Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies

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Abstract
Objective—To compare a recently developed immunoprecipitation assay (IPA) to the mouse protection bioassay (MPB), currently considered the “gold standard”, for detecting antibodies against botulinum toxin A (BTX-A) and to correlate these assay results with clinical responses to BTX-A injections.

Methods—MPB and IPA assays were performed on serum samples from 83 patients (38 non-responders, 45 responders) who received BTX-A injections. Six non-responders had serum tested on two separate occasions. Some patients also received a “test” injection into either the right eyebrow (n=29) or right frontalis (n=19).

Results—All patients antibody positive (Ab+) by MPB were also Ab+ by IPA, whereas an additional 19 patients (17 with reduced or no clinical response) who were MPB Ab− were Ab+, with low titres, by IPA. Two of these 19 patients (non-responders) were initially MPB Ab− but later became MPB Ab+. Similar to previous studies, the sensitivity for the MPB was low; 50% for clinical, 38% for eyebrow, and 30% for frontalis responses whereas the IPA sensitivity was much higher at 84% for clinical (p<0.001), 77% for eyebrow (p=0.111, NS) and 90% for frontalis responses (p=0.02). The IPA specificity was 89% for clinical, 81% for eyebrow, and 89% for frontalis responses, whereas the MPB specificity was 100% for all three response types, which were all non-significant differences.

Conclusions—Both assays had high specificity although the sensitivity of the IPA was higher than the MPB. In addition, the IPA seems to display positivity earlier than the MPB, and as such, it may prognosticate future non-respondiveness. Eyebrow and frontalis “test” injections correlated well with clinical and immunological results and are useful in the assessment of BTX non-responders.

Methods—Eighty three patients (17 men and 66 women) with a mean age of 56 (SD 12.2) years; range 19 to 81) were selected for this study. Most of the patients were treated primarily for dystonia; cervical (n=62; 32 non-responders), cranial and cervical (n=10; four non-responders), and cranial (n=7, all responders). Other conditions included spastic hemiplegia (n=1; responder), hemifacial spasm (n=1; responder), focal leg dystonia (n=1; non-responder), and segmental myoclonus (n=1; non-responder). Clinical response to BTX-A (Botox®, Allergan Pharmaceuticals, Irvine, CA, USA) injections was rated on a 0 to 4 “peak effect” scale (0=no effect; 1=mild effect, no functional improvement; 2=moderate improvement, no change in botulinum toxin type A (BTX-A). In addition, BTX-A is also being used for various non-neurological (for example, cosmetic) indications. As the range of uses for BTX-A continues to expand, there is a growing concern regarding the development of immunoresistance secondary to blocking antibodies (Ab). The reported frequency of such antibodies has ranged from 3% to 57% depending on the assay method used.

The standard assay for detecting BTX Ab is the in vivo mouse protection bioassay (MPB), which evaluates the ability of increasing dilutions of a patient’s serum to protect mice from lethal doses of BTX-A. In vitro assays, including the sphere linked immunodiagnostic assay (SLIDA), enzyme linked immunosorbent assay (ELISA), a monoclonal antibody based immunoassay, and western blot technique have also been reported to detect such antibodies. These assays, however, do not correlate well with clinical responses because they do not detect specific blocking Ab.

The MPB has been shown to have high specificity, but its sensitivity is relatively low. The primary aim of this study was to compare the MPB with a more recent immunoprecipitation assay (IPA) developed by Palace et al and to correlate the presence of antibodies detected by these two assays to the patients’ clinical response to BTX-A injections. The results described by Palace et al needed to be confirmed using a larger number of patients, as well as incorporating more clinical details including correlation with facial (eyebrow and frontalis) “test” injections. Additionally, we evaluated the utility of eyebrow or frontalis injections as clinical “tests” for immunoresistance.
functional disability; 3=moderate change in severity and function; 4=marked improvement in severity and function). There were 38 non-responders (0 or 1 “peak effect” response rating after their last injection), and 45 responders randomly chosen from the botulinum toxin clinic population. Six patients (all non-responders) had samples drawn on two occasions (with a minimal latency between sample collections of 4 months; mean 4.3 months). Thus, there were 89 total serum samples on 83 patients included in this study. This low ratio of responders/non-responders does not represent the actual patient response rate in the BTX clinic as we did not collect samples on all patients seen in the clinic.

The blood collected was separated and sent to Northview Pacific Laboratories, Berkeley, California, USA for the MPB assay and to the Institute of Molecular Medicine, John Radcliffe Hospital, Oxford University, UK for the IPA assay. The individual laboratories were “blinded” to the clinical information before sample testing to maintain objectivity.

The MPB is a qualitative test reported as either positive (Ab+) indicating that the patient’s serum neutralises the effects of BTX-A injected intraperitoneally with survival of 3/4 mice. In a negative result, two or more of the mice die, presumably indicating the lack of blocking Ab in the patient’s serum.

The IPA method was performed as described by Palace et al with slight modifications. After the iodination reaction, the 125I-BTX was microfiltered and stored at 4°C in phosphate buffered saline (PBS). When required, it was diluted in PBS and centrifuged to remove any aggregates immediately before use. Supernatant (25 µl) containing 30 000–50 000 125I-BTX precipitated/l serum, was incubated with 2.5 µl of each serum in a total volume of 50 µl PTX buffer PBS (0.02M phosphate, pH 7.4 m 0.1% tritonx100). After 2 hours at room temperature or overnight at 4°C excess goat antihuman Ig was added. When a precipitate had formed, 600 µl PTX was added before centrifuging. The pellets were washed twice briefly in PTX buffer and counted on a Cobra Packard gamma counter. Results were expressed as pM (pmoles and counted on a Cobra Packard gamma)

Results of both controls were below the range of sensitivity of the test. The control samples were therefore considered false positive as they continued to give a precipitate.

Sensitivity, specificity, and positive predictive value of the two assays was determined as follows:

Sensitivity=A/(A+C); specificity=D/(D+B);
positive predictive value=(PPV) A/(A+B);
negative predictive value=(NPV): D/(D+C)

where A=true positive (Ab+ with negative response to injection), B=false positive (Ab+ with positive response to injection), C=false negative (Ab− with negative response to injection), D=true negative (Ab− with positive response to injection).

Comparisons of the above parameters of the two assays were performed using the Fisher’s exact test.

Results
The distribution of results of the first samples on the 83 patients is shown in fig 1. The threshold for positivity, 50 pM of 125I-BTX binding sites precipitated/l of serum, was lower than that reported previously due to slight improvements in the assay that reduced non-specific precipitation by control serum samples.

There was a clear correlation between the results of the IPA and MPB assays (fig 2). All serum samples which were Ab+ by MPB were Ab+ by IPA, and all Ab− by MPB were Ab− by IPA. However, 20 serum samples (from 19 patients) were Ab− by MPB but Ab+ by IPA. The antibody titres in this group, with a mean of 183.2 pM (SD 111.8): range 51 to 459 pM were, however, significantly lower (p<0.0001, Kruskal-Wallis test) than those in the MPB Ab+ group, in which the mean was 1378.1 (SD 921.5): range 101 to 3663 pM. Of the 19 IPA Ab+/MPB Ab− patients, 14 were non-responders and two of these non-responders became Ab+ by MPB on repeat testing as shown in figure 2. The remaining five were considered false positive as they contin-

![Figure 1](http://jnnp.bmj.com/)  
**Figure 1** Frequency distribution of IPA results (pM of 125I-BTX precipitated/l serum) on the initial samples from the 83 patients, divided on the basis of clinical response. Results from healthy control serum samples were subtracted from all test values.
ued to respond to BTX-A despite low, but positive, titres (112–353). Three of these five patients had a reduced, peak effect score 2, response (fig 3).

In a previous report, we showed that lack of response to a test injection into the facial muscles is a more sensitive measure of non-responsiveness than the MPB.18 In the present study, 29 and 19 patients respectively were given eyebrow or frontalis “test” injections, and the IPA titres corresponded well with responses to the facial “test” injections. Four patients showed no response to the eyebrow test injections despite continuing clinical response. However, three of these patients were border-line (reduced) clinical responders (peak effect score 2), who previously had a more robust response to BTX-A, and two of these patients were IPA Ab+ suggesting that the eyebrow and IPA may both be early predictors of immunoresistance.

Of the 10 clinical non-responders who also had eyebrow injections, only one had a good eyebrow response. This patient was MPB Ab− but IPA Ab+ (titre of 409 pM). Seven patients who were responders had a frontalis injection, and all seven had a good frontalis response. Of the 12 patients who were clinical non-responders and who received a frontalis injection, two had a good frontalis response. Both patients were MPB Ab− whereas one was IPA Ab+ (with a low titre, 82 pM) (see fig 4 for correlation of clinical responses with responses to “test” injections).

The specificity of both assays was relatively high, although the sensitivity of the IPA was substantially higher than the MPB (tables 1 and 2). Specificity of the MPB was 100% on all three parameters (clinical, eyebrow, and frontalis) whereas the IPA specificity was 89% for clinical (p=0.056, NS, Fisher’s exact test), 81% for eyebrow (p=0.226, NS), and 89% for frontalis responses (p=0.99, NS). Sensitivity for the MPB was low; 50% for clinical, 38% for eyebrow and 30% for frontalis whereas the IPA sensitivity was much higher at 84% (p<0.001) for clinical, 77% for eyebrow (p=0.111, NS) and 90% for frontalis responses (p<0.02).

The PPV of the MPB was 100% for clinical, eyebrow, and frontalis responses, whereas the NPV was 67% for clinical responses, 66% for eyebrow, and 56% for frontalis responses. The PPV of the IPA was 88% for clinical, 77% for eyebrow, and 90% for frontalis responses, whereas the NPV was 85% for clinical, 81% for eyebrow, and 89% for frontalis responses.

