LETTERS TO THE EDITOR

A novel de novo point mutation in the GTP cyclohydrolase I gene in a Japanese patient with hereditary progressive and dopa responsive dystonia

Hereditary progressive dystonia is characterised by lower limb dystonia of childhood onset with marked diurnal fluctuation and shows a dramatic and stable response to low dose levodopa. The disease is transmitted in autosomal dominant inheritance, and Segawa et al. proposed hereditary progressive dystonia as a new disease entity in the early 1970s. Dopa responsive dystonia, which was first proposed by Nygaard et al. in 1988, is essentially identical to hereditary progressive dystonia although it may include some other heterogeneous dystonias. The GTP cyclohydrolase I (GTP-CH I) gene on chromosome 14 is the causative gene of hereditary progressive/dopa responsive dystonia and more than 20 different mutations have been reported. We report a novel non-sense mutation in the GTP-CH I gene in a genetically confirmed sporadic Japanese patient. A 12 year old Japanese girl developed gait disturbance with a dystonic pes equinovarus posture in the right leg at the age of 4 years. These symptoms showed diurnal fluctuation, they were mild in the morning and worsened later in the day, and sleep improved the symptoms. They dramatically and continuously responded to low dose levodopa/carbidopa (100 mg/day) without adverse effects. Other members of her family, comprising the parents and one sister, had no symptoms.

Blood specimens of the patient and of the parents and sister were available for genetic analysis. For mutation analysis, genomic DNA was extracted from EDTA anticoagulated peripheral blood. Fragments of DNA containing the entire coding region of the GTP-CH I gene were obtained from genomic DNA by polymerase chain reaction (PCR) according to the method of Ichinose et al. Direct nucleotide sequencing of PCR products was performed with an automated DNA sequencer (Applied Biosystems 310) using the same primers as were used for amplification.

Direct nucleotide sequencing of genomic DNA of the patient showed a G to A transversion in exon 1 of the GTP-CH I gene (data not shown). This mutation produces a substitution of the tryptophan residue (TGG) with a stop codon (TGA) at position 96, which creates a new Eco57I cleavage site. The sequencing of the parents and the sister of the patient showed no mutation. To confirm the mutation, exon 1 was amplified and digested by Eco57I in all the four subjects. The restriction fragment length polymorphism consisted of two fragments (370 and 132 bp) in the mutant allele and one fragment (502 bp) in the normal allele (figure). The restriction pattern in the patient was consistent with heterozygous status, consisting of one each of the mutant and normal alleles, whereas that of the parents and sister, with homozygous status of two normal alleles. No other mutations were detected in the coding region of the gene.

The patient presented with typical clinical features of hereditary progressive dystonia. A new mutation in the GTP-CH I gene of the present patient causes a stop codon, and this mutation is most likely the pathogenic mutation. GTP-CH I catalyses the initial and rate limiting steps of tetrahydrobiopterin synthesis. Tetrahydrobiopterin is an essential cofactor for tyrosine hydroxylase, the rate limiting enzyme in the dopamine synthesis pathway. GTP-CH I activity in patients with hereditary progressive dystonia is less than 20% of that in normal subjects. The non-sense mutation in exon 1 confirmed in the present patient would have caused premature truncation of the GTP-CH I protein with a loss of an estimated 60% of the amino acid residues from the C terminal, and GTP-CH I activity, though it was not measured, may have been reduced below the critical threshold. To date, 22 different mutations in the GTP-CH I gene have been identified worldwide, and there seems to be no evidence of the founder effect.

To our knowledge, only a single case (patient 2 of Furukawa et al.) was confirmed to be genetically sporadic. The present patient 1 is the second report of de novo mutation in the GTP-CH I gene.

We thank Dr Hiroki Takano, Department of Neurology, Brain Research Institute, Niigata University, for his invaluable advice. This work was partially supported by grants in aid for scientific research on priority areas from the Ministry of Education, Science and Culture, and from the Research Committee of Health and Welfare of Japan.

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Central nervous system involvement in four patients with Charcot-Marie-Tooth disease with connexin 32 extracellular mutations

In a recent issue of this journal there was a report of two cases of multiple sclerosis with duplicated CMT1A. Here we present four additional patients with Charcot-Marie-
Tooth disease with CNS involvement, as shown by electrophysiological studies and the presence of myelin lesions in brain MRI. In our patients point mutations were identified in GJB1, a gene coding for connexin 32 (GenBank acc number 117688). We also point the possible importance of the position (intracellular or extracellular) of the mutations in the involvement or not of the CNS.

In the process of investigating a panel of patients with Charcot-Marie-Tooth disease for mutations leading to the disease, we have screened the GJB1 gene for mutations in six patients (C12, C64, C10, and C13 (all unreported), and C2–1 and C2–2 (brothers) who did not have a CMT1A duplication and had a family history compatible with an X linked mode of transmission. GJB1 is a gene coding for connexin 32 (Cx32), a gap junction protein that is found in both the peripheral and the central nervous systems and that has been reported by many to be responsible for CMTX, the X linked subtype of Charcot-Marie-Tooth disease. We performed our search using SSCP and nucleotide sequencing when additional bands were detected.

Mutations leading to amino acid sequence changes and transmitted with the disease were detected in all six patients, whereas those exhibiting variation were not detected in 150 healthy control X chromosomes. Because Cx32 is a protein expressed in both the peripheral and the central nervous systems we proceeded to test for CNS involvement in those patients using electrophysiological (table) and MRI techniques. The clinical and laboratory findings for our patients were as follows.

In 1995 a 19 year old man, had a history of 5 hour to 3 day long episodes of weakness—generalised or at other times localised to the left or right half of the body—dysarthria, and difficulty in swallowing. Neurological clinical examination showed muscle weakness and peripheral atrophy of the limbs, absence of tendon reflexes, distal loss of vibration in the legs, dysmetria, fine tremor, positive Romberg’s sign, and bilateral pes cavus. The CSF showed an IgG index of 1.0 (normal<0.85) and oligoclonal bands. Brain MRI showed demyelination in the white matter of the cerebral hemispheres. Electrophysiological studies also showed that both the central and peripheral nervous system were affected. The patient had the same mutation as his brother C2–1, as was expected.

Patient C12, a 63 year old man, had progressive muscle weakness and peripheral atrophy of the extremities since the age of 9 years. When admitted he had severe muscle weakness, absence of tendon reflexes, distal loss of vibration in the legs, dysmetria, fine tremor, positive Romberg’s sign, and bilateral pes cavus. The CSF showed an IgG index of 1.0 (normal<0.85) and oligoclonal bands. Brain MRI showed demyelination in the white matter of the cerebral hemispheres. Electrophysiological studies also showed that both the central and peripheral nervous system were affected. The patient had the same mutation as his brother C2–1, as was expected.

Patient C64, a 58 year old man, presented with progressive muscle weakness and peripheral atrophy since the age of 10 years. His CSF was not sampled. Brain MRI showed high density areas of demyelination in the white matter on the left side in the frontoparietal area. The patient had a G to A transition at position 491 (novel mutation).

Patient C10, a 74 year old woman, presented with progressive muscle weakness and peripheral atrophy of the legs since the age of 11. The clinical picture was the same as that of patient C64. The CSF and brain MRI were normal. The patient had a C to T transition at position 359 (novel).

Patient C13, a 40 year old man, presented with progressive muscle weakness and peripheral atrophy starting at the age of 7 years. His CSF and brain MRI were normal. The patient had a C to T transition at position 43 (already reported). Sural nerve biopsy performed in patients C2–1, C2–2, C64, and C10 showed loss of myelinated fibres and “onion bulb” formation. It is of particular interest, possibly implying an underlying mechanism, that the four patients with evidence of CNS involvement (C2–1, C2–2, C12, and C64) had mutations in the extracellular domain of Cx32, and by contrast, in the two patients with no evidence of CNS involvement (C10, C13) the mutations were in the intracellular domain of the protein.

The exact pathogenetic mechanisms of the various types of myelin damage are not yet fully understood. Therefore, we cannot reach any convincing conclusions about the possible relations between those degenerative processes and the position of Cx32 mutations. However, we hope that our findings will contribute to a better understanding of some myelin damage mechanisms.

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Lack of mutation G209A in the α-synuclein gene in French patients with familial and sporadic Parkinson’s disease

Polymeropoulos et al described the genetic linkage of a large Italian Parkinson’s disease pedigree (Contursi) to chromosome 4q21-q23; more recently the sequence of the α-synuclein gene located in this chromosomal region in affected patients from this kindred disclosed that most of the affected members were heterozygous for a missense mutation (alanine→threonine) at position 53 of the protein. This same missense mutation was also found in three additional unrelated families of Greek origin with Parkinson’s disease.

