Copper concentration in CSF during the course of treatment in a 41 year old patient with Wilson's disease. The arrow marks the time when the patient started to take his zinc in reduced doses and irregularly.

copper and ceruloplasmin were unchanged. Confronted with these results the patient admitted that he had been non-adherent to his zinc regimen for the past 2 years by reducing the daily zinc intake to less than 400 mg a day. One established parameter for the efficacy of treatment in Wilson's disease is the balancing of the intake and excretion of copper. This, however, was not feasible as the patient refused to take a standardised diet, rendering the daily copper intake unknown. As is displayed in the figure there had been a continuous decrease of the CSF copper concentrations over the past years, although the treatment consisted only of 800 mg zinc a day without a restriction in copper intake. The repeated determination of the CSF copper allowed for the demonstration of a sufficient treatment and for the detection of non-adherence to the treatment regimen before the reappearance of clinical symptoms. We conclude that the determination of CSF copper reliably detects copper accumulation in the CNS and may be used to monitor the treatment efficacy, particularly in patients with non-adherence to (copper free) diet and drug treatment.

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CORRESPONDENCE

Between will and action

I read with great interest the recent paper by Bundick and Spinella¹ and the related commentary by Goldberg.² These articles address the neurological substrates of volitional disturbance and in places they adopt the vocabulary of the philosophy of action—for example, Goldberg refers to the “will”. However, their uses of action related terms are mutually inconsistent and some clarification might assist in elucidating the functional anatomical relevance of the disorders described.

If we are to use the terms “will” and “action” then their use should be internally consistent. The “will” is that process that deliberates (consciously) on what is to be done, and the “action” is the performance, which follows on from that deliberation.³⁻⁴ (It should be noted that the temporal sequence of this philosophical model of volition is substantially undermined by the classic EEG experiments of Libet *et al* on “intention”.⁵⁻⁶) An “action” is consciously chosen; there is no such thing as an “involuntary action” (according to this model). Involuntary movements are movements not the intended actions of the agent (“the one who acts”).⁴ It follows that the movements initiated by an “alien hand” may seem purposeful, but they are not actions (chosen by the patient). They are failures of action in so far as the patient cannot make the limb “behave”. Hence, although Goldberg refers to the “will” being involved in action generation, his terminology is extrapolated inconsistently: he refers to alien hands performing “purposeful acts” and “involuntary actions”; the first is an attribute of an agent, the second is an oxymoron.⁴

Bundick and Spinella, by contrast, refer to “involuntary motor activity” and “non-purposeful” movements.¹ These terms are coherent within the context of the “will” vocabulary being used.

The above points are not merely pedantic, as a case can be made for “action” and “agency” implicating different brain systems,⁷ and thus the volitional deficit demonstrated in each form of the alien hand syndrome may have some cognitive-neurobiological relevance.

In the medial-prefrontal and callosal forms of alien hand syndrome, the patients, although they have a failure of motor control, and an inability to impose their “will” on the alien limb, do not generally attribute alien agency to that limb—that is, they do not experience it as belonging to an “other”. However, in the posterior alien hand syndrome, personal agency may be lost, and the limb experienced as belonging to someone else. Consider the case of Leiguarda *et al*,⁸ cited by neither Bundick and Spinella nor Goldberg.^{1,2} This alien limb (associated with ictal activity from a right parietal lesion) was experienced thus by the patient:

“Suddenly I had a strange feeling on my left side; later I could not recognize the left arm as my own; I felt it belonged to someone else and wanted to hurt me because it moved towards me.”⁸

This third form of alien hand syndrome has been referred to previously.⁷ The loss of

agency it comprises is consistent with that alienation noted in “somatoparaphrenia” by Critchley⁹ and is congruent with that attribution of agency to external forces so characteristic of schizophrenic “alien control”; itself associated with functional abnormality of the right parietal region.¹⁰

Hence, a consistent application of action terminology may help to elucidate the functional anatomical correlates of disorders of volition.⁷

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Progressive dementia and gait disorder in a 78 year old woman

Although the provisional diagnosis of gliomatosis cerebri in the *clinicopathological case conference* by Tagliati *et al* was the one eventually validated at necropsy,¹ the discussion should also have entertained the possibility that the occurrence of signal hyperintensity on MRI, in the context of dementia, ataxia, and Babinski's sign could also be consistent with the diagnosis of cerebral amyloid angiopathy (with giant cell inflammatory reaction to B4-amyloid and vasculitis), exemplified by a 63 year old man presenting with some of these stigmata.² In the classic triad, consisting of cognitive impairment, upper motor neuron signs, and lobar haemorrhage,³ the third might well be a criterion potentially interchangeable with, or antedated by amyloid related vasculitis and attendant stigmata such as focal non-specific hyperintensity on MRI.