Sensitivity, specificity, PPV, and NPV of the individual test injections were determined in relation to clinical responses. False positives in this determination were a positive test injection response with a negative clinical response. False negatives were a negative test response with a positive clinical response. Thus, for the eyebrow injections, sensitivity was 79%, specificity was 90%, PPV was 94%, and NPV was 69%. For the frontalis injections, sensitivity was 100%, specificity was 83%, PPV was 78%, and NPV was 100%. For the test injections combined, sensitivity was 85%, specificity was 86%, PPV was 88%, and NPV was 83%.
As the number of patients treated with BTX-A continues to grow, the prevention and accurate detection of immunoresistance have become high priorities. The MPB, originally described by Hatheway and Dang,14 has been considered by many to be the “gold standard” assay for the detection of BTX-A Ab. Here we show that an assay based on immunoprecipitation of radio-labelled BTX-A is a highly reliable test which is slightly less specific, but considerably more sensitive than the MPB. Six non-responding patients were tested twice by both assays, typically secondary to patient request or for verification purposes. Two of these were initially MPB Ab− but became Ab+ by MPB on repeat testing; the IPA values were positive on first testing and the titres rose over the 4 months between the samples (fig 2) suggesting the early detection of immunoresistance by IPA. Furthermore, there were five false positives (clinical responders with Ab+ result by IPA), but three of these patients have had declining response to BTX as well as relatively low titres by IPA, which is a quantitative test. Thus, positivity by the IPA may be a useful predictor of future non-responsiveness.

The IPA correlated well, not only with the overall clinical responses, but also with the eyebrow and frontalis “test” injections, with a specificity of 81% and 89% respectively to these upper face injections. Additionally, the strong correlation of these “test” injections with clinical response ratings provides a strong support for using these simple biological tests to evaluate patients for immunoresistance. Overall, we prefer the eyebrow injections as these are more cosmetically acceptable in that the asymmetric responses are present only during voluntary contractions whereas unilateral disappearance of frontalis wrinkles may not be desirable.

The only commercially available in vitro test utilizes a western blot assay. Although this test offers potential advantages over MPB in that it is less cumbersome and does not require the use of experimental animals, our previous study18 showed that this in vitro test does not correlate as well as the MPB with clinical responses.

Based on the results or our study, we offer the following guidelines for evaluation of patients who fail to respond to BTX injections (secondary non-responders) (fig 5). When such a patient returns to the clinic after obtaining a poor or no response to the previous injection, the clinician may re-inject with the same or higher dose and/or an alteration of the site and at the same time inject 15–20 units of BTX into the right eyebrow or right frontalis. If the patient shows no response to both (clinical and test) injections, the use of serological assays, such as IPA or MPB may be considered, before precedings to the next step of using other BTX serotypes,21–23 plasma exchange, immunoabsorption, or surgery.

Table 1 Clinical-immunological correlation

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<th>Mouse bioassay (MPB)</th>
<th>Immunoprecipitation assay (IPA)</th>
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<tr>
<td></td>
<td>+ + − −</td>
<td>+ + − −</td>
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<tr>
<td>Clinical (n=83 subjects, 89 samples)</td>
<td>+ + − −</td>
<td>+ + − −</td>
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<tr>
<td>Eyebrow (n=29 subjects)</td>
<td>+ + − −</td>
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<td>Frontalis (n=19 subjects)</td>
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<td>Total responses</td>
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+ = Responder; − = non-responder.

Table 2 Mouse bioassay - immunoprecipitation assay comparison

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<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
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<tr>
<td>Clinical</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Eyebrow</td>
<td>38</td>
<td>100</td>
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<td>Frontalis</td>
<td>30</td>
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PPV=Positive predictive value; NPV=negative predictive value.

Discussion

As the number of patients treated with BTX-A continues to grow, the prevention and accurate detection of immunoresistance have become high priorities. The MPB, originally described by Hatheway and Dang,14 has been considered by many to be the “gold standard” assay for the detection of BTX-A Ab. Here we show that an assay based on immunoprecipitation of radio-labelled BTX-A is a highly reliable test which is slightly less specific, but considerably more sensitive than the MPB. Six non-responding patients were tested twice by both assays, typically secondary to patient request or for verification purposes. Two of these were initially MPB Ab− but became Ab+ by MPB on repeat testing; the IPA values were positive on first testing and the titres rose over the 4 months between the samples (fig 2) suggesting the early detection of immunoresistance by IPA. Furthermore, there were five false positives (clinical responders with Ab+ result by IPA), but three of these patients have had declining response to BTX as well as relatively low titres by IPA, which is a quantitative test. Thus, positivity by the IPA may be a useful predictor of future non-responsiveness.

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Figure 5 Decision tree for the evaluation and subsequent treatment of patients based on response to BTX injections.
of our study, we recommend the IPA assay (given the high sensitivity and specificity) as the assay of choice to confirm immunoresistance. Eight of nine patients who were clinical and test (eyebrow) non-responders were IPA Ab+, and nine of 10 patients who were clinical and frontalis non-responders were IPA Ab+. As it can be predicted with relative certainty that if both the clinical and test injections result in no response, the IPA will be positive, there may be no need to test for antibodies by the IPA in this category of patients. Given the low sensitivity of the MPB, this assay has a limited value compared with the IPA. Furthermore, the IPA does not require the use of experimental animals and it quantitatively assesses the degree of immunoresistance by providing antibody titres which can be measured serially.

It is important to recognise some possible shortcomings of our study. Although the "0–4 peak effect" scale is an established method of assessing response to BTX injections, it may not always reliably differentiate responders from non-responders. Patients were considered non-responders if they described no effect or only mild effect with no functional improvement from their most recent injection. These patients may have had suboptimal benefit from their recent injection secondary to technique, injection of inappropriate muscles, low potency of the BTX batch, or inadequate dose, and as such, the reported sensitivities of the two assays may be artificially low. A wide range of doses was given per visit at different intervals making a correlative analysis difficult. A further possible shortcoming is the definition of sensitivity and specificity used. "True positive" assumed that the Ab+ patient must be a non-responder, which is supported by our previous finding that all 20 MPB Ab+ patients had no response to BTX-A injections on at least two consecutive treatment sessions. "False negatives" refer to those patients who do not respond to BTX injections despite an Ab− test.

In conclusion, our study shows that both assays have a high specificity, but because the IPA is more sensitive than the MPB and because the IPA is an in vitro assay, it may have relative advantage over the MPB. A further advantage of the IPA is that this is a quantitative assay which may be useful for serial evaluations and may have a predictive value in determining impending or future unresponsiveness. Eyebrow and frontalis "test" injections correlated well with the clinical and immunological results and can be used as reliable screening tests in patients who have either no response or an equivocal response to BTX injections.

The study was supported by grants from Allergan Pharmaceuticals and the Medical Research Council of Great Britain. We had complete control over the collection and analysis of the data.

LETTERS TO THE EDITOR

Cerebral metabolism during vegetative state and after recovery to consciousness

One way to approach the study of consciousness is to explore lesional cases in which impairment of consciousness is the prominent clinical sign. Vegetative state is such a condition wherein awareness is abolished whereas arousal persists. It can be diagnosed clinically soon after a brain injury and may be reversible (as in the following case report) or progress to a persistent vegetative state or death. The distinction between vegetative state and persistent vegetative state is that the second is defined as a vegetative state that has continued or endured for at least 1 month.1 We present a patient who developed a vegetative state after carbon monoxide poisoning and in whom we had the opportunity to measure brain glucose metabolism distribution during the vegetative state and after recovery to consciousness. Using [18F]fluorodeoxyglucose (FDG) PET and statistical parametric mapping (SPM) we compared both patient’s sets to a normal control population. Our findings offer an insight into the neural correlates of “awareness”, pointing to a critical role for posterior associative cortices in consciousness.

A 40 year old right handed woman attempted suicide through CO intoxication and was found unconscious. She was treated with hyperbaric oxygen but evolved to a vegetative state diagnosed according to the following criteria:1 (1) spontaneous eye opening without evidence of awareness of the environment; (2) no evidence of reproducible voluntary behavioural responses to any stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness and behaviourally assessed sleep-wake cycles; (5) normal cardiorespiratory function and blood pressure control; (6) preserved pupillary, oculocephalic, corneal, and vestibulo-ocular reflexes. Brain MRI performed 14 days after admission was normal. Electroencephalography showed a 6 Hz basal activity with more pronounced slowing on the left parietal regions. Auditory evoked potentials were normal. Somaesthetic evoked potentials of the median nerve showed normal latency and amplitude of P14 and N20 potentials without any late cortical components. After remaining in a vegetative state for 19 days the patient regained consciousness. Her sequelae consisted of a bilateral spastic paraparesis of upper and lower limbs. Neuropsychological testing 1 month after admission showed an attention deficit with moderate impairment of short term memory. One year after the accident she showed a spastic gait with altered fine motor function, most prominent on the right, a slurred speech, and minor short term memory disturbances. FDG-PET was performed during the vegetative state (day 15 after admission) and after recovery to consciousness (day 57).

The control population consisted of 48 drug free, healthy volunteers, aged from 18 to 76 years (mean: 42 (SD 21) years). The study was approved by the ethics committee of the University of Liége. Informed consent was obtained by the husband of the patient and for all control subjects. Five to 10 mCi FDG was injected intravenously; PET data were obtained on a Siemens CTI 951 R 16/31 scanner in bidimensional mode. Arterial blood samples were drawn during the whole procedure and cerebral metabolic glucose rates (CMRGlu) were calculated for all subjects. PET data were analysed using SPM software (SPM96 version; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The use of SPM to assess between subject (rather than within subject) variability is unlikely to alter the relevance of our results given their high degree of significance. Data from each subject were normalised to a standard stereotactic space and then smoothed with a 16 mm full width half maximum isotropic kernel. The analysis identified brain regions where glucose metabolism was significantly lower in each patient scan compared with the control group. The resulting foci were characterised in terms of peak height over the entire volume analysed at a threshold of corrected p<0.05.