The mutation was found by DNA sequence analysis of the fourth exon of the α-synuclein gene, disclosing a single base pair change at position 209 from G to A (G209A), and creating a novel Tag45 I restriction site. Using a polymerase chain reaction (PCR) assay and Tag45 I restriction, we have found some French patients with Parkinson’s disease. Genomic DNA was amplified with primers 3 and 13 of the DNA sequence (GenBank ID U46898) in a 50 μl reaction volume (10 mM Tris-HCl, pH=8.3; 50 mM KCl; 1.5 mM MgCl2; 200 μM of each dNTP and 1 U Taq polymerase); cycling parameters were: one initial step of denaturation at 94°C for 45 seconds; 25 cycles of 30 seconds 94°C, 40 seconds at 55°C and 40 seconds 72°C; and a final extension step (5 minutes at 72°C). A 2 μl aliquot of the 121 base pair (bp) product was restricted with the

Electrophysiological data from the six patients

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MNC=Motor nerve conduction; Amplitude=amplitude; DL=distal latency; CV=conduction velocity; SNC=sensory nerve conduction, BAERs=brain stem auditory evoked responses: waves I, III, and V; VEPS=visual evoked potentials; Lat=latency; NE=not evoked; NP=not performed.

References:
Electrophoresis patterns of Tsp45I digestion of polymerase chain reaction (PCR) products. Lane P shows pUC19 plasmid restricted by the enzyme (the four restriction fragments at 1588, 576, 311, and 2116p). All the nine subjects tested were wild type, producing a single 216bp PCR product which was resistant to Tsp45I digestion. M=DNA size marker.

Tsp45I enzyme at 65°C for 5 hours; the efficiency of the Tsp45I restriction was verified by monitoring for the pUC19 plasmid restriction (four fragments at 1588, 576, 311, and 2116 bp). The digested PCR products were separated by electrophoresis on a 3% agarose gel and visualised by ethidium bromide staining.

Fourteen French families1 with at least two members in each family meeting clinical criteria for idiopathic Parkinson’s disease were tested. Affected members in all families exhibited at least two of the three cardinal signs of Parkinson’s disease (bradykinesia, rigidity, and resting tremor), as well as marked improvement with levodopa treatment. The G209A mutation was not found in 27 patients with Parkinson’s disease belonging to these 14 French pedigrees. The Tsp45I restriction site was also absent in the genomic amplificates of 79 patients of French origin with sporadic Parkinson’s disease.

We conclude that the G209A mutation is rare, or absent, in French patients with familial and sporadic Parkinson’s disease, and similar results were obtained recently from American patients. The main age at onset of disease in our patients with Parkinson’s disease, both familial and sporadic, was 64.5 (range 25–88) years. The major kindred published1 in which the G209A mutation was found originates in Contursi (southern Italy) and is fairly typical Parkinson’s disease, albeit with relatively early onset of symptoms and rapid subsequent progression; little has been reported until now about the three Greek families with Parkinson’s disease with the G209A mutation, except that they too have relatively early onset. Probably the G209A mutation concerns a small set of families with Parkinson’s disease, originating from some focal localities on the Mediterranean coast.

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Resolution of extensive spinal epidural haematoma with conservative treatment

Spontaneous spinal epidural haematoma (SSEDH) is an uncommon condition presenting with local and radicular pain associated with clinical features of rapidly progressive spinal cord compression. The cause of the bleeding is varied, with anticoagulant therapy recognised to be the commonest known aetiologic factor. Surgery is the preferred treatment, regardless of aetiopathology, especially in cases of rapidly progressive neurological deficits.1,2 Spontaneous resolution of the haematoma is reported but rare.3 We report a case of an extensive spontaneous spinal epidural haematoma extending from the upper cervical to lower thoracic region secondary to anticoagulant therapy, with remarkable clinical and radiological improvement with conservative management.

An 82 year old woman was admitted with a one week history of neck pain and upper thoracic pain, which had worsened during the preceding 4 days. On the day before admission, she developed sudden onset of complete paraplegia with urinary retention. She had noticed some improvement in power in her legs and back pain on the day of referral to our institution. She has a medical history of ischaemic heart disease with congestive cardiac failure and was on long term warfarin therapy for atrial fibrillation. At the referring hospital, her international normalised ratio (INR) was 10 and she was transferred to our neurosurgical unit after vitamin K and fresh frozen plasma were administered.

When assessed on arrival, she was complaining of mild thoracic pain. There was no neurological abnormality in the upper limbs. Tone was increased in the lower limbs with grade 2 (MRC) power on the left and grade 3 on the right. She had sensory loss to pin prick below D10 with saddle anaesthesia. Posterior column sensation was preserved. Deep tendon reflexes were pathologically brisk in the lower limbs and planter responses were extensor bilaterally.

Her INR was 1.9 and radiography of the cervical spine showed spondylotic changes and thoracic spine radiography showed evidence of osteoporosis. There was no fracture. Brain MRI showed an intermediate to high signal intensity epidural lesion suggestive of haematoma from C-1 extending to the lower thoracic region, compressing the dorsal aspect of the cord (figure). As the power in her lower limbs was improving, we elected to treat her conservatively. Her clotting derangement was corrected with vitamin K and fresh frozen plasma while monitoring her INR. Her power continued to improve and at the time of her discharge she had grade 4 power in her legs with associated mild distal sensory loss. Eight weeks later, she had grade 5 power but was slightly unsteady on her feet due to spasticity. Sensory testing was normal. Repeat MRI showed almost complete resolution of the haematoma.

Cervical and thoracic MRI showing the extent of epidural haematoma.

Spontaneous spinal epidural haematoma (SSEDH) is an uncommon disorder first described by Jackson in 1869. It usually affects patients in the age group 20 to 70 and the thoracic spine is the commonest region affected. Spinal MRI is the investigation of choice in establishing diagnosis, characteristically showing increased signal intensity in T1 weighted images in an epidural mass at the first examination or increasing signal intensity with time; and in T2 weighted images, showing focal low signal intensity in early stages. The aetiopathology includes vascular malformations, coagulopathies, anticoagulant therapy, aspirin intake, minor trauma and hypertension.1,4 In about 40% of cases, the cause is unknown despite extensive investigations. About 300 cases of SSEDH have been reported in the world literature.5 Anticoagulant therapy is the commonest known cause of SSEDH, but prothrombin time or INR values do not seem to correlate with the risk of haemorrhage.6

Surgery is generally the treatment of choice as the rapid decompression of the spinal cord ensures maximal neurological recovery. It is generally held that early (<12 hours) surgery and good preoperative neurological status promise the best possible outcome, although delayed surgery after total loss of spinal cord function does not completely exclude the possibility of some recovery.7,8

We report a case of SSEDH in an 82 year old lady who was on anticoagulant therapy (warfarin), for cardiovascular disease, and presented with features of spinal cord compression associated with back pain. Spinal MRI disclosed spinal epidural haematoma extending from C-1 to the lower thoracic...
region. Such an extensive haematoma is very uncommon. Literature review suggests that SSEHD involving more than two vertebral levels carries a worse prognosis. Hence, the rapid recovery seen in our patient despite such an extensive haematoma is remarkable.

Improving the clinical condition, extensive haematoma, age, and poor medical condition of the patient prompted us to pursue conservative treatment with good clinical and radiological improvement. Although emergency surgery or the treatment of choice, non-surgical therapy in the medically unfit, patients with minor deficits, and in patients with initial clinical improvement, has yielded good results in the aetiological group, it fits with our experience. Fresh frozen plasma, Vitamin K, and monitoring of INR have been the mainstay of conservative treatment in patients on anticoagulants, who need repeat MRI for follow up. With the ever increasing number of patients on anticoagulant therapy for cardiovascular diseases, SSEHD is likely to become a more common problem. When to restart anticoagulant therapy and the optimal INR values to be maintained after restarting are the questions still unanswered in the literature.

In summary, SSEHD in patients taking anticoagulant drugs with initial clinical improvement were successfully treated with regular clinical, haematological, and MRI monitoring even if they have extensive clots.

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Flail arm syndrome: a distinctive variant of amyotrophic lateral sclerosis

In a retrospective case note study of patients referred to a specialist clinic for motor neuron disorders we identified a subgroup of patients with severe wasting and weakness of the arms without significant functional involvement of other regions. This “flail arm syndrome” was identified in 39/395 (10%) of the subjects studied. Their clinical characteristics were compared with the amyotrophic lateral sclerosis (ALS) group as a whole. The age of onset was similar between the two groups but the male:female ratio was 9:1 in the flail arm group, compared with 1:5:1 in the ALS group (p=0.0015). Although there was a trend towards improved survival in the flail arm group (median survival 57 (95% CI 43–69) months) compared with the ALS group (39 (95% CI 35–43) months), this did not reach significance (p=0.024) and was not an independent prognostic factor. As many patients with flail arm syndrome develop upper motor neuron signs in the lower limbs this syndrome probably represents a variant of ALS. It seems likely that unknown factors linked to male sex predispose a proportion of patients to develop the flail arm phenotype.

