The male to female ratio was strikingly different between the two groups, being 9:1 in the flail arm group and 1.5:1 in the ALS group (Student's *t* test, $p=0.0015$). The mean age of symptom onset was similar (flail arm 58 (SD 13) years and ALS 55 (SD12) years) and there was no significant difference in the duration of follow up (flail arm 24 (SD 17) months and ALS 20 (SD 13) months, $p=0.17$) or the proportion of familial cases (both 9%).

Using Kaplan-Meier analysis, the median survival in the flail arm group was 57 (95%CI 45–69; range 6–109) months, compared with 39 (95%CI 35–43; range 2–577) months in the ALS group, but this did not reach significance (log rank test, $p=0.204$). There was no significant difference between the mean survival of flail arm and limb onset ALS groups. Using the Cox proportional hazards model, the flail arm syndrome was not identified as an independent risk factor determining survival.

The features of this distinctive ALS variant have not previously been characterised but it was probably first described by Gowers in his 1888 text *Diseases of the Nervous System*. In the chapter on the progressive muscular atrophies he noted that “when the arms are the seat of (such) atrophy as has been described, the legs, if not also wasted, may be normal, but they are often paralysed without being wasted” suggesting a pyramidal lower limb weakness.² Indeed, the illustration of a patient with primary muscular atrophy depicts the typical appearance of the patient with flail arm syndrome.

The predominant clinical feature of this syndrome is the relatively symmetric and proximal involvement of both arms, causing severe wasting and functional disability, with little or no weakness of the leg or bulbar musculature. Signs of corticospinal tract involvement are common in the legs and although denervation may be present in other regions this pattern of flail arms may persist for many years. Despite a severe loss of motor neurons in the cervical cord of patients with flail arm syndrome the higher cervical segments innervating the diaphragm seem to be spared early in the course of the disease.

What is the relation between the flail arm syndrome and other forms of ALS? The demonstration of upper motor neuron signs in most patients distinguishes this syndrome from primary muscular atrophy although there is probably an overlap. Our findings suggest that in most instances the flail arm syndrome represents a variant of classic ALS and most patients fulfil the probable or definite ALS El Escorial categories.¹ Although our clinic based ALS population is selected by referral it seems to be broadly representative judging by the demographic features described in other clinic and population samples.^{3,4}

We, and others, have previously reported the influence of genotype on ALS phenotype with the apolipoprotein E $\epsilon 4$ allele being associated with a bulbar onset of disease.^{5,6} It is interesting to note that whereas the male:female ratio in most studies is around 1.5:1 for ALS overall, women predominate in the late onset bulbar palsy group.^{3,4} The most striking finding of our study is the predominance of males in the flail arm group with a ratio of 9:1. It may be that factors linked to male sex predispose a proportion of patients to develop the flail arm phenotype. Curiously a male preponderance is also described in other lower motor neuron syndromes such as

multifocal motor neuropathy and monomelic amyotrophy.^{7,8}

We suspect that survival of patients with flail arm syndrome might be better than those with other forms of ALS as the median survival in the flail arm group was 57 months, compared with 39 months in the ALS group. Although the difference was not significant, our numbers are still small and larger studies are needed. We conclude that the flail arm syndrome is a distinctive clinical variant of ALS that is strikingly more common in males and may have a better prognosis.

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Multifocal cortical myoclonus and cerebral amyloid β -peptide angiopathy

The commonest clinical presentations of the sporadic cerebral amyloid angiopathies are with either recurrent lobar haemorrhages or with dementia.¹ In addition, transient focal neurological syndromes have occasionally been reported in association with cerebral amyloid angiopathies. These may represent transient ischaemic events or possibly focal seizures related to petechial intraparenchymal haemorrhages which are not associated with neuroimaging abnormalities; large haemorrhages may follow the onset of transient symptoms by weeks or months.^{2,3} We report on a patient with multifocal cortical myoclonus who subsequently proved to have amyloid β -peptide cerebral amyloid angiopathy, an association not previously described. We consider possible pathogenetic interrelations of these findings.

A 65 year old woman presented with a 4 year history of involuntary movements. She had been noted to have abnormal jerking movements of her legs—for example, when climbing the stairs—which, on occasion had caused her to fall. Using an electric vacuum

cleaner or hearing the telephone ring had been noted to trigger these involuntary movements. There was no history of cognitive impairment. Her medical history was unremarkable aside from treated hypothyroidism. Family history was positive for sudden death, all three of her elder siblings (one sister, two brothers) dying in their mid-60s. One had previously had angina, the other two had been healthy until the time of their deaths, which were ascribed to a “heart attack” and a “clot on the brain”, respectively.