During the vegetative state, average grey matter glucose metabolism was 38% lower than in controls (4.5 ± 7.3 (SD 1.4) mg/100 g/min). No substantial change in mean CMRGlu was found after recovery (4.7 ± 100 g/min). During the vegetative state, significant regional CMRGlu decreases were found in the left and right superior parietal lobule; the left inferior parietal lobule; the precuneus; the left superior occipital, superior and middle temporal gyri; and the premotor and postcentral and precentral cortex (figure, yellow colour). After recovery, metabolic impairment was confined to the left and right precentral and postcentral gyri and premotor cortices (figure, blue colour).

This case report offers an insight into the neural correlates of human consciousness (at least, external awareness as it can be assessed at the patient’s bedside). Given that global glucose utilisation levels remained essentially the same, the recovery of consciousness seems related to a modification of the regional distribution of brain function rather than to the global resumption of cerebral metabolism. The main decreases in metabolism seen during the vegetative state but not after recovery were found in parietal areas, including the precuneus. This is in agreement with postmortem findings in persistent vegetative state, in which involvement of the association cortices is reported as a critical neuroanatomical substrate1 and with PET studies in postanoxic syndrome, in which the parieto-occipital cortex showed the most consistent impairment.2 The functions of these areas are manifold: lateral parietal areas are involved in spatial perception and attention, working memory, mental imagery, and language, whereas the precuneus is activated in episodic memory retrieval, modulation of visual perception by mental imagery, and attention.2 Our data point to a critical role for these posterior associative cortices in the emergence of consciousness experience.


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Electrical inexcitability of nerves and muscles in severe infantile spinal muscular atrophy

Spinal muscular atrophy (SMA) is one of the most common fatal autosomal recessive disorders, characterised by progressive degeneration of anterior horn cells. Before the advent of genetic testing, the diagnosis of SMA was based on clinical, histopathological, and electrophysiological features. In 1992, the International SMA Consortium defined diagnostic criteria of proximal SMA based on clinical findings.1 In SMA type I (severe; Werdnig-Hoffmann disease), affected persons have onset of symptoms before 6 months of age and are never able to sit without support. Electromyography demonstrates denervation features. In early 1995, the candidate gene, the survival motor neuron (SMN) gene, was identified, making the confirmation of SMA by DNA analysis possible.

With the availability of a genetic test for SMA, many investigators are refining the diagnostic criteria published by the Consortium. Studies involving hundreds of patients with SMA have disclosed a subset of patients who fulfil at least one exclusion criterion defined by the Consortium.2 We identified an infant with severe SMA who fulfilled two exclusion criteria and also showed inexcitability of all nerves as well as muscles. This report will further delineate the wide range of phenotypes for this particular gene mutation.

A 2945 g male infant was born at term. First fetal movements were noted at 13 weeks of gestation. Chorionic villus sampling at 10 weeks of gestation disclosed normal chromosomal decreases. Decreased fetal movement and polyhydramnios were noted at about 34 weeks of gestation. At delivery, the infant was cyanotic with no respiratory effort and was subsequently intubated. On physical examination, the infant had no spontaneous movements. He opened his eyes with brief fixation but no following. Tongue fasciculations were present. Other cranial nerves seemed intact. Mild flexion contractures of both elbows, knees, and ankles were noted. Tone was flaccid in the upper and lower limbs, and there was no movement response to painful stimulus. Deep tendon reflexes were absent.

Brain MRI disclosed mild diffuse cortical atrophy. His EMG was severely abnormal, with widespread fibrillations and absent voluntary motor units except in the genioglossus, where mildly neurogenic motor units with decreased recruitment were seen. Stimulation of the median, ulnar, and peroneal nerves with a maximal stimulus resulted in no clinical or electrical response. The biceps brachii and rectus femoris muscles were electrically inexcitable by direct nerve stimulation. Median, ulnar, and sural sensory potentials were not obtainable. DNA testing showed a homozygous deletion of exons 7 and 8 of the telomeric SMN gene, all three siblings showed a large deletion in the region that includes all alleles of the multlocopy markers Ag1-C1 and C212, localised at the 5' end of the two SMN gene copies. It has been postulated that the severity of disease may be correlated to the extent of a deletion involving the SMN gene and the multilocopy markers.1-4 The infant in our report with SMA type I showed electrical inexcitability of motor nerves as well as the characteristic alteration of the SMN gene.

Although it has been known for some time that histological studies that sensory systems are involved in SMA, electrophysiological sensory findings have been previously reported only once. Sensory nerve conduction velocity was tested in a series with severe SMA and showed no recordable potential, but the infant in our report also exhibited universal absence of sensory potentials. In both cases, DNA analysis disclosed the 5q deletion. It is unclear whether this finding represents a distinct entity or merely the severe end of classic Werdnig-Hoffmann disease. The diagnostic criteria produced by the International SMA Consortium currently lists "abnormal sensory nerve conduction potentials" as an exclusion criterion.1 Our finding of absent sensory potentials in a 5q deletion established case of SMA indicates further need for revision of the Consortium criteria.

Sma studies involving large series of patients with SMA have identified cases of SMA variants.1 These patients were diagnosed as infantile SMA by the presence of proximal weakness and atrophy, hypotonia, and evidence of neurogenic alterations in EMG and muscle biopsy. In addition, these patients also exhibited one of the exclusion criteria defined by the Consortium—for example, diaphragmatic weakness, involvement of the CNS, or arthrogryposis. Although these patients did not show the typical SMA deletion and were therefore probably not linked to chromosome 5q, they could have had point mutations. The infant in our report showed no respiratory effort after birth, indicating diaphragmatic weakness. He did, however, preserve the characteristic SMN gene alterations. This finding suggests that diaphragmatic weakness should be reconsidered as an exclusion criterion by the Consortium.

Review of the literature disclosed no previous reports of electrophysiologically inexcitable muscles in SMA. This phenomenon is known to occur in a few other neuromuscular conditions such as periodic paralysis and critical illness polyneuropathy. Fibillations, as seen in the infant in our report, are commonly seen in acute denervation and are thought to be caused by perturbation of the sarcoclemmal membrane, rendering it unstable. One possibility may be that SMA type I denervation in SMA type I can result in abnormal function of the membrane to make it electrically inexcitable. Further electrophysiological studies at the cellular level are required to delineate this interesting finding.

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Acute overdosage and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-O-methyldopa

Although the effects of a chronic overdosage with levodopa are well known, few cases of acute intoxication have been described.1–4 A particular problem in establishing a diagnosis of levodopa overdosage is the relatively short half life in the circulation of levodopa.1 If there is a delay in bringing an acutely intoxicated patient to hospital, perhaps due to late discovery, the blood concentration of levodopa could already be normal, corresponding to the peak levodopa concentration in Parkinson's disease therapy) after 6–8 hours. Depending on the extent of the overdosage, the time could be even shorter. This report describes the clinical effects and the plasma concentrations of levodopa and specific metabolites over a period of 132.5 hours after ingestion of 30 tablets of carbidopa/levodopa (50 mg/200 mg tablets).

A 76 year old patient had a pre-existing mild akinetic rigid Parkinson's syndrome, which had been treated for the past 1.5 years with 3×1 tablets of carbidopa/levodopa (50 mg/200 mg) a day without a substantial response. The weight of the patient was 74 kg. A known chronic obstructive airway disease was treated with a home oxygen appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 0.00 hours he appeared psychically altered, crying without reason, anxious, and depressed. After about 30 minutes he was increasingly inadequate, with rest, and subepisodic and was experiencing visual hallucinations; he was restless, tossing and turning, and getting out of bed. He did not represent peak dose dyskinesia or other extrapyramidal clinical features. At 10.00 pm he showed bilaterally maximally dilated pupils. The muscle stretch reflexes were lively, there were no pyramidal tract signs, and he did not show any signs of Parkinson's syndrome or dyskinesia. Arterial hypotension and sinus tachycardia could be registered.

After an empty box of Striaton (carbidopa/levodopa, 50 mg/200 mg) was found in the patient's flat, 1 g of carbon was given by stomach tube after gastric lavage. At 11.00 pm the patient was moved to the medical intensive care unit and observed for 24 hours. The ECG showed a P pulmonale, but no other unusual features. Echocardiography showed normal right and left ventricular function with suspicion of right ventricular hypertro-

References

Distribution into muscles rather than metabolism may largely determine the plasma half-life of levodopa and explain why this was only slightly altered with overdose. The measured peak concentration of 66 763 ng/ml is about 30 times higher than the peak concentration to be expected after taking one tablet of carbidopa/levodopa (50 mg/200 mg). It is apparent that the 30 tablets did not interfere with absorption or lead to a gastrointestinal paralysis due to the high dose of levodopa; the relation between amount ingested and plasma concentration seems to be linear, at least in this dose range.

We conclude from these findings that in cases of suspected levodopa intoxication some hours previously, it could be important to measure the concentration of 3-o-methyldopa, so as not to overlook an overdose with levodopa, which may be due to a suicide attempt. In addition to the diagnostic uncertainty in relation to the immediate treatment of the patient, this would also have an effect on further psychiatric and psychological therapy.

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The use of olanzapine for movement disorder in Huntington's disease: a first case report

Movement disorder is a prominent feature of Huntington's disease and consists of involuntary and voluntary components as well as associated bradykinesia. Pharmacological treatment is problematic because of the side effects of the drugs used, which may further compromise cognitive functioning and mobility. Patients are often not subjectively aware of their movements but can be considered disabled by them and carers are often distressed and enquire about treatment options. If drug treatment is considered it is important to achieve the maximum improvement in movements with the minimum of negative side effects. This paper describes the effect of olanzapine on movements when other treatment options had been ineffective or limited by side effects.

Huntington's disease is a hereditary progressive neurodegenerative disorder. It consists of a triad of symptoms comprising motor, psychological, and cognitive abnormalities. The motor component consists of involuntary choreiform movements and increasing difficulties with voluntary movement. The degree of the involuntary movements is variable but in some patients can be very marked. Progression over time of the movement disorder in Huntington's disease can be monitored using the quantitative neurological examination (QNE). This measure has three subscales, an eye movement scale, a motor impairment scale (MIS) quantifying voluntary movement, and a depressive scale measuring involuntary movement.