Historically, physicians have categorised illnesses according to their clinical characteristics. As a result the adult sporadic motor neuron syndromes have been described according to the site of lesion onset. Most patients present with both upper and lower motor neuron signs in the limbs (classic motor neuron disease or ALS). Rarer forms of predominantly upper and lower motor neuron syndromes are also recognised (primary lateral sclerosis and progressive muscular atrophy respectively). We have noted that a subgroup of patients with classic ALS present with progressive wasting and weakness of the arms, with little or no functional impairment of the bulbar muscles or legs (figure). Here we describe their clinical features and natural history in comparison to the ALS group as a whole. We have used the term “flail arm syndrome” to describe this variant of ALS.

All patients attending our specialist motor neuron disorders clinic between 1 January 1990 and 30 September 1996 were studied in a retrospective case note study. Patients with alternative diagnoses, such as Kennedy’s disease, spinal muscular atrophy, and multifocal motor neuropathy were excluded after full neurological, spinal muscular atrophy, and multifocal motor neuropathy were excluded after full clinical, haematological, and serological investigation, leaving 395 patients with a firm diagnosis of ALS. The censoring date for survival analysis was 31 January 1996.

Patients were classified according to the El Escorial criteria and included in a detailed database incorporating key characteristics of the disease. Most fulfilled probable or definite ALS El Escorial categories having upper and lower motor neurone signs at first review. A minority with predominantly lower motor neuron features at presentation fulfilled suspected or possible ALS El Escorial categories. The flail arm syndrome was defined as a predominantly lower motor neuron disorder of the upper limbs without significant functional involvement of other regions at clinical presentation. Specifically, the wasting and weakness of the upper limbs had to be profound, symmetric, and involve proximal muscle groups (MRC grade <3). Those fulfilling the flail arm criteria were identified and compared with the rest of the ALS population based on the clinical assessment made at the time of the first clinic visit. Follow up was complete.

Demographic variables were compared using Student’s t test. The χ2 test and linear regression were used to test the independence of two variables. Survival of patients with ALS was estimated using the Kaplan–Meier curves and the log rank test was used to compare different categories. The Cox proportional hazards model was used to assess the simultaneous effects of several variables on survival. Results are expressed as the mean ±1 SD and a p value of <0.05 was considered significant.

Of 395 patients, 39 (10%) were identified as having the flail arm syndrome. Nine out of 39 (23%) of the patients with the syndrome had solely lower motor neuron features at the time of presentation. Upper motor neuron signs in the legs were present in most patients (77%) and although bulbar signs were present in 22 (56%) during the follow up period they were commonly asymptomatic at presentation.

(A) This 54 year old man with the flail arm syndrome has severe wasting of the arms causing profound weakness. Note the symmetric distribution and involvement of proximal muscle groups. Muscle bulk and strength were relatively preserved in the legs but lower limb reflexes were pathologically brisk and the plantar responses extensor. (B) Note the very similar pattern of wasting in a patient with “progressive muscular atrophy” depicted in a 1888 text of Gowers.
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 1886 text Diseases of the Nervous System. In the chapter on the progressive muscular atrophy 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 there is often paralysis of the limbs without being wasted” suggesting a pyramidal lower limb weakness. 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 muscle. 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 lower motor neuron syndromes 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

**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 ischemic 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.1

We report on a patient with multifocal cortical myoclonus who had previously been proven 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 brothers (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 B<sub>12</sub> red cell folate, serum electrophoresis, quantitative immunoglobulins, angiotensin converting enzyme (ACE) concentrations, autoantibodies (including ANCA, anti-endomysial antibodies, and anti-GAD antibodies), and CSF protein E genotyping in sporadic amyotrophic lateral sclerosis (ALS) patients with either recurrent lobar haemorrhages or multifocal cortical myoclonus of unknown cause. Brain MRI showed a 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 nonspecific 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 averaged 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 each 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 µV; left 15 µV). 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 transient 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 weakness, which recovered. CT disclosed a large right sided parieto-occipital intracranial 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 thrombosed, were thickened 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 βA4. 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 neurites, neuritic plaques, or cortical dystrophic neurites. According to the criteria of the Boston Cerebral Amyloid Angiopathy Group,1 the histological findings and clinical data indicated a diagnosis of “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, neurodegenerative, parasitic, toxic), degenerations (basal ganglia, spinocerebellar), malabsorption syndromes (coeliac disease, Whipple’s disease), storage disorders, and dementias (Cerebral, Alzheimer, Parkinson-Korsakoff 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 occurrence, it is possible that recurrent small intraparenchymal bleeds from angiopathic 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 cerebral biopsy; Dr Lisa Cipolotti and Professor Thanks are due to Mr W Harkness for performing the cerebral biopsy; Dr Lisa Cipolotti and Professor

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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 antibody titres to GM1 to GM1a. Antibodies against several gangliosides are present in the acute phase in serum samples from patients with Guillain-Barré syndrome.3 There have been no previous reports, however, on anti-ganglioside antibody titres in patients with recurrent disease. We report finding anti-ganglioside antibodies in a patient with recurrent Guillain-Barré syn-
drome during the third and fourth episodes. Ten days after a bout of upper respiratory tract infection, he 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 16. In 1989, he was seen again and experienced a fourth episode. Three days after an upper respiratory tract infection, he rapidly developed dysarthria, digital paraesthesias, and leg weakness. Neurophysiological 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 assay2 showed IgG antibody titres to GM1 (<500), GM2b (128 000), GD1a (128 000), GalNAc-GD1a (<500), GT1a (64 000), GD1b (400), 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 antibody 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 immunostaining 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 recurrent 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 protein concentrations are normal within 1 week of the onset of Guillain-Barré syndrome, which may provide a way of distinguishing it from CIDP.4 Only low anti-ganglioside antibody titres, which were unlikely to have clinical signifi-
cance, 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 In one patient, however, had similar upper respira-
tory symptoms before each onset of neuro-
logical symptoms. Antecedent agents such as Campylobacter jejuni and cytomegalovirus have ganglioside epitopes,6 and therefore may present as the Gistganglioside antibodies in Guillain-Barré syndrome.

This research was supported in part by grants in aid from the Uehara Memorial Foundation, Ciba-Geigy Foundation (Japan) for the Promotion of Science, Nakabayashi Trust for Research, Ryoichi Naito Foundation for Medical Research, and Research Grant for Intractable Diseases from the Ministry of Health and Welfare of Japan.

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The disease can be triggered by vaccination or a variety of infections. Both viral and bacterial infections can lead to the production of autoantibodies that cross-react with specific gangliosides. These antibodies can cause neuronal damage, leading to the development of symptoms such as muscle weakness and difficulty in movement.

This patient presented with recurrent episodes of Guillain-Barré syndrome, characterised by progressive weakness and a loss of sensation. The diagnosis was confirmed by the presence of anti-ganglioside antibodies in the blood and cerebrospinal fluid. The antibodies targeted specific gangliosides, such as GM1, which are present on the surface of nerve cells.

The patient was treated with plasmapheresis, where blood is removed from the body and the plasma is replaced with albumin. This helps to remove the antibodies and reduce the inflammation in the nervous system. The patient also received immunoglobulin therapy, which provides the body with additional antibodies to fight off the disease.

The treatment was effective in improving the patient's condition, and they were able to recover from each episode. However, the patient experienced four episodes of the disease, indicating a chronic and recurrent nature.

Despite the challenges, the patient's recovery after each episode provided hope for the future. The research into anti-ganglioside antibodies in Guillain-Barré syndrome continues to advance our understanding of the disease and offer potential new treatment options.
Urinary retention associated with a unilateral lesion in the dorsolateral tegmentum of the rostral pons

The existence of a brainstem region concerned with micturition has been known since the report of Barrington more than 70 years ago. In animals such a pontine micturition centre has been located in the dorsolateral tegmentum of the rostral pons, corresponding to Barrington’s micturition centre, but such a centre has not been precisely localised in humans. We describe a patient with presumed rhombencephalitis presenting with urinary retention and present his MRI findings. To our knowledge, this is the first MRI demonstration of a circumscribed lesion related to the putative pontine micturition centre in humans.