Examination of the patient disclosed a pronounced startle response, and action myoclonus in all limbs. There was no consistent stimulus sensitivity of the jerks. Otherwise, neurological examination was within normal limits.

Investigations, which proved either normal or negative, included standard tests of haematological and biochemical indices, thyroid function tests, serum vitamin B₁₂, red cell folate, serum electrophoresis, quantitative immunoglobulins, angiotensin converting enzyme (ACE) concentrations, autoantibodies (including ANCA, anti-endothelial antibodies, and anti-GAD antibodies), and anti-neuronal antibodies (Hu, Purkinje). Blood film was negative for acanthocytes. Analysis of CSF showed a raised protein (0.82 g/l) but normal glucose concentration, cytology, and ACE; oligoclonal bands were not present. T2 weighted brain MRI showed a few small foci of high signal in the periventricular white matter, thought to represent age related small vessel disease. Carotid angiography was normal. Small bowel biopsy showed a normal mucosa with no evidence of coeliac disease. Analysis of mitochondrial DNA for common mutations (positions 3243, 3271, 8344, and 8356) proved negative. Psychometric assessment showed the patient to have a verbal IQ of 94, performance IQ of 95, indicative of functioning in the lower half of the average range but within the patient's estimated average optimal level of ability. She was noted to show signs of inefficiency and slowness, particularly in word retrieval and frontal lobe tasks, but there was no unequivocal evidence of focal deficits.

Peripheral, cervical, and cortical somatosensory evoked potentials after electrical stimulation of the median nerve at either wrist were of normal latency and morphology. However, although the amplitude of peripheral and cervical potentials was normal, the cortical responses were abnormally large, particularly from the right arm (22 μ V; left 15 μ V). Hence, on clinical and neurophysiological grounds, a diagnosis of multifocal cortical myoclonus of unknown cause was made. The patient was treated with clonazepam (0.25 mg twice daily), with marked symptomatic benefit at follow up.

Ten months after these investigations, the patient presented to an ophthalmologist with episodes of metamorphopsia for which no ocular cause was found. A further 3 months later she presented with a sudden onset of right parietal headache associated with vomiting and left sided pyramidal signs. Brain CT disclosed a large right sided parieto-occipital intracerebral haematoma with mass effect. At surgical drainage of the haematoma, a small piece of brain tissue was removed from the right parieto-occipital region. Histological examination showed small, irregular fragments of cortical grey and minimal amounts of white matter. The first included vessels, some of which were in obvious continuity with meningeal vessels. Most of them had

thickened hyaline walls which stained with Congo red, showing the characteristic apple green birefringence under polarised illumination, and were positive with immunostaining for β A4. This immunostaining also showed diffuse plaques, a few containing cores most of which could not be seen on routine staining. No abnormalities were seen in the white matter. Silver impregnation (Bielschowsky) and tau immunohistochemistry did not show neurofibrillary tangles, neuritic plaques, or cortical dystrophic neurites. According to the criteria of the Boston Cerebral Amyloid Angiopathy Group,³ the histological findings and clinical data indicated a diagnosis of "probable cerebral amyloid angiopathy with supporting pathological evidence". DNA was screened by polymerase chain reaction amplification for the presence of mutations in the amyloid precursor protein (APP) gene, which are known to cosegregate with hereditary cerebral haemorrhage with amyloidosis Dutch type (HCHWA-D; codons 670/671 of exon 16 and in codons 692, 693, 713, and 717 of exon 17). No mutation was found.

The patient underwent psychometric reassessment 1 month after the intracerebral haemorrhage and surgical drainage, from which she had made a good physical recovery. In keeping with the location of the haemorrhage, she was found to have significantly impaired visual perceptual functions, with left unilateral neglect, an inability to discriminate shapes, and a severe deterioration in her performance on the visual version of the recognition memory test (verbal version remained within the average range). Additionally, a mild degree of verbal intellectual deterioration was noted (verbal IQ 83).