Pharmacological control of the symptoms has been shown to be effective with dopamine antagonists, but their use is limited because of the side effects. Clinically the most problematic of these are sedation, cognitive slowing, increased mobility problems, and hypotension. The inability of traditional dopaminergic antagonists to improve functional capacity, despite amelioration of the parkinsonian symptoms, is probably due to suppression of voluntary motor activity. Tardive dyskinesia has occasionally been reported in patients with Huntington's disease treated with these drugs. The atypical antipsychotic clozapine has been shown to be effective in improving the movement disorder. However, in a double blind randomised trial of clozapine which included patients who were already receiving traditional antipsychotic medication, only one group who had not received drug treatments for their movement disorder, chorea, was reduced in those who were antipsychotic naive only and the authors concluded that clozapine was of little added value in Huntington's disease. Olanzapine is a new atypical antipsychotic drug. It is a thienobenzodiazepine structurally very similar to clozapine. Unlike clozapine it is not associated with the potentially serious side effects of agranulocytosis and therefore frequent blood monitoring is not necessary.

This report describes the progress of a man who has Huntington's disease. He developed a marked movement disorder and was unable to tolerate both sulphpride and risperidone but had symptomatic improvement when treated with olanzapine.

He is a man in his early 50s who had a confirmatory genetic test for Huntington's disease in 1994, after the development of clinically obvious motor symptoms. It is likely that the onset of symptoms had occurred a few years previously as he had experienced difficulties in concentration, at work, attributed at the time to stress, leading to the loss of employment. In addition he has a family, watching family videos of a few years earlier, thought that there were early signs of his movement disorder. However there was no known family history of Huntington's disease which might have led to an earlier diagnosis. By May 1995 his involuntary movements were becoming more noticeable, although control of voluntary movement was good. A trial of sulpiride commencing at 200 mg twice daily and increasing over 1 week to 800 mg daily was undertaken with a subsequent decrease in the frequency and extent of involuntary movement recorded in case notes; unfortunately the QNE was not repeated at this time. However, the patient experienced a subjective slowing of his cognitive processes, concurrently became depressed, and decided to stop the treatment within 3 weeks. Paroxetine, a selective serotonin reuptake inhibitor antidepressant, was started at a dose of 20 mg a day, which led to an improvement in his low mood. His involuntary movements continued to cause difficulties in his daily living. He was unable to sit comfortably in a chair and when out he felt that he was being watched, knocking into them. He agreed to a trial of
risperidone. This was started at a dose of 1mg twice daily, increasing to a dose of 1mg four times a day over a period of 2 weeks, stopped after a brief period. He developed hypotension (blood pressure 100/60 mm Hg), complaining of dizziness after the initial dose. His blood pressure remained stable, although low, after this and as there was improvement in his movements the drug was continued. However, he decided to stop the risperidone after 4 months because of his subjective experience of slowed thinking and occasional dizziness. A repeated trial of sulpiride was carried out in March 1997. Sulpiride was started at a dose of 200 mg twice a day and increased to a total daily dose of 1000 mg over 2 weeks. He was on sulpiride for 4 weeks with no improvement in his movements, so it was discontinued. The patient continued to experience low mood and after the discontinuation of sulpiride, his antidepresant drug was changed to lofepramine commencing at 70 mg once a day and increasing after a few days to 140 mg daily. There were no changes noted in his movements during this change. Although the patient was subjectively unaware of the extent of his movements his everyday life continued to be affected. The social venues he felt able to attend were becoming more limited and activities he wanted to pursue such as travelling abroad by air were problematic. A trial of olanzapine was then instituted. He was started on 5 mg a day in the morning. There was a marked improvement in his involuntary movements within 1 week but once again he experienced slowed thinking. However, adjusting the time of medication to the evening led to an improvement in this. Six months later the improvement in his involuntary movements is maintained. Serial quantitative neurological examination scores are illustrated in figure 1.

In the absence of a cure for Huntington's disease, it is very important that any interventions considered enhance the quality of life of the patient and improve overall functioning. It may not always be in the best interests of the patient to use drug treatments for the movement disorder. In those patients who have severe movements, however, a trial of treatment may be appropriate and continued if a clear benefit has been achieved. Neurological monitoring and the patient's own perception of the effect of the drug must be taken into account.

The mechanism by which olanzapine may have beneficial effects is unclear. Olanzapine has been shown to have high affinity for a large number of receptors including D1, D2, D4, 5HT2A, 5HT2C, 5 HT3, α-1-adrenergic, histamine H1, and 5 muscarinic receptors. This binding profile is similar to clozapine, another atypical antipsychotic drug, but substantially different to the conventional antipsychotic haloperidol.1 Preferential loss of D2 projection neurons which are involved in a feedback loop normally active in the suppression of involuntary movements is thought to be the pathophysiological basis of chorea in patients with Huntington's disease.2 The D2 antagonist properties of olanzapine may explain its possible benefits in the improvement of chorea. However, the effect at other receptors such as D4 may also be important, as D4 receptor density has been shown to be raised in Huntington's disease, therefore the D4/D2 ratio of activity may also be relevant. Differences in binding profile across a range of receptors may explain clinical differences in outcome when comparing different antipsychotic drugs.

This case report indicates that olanzapine may be a useful addition to the treatments for movement disorder, for some patients, and controlled trials of its use in Huntington's disease would be welcome.

**Patient characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at surgery</th>
<th>Sex</th>
<th>Years with PD</th>
<th>H and Y*</th>
<th>UPDRS off</th>
<th>putalidotomy</th>
<th>Pallidotome side</th>
<th>Transient side effects</th>
<th>Medication additional to levodopa</th>
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<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>8</td>
<td>2/5</td>
<td>57/NP</td>
<td>R</td>
<td>L</td>
<td>Slight facial paresis, swallowing problems, drooling</td>
<td>Trzyptirol, remazepam, alprazolam, apomorphine</td>
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<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>7</td>
<td>2/2.5</td>
<td>24/NP</td>
<td>L</td>
<td>L</td>
<td>Slight dysarthria</td>
<td>Trihexifenidyl</td>
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<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>15</td>
<td>2/3</td>
<td>55/NP</td>
<td>L</td>
<td>L</td>
<td>Facial paresis</td>
<td>Perigolide, amantadine</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>12</td>
<td>2/2</td>
<td>40/22</td>
<td>L</td>
<td>L</td>
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<td>Selegeline, biperiden</td>
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<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>14</td>
<td>2/5.4</td>
<td>69/36</td>
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<td>L</td>
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<td>Perigolide, selegeline</td>
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<td>58</td>
<td>M</td>
<td>13</td>
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<td>Facial paresis, aphasia</td>
<td>Selegeline, biperiden</td>
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<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>15</td>
<td>2.5/4</td>
<td>55/NP</td>
<td>L</td>
<td>L</td>
<td></td>
<td>Clozapine, temazepam, cisapride</td>
</tr>
</tbody>
</table>


**Transient hiccup after posteroventral pallidotomy for Parkinson's disease**

Hiccup is defined as an abrupt intermittent, involuntary, contraction of the diaphragmatic and external (inspiratory) intercostal muscles, with inhibition of expiratory intercostal activity. This results in a sudden inspiration, abruptly opposed by closure of the glottis.1 Hiccup may result from various structural or functional disorders of the medulla, the afferent or efferent nerves to the respiratory muscles, and the gastrointestinal tract.1,2 Newson Davis performed a study of hiccup with electrophysiological techniques and concluded that hiccup is served by a supraspinal mechanism distinct from that generating rhythmic breathing.3 The principal site of interaction of the hiccup discharge with other descending drives to the respiratory motoneuron is at the spinal level. Neurogenic hiccup is particularly associated with structural lesions of the medulla oblongata.

Since 1994 we have performed 66 pallidotomies for Parkinson's disease in 60 patients. So far, we have seen transient hiccups in seven patients after the operation (table). Our target coordinates for the posteroventral globus pallidus at the border of the medial and lateral segments are 2–3 mm anterior to the midcommissural point, 5 mm below the intercommissural line and 22 mm lateral to the midline of the third ventricle. Ventriculography was performed for target

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**Quantitative neurological examination scores showing the progress of the movement disorder. 06/95: before trial sulpiride, no medication; 05/96: before risperidone, 20 mg paroxetine daily; 07/96: 1 mg risperidone four times daily and 20 mg paroxetine daily; 03/97: before retrial sulpiride, 20 mg paroxetine daily; 04/97: 400 mg sulpiride in the morning, 600 mg at night and 20 mg paroxetine; 04/97: before olanzapine, 140 mg lofepramine daily; 06/97: 5 mg olanzapine at night, 140 mg lofepramine daily.**
localisation. Patients started with a short schedule of corticosteroids (5 days) the night before surgery.

The hiccups started immediately after the operation or the next day, were intermittent, and the bouts of hiccup of six patients, with a duration of hours, resolved within 3 days after the procedure. One patient complained of yawning more often and frequent bouts of hiccup for 6 months.

Five patients were men. All patients were right handed. The mean age at surgery was 54 years and the mean duration of Parkinson’s disease was 12 years. All patients were taking levodopa. In four patients the hiccups appeared after a left sided pallidotomy. Patient 2 had a right sided thalamotomy 4 years before the pallidotomy. Patient 5 underwent a left sided pallidotomy 10 months before the right sided pallidotomy which caused the hiccups. The pallidotomies improved parkinsonism in the “off” state (table), contralateral dyskinesias, and pain accompanying Parkinson’s disease. Six patients had transient adverse events: four patients had a transient facial paresis postoperatively and two a slight transient dysarthria. Two patients had choreatic movements after the pallidotomy and the contralateral side which resolved spontaneously within 2 hours and is associated with a favourable surgical outcome.3 Postoperative MR scans were obtained in the first six patients, and showed that in five patients the lesions were located in the posterior part of the globus pallidus pars externa (GPe) and interna (figure). In patient 5 the lesion was situated slightly more anterior in the GPe and putamen. In patient 3 there was a small separate lesion more dorsal, probably an infarct.

