Anti-GQ1b IgG antibodies were present in 68% of these Bickerstaff-phenotype patients and 83% of the Fisher-phenotype patients. One of the authors went on to propose the term ‘Fisher–Bickerstaff syndrome’ (Yuki, 2009), and pointed out that GQ1b is not only expressed at the neuromuscular junction of the extraocular muscles and of muscle spindles (Liu et al., 2009), but also that serum IgG with anti-GQ1b reactivity stains the cerebellar molecular layer in humans (Kornberg et al., 1996).

The Bickerstaff story may tell us, among other things, that the brainstem is particularly susceptible to immune attack, indeed offering a precise humoral mechanism. The separate but no less brainstem is particularly susceptible to immune attack, indeed requires an update on how Bickerstaff’s ‘mesencephalitis and Fisher syndrome form a continuous spectrum with variable CNS and PNS involvement’ to this picture.

There is no suggestion in any of the original CLIPPERS cases, or those now published, of a paraneoplastic link. The Mayo–Ghent group also naturally considered very carefully the relationship between CLIPPERS and Bickerstaff’s brainstem encephalitis. They concluded that the disorders are distinct for several reasons, including ‘the observed neuropathology and radiological features and lack of peripheral nerve involvement’, and also since the ‘diagnostic features of Bickerstaff brainstem encephalitis include drowsiness or coma, progressive external ophthalmoplegia, ataxia and corticospinal tract signs’ (Pittock et al., 2010). The implication is that two distinct forms of idiopathic brainstem encephalitis can be recognized—GQ1b-related Bickerstaff–Fisher syndrome (or rather, one end of the spectrum of that disorder) and CLIPPERS, and that the brainstem might additionally be involved in other (slightly) less idiopathic disorders, including para-neoplasia [in which magnetic resonance scanning is characteristically normal (Saiz et al., 2009)] and, of course, multiple sclerosis. A more cautious view, one that William of Ockham might have offered, might be that the distinction of Bickerstaff’s from CLIPPERS remains to be nailed, as it were. Thus, the core clinical features of Bickerstaff’s—external ophthalmoplegia and ataxia—were seen in all the Mayo–Ghent patients, and spinal signs appeared to be present in five out of eight patients with CLIPPERS. Impaired consciousness occurred in only 9% of the Bickerstaff-phenotype patients at onset (Ito et al., 2008), and at any time in the illness in 11/16 of the Birmingham cohort (Ito et al., 2008)—while ‘cognitive deficits and psychomotor slowing’ are now reported in one of the patients with CLIPPERS reported by Kastrup et al. (2011). Peripheral nerve features were not described in the Mayo–Ghent series, and neurophysiological tests (and anti-ganglioside antibody testing) were not performed, but more importantly, peripheral nerve features are not characteristic of the Bickerstaff end of Bickerstaff–Fisher syndrome. Relapsing Bickerstaff’s encephalitis is reported (Mondejar et al., 2002). Concerning the neuropathology, Al Din et al. (1982) and Odaka et al. (2003), reporting autopsied cases of Bickerstaff’s, both describe (in the brainstem) ‘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’—features not wholly dissimilar to CLIPPERS.

This leaves the very striking MRI changes seen in CLIPPERS. It is the gadolinium enhancement images that are particularly distinctive; but MRI descriptions in historical Bickerstaff case reports, while admittedly not strongly suggestive of CLIPPERS, often lack detail (indeed often lack contrast scanning). Also with the fast-changing quality of magnetic resonance scanning, arguably only the last decade or so of ‘Bickerstaff’ reports may reasonably be compared. Some Bickerstaff’s cases clearly exhibit no contrast enhancement (Chataway et al., 2001); and Mondejar et al. (2002), specifically describing magnetic resonance findings in (one) Bickerstaff case, also report that lesions do not show contrast enhancement. However, their patient did not in fact have an enhanced scan at presentation, while other Bickerstaff cases had gadolinium-enhanced magnetic resonance scans that do appear, from the images presented, reminiscent of CLIPPERS (Weidauer et al., 2003; Roos et al., 2008). Furthermore, Taieb et al.’s (2011) case study suggests that CLIPPERS MRI changes can be rather variable.

But this attempt to wield Occam’s razor remains problematic, and I am not sure that CLIPPERS can be elided with Bickerstaff’s. Other authors stress drowsiness as a defining feature of Bickerstaff’s (Ito et al., 2008); while the clinical course varies, in
the main Bickerstaff’s encephalitis appears monophasic; and the scan appearances described for CLIPPERS are clearly remarkable. Some neurologists may hesitate before accepting a new disorder based largely on imaging appearances, with relatively non-specific neuropathological changes, and (most importantly) with no clues as to cause. Interestingly, Bickerstaff himself was also sensitive to such concerns (his first report lacked even neuropathology), and his conclusion 60 years ago concerning his cases remains curiously apposite to CLIPPERS: ‘Despite the advances of the recent decades in scientific methods of investigation, conditions are not infrequently seen, particularly in neurological practice, which fall outside the well-recognized syndromes and in which it is possible to hazard only a guess at the aetiological and pathological processes involved. If the patient recovers the exact explanation may never be certain, but one experience of such a condition may enable it to be recognized again, and, even in the face of ignorance about its nature, some idea of its likely course and prognosis may be formed’ (Bickerstaff and Cloak, 1951).

Bickerstaff–Fisher syndrome at least now has an antibody—and how the erstwhile similarly cryptic Devic’s syndrome has blossomed since acquiring its marker!—though it must be stressed that the GQ1b antibody is an association, lacking evidence for causality. Regarding CLIPPERS, the steroid responsiveness, lymphocytic infiltrate, gadolinium enhancement and spinal fluid changes all point to an immune cause, as Pittoc et al. (2010) point out, and immunological studies clearly represent the next process of involved. If the patient recovers the exact explanation may never be certain, but one experience of such a condition may enable it to be recognized again, and, even in the face of ignorance about its nature, some idea of its likely course and prognosis may be formed’ (Bickerstaff and Cloak, 1951).

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