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=0.11, 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-responsiveness. Eyebrow and frontalis “test” injections correlated well with clinical and immunological results and are useful in the assessment of BTX non-responders.

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Keywords: dystonia; botulinum toxin; antibodies; immunoresistance

An ever increasing number of disorders including dystonia, tremors, tics, hemifacial spasm, spasticity, sphincter dysynergia, and achalasia are now being treated effectively with 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.

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...
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 cpm, 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 and counted on a Cobra Packard gamma counter. Results were expressed as pM (pimoles of 125I-BTX precipitated /l serum) after subtraction of the mean results (<1000 cpm) from healthy control serum samples run in parallel.

Twenty nine patients were also injected with a test dose of 15 units (n=26) to 20 units (n=3) of BTX-A into the medial aspect of their right eyebrow (one site), and 19 patients received 15 units (in two divided doses) into the frontalis muscle on the right side. For the eyebrow injections, a positive (good) response is indicated by the presence of asymmetry on frowning after unilateral BTX-A injections, whereas a negative (no) response (immunoresistance) is present when there is no asymmetry with frowning. A positive response to unilateral frontalis injections is strongly suggested by asymmetry of eyebrow elevation or forehead wrinkling on raising of eyebrows whereas a symmetric contraction of forehead muscles indicates a negative response (immunoresistance).

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− samples by IPA were Ab− by MPB. 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-

![Clinical response vs. reduced or no clinical response](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 e

ECT 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 borderline (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% for clinical (p<0.001), 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 83% 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%.

Figure 2 IPA results on the 89 samples (from 83 patients) depicted on the basis of whether the sample tested negative (open circles) or positive (shaded triangles) by MPB. The lines join the values from the two patients whose MPB Ab status changed. IPA titres > 50 pM are considered positive.

Figure 3 IPA results separated on the basis of the patient’s clinical response to BTX injections. Grade 0 or 1 response indicates non-responders (shaded triangles), grade 2 response (open triangles) indicates reduced response, and grade 3 or 4 (open circles) are responders.

Figure 4 Correlation of clinical response (grade 0 or 1 response indicates non-responders, grade 2 response indicates reduced response, and grade 3 or 4 are responders) with response to test injections.
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.

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 frontal wrinkles may not be desirable.

The only commercially available in vitro test utilises 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 of 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 preceding to the next step of using other BTX serotypes, plasma exchange, immunoabsorption, or surgery. Based on the results

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<th>Clinical-immunological correlation</th>
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<tr>
<td><strong>Mouse bioassay (MPB)</strong></td>
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<tr>
<td>Ab+ (n=22)</td>
</tr>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Clinical (n=83 subjects, 89 samples)</td>
</tr>
<tr>
<td>Eyebrow (n=29 subjects)</td>
</tr>
<tr>
<td>Frontalis (n=19 subjects)</td>
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<tr>
<td>Total responses</td>
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+=Responder; −= non-responder.

<table>
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<th>Mouse bioassay - immunoprecipitation assay comparison</th>
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<tr>
<td><strong>Response</strong></td>
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<td>Clinical</td>
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<td>Eyebrow</td>
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PPV=Positive predictive value; NPV=negative predictive value.

Clinical response to BTX

- (good) Response
  - Reinject with the smallest dose needed to achieve optimal response
  - (good) Response to clinical and/or test injection (asymmetric contraction)

- (no) Response
  - 1) Reinject; adjust dose and/or site
  - 2) Administer “test” injection (eyebrow or frontalis)
  - 3) Collect serum for assays
  - (no) Response to both clinical and test injection (symmetric contraction)
  - IPA or MPB assay
  - Other BTX serotypes, plasma exchange and immunoabsorption, or surgery

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 it 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.

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Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies

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Cerebral metabolism during vegetative state and after recovery to consciousness

One way to approach the study of consciousness is to explore lesion 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 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).² 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<0.05.³

During the vegetative state, average grey matter glucose metabolism was 36% 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 mg/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 substrate⁴ and with PET studies in postanoxic syndrome, in which the parieto-occipital cortex showed the most consistent impairment.⁵ 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.⁶ Our data point to a critical role for these posterior associative cortices in the emergence of consciousness.

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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.2

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 worldwide have disclosed a subpopulation of patients who fulfill at least one exclusion criterion defined by the Consortium.3 We identified an infant with severe SMA who fulfilled two exclusion criteria and also showed abnormalities on Nerve as well as muscles. This report will further delineate the wide range of phenotypes for this particular gene mutation.