We never encountered hiccups in 150 other stereotactic procedures for Parkinson’s disease, such as thalamotomies or deep brain stimulation electrode implantation in the thalamus and therefore it is unlikely that medication or positive contrast medium ventriculography with Iohexol evoked the hiccups. A possible cause for the transient hiccups could be the lesion in the ventral medial segment of the globus pallidus or pressure, due to oedema, on an adjacent structure like the internal capsule or putamen. We could not find other reports of hiccups as an adverse event after functional stereotactic surgical interventions, nor after lesions of other aetiology involving the striatum.4 Based on our experience we hypothesise that the globus pallidus or a neighbouring structure may be involved in a supramedullary system involved in triggering hiccups.

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5 Bathia KP, Marsden CD. The behavioral and motor consequences of local lesions of the basal ganglia in man. Brain 1994;117:859–76.

Psychological adjustment and self-reported coping in stroke survivors with and without emotionalism

Emotionalism after stroke is common, occurring in 10%–20% of a community sample.1 Psychological factors in its cause or maintenance have not been studied; research has tended to concentrate instead on location of the stroke lesion. We suspect that one reason for this neglect of psychological aspects of emotionalism is that most people do not make a distinction between emotionalism, and pathological crying and laughing. As a result all disorders of emotionality after stroke are stereotyped as being related to brain damage and therefore psychologically meaningless.

None the less, many patients with emotionalism describe their crying as provoked by emotionally congruent experiences, which makes the tearfulness seem understandable.1 In two previous studies2 we have shown that stroke patients with emotionalism have more symptoms of psychological disorder than do patients without emotionalism. In the present study, we explored further the psychological characteristics of stroke patients with emotionalism. Our aim was to determine whether they differed from patients without emotionalism in their psychological reactions to stroke, or in the coping strategies they reported.

Post-traumatic stress disorder is also characterised by recurrent episodes of intrusive and uncontrollable emotion, and we were therefore interested in whether patients with emotionalism also experienced intrusive thoughts typical of post-traumatic stress disorder. Because emotionalism is often described as uncontrollable, we were interested in the possibility that patients were more generally helpless, passive, or avoidant in their responses to stroke. Again, because of the reported uncontrollability of emotionalism, we postulated that patients with emotionalism would report a more external locus of control than those without emotionalism.

Participants were adults admitted to local general hospitals after stroke, and were interviewed within 1 month of admission. Exclusions were due to poor physical health, cognitive impairment, communication difficulties, or lack of consent. Approval for the study was obtained from the local research ethics committees.

All participants completed a standardised measure of distress—the general health questionnaire, GHQ-12; a widely used measure of intrusive thoughts of the sort encountered in post-traumatic stress disorder—the impact of events rating scale;4 a measure of cognitive coping—the mental adjustment to stroke scale (O’Rourke S, Dennis M, MacHale S, Slattery J. The development of the mental adjustment to stroke scale: reliability, patient outcome and associations with mood and social activity, manuscript in preparation); and a measure of beliefs about responsibility for recovery from illness—the recovery locus of control scale.5 All the measures are self-report questionnaires.

A total of 177 stroke patients were screened, of whom 112 were excluded. The 65 participants (29 men, 36 women) had a mean age of 71.8 years (range 43 to 88 years). Nineteen (29.2%) patients met our criterion for emotionalism,1 a rate similar to that found in other studies. Their scores on the study measures are compared with the scores of patients without emotionalism in the table. It might be that these associations with emotionalism were accounted for by the greater general levels of distress experienced by those with emotionalism. We therefore undertook analysis of covariance with GHQ-12 and presence of emotionalism as the covariates, and each of the other test items in turn as the independent variable. The results showed an association, after adjustment for GHQ-12 score, between emotionalism and the impact of events subscales intrusions.
Comparison of stroke survivors with and without emotionalism, assessed in hospital 1 month after stroke

**MASS Helplessness/hopelessness subscale** 10.9 (2.5) 14.1 (3.5)

**GHQ-12** 3.2 (2.4) 5.3 (3.5)

**Recovery locus of control scale** 33.2 (3.3) 34.2 (3.7)

**Impact of events scale intrusion subscale** 2.9 (4.6) 9.2 (6.6)

**Impact of events scale avoidance subscale** 4.7 (4.6) 9.9 (6.1)

**MASS Anxiety preoccupation subscale** 49.1 (4.2) 48.6 (4.2)

**MASS Fatalism subscale** 22.2 (2.8) 25.2 (4.0)

**MASS Avoidance subscale** 20.0 (1.9) 21.3 (2.2)

**Mass = Mental adjustment to stroke scale**.

\(F=15.33, \ p<0.001\), and avoidance \((F=11.84, \ p<0.001)\); the mental adjustment to stroke scale subscales helplessness/hopelessness \((F=11.71, \ p=0.001)\) and anxious preoccupation \((F=8.05, \ p=0.006)\). The associations with fatalism \((F=14.79, \ p<0.052)\) and avoidance \((F=0.06, \ p=0.8)\) on the mental adjustment to stroke scale were no longer significant after adjustment for GHQ-12 score.

We thank those patients who participated in the study and the staff of local hospitals and the Leeds Stroke Database for their invaluable help. We also thank Dr Louise Dye for her statistical advice. This study was completed as part of work for the degree of DClinPsych at Leeds University (SE).

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Paraneoplastic stiff limb syndrome

Stiff man syndrome (SMS) is a rare, severe progressive motor disorder characterised by painful spasms, symmetric axial muscle rigidity, and uncontrollable contractions leading to distorted posturing. The disorder has been associated with the autoantigens, glutamic acid decarboxylase (GAD), and amphiophysin, which are cytoplasmic proteins in neurons of the CNS. A large series of patients with SMS found that most have autoantibodies against GAD, whereas amphiophysin is presumably the predominant autoantigen in paraneoplastic SMS. Recently, Barker et al. proposed that the nomenclature

"stiff limb syndrome" refers to the focal form of SMS when one or more distal limbs are involved; two of their patients were also anti-GAD antibody positive, but none were tested for antibodies to amphiophysin or identified as having an underlying neoplasm. We present a patient clinically consistent with paraneoplastic SMS who was found to have autoantibody to GAD and breast cancer. A 68 year old woman presented with a 1 month history of painful spasms in her legs. Cramps were associated with tactile stimuli and emotional upset. Within weeks, inversion began at the left and then right ankle, making ambulation difficult. Her medical history was significant for Graves’ disease treated with thionamide and radioactive therapy, and hyperlipidaemia. She was a chronic smoker. General examination was noteworthy for lymphadenopathy in the right axilla. Her mental status was worse during periods of lower extremity spasms, during which she became anxious, diaphoretic, and tachycardic. Cranial nerve and motor evaluations were unremarkable, but assessment of the left leg, due to painful spasms elicited by light touch, was difficult. Inversion and plantar flexion were essentially fixed at the left ankle, but could be overcome on the right. Deep tendon reflexes were 3+ in the upper and lower extremities, with sustained clonus at the right ankle. Sensory examination and spinal flare were normal. The exception of hyperesthesia in the distal lower extremities, and coordination testing were grossly normal. No hyperlordosis or myoclonus was noted. Gait was limited due to ankle posturing.

The laboratory evaluation was noteworthy for a CSF with increased IgG indices (2.5, 3.4; normal, 0.2–0.8) and oligoclonal bands (3, 5) but no pleocytosis. Serological testing for anti-Hu, anti-Yo, and anti-Ri antibodies was unremarkable, and the haemoglobin A1C was 6.6 (5.6–7.7%). Skin biopsy at three sites on the patient’s leg showed diminished epidermal nerve fibre density and terminal axonal swelling distally, consistent with a small fibre sensory neuropathy. The patient was not recommended EMG. Magnetic resonance images of the brain and the entire spinal cord were normal. Fine needle aspiration of the left abdominal wall revealed a metastatic adenocarcinoma. On an open surgical procedure, infiltrating duct carcinoma of the breast was identified. Anti-GAD antibodies were positive by the chemical assay and immunoprecipitation, but antibodies to amphiophysin were not detected by immunocytochemistry, immunoprecipitation, or western blotting (Dr P De Camilli, Yale University).

Ongoing therapy with clonazepam and a trial of oral dexamethasone did not improve the lower extremity symptoms. The patient’s ankle posturing continued a slow progression to marked inversion, with spontaneous extension of hallucis longus. The patient died 18 months after symptom onset. Gross necropsy attributed the cause of death to aspiration pneumonia. Neuropathological evaluation showed a grossly normal spinal cord. Microscopically, the lumbar cord had mild reactive gliosis in the anterior horns but no evidence of inflammation. Sections of the frontal cortex, pons, and medulla showed mild diffuse reactive astrocytosis.

Stiff man syndrome is increasingly recognised as a heterogeneous disorder. Other case reports have documented patients with “focal” disease involving either lower or upper extremity posturing, which contrast
with the “diffuse” axial and subsequent proximal muscle distribution of the classic disorder.

Our patient differs from those reported with stiff leg syndrome in that an occult malignancy was present. Unfortunately, we were unable to obtain electrophysiological studies for comparison. The search for a paraneoplastic process was based on the findings of axillary lymphadenopathy and an abnormal CSF. Our patient is only the second reported patient with paraneoplastic SMS associated with anti-GAD antibody; the other had upper limb rigidity in the setting of breast cancer.

For a paraneoplastic process was based on the patient's findings of axillary lymphadenopathy and an abnormal CSF. Our patient is only the second patient with paraneoplastic SMS associated with anti-GAD antibody; the other had upper limb rigidity in the setting of breast cancer. A neurological evaluation by skin biopsy. J Neurol Neurosurg Psychiatry 1990;51:633–40.

Electrophysiologic examination suggested by its binding to dynamin in nerve terminals. Proc Natl Acad Sci USA 1997;94:1555–60.