A 30 year old man with no history of voiding problems developed high fever, light headedness, frequent urination, and voiding difficulty. One day after onset, urinary retention occurred despite his sensation of needing to void. Two days later, in addition to urinary retention, the patient also had left cheiro-oral dysaesthesia and horizontal diplopia. Prostate examination did not show abnormalities. Urinary retention was managed with an indwelling catheter until 7 days after onset of his symptoms. The patient did not have a history of overdistension of the urinary bladder. Even though all his symptoms began to improve, the patient was referred to our hospital for an evaluation of neurological abnormalities.

Examination 9 days after onset showed mild right horizontal gaze paresis with intact vestibulo-ocular reflex, ipsilateral saccadic pursuit, and hypaesthesia around the left mouth angle and thumb and index finger, suggesting involvement of the right pontine tegmentum. Indeed, in addition to scattered amorphous lesions in the pons and cerebellum, brain MRI (1.5 tesla) showed a discrete lesion in the right upper pontine tegmentum (figure). An MRI of the spinal cord disclosed no abnormal intensity areas. Lumbar puncture yielded CSF with normal cell counts (3/µl) and mildly increased protein (52 mg/dl). Neither oligoclonal bands nor myelin basic protein were present in the CSF; intrathecal IgG synthesis was within the normal range. Serum autoantibody and viral antibody tests did not contribute to diagnosis. A CO2 cystometry with sphincter EMG 3 weeks after onset showed increased bladder volume over 555 ml and atomic cystometrogram (detrusor areflexia), despite the absence of subjective urinary symptoms. Organic obstructive urological disease was radiologically excluded. All neurological and MRI abnormalities cleared by 1 month after onset. One year follow up showed no recurrence of the neurological symptoms.

Based on neurological findings, the patient was thought to have incomplete involvement of the right paramedian pontine reticular formation, smooth pursuit pathway, and medial lemniscus, suggestive of a right pontine tegmental lesion. The association of acute and reversible urinary retention was consistent with a lesion in the rostral portion of the pontine tegmentum. Indeed, the MRI with a special focus on the rostral brainstem substantiated our neurological assessment and showed a discrete lesion in the right dorsolateral portion of the upper pontine tegmentum. Other less distinctive lesions in the pons and cerebellum were seen on MRI, but no relevant neurological abnormalities were detected. Simultaneous involvement of the spinal cord was excluded by neurological and radiological examinations. Although the patient was considered to have possible rhombencephalitis, the question of whether it was caused by a direct virus invasion or parainfectious demyelination remains unclear.

In humans, an association between micturition disturbances and brainstem involvement has been suspected on pathological and radiological bases. Early in 1926, Holman documented a relation between micturition disturbance and posterior fossa tumours. Later, a pathological study of brain tumours disclosed a high frequency (63%; 50/79) of voiding difficulties and urinary retention with pontine and fourth ventricle tumours. Histological abnormalities were concentrated in the tegmentum of the rostral pons in all such patients. The locus coeruleus and adjacent neural tissue were more often involved than other nuclei or regions of the pons. However, because of the extensive involvement of these tumours, no localised lesions were noted. One recent study with MRI on brainstem stroke disclosed similar results. Despite numerous reports on the association between multiple sclerosis and micturition disturbances, MRI studies to date have not delineated brainstem lesions specific to the impaired micturition.

In experimental studies, by contrast, Barrington had suggested that in the cat the micturition region was located in the dorsal part of the pontine tegmentum. Recent investigators have reported that it can be located more precisely, in the nucleus locus coeruleus, locus coeruleus alpha, or the dorsomedial part of the dorsolateral pontine tegmentum. Neurons in the pontine micturition centre may activate the parasympathetic excitatory outflow to the urinary bladder (detrusor), while there also exists a pontine storage centre ventral or lateral to the pontine micturition centre that controls external urethral sphincter function. Because our patient hadatomic bladder and urinary retention, the pontine micturition centre may have been the main site of brain involvement. Atomic bladder may reflect a “shock” state, as has been documented in some stroke patients. However, Sakakibara et al described three patients with atomic cystometrogram 3 months, 6 months, and 3 years after brain...
stern stroke, suggesting a prolonged atomic curve as a supranuclear type of parasympathetic pelvic nerve dysfunction.

Griffiths et al reported bilateral lesions of the pontine micturition centre leading to a period of urinary retention lasting from 2 to 9 weeks, whereas lesions located on only one side had no obvious specific effect on lower urinary tract function. This may be accounted for by bilateral innervation of the spinal parasympathetic nucleus by the pontine micturition centre. However, histology verified that only 15% of the right pontine micturition centre was destroyed. A recent PET imaging study disclosed that cortical and pontine micturition sites in humans are predominantly on the right side. It is therefore possible that extensive involvement of a unilateral pontine micturition centre, especially the right side, may cause transient urinary retention as found in our patient. Another possibility is that the amorphous lesions in the pons could have interrupted outflow pathways from the opposite pontine micturition centre.

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Splicing of the glutamate transporter EAAT2: a candidate gene of amyotrophic lateral sclerosis

Defective glutamatergic neurotransmission may have a critical role in the pathogenesis of amyotrophic lateral sclerosis (ALS). A reduced synaptic glutamate reuptake has been described as disease specific. In vitro expression studies suggested that proteins translated from these transcripts were rapidly degraded and show a dominant negative effect on normal EAAT2 protein which appears to be the predominant glutamate transporter in the CNS. A loss of EAAT2 can lead to neuronal degeneration through abnormal presynaptic glutamate excitotoxic mechanisms. This pathogenetic concept was supported by the clinical efficacy of ant glutamatergic drugs in patients with ALS and transgenic models. One of the reported transcripts was characterised by the skipping of the protein coding exon 8 of the EAAT2 gene. This transcript was amplified by polymerase chain reaction from ALS-CSF and suggested a role of this splice variant in ALS.

Interestingly, this is identical to an alternative splicing product of the EAAT2 transcript which we have recently reported and named EAAT2/C1. This and another splice product, named EAAT2/C2, have been cloned from normal human brain RNA. Here we report the cloning of two further EAAT2 transcripts, named EAAT2/C3 and EAAT2/C4. Based on the EAAT2 sequence information we designed specific primers for reverse transcription (RT) of the EAAT2-mRNA using control human poly-A+ RNA as template (Clontech, Palo Alto). RT and PCR amplification were performed as described (RT primer: 5' CAGTACACATAG-GATACGGTGC; PCR primers: 5' GATATGTTGCTGAAGAG-3'). Sequencing disclosed two novel EAAT2 transcripts which resulted from splicing of protein coding sequences. EAAT2/C3 originated from a deletion of 12 nucleotides (891-1012) leading to a frame shift. EAAT2/C4 resulted from deletion of exons seven to nine and parts of exons six and 10 (figure) with the downstream sequence still in frame. At the putative protein level EAAT2/C4 showed a loss of 234 amino acids located in the middle and C-terminal part of the polypeptide.

Our findings contribute to the notion that the EAAT2 transcript is highly variable. Splicing of the EAAT2 transcript is also found under normal conditions and may be part of post-transcriptional EAAT2 gene regulation. Furthermore, alternative EAAT2 transcripts were identified in other species. We conclude that splicing of the EAAT2 transcript is unlikely to be ALS specific. The EAAT2 gene regulation and its pathogenetic relevance are far from completely understood. The use of EAAT2 splicing products as diagnostic tools in ALS would be extremely valuable, but further evidence is necessary before concluding that these splice variants are specifically associated with ALS. However, the evolving knowledge on EAAT2 gene regulation will provide the basis for a comprehensive association study of EAAT2 splicing products in ALS and other neurodegenerative diseases.

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Lhermitte's sign in cavernous angioma of the cervical spinal cord

The sudden feeling of “painless but unpleasant electric shock-like discharges” originating in the neck or upper back and spreading down the spine into the limbs on flexion of the head was first described in 1917 by Marie and Chatelin and later by Lhermitte in his seminal paper of 1924. It is not a specific symptom but is most commonly encountered in cervical spinal cord demyelination caused by multiple sclerosis. The sign has been found in many other conditions that cause a traumatic or compressive cervical myelopa-
thy, such as cervical spondylosis and epidural, subdural, and intraparenchymatous tumours. It has also been reported infrequently in radiation myelitis, pernicious anaemia (subacute combined degeneration), pyridoxine toxicity, nitrous oxide misuse, cisplatin and docetaxel neuropathies, cervical herpes zoster myelitis, paroxetine withdrawal, Behçet’s disease, and systemic lupus erythematosus. Vascular disease of the cervical spine or intraspinal cord has never been noted to produce Lhermitte’s sign.