A 4-month-old 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. The muscle stretch reflexes were absent. 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 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 multi-copy markers Ag1-CA and C212L2, 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 multicopy markers.4 5 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.6

Although it has been shown for some time that histological studies that sensory systems are involved in SMA, electrophysiological sensory findings have been previously reported only once.7 Sensory nerve conduction velocity was tested in an 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 neurophysiological function potentials” as an exclusion criterion.8 Our finding of absent sensory potentials in a 5q deletion established case of SMA indicates further need for revision of the Consortium criteria. Studies involving large numbers of patients with SMA have identified cases of SMA variants.9 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 weaknes, 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, possess the characterstic 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 electrically inexcitable muscles in SMA. This phenomenon is known to occur in a few other neuromuscular conditions such as periodic paralysis and critical illness polyneuropathy. Fibrillations, as seen in the infant in our report, are commonly seen in acute denervation and are thought to be caused by perturbation of the sarcocell membrane, rendering it unstable. One possibility may be that EMG fibrillations on onset in SMA type I can result in abnormal function of the membrane to make it electrically inexctible. Further electrophysiological studies at the cellular level are required to delineate this interesting finding.

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1 The International SMA consortium. Meeting report. Neuromuscular Disorders. 1992; 2

Acute overdosage and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-0-methylpyridyldopa

Although the effects of a chronic overdose with levodopa are well known, few cases of acute intoxication have been described.1 2 A particular problem in establishing a diagnosis of levodopa overdosage is the delay in bringing an acutely intoxicated patient to hospital, perhaps due to late discovery, the blood concentration of levodopa could already be normal or even supranormal (peaking 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 3x1 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 5 tablets of carbidopa/levodopa. About 12.00 pm he appeared psychically altered, crying without reason, anxious, and depressed. After about 30 minutes he was increasingly inadequate, restless, and subepileptic, 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. 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 hyperto-
can be assumed that the e...ardinal examinations of a...adrenaline, and dopamine were raised...patient was 66.763 ng/ml, the concentrations...levodopa intoxication in the subacute stage is...elevations of levodopa concentration were...and dopamine. The time of levodopa, 3-...the plasma concentrations of levodopa, 3-...o-methyldopa, dihydroxyphenylacetic acid, homovanillic acid, noradren-...lination, we measured the plasma concentrations...tions is variable but in some patients can be...in movements with the minimum of...plemay be highly disabling by them and carers are often...Huntington's disease: a first...trophic genetic test for Huntington's dis-...tent is variable but in some patients can be...tary antipsychotic clozapine has been shown to...ery marked. Progression over time of the...n is variable but in some patients can be...elevations of levodopa concentration were...ed by assuming a rate limited metabo-...therapy. The atypi-...neurological examination (QNE). This mea...ur to overlook an overdosage with levodopa, which may be due to...the diagnosis...of the side effects. Clinically, the most problem-...s depression, cognitive slowing, increased mobility problems, and...es. The inability of traditional antipsychotic dopamine antagonists to improve functional capacity, despite ameliorating it pro-...lindrical, 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-...olution in relation to the immedi-...t rate of the side effects. Clinically, the most problem-...tivation from animal experiments of a spe-...elevations of levodopa concentration were...ed by assuming a rate limited metabo-...and dopamine. The time course of the concentrations of levodopa and 3-o-methyldopa are shown in the figure. After 24 hours the patient was moved from the intensive care unit to a normal medical...s. If drug treatment is considered it is...cantly due to suppression of voluntary motor activity. Tardive dyskinesia has occasionally been reported in patients with Huntington's disease treated with these drugs. The atypi-...s antidepressant clozapine. It is a thieno-...treatment of the patient, this would also...t rate of the side effects. Clinically, the most problem-...highest. The peak of 3-O-MD appears after a delay, and the concentration then falls very slowly, corresponding to a half life in plasma of 16.7 hours.

Distribution into muscles rather then metabolism may lastly 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 gastro-...tions was variable but in some patients can be

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 mo-...dopamine antagonists to improve functional capacity...m, thought that there was evidence of...early, thought that there was evidence of...cases, Neurology 1975;25:792-794. 2. Spoerri KA, Carbidopa-levodopa overdose. Ann Emerg Med 1991;19:49-54. 3. Conlin M, Riva R, Martinelli P, et al. Longitudi-...vations in rats following different routes of administration. Pharm Res 1994;11:549-55. 4. Korczyn AD, Keren O. The effect of L-dopa on pupillary diameter in mice. Experimenta 1982; 38:481-2.