Tetrad toxin intoxication in a uraemic patient

Tetrad toxin intoxication results from ingest- ing puffer fish or other animals containing the toxin. Clinical presentation is mainly acute motor weakness and respiratory paralysis. Death is common in the worst affected victims. Although the severity of the symp- toms generally depends on the amount of toxin ingested, it may be influenced by the victim's medical condition, as described in this report. The patient was a 52 year old uraemic woman. The uraemia was of undif- fered aetiology. Over the past 3 years she has received regular haemodialysis. One day both she and her husband, a healthy 55 year old man, ate a fish soup. About 12 hours after the meal she developed a headache and a lingual and circumoral tingling sensation and num- kinds at the distal parts of all four limbs. She was dizzy and unsteady, had difficulty in swallowing, and became very weak. She was taken to the emergency service and was placed on machine assisted ventilation as respir- itory distress and cyanosis developed. Her husband remained asymptomatic throughout this time.

The patient's condition kept on deteriorating, developing eventually into a comatous- like state with no spontaneous or reflexive eye opening or limb movement within 30 min- utes of intubation. On neurological examina- tion, the pupillary light reflex was absent and oculocephalic manoeuvre elicited no ocular movements. All four limbs were areflexic and Babinski's signs were absent. Brain CT and laboratory studies of arterial blood gas (under assisted ventilation), electrolytes, liver func- tion, blood glucose, and CSF study were unremarkable. An examination of renal func- tion indicated chronic renal insufficiency with mild azotaemia (urea nitrogen 70 mg/dl, creatinine 9.1 mg/dl). An EEG, recorded 18 hours after the onset of symptoms when the neurological condition was unchanged, showed posterior dominant alpha waves intermixing with trains of short duration, diff- use theta waves. When brief noxious stimuli were applied to the sternum, they were replaced transiently by beta activities. The findings suggested that the profound neuro- logical dysfunction might be peripheral in origin. The patient was given a course of haemodialysis according to the set schedule for uraemia at 21 hours after onset of the symptoms. Her condition improved dramati-
ably within an hour. She could open her eyes and she communicated and answered questions correctly by blinking. Pupillary reflex recovered and voluntary eye movements were limited only at the extreme lateral gaze. Muscle power was grade 3 and 4 in the proximal and distal parts of the four limbs. Tendon reflexes were absent. She was taken off mechanical ventilation the next day. Her clinical condition continued to improve and her symptoms subsided in a stepwise pattern, in response to each course of haemodialysis (figure). When recalling, she could remember certain events such as the recording of the EEG, but was “too weak to move” at that time. She regained her initial strength by the time she was discharged on day 16.

When analysing the remains of the cooked fish (identified as *Ogcocephalus naso*), tetrodotoxin was demonstrated by thin layer chromatography, high performance liquid chromatography, and cellulose acetate membrane electrophoresis. Toxicity was assayed by using Institute of Cancer Research strain adult male mice and the toxicity score was 25 mouse units (MU)/g in fish muscle (1 MU = 0.178 µg) of the ICR strain mouse). Tetrodotoxin exerts its effect through binding with and blocking the voltage dependent sodium channel. The voltage clamp experiments showed that tetrodotoxin diminished the sodium inward current responsible for the depolarization of excita-
tory membrane. The gating properties of the sodium channel, such as the activation and inactivation mechanism, are not altered—that is, the sodium channel is not perm-
amently damaged and its function recovers when the bound toxin is released. In uraeinia, ion conductance through the sodium channel is also impaired. Sodium permeability through excitory membranes is reduced and small inward sodium current and re-
duced action potential amplitudes are noted in experimental uraeinic neuropathy. By contrast with the effects of tetrodotoxin, uraeinia changes the basic property of the sodium channel by an increased inactivation and an impaired activation mechanism. The excitability of peripheral nerves will be more significantly depressed when these two conditions coexist, because the synergistic effect of uraeinia and tetrodotoxin is obvious in this incident in which the patient and her husband ingested roughly an equal amount of tetrodotoxin (about 200 µg, calculated from toxic score times the weight of ingested fish). The amount is about 10% of the estimated lethal dose in humans—2200 µg/60 kg body weight (body weights of the patient and her husband were 54.5 and 62 kg respectively)—and caused no clinical evidence of poisoning in the healthy person. It was of interest that the CNS was relatively spared from the toxicity as the EEG showed a posterior dominant, promptly reactive alpha rhythm and the patient retained consciousness when the symptoms were at their most severe.

One of the most striking clinical features in our patient was the response to haemodialysis. Despite the small amount of tetrodotoxin ingested, the dramatic improvement of her clinical condition was most likely attributed to the rapid elimination of absorbed toxin in the course of haemodialysis, rather than spontaneous recovery. The physical and chemical properties of tetrodotoxin are also supportive to this hypothesis. It has a low molecular weight (C11H17N3O8), is water soluble, and not significantly bound to protein—all these features are found common to toxins amenable to haemodialysis. Traditionally, the management of tetrodotoxin intoxication is mainly supportive, such as gastric lavage to remove unabsorbed toxin and machine as-
sisted ventilation when respiration is severely affected. We suggest that haemodialysis may be an effective method in the treatment of tetrodotoxin intoxication.

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3 Brismar T, Tegner R. Experimental uraeinic neu-
4 Tani I. Toxological studies of puffers in Japan. Teshokan-Tsusho (Tokyo) 1945:103.

Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome

The clinical entity critical illness polyneuropa-
athy occurs almost exclusively in patients in critical care units and has been character-
ised as a complication of sepsis and multiple
minor illness or inoculation. Except for sepsis, but in Guillain-Barré syndrome there is a brief period of recovery after a relatively minor illness or inoculation. Critical illness polyneuropathy may be a common cause of the difficulty in weaning patients from the ventilator, particularly those who show intractable ventilator dependence. All the measures used to prevent or treat this severe complication of multiple organ failure are the main methods now used to deal with critical illness polyneuropathy. Knowledge of this type of polyneuropathy is of help in making clinical respiratory, nursing care, prognosis, and overall management. Moreover, recognition of critical illness polyneuropathy indicates the need for physiotherapy, rehabilitation, and other supportive measures as the patient recovers. Bolton et al have made an impor-
tant positive contribution to the care of patients with critical illness polyneuropathy. The actual aetiology, however, has yet to be determined. The pathogenesis needs to be further clarified to treat patients more effectively.

Critical illness polyneuropathy invariably occurs at the peak of critical illness and sepsis, but in Guillain-Barré syndrome there is a brief period of recovery after a relatively minor illness or inoculation. Critical illness polyneuropathy is considered as having early axonal degeneration and demyelination. Patients with Guillain-Barré syndrome who were studied in their EMG laboratory, they found marked differ-
ces between the two types of polyneuropath-
y. Patients with Guillain-Barré syndrome had greater slowing of the speed of impulse conduction, and, in the initial stages, abnor-
mal spontaneous activity in the muscle was absent, indicative of a predominantly demy-
elinating polyneuropathy. The CSF was only mildly increased in patients with critical illness polyneuropathy, but it was much increased in patients with Guillain-Barré syndrome. Comprehensive studies done at necropsy and nerve biopsies of patients with critical illness polyneuropathy showed the presence of primary axonal degeneration of the motor and sensory fibres, mainly distally, with no evidence of inflammation. Zochodne et al (excluding Bolton) therefore concluded that the two types of polyneuropathies most probably are separate entities.

Guillain and colleagues enumerated the clinical and spinal fluid features of a patient with acute flaccid paralysis without regard for the underlying pathology or pathology. Clas-
ic pathological studies of Guillain-Barré syndrome, however, have identified promi-
tent demyelination and inflammatory infil-
trates in the spinal roots and nerves. Guillain-Barré syndrome often has been considered to be synonymous with the pathological desig-
nation of acute inflammatory demyelinating polyneuropathy, and patholo-
comings consistent with demyelination have been taken as supportive evidence for the diagnosis of Guillain-Barré syndrome. Feasby et al (excluding Bolton) therefore directed the attention to patients who were clinically con-
sidered as having Guillain-Barré syndrome, but who were characterised electrophysi-
ologically as having early axonal degeneration of the motor and sensory nerve fibres. The evidence included a rapid fall in compound muscle action potentials and sensory nerve action potentials, and no evidence of demyelination. Such patients often had severe paralysis and may have a slow recovery, presumably reflecting the need to regenerate axons rather than remyelination. Pathological find-
ings are consistent with axonal degeneration without demyelination. Feasby et al termed this pattern axonal Guillain-Barré syndrome and suggested that there is a fundamental difference in the underlying pathophysiology, resulting in primary axonal damage rather than demyelination. Griffin et al then con-
firmed the existence of the acute motor-
sensory axonal neuropathy (AMSAN) pat-
tern of Guillain-Barré syndrome described by Feasby et al. Infection caused by the gram negative bac-
terium *Campylobacter jejuni*, a leading cause
of acute diarrhoea, commonly precedes the development of Guillain-Barré syndrome.1 There is a close association between axonal Guillain-Barré syndrome and antecedent C jejuni infection.3 The antecedent infectious symptom was diarrhoea in three of five patients with axonal Guillain-Barré syndrome described by Feasby et al. Observations by Griffin et al2 confirmed that AMSAN follows C jejuni infection. Serum samples from patients with axonal Guillain-Barré syndrome subsequent to C jejuni enteritis often have detectable class autoantibodies to gangliosides GM1, GM1b, GD1a, or GalNAc-GD1a in the acute phase of the illness, and there is molecular mimicry between these gangliosides and the lipopoly-saccharides of C jejuni isolates from patients with Guillain-Barré syndrome. This ganglioside mimicry may trigger high production of the IgG anti-ganglioside antibodies, and these autoantibodies may cause motor nerve dysfunction in patients with GBS.