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Guillain-Barré, Fisher, and Bickerstaff syndromes: nature versus well established ideas

As the author of the first ever report documenting central nervous system involvement in Miller Fisher syndrome,¹ I beg permission to discuss certain aspects of the work of Yuki *et al* on Guillain-Barré syndrome and Bickerstaff's brainstem encephalitis, an example of which was published in this *Journal*.² Twenty three years ago, I perused the literature in search of a diagnosis for a child I had seen in Iran. Eyeing incessantly a few certain guide posts in the neurological heavens (Babinski's response, internuclear ophthalmoplegia, spasticity) I sailed the lore diligently, arriving at two inescapable conclusions: (a) that my patient with a midbrain lesion demonstrated by CT was an instance of Miller Fisher syndrome, hitherto a variant of Guillain-Barré syndrome; (b) that Bickerstaff's brainstem encephalitis and Miller Fisher syndrome are one and the same entity. With that perusal behind me, I thought it entirely sufficient to include Bickerstaff's work in my references and ended the article by the following statement: It is evident that our finding, if confirmed, raises questions regarding pathophysiology of Landry-Guillain-Barré syndrome, of which Fisher syndrome is a limited form. That pivotal observation has since been amply substantiated (see below for an incomplete list of references).

In 1982 the article became the subject of an editorial in the *Archives of Neurology* in opposition to my position. It was acknowledged parenthetically by Bickerstaff himself who eventually embraced my second conclusion even though he sided with the splitters, considering the entity of a separate disease. The arrival of MRI turned the tide entirely in favour of the lumpers soon after³, confirming my impression of a need for a reappraisal indicated above. Electrophysiological studies pointed to the same conclusion—that is, Miller Fisher syndrome often, if not always, is superimposed on a Guillain-Barré syndrome background sometimes so mild requiring complex techniques to disclose its presence.⁴ Frequent shuttling of Yuki *et al* between Guillain-Barré syndrome, Bickerstaff's brainstem encephalitis, and Miller Fisher syndrome when reporting "overlapping" hybrid cases means the same thing as well. Many others have made similar observations describing an ascending or descending march of the pathology along the brainstem, displaying corresponding neurological features.⁵ The report of Odaka *et al* concerning ballism⁶ in a case of Guillain-Barré syndrome/Miller Fisher syndrome is a novel observation, and another warning to those remaining sceptics who, while ignoring other guide posts, consider Miller Fisher syndrome strictly a peripheral nervous system disease. But when Yuki *et al* draw any distinction between Fisher and Bickerstaff syndromes they are displaying a lack of historical perspective and paucity of clinical perspicuity which I am rectifying here, as this is an important area of neurology where the stakes are high and simple logic must prevail. It is this blurring of traditional border between certain maladies affecting the peripheral and central nervous system that is the thrust of what has followed our ground breaking observation, including the work of Yuki *et al* (whatever its eventual immunological import may be).

The role of MRI in the ensuing events which sometimes resembled an eponymous war deserves a comment. Whereas Ropper and others mistakenly relied on the absence of a lesion in conventional MRI to refute the role of a central nervous system lesion in Miller Fisher syndrome such instances are more cogently explained as follows: (a) the existence of a pathological difference between a signal producing inflammation and mere presence of a viral infection in the central nervous system; for example, in a recent report 30% of clinically proved enterovirus 71 related rhombencephalitis had negative conventional MRI⁷; (b) the subject of "normal appearing" white matter when in fact it is not normal may one day loom large here as it has in the case of multiple sclerosis.