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 involun-...tary motor symptoms. It is likely that the onset of symptoms had occurred a few years previously as he had experienced difficulties in concentration and memory work, attributed at the time to stress, leading to the loss of employment. In addition his family, watching family videos of a few years earlier, thought that there were difficulties in his concentration and memory, a problem which they thought had started 6 years earlier. In May 1995, thought that there was evidence of...he was unable to sit comfortably in a chair and when...directed to stop the movement within 3 weeks. Paroxetine, a selective serotonin reuptake inhibitor antide-...able to sit comfortably in a chair and when out...on the other hand, the plasma half life of levodopa was 111 minutes; this is...sibly due to suppression of voluntary motor activity. Tardive dyskinesia has occasionally been reported in patients with Huntington’s disease treated with these drugs. The atypi-...lastly 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 gastro-...to measure the concentration of 3-o-...it the effect is caused by the peripheral conversion of levodopa into noradrenaline, which stimulates α-adrenergic receptors in the dilator iridis. There is no indication from animal experiments of a spe-...lastly 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 gastro-...tions was variable but in some patients can be

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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 mg 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 antidepressant 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 more limited and venues he felt able to attend were becoming problematic. A trial of olanzapine was then carried out in March 1997. Olanzapine was started at a dose of 200 mg at night and 400 mg on the morning of the first day. After 2 weeks it was increased to a total daily dose of 1000 mg at night and 200 mg lofepramine daily; 04/97: before olanzapine, 140 mg lofepramine daily; 06/97; 5 mg olanzapine at night, 140 mg lofepramine daily.

Quantitative neurological examination scores showing the progress of the movement disorder. 06/95: 5 mg olanzapine at night, 140 mg lofepramine daily; 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, 400 mg at night and 200 mg lofepramine daily; 04/97: before olanzapine, 140 mg lofepramine daily; 06/97: 5 mg olanzapine at night, 140 mg lofepramine daily.

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, α1-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. 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. 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.

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Transient hiccups after posteroventral pallidotomy for Parkinson’s disease

Hiccups are 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. Hiccups may result from various structural or functional disorders of the medulla, the afferent or efferent nerves to the respiratory muscles, and the gastrointestinal tract.1-3 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.4 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 intercommisural line, and 22 mm lateral to the midline of the third ventricle. Ventriculography was performed for target

**Letters, Correspondence, Book reviews, Correction**

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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 staging</th>
<th>UPDRS off</th>
<th>UPDRS off total pallidotomy</th>
<th>Pallidotomy side</th>
<th>Transient side effects</th>
<th>Medication additional to levodopa</th>
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<tbody>
<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>Slight facial paresis, swallowing problems, drooling</td>
<td>Tranylcypromine, levodopa, apomorphine</td>
<td>Apomorphine</td>
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<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>7</td>
<td>2/2</td>
<td>2/7</td>
<td>L</td>
<td>Slight dysarthria</td>
<td>Trihexyphenidyl</td>
<td>Levodopa</td>
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<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>15</td>
<td>2/3</td>
<td>5/15</td>
<td>L</td>
<td>Facial paresis</td>
<td>Persantin, amantadine</td>
<td>Persantin</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>12</td>
<td>2/2</td>
<td>4/22</td>
<td>L</td>
<td>Slight dysarthria</td>
<td>Levodopa, selegiline</td>
<td>Levodopa</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>14</td>
<td>2/3</td>
<td>6/95</td>
<td>R</td>
<td>Facial paresis, hypophonia</td>
<td>Persantin, selegiline</td>
<td>Persantin</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>M</td>
<td>13</td>
<td>2/2</td>
<td>48/27</td>
<td>L</td>
<td>Facial paresis, aphasias</td>
<td>Levodopa, biperiden</td>
<td>Levodopa</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>15</td>
<td>2/5</td>
<td>5/55</td>
<td>R</td>
<td></td>
<td>Clozapine, temazepam, cиспирати</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>

*H and Y=Hoehn and Yahr; †UPDRS off=unified Parkinson’s disease rating scale part 3 (motor examination), in a standardised off state, 12 hours without antiparkinson medication; SNP=not performed.
localization. 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 (table). Two patients had choreatic movements after the pallidotomy at the contralateral side which resolved spontaneously within 2 hours and is associated with a favourable surgical outcome.

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 stratum. 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. 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. In two previous studies 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 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; 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. 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, 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 intrusion

![Image](image_url)
Comparison of stroke survivors with and without emotionalism, assessed in hospital 1 month after stroke

GHQ-12* Recovery locus of control scale
Impact of events scale intrusiveness subscale**
Impact of events scale avoidance subscale*
MASS Fighting spirit subscale
MASS Sense of control subscale
MASS Anxiety preoccupation subscale**
MASS Fatalism subscale*
MASS Avoidance subscale
MASS Helplessness/hopelessness subscale**

MASS = Mental adjustment to stroke scale. *p<0.05; **p<0.01, t tests.