Interestingly, Hagensee et al4 reported a case of "C jejuni bacteremia and subsequent Guillain-Barré syndrome" that occurred in a patient with chronic graft versus host disease and severe aplastic anemia following transplantation. Because there was acute flaccid paralysis associated with sepsis, some physicians might have diagnosed critical illness polyneuropathy. Conversely, the existence of this case strongly suggests that some diagnosis of critical illness polyneuropathy should actually be axonal Guillain-Barré syndrome or AMSAN. Our hypothesis of the nosological relation between critical illness polyneuropathy and Guillain-Barré syndrome is shown in the figure. Serum IgG antibodies against GM1, GM1b, GD1a, or GalNAc-GD1a could be used as immunological markers for axonal Guillain-Barré syndrome.5 To examine the aetiology of critical illness polyneuropathy and its nosological relation to axonal Guillain-Barré syndrome, it is necessary to investigate whether patients with critical illness polyneuropathy have anti-ganglioside antibodies during the acute phase of the illness.

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Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study

Recently, a new technology known as repetitive transcranial magnetic stimulation (RTMS) has been developed.1 In 1994, the use of magnetic stimulation in clinical psychiatry was suggested.2 Since then, it has been used in the study or treatment of obsessive-compulsive disorder, conversion disorder, schizophrenia, and particularly, depression.3

Our pilot study aimed to assess the possible adverse effects of this treatment in chronic schizophrenic patients with severe negative symptoms; to evaluate if direct RTMS of the prefrontal cortex might improve negative symptoms or cognitive impairments in patients with chronic schizophrenia; and thirdly, to note if RTMS might modify the deficit in prefrontal cortical activity, often reported to hypertend to be established in schizophrenia,4 specially under conditions of task activation.

Six right-handed patients with chronic schizophrenia were identified at the outpatient psychiatric clinic of the Hospital Clinic of Barcelona. There were two men and four women (mean age 39).

Exclusion criteria included alcohol or substance abuse dependence disorder in the past 5 years, focal neurological disorder, systemic neurological illness, taking cerebral metabolic activator or vasodilator medications, electro-convulsive therapy within 6 months, and significant abnormal findings on laboratory examination.

All patients were taking neuroleptic drugs, but a stable dose for at least 3 months was required. All patients were studied off benzodiazepines for at least 1 week before beginning the treatment. During the RTMS, psychotropic medications were continued at the initial dosage.

All patients were admitted to hospital. Inpatients underwent the UKU side effect scale,2 the positive and negative syndrome scale (PANSS), and a neuropsychological battery, the day before beginning the treatment and at the end of the treatment. The UKU scale was also administered after each session.

An equivalent neuropsychological battery was used on both occasions, which consisted of the blocks test, the Trail making test, the Wisconsin card sorting test (WCST), the FAS verbal fluency test, and two subtests of the Wechsler memory scale (the visual memory reproduction and the verbal paired associates subtest).

A brain SPECT study was performed using a rotating dual head gamma camera, fitted with high resolution fanbeam collimators. Two Tc-HMPAO SPECT scans with cognitive activation, such as the Wisconsin card sorting test (WCST), were performed on each patient (24 hours before the beginning of the treatment and 24 hours after the last session).

RTMS was given with a Mag Pro magnetic stimulator, 5 days a week, during 2 weeks, at a constant intensity of 110% of the stimulation threshold, with minimal side effects (mild headache and tinnitus).

Table Neuropsychological tests and PANSS scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Block design</td>
<td>Pre 49 (11.95) NS Post 50 (8.69) NS</td>
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| Trail making test | A Pre 38.3 (4.5) NS Post 42.6 (14.1) NS B Pre 38.3 (4.5) NS Post 41 (10.03) NS Immediate visual reproduction | Delayed visual reproduction Pre 64.2 (6.23) p<0.05 Post 53.8 (12.46) p<0.05 Immediate verbal paired associates Delayed verbal paired associates | Pre 8.8 (1.17) NS Post 8.8 (1.17) NS PANSS-PG Pre 37.67 (11.15) NS Post 36.5 (11.47) p<0.02 PANSS-N Pre 31.67 (8.20) NS Post 27.83 (8.47) p<0.02 PANSS-P Post 16.83 (7.28) NS Post 15.33 (7.55) p<0.02
| p<0.02 | p<0.02 |
| NS | NS |

In 1994, the path of research was changed under the direction of the Wechsler. The Trail making test was always within the normal range) diminished their number of perseverative answers (which was usually significant) explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, although there are methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

We found that all patients (except one, who was always within the normal range) diminished their number of perseverative answers and errors on WCST (items characteristically altered in schizophrenia) after the RTMS. However, significance was not achieved on any WCST scores.

Two patients who initially did not perform any categories on WCST, after the treatment, achieved one category, a possible indication of improvement of their abstract thinking. This change leads us to consider a research strategy previously reported in which the WCST is used as a screening test for selecting schizophrenic patients. Those initially achieving low category scores would be compared to higher category scorers in an effort to identify a subgroup most likely to benefit from RTMS.

Taking into account these mild improvements together, and the lack of changes in


2 Zochodne DW, Bolton CF, Wells GA, et al. Brain SPECT study was performed A and B, the FAS verbal fluency test, and two of the block design subtest of the Wechsler battery, the day before beginning the treatment. During the RTMS, psychotropic medications were continued at the initial dosage.


Sensory alien hand syndrome

The case report by Ay et al. of alien hand syndrome and review of the literature neglected the intriguing issue of why in every case so far reported the patient seems to be terrified of the alien limb. Not believing that you are any more in control of a limb is not likely to be a pleasant experience.

Those with alien hand syndrome seem to jump to extremely negative conclusions concerning the intent of the limb. Typically, as in the report of Ay et al., the common belief is that the limb has deeply malevolent intentions towards the victim.

It is this aspect of alien hand syndrome that I suggest also needs incorporating into its neurological explanations, and which provides a clue as to why our everyday experience of being in charge of our bodies, and so initiating all personal action, itself has a neurological basis. In other words, while the brain is the seat of our conscious experience, there is also a part of our nervous system which is responsible for our belief that we have free will over our behaviour. Patients with alien hand syndrome think that they are no longer in control of a limb because the part of the brain that gives us the sensation of control over our bodies has been damaged. When that happens, our limbs seem to act independently of us.

Research conducted in the 1980s has found that the same electrical brain wave changes that characteristically precede all limb movements, occur several 100 ms before we seem to consciously decide to move a limb. If our conscious decision to act is preceded by brain changes that anticipate action, then our “decision” to choose how to behave or “freedom”, as in free will, is in fact illusory. Our choices have in a sense been decided beforehand by our brains.

Spence asserts that evidence such as this, combined with phenomena such as alien hand syndrome, means that philosophers have to reconsider whether we have free will. He argues that these data suggest that our sense of agency is illusory and it follows that most of us share in common the useful delusion that we have free will. Patients with alien hand syndrome have lost this experience in relation to a particular limb. There is a sense then that those who experience the syndrome are closer to the reality of how much we are responsible for our actions than the rest of us. This is because it is the function of the part of the brain that normally works to make us think that we have conscious freedom of will. They develop the experience, therefore, of becoming mere remote spectators to the actions of our bodies.

Defenders of human “free will” argue what happens before the brain itself decides to act is still unknown, and there may be a role for our own autonomy there. But even these free will guardsians concede the neurological research indicates that whatever happens before the brain is roused, must occur below the level of consciousness.

Yet in alien hand syndrome the patient thinks that the hand has hostile motivations; it is invariably the case that the patient not only thinks that the limb is “not self” but finds that the limb behaves towards the self in a destructive and aggressive manner. This could be explained by the stressors that we lose our conscious sense of voluntary control over our bodies, our minds have to come to terms with the fact that our bodies are not in control then someone or something else must be. We would offer that the value of our particular case is that it was due to a central deafferentation—the term “sensory alien hand syndrome.”
opposed to the idea that “we know our limbs belong to us because they obey us”, we know that our limbs belong to us because they provide us with sensory input that is recognised as self. Many patients with movement disorders or paralysis lose control of their limbs but still have no difficulty in realising them as self. Indeed even in “phantom limb” there is sense of self due to central processes in the absence of a limb. Our patient, as do others with agnosia and primary abnormalities of central sensory systems, shows perhaps that it is central sensory processes that are the key to identifying “self”. We know our limbs not because they obey us but because there is pattern of sensory innervation that accompanies our own limb movements. When this pattern never reaches specific cortical regions, then the limb is not perceived as self; called “amorphosynthesis” by Denny-Brown and Banker.

Vasomotor reactivity is exhausted in transient ischaemic attacks with limb shaking

The article of Baumgartner and Baumgartner entitled “Vasomotor reactivity is exhausted in transient ischaemic attacks with limb shaking” provides interesting new information regarding the nature of involuntary limb movements contralateral to haemodynamic failure from severe carotid artery occlusive disease. The authors evoke an “exhausted cerebral vasoreactivity in the hemispheres opposite the involuntary limb movements”. In their report, involuntary movements affected only the limbs, and displayed no tonic contraction, tonic-clonic jerking, or Jacksonian march and no epileptic activity during attacks. These findings led the authors to strongly argue against seizures as the cause of limb shaking in these transient ischaemic events.

In contradistinction, a 72 year old right handed man was admitted to our hospital with a 3 month history of episodic weakness and numbness of the right arm. The patient then had six discrete stereotypic episodes of right arm weakness and clumsiness that were also associated with the inability to speak.

Several episodes of dysarthria, numbness and weakness of the right arm and leg (MRC grade 4/5) were seen, unrelated to posture, some of which occurred when the patient was supine. Most disturbing was that characterised by slight tremulousness and asterixis-like movements of the outstretched right arm. There was a return to baseline functioning between events.