A wide variety of disorders may produce cortical myoclonus: the differential diagnosis includes anoxic injury, focal CNS damage (vascular or neoplastic lesions of sensorimotor cortex), encephalopathies (metabolic, mitochondrial, viral, paraneoplastic, toxic), degenerations (basal ganglia, spinocerebellar), malabsorption syndromes (coeliac disease, Whipple's disease), storage disorders, and dementias (Creutzfeldt-Jakob disease). Myoclonus may also be encountered in Alzheimer's disease, in which it is associated with increasing severity of dementia. We are not aware of previous reports of cortical myoclonus as a clinical feature of sporadic cerebral amyloid angiopathy. Although this could be a chance concurrence, it is possible that recurrent small intraparenchymal bleeds from angioathic vessels may have been causal, as vascular lesions are a recognised cause for cortical myoclonus. Another possibility which may be worth considering relates to the effects of amyloid β -peptide ($A\beta$) and its metabolic fragments on neuronal membrane ion channels and their associated currents.⁴ Because the pathophysiology of cortical myoclonus is thought to reflect both increased excitability and deficiency of inhibitory processes in the cortex,⁵ the effects of $A\beta$ on a variety of ion currents, both excitatory and inhibitory, might theoretically produce such an imbalance and hence contribute to the development of cortical myoclonus.

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Antiganglioside antibodies in various episodes in a patient with recurrent Guillain-Barré syndrome

Guillain-Barré syndrome is defined as an acute, monophasic polyneuropathy. It recurs in 2%-5% of patients.¹ Both the initial and recurrent episodes are preceded by an infection. Antibodies against several gangliosides are often present in the acute phase in serum samples from patients with Guillain-Barré syndrome.² There have been no previous reports, however, on anti-ganglioside antibodies in patients with recurrent disease. We report finding anti-ganglioside antibodies in a patient with recurrent Guillain-Barré syndrome during the third and fourth episodes.

Ten days after a bout of upper respiratory tract infection, a 26 year old man noted paraesthesias in his fingers and toes, and rapidly developed limb weakness. He had bulbar palsy and areflexic tetraparesis on day 1, and underwent three sessions of plasmapheresis on days 3, 4, and 5. Disability was maximal on day 6. Bulbar weakness disappeared on day 8, and he could walk without support on day 14. He had had similar episodes of acute, monophasic paralytic disease at the ages of 14 and 19. Six years later, he experienced a fourth episode. Three days after an upper respiratory tract infection, he rapidly developed dysarthria, digital paraesthesias, and leg weakness. Neurological examination on day 2 showed bilateral external ophthalmoplegia, facial diplegia, and areflexic tetraparesis. He required mechanical ventilation from days 2 to 19, and underwent five sessions of plasmapheresis on days 2, 3, 4, 6, and 9, then intravenous immunoglobulin therapy from days 11 to 15. His disability began to lessen on day 11 and had disappeared by day 34.

An enzyme linked immunosorbent assay³ showed IgG antibody titres to GM1 (<500), GM1b (128 000), GD1a (128 000), GalNAc-GD1a (<500), GT1a (64 000), GD1b (4000), and GQ1b (32 000) on day 3 during the third episode. No IgM anti-ganglioside antibodies were detected. On day

113, during the recovery phase, the anti-ganglioside IgG titres were <500. Serum on day 3 of the fourth episode had IgG antibodies titres to GM1 (<500), GM1b (256 000), GD1a (128 000), GalNAc-GD1a (<500), GT1a (64 000), GD1b (1:4000), and GQ1b (1:64000). Thin layer chromatography with immunostaining⁴ confirmed that the IgGs in the acute, progressive phase of both attacks reacted with the same gangliosides (data not shown).

Differentiation between Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) relies on the time needed to reach maximum disability. Our patient had four episodes of typical Guillain-Barré syndrome, not of CIDP. Neurological function in each episode reached a nadir within 2 weeks of onset and returned to normal within 5 weeks. The distinction between Guillain-Barré syndrome and CIDP, however, is blurred in the early onset phase in some patients. Protein concentrations in CSF in CIDP tend to remain raised during remission and at the onset of recurrence; whereas CSF protein concentrations are normal within 1 week of the onset of Guillain-Barré syndrome, which may provide a way of distinguishing it from CIDP.¹ Only low anti-ganglioside antibody titres, which were unlikely to have a role in the pathogenesis, were found in some patients with CIDP.⁵ The presence of high anti-ganglioside antibody titres at the onset of a recurrence may be of use in confirming the diagnosis of recurrent Guillain-Barré syndrome.

In recurrent Guillain-Barré syndrome, the nature of the antecedent illness usually tends to differ from episode to episode.¹ Our patient, however, had similar upper respiratory symptoms before each onset of neurological symptoms. Antecedent agents such as *Campylobacter jejuni* and cytomegalovirus have ganglioside epitopes,^{4,5} and therefore may produce the anti-ganglioside antibodies in Guillain-Barré syndrome.

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