A 48 year old left handed man presented with a history of a “burst, very brief electrical tingling” in the left forearm, hand, and lower leg for almost 2 years. The symptom occurred only on flexion of the neck and abated even when the neck was kept flexed. No other neck movements caused this symptom. A year later, the patient noted mild dysesthesia in the left arm and leg. A sagittal heavily T2 weighted fast spin echo MR image of the cervical spine showed a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3–4 level with minimal mass effect. Subtle low signal intensity about its rim suggested hemosiderin deposition (figure). A few weeks later, after raking his yard, the patient experienced acute neck pain. A day later, he noticed diminished coordination of the left arm and leg. A sagittal T2 weighted fast spin echo MRI of the cervical spine obtained a few days later showed an extensive intramedullary low signal intensity area in the midposterior spinal cord compatible with interval haemorrhage, spinal cord atrophy, and oedema. Results of spinal angiography were normal. The pain resolved in 10 days, and only mild numbness in the left hand and to lesser degree in the foot persisted. At operation, the lesion was found to be a cavernous angioma. After resection of the malformation, sensory deficits in the left hand and foot worsened, and discomfort with an unpleasant sensation of swelling developed in the hand. For 1 month after the operation, the patient also complained of spontaneous “electrical bursts” in the right arm and both legs. Neurological examination 6 months after the operation disclosed mild weakness of the left arm and hand with diminished stretch reflexes and equivocal plantar response in the left foot. Abnormalities elicited in the sensory examination were decreased pain sensation in the left hand, mild attenuation of two point discrimination, and dysgasthesia in the left fingers. Mild sensory ataxia on finger to nose testing and mild pseudoneuroathetotic movements of the left hand were also noted. Lhermitte’s sign is a common symptom in neurological practice. However, the pathophysiology of the sign is not well known. Because flexion of the neck causes the dysesthetic symptoms, it has been suggested that an increased mechanical sensitivity of these damaged myelinated axons causes an abnormal origin or transmission of sensory information. In the cat model, deformation of experimentally demyelinated dorsal columns by <1 mm increased the frequency of action potentials in both spontaneously active and previously silent fibres. Routine flexion of the neck can lengthen and deform the cervical cord slightly and provide synchronisation of a volley of aberrant activity in damaged dorsal column myelinated axons. Nordin et al. reported activation of multiple units in the neuropeptide of the median nerve, presumably arising from afferent sensory fibres in the dorsal columns of a patient with Lhermitte’s sign on flexion of the neck. As expected, multiple sclerosis is the most common cause of Lhermitte’s sign, occurring in about one third of patients. The sign, however, is not specific and may be present in other clinical conditions that compress or damage myelinated sensory axons of the dorsal columns of the cervical cord. Occasionally, Lhermitte’s sign is the presenting complaint of the underlying medical cause.

To our knowledge, this is the first reported case of Lhermitte’s sign caused by a vascular disease in the cervical spinal cord. It was, in fact, the presenting symptom in our patient. The pathological findings confirmed the MRI diagnosis as a cavernous angioma. It is probable that the underlying lesion acted by producing compression or ischaemia on the dorsal columns of the cervical spinal cord.

Sagittal T2 weighted MRI (TR 3800/TE 96 ms) of the cervical spine shows a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3-4 level with minimal mass effect. Subtle low signal intensity about its rim suggests haemorrhoid deposition.

Autosomal dominant paroxysmal kinesigenic choreoathetosis: a clinical and genetic study of two families

Paroxysmal kinesigenic choreoathetosis (PKC), characterised by brief attacks of abnormal involuntary movements induced by sudden voluntary movements, is either neurologic (familial) or sporadic or symptomatic. A total of about 20 families with PKC have been reported, with autosomal dominant inheritance in most of them. No genetic study has been reported in familial PKC up to now.

We report two unrelated families with autosomal dominant PKC, in which we performed linkage analyses with loci involved in other paroxysmal movement disorders: (1) the locus for paroxysmal dystonic choreoathetosis (PDC), also known as paroxysmal nonkinesigenic dyskinesia, on chromosome 2q33–35; (2) the locus for AD paroxysmal choreoathetosis/spasticity (CSE), classified as “complicated” PDC, on chromosome 1p; and (3) the locus for episodic ataxia/myokymia (EA-1) on chromosome 12p13.

Family A was Portuguese and family B was French. They contained a total of 10 affected and nine unaffected family members, who were all interviewed and examined by the same physician. There was no family history of epilepsy. In one family, three of the five affected members also had migraine with visual aura. Except one patient, who had a parkinsonian resting tremor since the age of 52, neurological examination was normal. The phenotypes of the 10 patients were very homogenous. Age at onset of PKC attacks ranged from 1.5 to 13 years (median 6.5 years). Attacks occurred five to 20 times daily in nine patients and once a year in the other. Attacks were always triggered by a sudden movement of a lower limb (rising from a sitting position, running) that often occurred in response to an unexpected stimulus after sustained immobility. Embarrassment and stress were precipitating factors. In a few patients, fatigue, cold, or muscular tension, nausea, or fear of falling also favoured attacks. The latency between the triggering factor and dyskinesia was 0–2 seconds. Dyskinesias were usually preceded by a short aura (paraesthesias, n=4; muscular tension, n=3; visual aura, n=5) in the affected body. Duration of attacks was 3 to 40 seconds. Involuntary movements involved one side of the body, but sometimes extended rapidly to the whole body, with preservation of consciousness. During attacks, the intensity of the dyskinesias increased and decreased progressively. In addition to frequent dystathria (n=7) related to orofacial dyskinesia, breathing problems (n=1) and falls (n=5) sometimes occurred during violent movements. No other family history of movement disorders was noted.
attacks. One patient wore a helmet during early childhood because of frequent falls. PKC attacks occur at rest, are precipitated by caffeine and alcohol, not by sudden movements. PKC attacks are similar to those in PDC, except that physical exercise is a precipitating factor, and that some patients exhibit constant spastic paraplegia. Finally, although EA-1 consists of episodic myokymia and attacks of generalised ataxia, often prevented by acetazolamide, some features are shared with PKC—namely, the frequent kinesigenic origin of the attacks, the presence of a sensory aura, the short duration of the attacks (several seconds to 5 minutes), and the early onset. Moreover, an EA-1 family in which attacks of kinesigenic episodic ataxia and PKC occurred separately in some members, and jointly in one, has been reported. \(^1\)

After isolation of DNA from peripheral blood, a series of microsatellite markers were typed on: (1) chromosome 2q (D2S164–D2S173, D2S126, D2S377–D2S123); (2) chromosome 1p, with D1S197 (the CSE locus is situated in the 2 cm interval between D1S443 and D1S197); (3) chromosome 12p, with the markers D1S372, D1S299–D1S239. \(^1\) Inheritance of PKC was dominant in both families, with two male to male transmissions in one family, excluding X linked and mitochondrial transmission. There were no asymptomatic obligate carriers. Suggestive evidence for linkage was found in all three families. We assumed autosomal dominant inheritance with a gene frequency of 0.0002 and complete penetrance. We found autosomal dominant inheritance with a frequency of 0.0002, and complete penetrance by the age of 17 years. Allele frequencies for a white population were determined according to the genome database. Two point and multipoint lod scores were calculated using the MLINK program of the Fastlink package. \(^7\)

Results of the two point linkage analysis in both families are shown in the table. All markers tested generated negative lod scores at \(0.000 \) except for marker D2S377 in family B. Lod scores below the threshold of 2 were obtained for all candidate regions except for the PDC locus in family B. Multipoint linkage analyses excluded the following intervals including candidate loci in families A and B respectively: 26.5 and 25 cM on chromosome 2q including the PDC locus; 26.5 and 30 cM on chromosome 12p, including the intervals containing the voltage dependent potassium channel (KCNA1) gene responsible for EA-1. In conclusion, despite some clinical similarities between both families, our results suggest that PDC and PKC are genetically distinct from both forms of PDC and from EA-1.

We thank Dr Alexandra Durr for helpful comments and Giovanni Stevanin, Christiane Penet, Agnès Camuruz, Véronique Pothis, and Jacky Bou for technical support. We thank both families for their participation in this study, Dr. Marie Chane who referred one of the families, and Dr. Merle Ruberg for critical reading of the manuscript.

Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy

Granulomatous angiitis (GANS) of the CNS is a rare, idiopathic vasculitis confined largely to the small blood vessels of the CNS. It has also been referred to as “angiitis of the nervous system”, “idiopathic” angiitis of the nervous system. Clinical manifestations are usually the result of multifocal ischaemia and infarction and patients with GANS typically present with a chronic but progressively decompensating clinical course, with major and minor neurological deficits. Less commonly, haemorrhage can occur as a result of infarction, focal necrosis of a vessel wall, and aneurysm rupture, and the presentation may therefore be primarily neurosurgical. \(^4\) It is important to recognise this condition because long term clinical remission is possible with immunotherapy. In this paper we present a case of HIV-associated granulomatous angiitis. A forty-six-year-old woman was admitted to our unit with a 24 hour history of confusion, vomiting, dysphasia, and a generalised seizure. The patient also had a 30 month history of deteriorating work performance and had had episodes of nausea, vomiting, and headache lasting 1 to 2 days. After one of these episodes she was investigated by one of us (SM). Neurological examination and a CT were normal. Diagnoses of migraine and Ménière’s disease were considered. Four months before admission, she had experienced transient mild dysphasia and left hemianesthesia.

On admission to our unit, she was drowsy but opened her eyes to voice and obeyed simple commands. She had a left retinal haemorrhage and an expressive dysphasia. She was afebrile, there was no meningism, and general examination was normal. Brain CT showed an extensive area of low density involving both grey and white matter of the left frontal lobe, with three separate areas of intraparenchymal haemorrhage and mild mass effect. She was started on dexamethasone, phenytoin, and acyclovir and arrangements were made for MRI and MR angiography to be performed the following day. An improvement was noted overnight, but the next day her clinical condition deteriorated. Urgent CT was performed and this showed further haemorrhage into the left frontal lobe with appreciable midline shift (figure). Immediately after the scan her left pupil became fixed and dilated. An urgent left frontal lobectomy was performed.
Macroscopically the left frontal lobe was swollen, with multiple small areas of haemorrhage in the cortex and white matter, and thrombosis of superficial cortical veins. Histological examination disclosed a coexistent pattern of granulomatous and necrotising non-granulomatous vasculitits affecting the small leptomeningeal and intracerebral blood vessels. Occasional leptomeningeal vessels were occluded by thrombus. The granulomatous lesioned featured an infiltrate of lymphocytes and histocytes within blood vessel walls. The vascular intima was variably thickened by a fibrocellular proliferation and small numbers of Langhans and foreign body type giant cells were scattered individually within the media of some vessels. The leptomeninges contained a dense infiltrate of mononuclear inflammatory cells. The cerebral tissues were oedematous with extensive extravasation of erythrocytes and diffuse hypoxic neuronal changes but there was no evidence of a discrete area of infarction. Special stains for organisms (zinc, gram, PAS, PAS-D, Giemsa and GMS) were negative. Viral inclusions were not seen.

Haematological investigation disclosed a mild neutrophil leucocytosis, but haemoglobin, platelet count, and erythrocyte sedimentation rate were all in the normal range as were serological investigations including C reactive protein, complement assays, nuclear antibodies, double and single stranded DNA antibodies, and rheumatoid antibodies.

The patient was treated intensively with a combination of oral cyclophosphamide and intravenous methyl prednisolone for one week followed by oral cyclophosphamide and prednisone. Treatment was complicated by haemorrhagic cystitis (for which oral cyclophosphamide was changed to pulsed intravenous cyclophosphamide), and organic psychiatric. At 2 years the patient is clinically stable. Immunoallergy is being gradually reduced. She has a fixed frontal lobe deficit consisting of impulsivity, a loss of control of emotions, reduced verbal fluency, and impaired insight. Serial CT and MRI show only post-surgical change in the left frontal lobe. The importance of this case is firstly that it draws attention to the protein manifestations of this rare but treatable condition. Other reported presentations include recurrent intracerebral haemorrhage, radiculomyelopathy, cerebral and spinal aeriectasia, subarachnoid haemorrhage, seizures, and mass lesions.1, 2, 3

Secondly, this case emphasises the fact that the disease mostly affects small vessels of the leptomeninges. Neurosurgeons are most likely to encounter this disease in the setting of a request by their neurology colleagues for a diagnostic brain biopsy. Moore suggested that the ideal biopsy in these patients is a 1 cm wedge of cortex including leptomeninges and preferably containing a cortical vessel.2 Our patient ultimately required urgent decompressive frontal lobectomy. The diagnosis of GANS was not suspected preoperatively and the inclusion of leptomeninges in the surgical specimen was fortuitous. We would advise others undertaking the evacuation of an intracranial haemorrhage of uncertain aetiology to obtain a leptomeningeal biopsy at the same time, particularly when there is a background of neurological symptoms.

Other investigations may not be helpful. Brain CT and MRI are abnormal in 30%-65% and 75%-100% of cases respectively and may show a wide variety of lesions. Angiographic abnormalities are present in 50%-90% of cases but are not specific for GANS. The CSF may be normal. It is essential to differentiate GANS, from the many secondary causes of cerebral vasculitis such as giant cell arteritis. The presence of markers of systemic, inflammaratory and immune disease should suggest an alternative diagnosis.

Because GANS is rare, our knowledge of its natural history and optimum management is incomplete. Early reported cases of GANS were invariably fatal but immunotherapy has now been shown to improve symptoms and result in sustained remission in some cases. The results with corticosteroids alone have been disappointing and the combination of prednisone with cyclophosphamide is the mainstay of treatment.1, 3, 4

Intravenous atropine suppression of detrusor hyperreflexia in multiple sclerosis

Multiple sclerosis commonly causes urinary frequency, urgency, and urge incontinence resulting from detrusor hyperreflexia. This might be associated with voiding difficulties due to detrusor sphincter dyssynergia. These symptoms can be treated effectively with antimuscarinic drugs (primarily oxybutynin) and clean intermittent catheterisation, but the antimuscarinic side effects limit clinical usefulness. Typically the antimuscarinic side effects include constipation, reflux oesophagitis, and flushing.

Oxybutynin, formulated for intravesical administration, has been reported to be effective for suppressing detrusor hyperreflexia with low incidence of side effects in various neuropathic disorders.5, 6 However, this preparation is not widely available.

Atropine is a cheaper, easily obtainable, antimuscarinic drug. Advocates have historically claimed that it was shown to be effective in increasing bladder capacities without side effects in patients with spinal cord injury.7 However, the only study was small and uncontrolled. Whereas the pathologies of multiple sclerosis and spinal cord injury are different, the bladder impairments are similar. This study was designed to investigate the efficacy of intravesical atropine in increasing bladder capacities in people with multiple sclerosis with detrusor hyperreflexia.

The study received ethics committee approval. Written informed consent was obtained from each patient.

Patients with a definite diagnosis of multiple sclerosis and urologically demonstrated detrusor hyperreflexia were recruited into the study. Each was taking oral antimuscarinic medication and using clean intermittent catheterisation. A sample size calculation based on previous data identified a target recruitment of 15 patients to achieve a significance level of 0.05 with a power of 0.80 using a crossover study design. Eighteen patients were contacted, of whom 16 consented and 15 completed the study.

Antimuscarinic drugs were stopped 2 days before cystometric testing. Patients attended on two occasions. They were allocated 30 ml of either atropine (6 mg) in normal saline or normal saline (as placebo). This was done according to random code with both patient and investigator blinded. An independent nurse performed the bladder study.

Standard static saline fill cystometry with a filling rate of 50 ml/min was performed before and 2 hours after intravesical instillation of the test preparations. As this was a first randomised study, a two-tailed test was used with comparisons between the difference in change in cystometric bladder capacities were made with Wilcoxon signed rank test was used quoting the 95% Wilcoxon confidence interval.

The study group consisted of 15 patients (six men and nine women) with a median age of 51 years (range 39–73 years). All patients retained their test solutions after each instillation. The results are shown in Table 1. After atropine the bladder volumes increased by a...
Cystometric bladder capacities (CBC) for atropine and placebo (saline)

<table>
<thead>
<tr>
<th></th>
<th>Atropine (ml)</th>
<th>Placebo (ml)</th>
<th>Change in CBC (ml) (Wilcoxon 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>183 (144.5-302.5)</td>
<td>135 (85.3-206.3)</td>
<td>0 (−3.3 to 3.3)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>159 (123.7-331.8)</td>
<td>179 (129.3-322.8)</td>
<td>−20 (−41.5 to −8.5)</td>
</tr>
</tbody>
</table>

median value of 93 ml (95% confidence interval 45.0–170 (p=0.001)). After saline the cystometric bladder capacity did not change significantly.

No significant changes were found in blood pressures or pulse rates. No side effects were reported by any patient. Atropine was not detected in blood samples 2 hours after intravesical instillation (limit of detection 0.05 mg/l).