Thus our novel observation of 1979 alleviated Fisher's "certain reluctance to upset well established ideas concerning the disease (Guillain-Barré syndrome)" and removed the stigma of "oddity" and "aberration" from the syndrome described by the two luminaries, Miller Fisher and Bickerstaff, who did not know of each others' contributions; nor could they have known of the fact that they were describing the same clinical entity. And for two good reasons—that is, sharing the above mentioned reluctance to upset the well established ideas concerning Guillain-Barré syndrome (as admitted by Fisher himself) and preceding the wonderful age of computerised neuroimaging by a quarter of a century. It was left to the serendipitous observation in a 7 year old Persian girl, and its aftermath, for the facts to be gleaned—as depicted here.

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Yuki replies:

Derakhshan wrote "when Yuki *et al* draw any distinction between Fisher and Bickerstaff syndromes they are displaying a lack of historical perspective", but we had described in detail the historical background in the introduction of our original paper,¹ which he did not cite. In 1951, Bickerstaff and Cloake² described three patients who had ophthalmoplegia and ataxia as a grave syndrome they called "mesencephalitis and rhombencephalitis". They speculated that the aetiology of Bickerstaff's brainstem encephalitis is similar to that of Guillain-Barré syndrome because prodromal upper respiratory infection, are-

flexia, and CSF albumino-cytological dissociation were detected. In 1956, Fisher³ described three patients who presented with acute ophthalmoplegia, ataxia of the cerebellar type, and areflexia as a variant of Guillain-Barré syndrome. One of the three patients showed mild drowsiness. In 1957, Bickerstaff⁴ added five more patients to the original study and named the condition "brain-stem encephalitis". In 1982, Al-Din *et al*⁵ (Bickerstaff being one of the authors) described 18 patients, and considered Bickerstaff's brainstem encephalitis to be a distinct clinical entity, not a variant of Guillain-Barré syndrome on the basis of radiological (three patients) and pathological (one patient) changes in the brainstem. In 1983, Ropper,⁶ however, criticised their report. He considered that six of the 18 cases reported by Bickerstaff's group were typical Miller Fisher syndrome, and that the other 12 represented obscure brainstem lesions without peripheral polyneuropathy. In 1987, Al-Din⁵ described two cases in which there was an altered state of consciousness and motor nerve dysfunction, in addition to the triad of Miller Fisher. He presented a "spectrum hypothesis", in which Guillain-Barré syndrome and the syndrome of ophthalmoplegia, ataxia, and areflexia are at opposite ends of a broad spectrum, although clinically and pathologically distinct. He regarded his reported cases as being in the middle of that spectrum.

Patients showing drowsiness, brisk reflexes, extensor plantar responses, and hemisensory disturbance, or central nervous system pleocytosis usually are considered to have Bickerstaff's brainstem encephalitis rather than Miller Fisher syndrome. Opinions differ as to whether these two conditions are distinct or related because the aetiology had yet to be established. While studying serum samples from patients with Miller Fisher syndrome, our attention was brought back to a patient with Bickerstaff's brainstem encephalitis previously treated in our hospital. In addition to acute ophthalmoplegia and cerebellar ataxia, this patient (patient 2 in Yuki *et al*)¹ had abnormal plantar responses and became comatose. These neurological symptoms, however, disappeared 2 months after onset. At that time, we thought that anti-GQ1b antibody testing could be used to differentiate between Bickerstaff's brainstem encephalitis and Miller Fisher syndrome. Unexpectedly, the patient had the anti-GQ1b IgG antibody. Therefore, we investigated whether two other patients with Bickerstaff's brainstem encephalitis had this antibody. All three patients had high anti-GQ1b IgG antibody titres, which decreased with their clinical improvement.¹ As prior infection is frequent in Bickerstaff's brainstem encephalitis, as in Miller Fisher syndrome and Guillain-Barré syndrome, an autoimmune mechanism was suggested in the pathogenesis of Bickerstaff's brainstem encephalitis. The finding that Bickerstaff's brainstem encephalitis and Miller Fisher syndrome share common autoantibodies suggested that the autoimmune mechanism is common to both and that they are not distinct, but closely related conditions. Bickerstaff and Cloake² speculated that the aetiology of Bickerstaff's brainstem encephalitis is similar to that of Guillain-Barré syndrome, but the nosological relation between the two had yet to be clarified because of the lack of pathological findings in overlapping cases. We therefore reported necropsy findings for a patient in whom overlapping Bickerstaff's brainstem encephalitis