Video/EEG monitoring, however, showed low voltage spikes in the left central-parietal region contralateral to the facial twitching and the right arm and right leg weakness. Although ongoing clinical and EEG seizures activity stopped after 2 mg intravenous lorazepam, they reoccurred after loading with phenytoin. Because angiography disclosed a greater than 95% stenosis of the right internal carotid artery (while the patient had 50% stenosis of the left common carotid artery), the patient was anticoagulated with heparin, but episodes continued. It was only after a left carotid endarterectomy that all episodes resolved. These findings of the outstretched right arm has been reported with asterixis-like movements as well as the sensorimotor deficits and diastolic dysfunction in Kaplan’s patient had a 95% stenosis of the left internal carotid artery, whereas that in virtually all reported cases, abnormal movements are more definitively resolved by carotid endarterectomy, argues in favour, at least in part, of an ictal contribution. The fact that in virtually all reported cases, abnormal movements are more definitively resolved by carotid endarterectomy, argues in favour of an underlying ischaemic aetiology that induces focal seizures. There are few reports that clearly delineate the interaction and association of inhibitory focal motor seizures and transient ischaemic attacks, as there are few sequential trials of antiepileptic drugs or anticoagulation (under EEG monitoring) and finally carotid endarterectomy. Several authors support the concept of an inhibition of motor function in parietal and secondary somatosensory re- gions by seizure activity which then interrupts the sensory feedback loop to motor integration with inhibition of subcortical and cortical areas.

BOOK REVIEWS


To the MRCP candidate neurology is one of the more daunting specialties. The unfamiliar nerve conduction study and the frankly mysterious EEG can distress an otherwise well rounded senior house officer. Despite the fact that much of neurology is commonly seen on a general medical ward—strokes, dementias and so forth—the general perception is of an unimaginable list of eponymous syndromes and obscure signs. Rather than dwell on the last, in this book Dr Smith tries to address the commoner complaints as examination style questions each with a “simple clinical les-
son”. The “grey case” section, for instance, includes questions on multiple sclerosis, cluster headache, and HSV encephalitis, while broadening the topics to include postinfective demyelination, chronic hemi-
crania, and acute haemorrhagic encephalo-
myelitis. There is, however, a tendency for the discussion after each question to be rather brief. A fuller explanation, with more allow-
ance for the reader’s ignorance, would have been appreciated. The data interpretation section is somewhat better, covering CSF, EEG, and other data extremely well. Perhaps a little too well; would an MRCP candidate really be expected to recognise the character-
istic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are disappointing. If anything, neurology lends itself best to this section of the written exam-
ination but it is let down by the poor quality of some of the images in this book. This is es
cially unfortunate, as other images in the same section are remarkably impressive. The Sturge-Weber skull radiograph and central pontine myelinolysis MRI are beautiful. In Sturge-Weber skull radiograph and central especially unfortunate, as other images in the
book. This is certainly a specialised book and will really only appeal to those interested in, or wishing to develop, expertise in transcranial colour coded ultrasound.

This book will be higher than expected as it is money. It may be that the circulation of this book will be higher than expected as it is expected. There is no doubting the aesthetic
expected. There is no doubting the aesthetic
expected.


This book, after a short introduction to some of the fundamental features of the disease goes on to provide some 117 illustrations of aspects of the disease from Cruveihier’s plates to histopathological specimens and also a heavy leaning to imaging particularly magnetic resonance scanning, as might be expected. There is no doubting the aesthetic impact of this short book. In addition, the fact that these illustrations emanate from a well established figure in the multiple sclerosis world and are likely to be a representative set of personal teaching slides from a successful academic career all vouch for the provenance and informative nature of the atlas. However the place of such a book within a neurologist’s library has to be questioned. There are a plethora of high quality textbooks devoted to all aspects of multiple sclerosis, all well illus-
trated and most in colour. They provide in depth analysis of all aspects of the disease and although their illustrations tend to be smaller this is where I would choose to put my money. It may be that the circulation of this book will be higher than expected as it is likely to be a popular choice for some pharmaceutical companies.


This monograph is the latest to be produced by the American Association of Neurological Surgeons as part of the Neurosurgical Topics series. It begins by tracing the history of cal-
varial reconstruction from ancient times. There follows a discussion of the different autologous donor sites and synthetic materi-
als currently used for craniotomies and facial defects. The merits, disadvantages, and contraindications of each are considered. Dural substitutes are then dealt with in simi-
lar fashion. Specific problems, such as scalp reconstructive management of commin-
uted frontal sinus fractures, and reconstruc-
tion of the anterior skull base are the subject of separate chapters. The final part of the book is devoted to craniosynostosis. A review of current knowledge on pathogenesis is followed by a good account of some of the more common techniques used to treat single suture synostosis. Understandably, in a book of this type there is space only for an overview of the treatment and complications of multi-
suture involvement, but the chapter provides well chosen references for further reading. The reconstruction of traumatic and post-
surgical calvarial defects is one of the bulk of this volume, and is dealt with very effectively. Operative techniques and the relative merits of various materials are covered in a clear and concise manner. By contrast, the section on aural substitutes is a little disappointing because it does not provide the reader with reasoned argument on how to select the most appropriate graft from the sometimes bewild-
ering variety of autologous, synthetic, and xenograft materials which are available when vascularised pericranial tissue is not an option.

Craniosynostosis is a topic which is covered very well in standard paediatric neuro-
surgical texts and it is not worth buying this book for that section alone. However, the account of techniques for repair of calvarial defects is excellent and merits the inclusion of this text in a departmental library.


Transcranial colour duplex sonography is an ultrasound technique which is becoming increasingly available for the non-invasive imaging of intracranial structures, parti-
cularly the basal cerebral arteries. There are now four principal components to the technique: B mode ultrasound which can be used to image the brain parenchyma; colour coded Doppler which provides a colour image of the basal vessels; spectral analysis of pulsed wave Doppler which is used to derive blood flow velocities; and latterly “power” Doppler which is also used to provide an aver-
ing following analysis of the amplitude rather than the frequency of the reflected ultrasound beam. In addition, echocontrast agents are now available which can increase the signal to noise ratio and thus help counteract some of the detrimental acoustic effects of the skull.

This volume of 400 pages and liberal colour diagrams and prints is edited by three exponents of the technique. Thirty one chapters contain a further 80 pages on topics from the history of transcranial ultra-

Letters, Correspondence, Book reviews, Correction


This is volume 47 of a series entitled Neurological Disease and Therapy, series editor W C. Koller. This volume is edited by an American surgeon and two British neuro-
physiologists. Most of the 45 contributors are American or British, almost half of whom, including Dr Cole, are from Southampton. The book begins with a pathophysiological
introduction setting the scene for the five main disease sections covering developmental/genetic disease, spinal injury, infection, tumour, and the effect of neurological and systemic disease on the spinal cord. This chapter covers a wide area from multiple sclerosis to motor neuron disease to vascular disease to metabolic diseases. Then follows a section on investigation considering imaging, neurophysiology, and urodynamics. Finally, there is a miscellaneous section covering clinically important entities such as pain, sexual problems, and terminal care associated with spinal cord disease but also including a highly specialised chapter on the role of oncology in spinal cord injury.

This is an ambitious attempt at being comprehensive. The editors themselves worry that the emphasis favours surgical conditions. Although this might be the case, many surgical conditions affect the neurologist or rheumatologist, care for spinal disease often falling between several specialties. Therefore, it is of benefit to the clinician to have all aspects of spinal disease in one volume. The standard and style of the individual chapters varies, that on motor neuron disease being up to date and topical, malignancies being covered in depth. That on sexual problems associated with spinal cord disease is excellent and particularly practical and a must for both doctors dealing with spinal disease and for patients themselves who are often untreated (our fault, not theirs). The chapter on depression will be food for thought for many doctors who enjoy recreational diving, for although studies have not yet shown adverse affects on the quality of life in those who dive frequently but without incident, their evidence for cumulative neurological damage from neurophysiological, imaging, and pathological studies is compelling.

The quality of illustration is high. Perhaps not surprisingly, this is particularly evident in the imaging section (where there is a rather spectacular sagittal T2 weighted MRI of a intramedullary arteriovenous malformation). In addition to imaging many of the chapters also make good use of schematic diagrams and line drawings to enhance the text.

Drs Engler, Cole, and Merton end their preface by commenting that “Our main hope, however, is that the chapters will read as a series of views on the spinal cord and its disease, so that a surgeon may learn about the complete disease picture which many of the sexes equally. There are also wider socioeconomic and legal issues that play a part in the complete disease picture which many of us neglect too often but which this book is careful to address (see below). Leaving content aside for a moment, this is a beautifully presented book; clearly headed and with wide use of well constructed tables. It encourages one to read on. It seems up to date and well referenced.

The contributors (40 in total) are exclusively American, and east coast American at that with only occasional forays westward. The text is divided into three sections. The first, entitled General/Neurological Disease in Women includes an anatomical chapter considering the sex differences of regional brain structure and function. More novel for this type of text, it contains two thoughtful chapters considering women’s health within the context of their lifestyles and women’s health and its relation with the law. This chapter considers issues such as coercive approaches to preventing foetal harm, those relating to informed consent to medical treatment, and difficult choices with neurological implications. The law and the case examples are exclusively American but the issues are universal. This opening section leaves no doubt that this is a book that has taken female issues extremely seriously.

The second section looks at neurological diseases as they affect females at different life stages, from birth through menarche, pregnancy, and menopause, to the elderly woman. As well as considering genetic diseases that strike at a particular age, these chapters consider the influence of changing physiology and hormonal balance on neurological disease. The third section is the most conventional. Each chapter considers a neurological disease representing these diseases with emphasis on their effect on women and there is, by necessity, some overlap between this and the previous section. As a non-American, I would feel more comfortable to believe that the high number of female patients with peripheral nerve injuries secondary to physical beings, knife wounds, or gunshot wounds reflected the country of origin of this book!

If pushed to criticise, the indexing could be more complete and certain conditions considered in more detail, in particular, paraneoplastic conditions associated with breast and gynaecological malignancies. However, that aside, I think this a rather special book and not only a good addition to any neurological library but a useful purchase for anyone interested in female medical issues.

GILLIAN HALL

The reader may be interested in the following:


CORRECTION


During the editorial process the descriptions of the histograms in figure 4 (p 614) were wrongly ascribed. The corrected figure is reproduced below.