This early study provides evidence in favour of the efficacy of intravesical atropine in increasing the cystometric bladder capacity in patients with multiple sclerosis. Cystometric bladder capacity was chosen as an outcome measure because it has been shown to be sensitive to the influence of orally administered antimuscarinic drugs used for the treatment of detrusor hyperreflexia in multiple sclerosis. It is therefore likely that urgency and urge incontinence will be improved with the administration of intravesical atropine. However, this will require testing in a randomised controlled therapeutic trial.

The patients did not identify any side effects during the 2 hours after the administration of the atropine. It has been shown that orally administered oxybutynin will induce antimuscarinic side effects in a similar period.

The absence of measurable drug in the blood at the time of the clinical effect is encouraging. The results show promise and if clinical efficacy were demonstrated this approach would be a useful addition to the therapeutic options for urinary incontinence in multiple sclerosis.

The study was funded by the MS trust fund of the Central Middlesex Hospital London. We thank Professor Stephen Senn of the Department of Epidemiology, University College London for statistical advice. Professor Stephen Senn of the Department of Epidemiology, University College London. We thank Professor Stephen Senn of the Department of Epidemiology, University College London for statistical advice.

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Prothrombotic mutations and ischaemic stroke at a young age in two sisters

We examined two sisters who had an ischaemic stroke at 32 and 41 years respectively. One had the prothrombin 20210 G to A variant and mild hyperhomocysteinaemia. The other had two prothrombotic mutations: the factor V Leiden mutation and the prothrombin 20210 G to A variant. We argue that these abnormalities may have caused the strokes.

Patient III-36 (pedigree, figure) was admitted at the age of 41 years with a left sided paraparesis. Her medical history was unremarkable, including the absence of migraine. Neurological examination showed a mild left sided paraparesis. Blood pressure was normal. She had no livedo reticularis. Brain CT showed a right parietal subacute infarct. Cardiovascular, carotid angiography, and laboratory testing were normal, including investigation of antiphospholipid antibodies, lipid profile, fasting and post-methionine loading homocysteine concentrations, antithrombin III, protein C, and protein S. The patient was treated with aspirin and did not have arterial ischaemic disease (or venous thrombosis) until now. Resistance to activated protein C (APC) was measured as described and the n-APC-SR of 1.09, and the factor V Leiden mutation was present in 1% to 2%.

The occurrence of a stroke in a young person is relatively rare. It is even more rare when both first degree relatives have a stroke at a young age. The second child of a family may suggest a genetic cause, which reduces the list of possible causes considerably. On clinical and radiological grounds and after laboratory and cardiac investigations, in the crawford patients many hereditary causes of stroke were excluded (mitral valve prolapse, atrial myxomas, cardiomyopathies, CADASIL, Sneddon’s syndrome, MELAS, and abnormalities of protein C, protein S, and antithrombin III). In homocystinuria thrombotic events are invariably more severe than in our probands, although the occurrence of mental retardation, epilepsy, and blindness in subject II-3 is compatible with homocystinuria (unfortunately, she could not be studied). III-37 had mild hyperhomocysteinaemia, but it is unlikely that this was the (only) cause for her strokes, as hyperhomocysteinaemia mostly causes premature atherosclerosis, preeclampsia, cardiomyopathy, and leukoencephalopathy, which were not found. We therefore considered the prothrombotic mutations as the most likely cause.

The factor V Leiden mutation occurs in about 4% of the Dutch population, and the prothrombin mutation in 1% to 2%. The simultaneous occurrence of both mutations in one subject can therefore be calculated as 0.04% to 0.08%—that is, 6000 to 12 000 persons in The Netherlands (about 15 million inhabitants). Nevertheless, so far only one Dutch family in which both mutations occur has been described. All members in this family with both genetic defects experienced venous thromboses. The only other published pedigree in which both mutations occur originates from France. In this pedigree only one subject carried both mutations, and she had recurrent stumps, but no arterial ischaemic events. The risk for venous thrombosis in patients with both mutations is probably high, as it is known that the factor V Leiden mutation enhances the risk for thrombosis in patients with other prothrombotic states, such as protein S and protein C deficiencies.

Although the association of prothrombotic mutations, such as the factor V Leiden mutation and the prothrombin variant, with carrier of the prothrombin 20210 G to A variant.

After informed consent, we prospectively investigated the family members of the probands. DNA testing was not performed in all family members (see pedigree). Medical histories of all family members were reviewed (no ischaemic heart disease, stroke, or deep venous thrombosis), except for III-39 who had mental retardation, epilepsy, and blindness (she could not be studied). The factor V Leiden and prothrombin variant were investigated in III-34, III-38, III-40, IV-65, IV-66, IV-68, and IV-70. The factor V Leiden mutation was present in III-34 and IV-70, the prothrombin variant in III-38 and III-39. The prothrombin variant was present in both variants in III-34, III-38, IV-65, IV-66, and IV-68, and no mutation in III-38. III-35 (who was not tested) may have had mutations, because her two daughters carry both mutations. III-61 (who is not a relative) probably carries the factor V Leiden mutation, as his wife has the prothrombin mutation, but their daughter has the factor V Leiden mutation. Fasting and post-methionine loading serum homocysteine concentrations were normal in III-34, III-38, III-40, IV-41, IV-65, and IV-67.

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Although the association of prothrombotic mutations, such as the factor V Leiden mutation and the prothrombin variant, with
(recurrent) venous thrombosis is now well established, the association with arterial thromboembolism is not clear. Population- and case-control studies have shown that the factor V Leiden mutation is not a risk factor for myocardial infarction or cerebrovascular disease. Nevertheless, this mutation has been associated with ischaemic stroke. The relationship between the more recently discovered prothrombin 20210 A to G mutation and arterial disease has not yet been intensively studied, but seems unlikely. It is, however, possible that the strokes in the probands can be attributed to the co-occurrence of two risk factors (prothrombin mutation and factor V Leiden mutation in one, and prothrombin mutation and hyperhomocysteinaemia in the other), because it is likely that a synergistic interaction occurs between thrombogenic risk factors. To study this further, a case-control study determining the importance of a combination of thrombogenic risk factors in unselected young patients with stroke is necessary.

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BOOK REVIEWS


The continuing rapid expansion of neuroimaging, with new technologies and improvements in more well established techniques, have sharpened the tools with which to examine neurological and psychiatric disorders, and schizophrenia of late onset continues this well referenced text. Besides presenting the data for the clinician, this comprehensive review will also be appreciated by researchers in this field.

The third part of this book returns to the application of these results to clinical practice. Both an American and European perspective on the clinical interpretations of the above data are presented and the conclusion can be quoted "Our ability to image the brain, however, has in some cases outpaced studies of schizophrenia, have led to new insights into the diagnosis, prognosis, and symptomatology of these ill understood diseases. However, there are two obstacles in the understanding of this expanding area of research for the interested neurologist and psychiatrist—namely, understanding of the basis of the technology and relating the research findings to best clinical practice. The remit of this text covers both these deficiencies.

For the non-physicist getting to grips with the basic principles and methodologies of neuroimaging can be daunting. The first section of this book explains the basic principles behind the hardware of the imaging department and this is aided by many excellent diagrams. The general clinical indications and safety issues of structural (CT and MRI) and functional (PET, SPECT, and EEG) imaging techniques are well reviewed and illustrated.

The second section of the text explores the research questions and summarises the answers so far in the field of old age psychiatry. Interpretation of imaging research in abnormal elderly patients, with regard to subject selection, imaging technique, and the relation to normal aging, is one of the main dilemmas in this field. This is fully discussed in the admirable chapter on normal aging, which commences this review of the research. Other chapters on Alzheimer’s disease, vascular dementia, other delirium, affective disorders, and schizophrenia of late onset continue this well referenced text. Besides presenting the data for the clinician, this comprehensive review will also be appreciated by researchers in this field.

our ability to understand the clinical implications of the structural and functional findings seen using modern imaging techniques”. In other words this interesting research which has been so excellently summarised here yet to make real impact on routine clinical practice.

CLARE GALTON


Stereotactic radiosurgery has been with us for about 30 years. The pioneering work of Lars Leksell was carried out at the Karolinska Institute in Stockholm, but in the United Kingdom, the National Stereotactic Radiosurgery Unit in Sheffield has now been active since 1985. In theory, indirect methods of treatment for neurosurgical conditions are to be preferred to direct open surgery and it already seems that in a number of areas indirect techniques have already largely replaced surgery as the treatment of choice, for example, in the endovascular coiling for the treatment of intracranial aneurysms where direct surgery seems destined to become a rare event for this condition in the not too distant future. It is therefore disappointing that the application of the stereotactic technique to radiosurgery has not been more productive in this respect, some progress has been made. This review in the series Progress in Neurological Surgery sets down the current state of play in this field. The experience recorded in this volume is entirely North American and, as most of the conditions treated by this technique are rare, it would have been valuable to have included the by now quite extensive experience from the Scandinavian and the United Kingdom units. The papers in the volume, as is usual in this type of publication, are of variable quality and of variable value - one wonders at the need for a chapter on the technology and physics of the technique. On balance however it is an interesting read and there are some useful data on the management of quite rare conditions. This may be particularly useful to the “modern” neurosurgeon who now has to discuss, using appropriate data, the alternatives to surgery with each patient as an integral part of the “informed consent” procedure. The chapters on Patient outcomes after Arteriovenous and Cavernous Malformations are potentially useful in this respect. The section on Radiosurgery is more problematic, and because of the small number of cases involved it is very difficult to form any useful conclusions about the place of this treatment technique in the management of these difficult conditions. One question, for example, whether it will ever replace tried and tested surgical techniques in the treatment of disorders such as trigeminal neuralgia or the involuntary movement disorders.

The book is compact and well presented and can certainly be recommended for the departmental library.

DAVID HARDY


Although recognised for more than 100 years, central pain has been poorly defined, poorly understood, intensively debilitating and, in the majority of patients, refractory to therapy. In this text, Professor Pagni attempts to define, classify, and review critically the multitude of treatments that have been proposed for this most challenging of conditions.

The book begins with a review of the history of the condition and a discussion of its definitions, nosology, and clinical spectrum. There follows a survey of the reasons which cause central pain, both spontaneous and iatrogenic, theories about its aetiology, and the various measures available to treat it. There is an extensive bibliography for further reading.

The book provides a critical review of the literature on central pain, interspersed with personal observations from over 30 years of experience in the field. It is written in a succinct style that presents theories and therapies in a historical sequence, followed by the author’s comments on current indications and clinical outcomes. If I have one criticism of this book it is the style of presentation which is by subject heading rather than strictly alphabetical sequence, making it cumbersome for cross-referencing. This, however, is a minor irritation.

In summary, this is a thoughtful and enjoyable book. It takes a logical look at a subject which, by its very nature, has a literature containing many anecdotal reports that can be hard to evaluate in isolation.

ROBERT MACFARLANE


This is a timely moment to publish a book which takes an analytical look at outcomes in the common neurological and neurosurgical procedures’ obsessed as we seem to be at present with evidence based medicine. In addition we are rapidly moving towards and era when therapies are becoming available for many neurological diseases, hitherto deemed more suitable for pastoral care, and our understanding of treatment trials and the importance of comparative treatment groups is essential for local and regional health planning. It places the work of the pioneering physicians effectively in context with the rest of medicine and provides a multitude of informative lessons on patient management and our interpretation of medical dogma and established practices.

Before embarking on the more traditional interpretation of current neurological and neurosurgical therapy there are four invaluable chapters in the introduction section. They take a practical view of papers designed to evaluate and measure outcome as well as their financial impact on the health services in a cost-benefit analysis. Although these subjects may seem a little stodgy to pure clinicians they provided

This book is a brave attempt to discuss the burgeoning field of gene therapy for neurological disorders. To many clinicians, gene therapy has not to date lived up to all the hype and excitement of when it was first suggested. However, as the editors point out in their preface, this has been a little unfair and it remains an exciting area that is worthy of a dejà vu phenomenon.

I cannot pretend that this is an essential book for neuroscience libraries, but it does provide important insights for those planning treatment or outcome studies and may also be of value for medicolegal work.

NEIL ROBERTSON


Currently the most exciting new developments in Parkinson's disease relate to the genetics and role of $a$-synuclein in the pathogenesis of this disorder, and the resurgence of neurosurgery that dominates new management strategies. These areas are therefore well covered in this book which (like others in this series) is a concise and topical review of, in this case, Parkinsonism. However, unlike previous volumes, abstracts are now provided along with a reference list in which the key articles are highlighted. This is a useful addition as it not only lays out the structure of the chapter, but allows the interested reader to supplement their understanding by the acquisition of a few essential source articles.

The book opens with a chapter on the clinical features of Parkinson's disease (Quinn) which is supplemented later on by chapters on other parkinsonian syndromes, including multiple system atrophy (Quinn and Wenning), progressive supranuclear palsy and corticobasal degeneration (Litvan), as well as other causes of parkinsonism (Tison). These chapters are helpful in defining the characteristic features of these diseases and by so doing the differences between them which should allow for a more accurate clinical diagnosis in life. However, the fact that all these conditions ultimately rely on pathology for diagnosis can create significant discordance between clinical features and disease state, and this is exacerbated by the desire to try and fit an atypical patient into one of these categories. In this respect the discussion on Lewy body dementia is timely, given its increasing recognition as a cause of dementia. The relation of this condition to Parkinson's disease is still far from clear and this is acknowledged by Lennox and Lowe in their chapter on dementia and Lewy bodies.

The book, however, does not stay purely within the realm of clinical phenotypes. Schapira provides a familiar chapter on the pathogenesis of Parkinson's disease and V伍 Good reviews the genetic literature and Ben-Shlomo the epidemiology. These are comprehensive chapters and again highlight the difficulties of conducting such work given the inability to make a definite diagnosis of Parkinson's disease in life. There is limited discussion on $a$-synuclein and the recent identification that this forms the major filamentous component of Lewy bodies and Lewy neurites is obviously not mentioned, although it may prove to be the gold standard for diagnosis in the future. Furthermore, the recent identification of a second gene (par- kin), this time in autosomal recessive juvenile parkinsonism, is also not covered in this book, which highlights the pace at which these books can become out of date.

The chapters on management are useful if not inspiring. Oertel and Quinn discuss the issue of drug therapy well, both in terms of overall aims and specific advice, and LeeWitt discusses rather turgidly newer pharmacological therapies. The controversy as to the treatment of young onset Parkinson's disease is touched on in both chapters, although no clear scientifically proved answers are provided. The surgical management is then discussed by Obeso and colleagues, who present data on the newer techniques of pallidotomy, deep brain stimulation, and transplantation. This is a burgeoning area of interest although the basic wiring diagram of the basal ganglia, that regularly turns up in chapters of this sort, is a gross simplification, which may explain some of the limited effects of these surgical manipulations. Since this book came out there is now much more information on the cognitive consequences of pallidotomy, as well as early studies addressing pallidal versus subthalamic stimulation in the treatment of Parkinson's disease. Furthermore the discussion on transplantation in this chapter is not especially critical both in terms of the failure of some centres to follow scientifically proved methods of tissue preparation and implantation as well as adherence to the CAPT-PD guidelines. This has meant that comparisons between centres with this experimental procedure cannot be done easily, if at all.

Overall the book is very rewarding and is probably more of interest to those not directly working in the field of movement disorders and Parkinson's disease. It is generally clear and concise and combines scientific research, and the contents of the book generally live up to the expectations that such a list generates. Aspects of experimental neuroprotection that were covered in individual chapters include glutamate receptor mediated ischaemic neuronal death, oxidative mechanisms, nitric oxide synthetase, ischemic injury, apoptosis, and neurotrophic factors. The chapters vary somewhat in character. For example, the chapters on glutamate neurotoxicity and inflammatory mechanisms...
provide an overview of the recent literature, whereas that on oxidant mechanisms provides focus on the use of transgenic and knockout animals to study free radical injury in ischaemia. Both types of chapter provide useful information, but the former variety seemed to me to sit better with my perception of the aims of the book.

The second part of the book contains three chapters. The first of these considers the current status of new drug development for stroke, with brief sections on both clinical trials of thrombolytic and neuroprotective therapy. It also contains a useful analysis of how protocols for clinical trials might be advanced, with consideration of clinical outcome assessment, the need for early enrollment, sample size issues, and the utility of surrogate end points. The second of these two chapters focuses on new MRI techniques in acute stroke. The final chapter provides a useful overview of future directions in stroke research.

The book provides an admirable review of current knowledge regarding experimental stroke research, and outlines the problems and some solutions in the clinical application of such knowledge. I think that this book will find a wide readership in both clinical and experimental stroke research, and will be useful reading for clinicians involved in stroke management. If I had a concern, it would be that the discussion of progress in clinical therapy seems more optimistic than justified. However, it might be argued that one of the prime function of monographs such as this is to arouse and sustain enthusiasm.

DAVID MENON

CORRECTION


On page S35, in the left hand column, paragraph 3 the statement: “However, these data may be affected by sampling bias, as the patients who received magnesium all had a condition (pre-eclampsia) which has a protective effect on cerebral palsy in preterm infants...” should read: “However, these data may be affected by sampling bias, as the patients who received magnesium sometimes had a condition (pre-eclampsia) which has a protective effect on cerebral palsy in preterm infants...”