(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=0.002) and avoidance (F=14.06, p=0.002) on the mental adjustment to stroke scale were no longer significant after adjustment for GHQ-12 score.

This study confirms earlier work by showing that stroke survivors with emotionalism have more harm mood symptoms (here rated by the GHQ-12) than do those without emotionalism. It goes further however, in showing that they also have intrusive thoughts about their condition and an emotionalism. This is a common response to threatening intrusive memories of the sort encountered in post-traumatic stress disorder. It may not that emotionalism is a direct manifestation of post-traumatic stress disorder, although that condition has been described after stroke, but the analogy raises the possibility that an abnormality in processing emotionally important stimuli may be one of the causes of emotionalism. If correct it suggests possible treatment strategies along the lines of those used in post-traumatic stress disorder.

A corollary is our finding of increased feelings of helplessness and hopelessness, coupled with avoidance—at least as a cognitive coping strategy reported on one of our measures. Avoidant coping may perpetuate the symptom of emotionalism, by preventing habituation to the social stimuli which provoke it. Alternatively it may lead to a reduction in social support, exacerbating coexistent mood disturbance. Thus, it may be that avoidant coping is not an integral part of emotionalism, but rather that it is an important maintaining factor.

We predicted that patients with emotionalism would have more "external" scores on the loci of control measure, reflecting their sense of lack of personal control over crying. They did not, perhaps because the emotional expression, although not apparently controlled by cognitive resources, is none the less perceived as having psychological meaning, so that responsibility for it cannot readily be devolved to others.

Our study used a relatively weak between-groups design, the number of patients was not large, and we cannot be sure that all co-founders were dealt with. None the less, our results suggest that future research into emotionalism could profitably concentrate not just on seeking its biological correlates, but should also explore the psychological factors which might contribute to its cause or continuation.

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 Dyer 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 amphiphysin, which are cytoplasmic proteins in neurons of the CNS. A large series of patients with SMS found that most have autoantibodies against GAD, whereas amphiphysin is presumably the predominant autoantigen in paraneoplastic SMS. Recently, Beal et al* presented four patients with a stiff limb syndrome marked by progressive rigidity and spasms of the lower extremities. This group of patients tested negative for anti-GAD antibody by immunoprecipitation and demonstrated distinct electrophysiologic features. By contrast, another report described two patients with stiff limb syndrome who tested positive for anti-GAD antibody.† Finally, in presenting a group of 13 patients, 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 amphiphysin or identified as having an underlying neoplasm. We present a patient clinically consistent with the stiff limb syndrome 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 thyroxine and radioactive iodine, 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 was normal and the exception of hyperaesthesia 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 (5, 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 density and terminal axonal swelling distally, consistent with a small fibre sensory neuropathy.‡ The patient would not tolerate EMG. Magnetic resonance images of the brain and the entire spinal cord were normal. Fine needle aspiration of the left thyroid nodule showed hyperplasia and a metastatic adenocarcinoma. On an open surgical procedure, infiltrating duct carcinoma of the breast was identified. Anti-GAD antibodies were positive by both chemical assay and immunoprecipitation, but antibodies to amphiphysin 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 sustained plantar flexion 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 and 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 reported patient with paraneoplastic SMS had upper limb rigidity in the setting of breast cancer and additionally mounted an immune response to amphiphysin.

Paraneoplastic processes can affect any component of the nervous system and, occasionally, multiple levels, as in the syndrome of sensory neuronopathy-encephalomyelitis. Our patient’s findings were not entirely consistent with criteria for classic SMS in that an apparent encephalopathy and a small fibre neuropathy were identified—for example, her dysautonomia (tachycardia and relative hypertension) during spasms may have been a manifestation of involvement of small fibres. The role of autoantibodies in the pathogenesis of SMS and cancer is unclear. Via its probable function in endocytosis, amphiphysin has been postulated to play a part in the regulation of growth factor internalisation; however, the absence of an autoimmune response to this toxin. Clinical presentation is mainly acute and circumoral tingling sensation and numbness 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 respiratory 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 minutes of intubation. On neurological examination, 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 function, blood glucose, and CSF study were unremarkable. An examination of renal function 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, diffuse theta waves. When brief noxious stimuli were applied to the sternum, they were replaced transiently by beta activities. The findings suggested that the profound neurological 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-

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### Tetrahydrozoline intoxication in a uraemic patient

Tetrahydrozoline 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 undefined 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 4 hours after the meal she developed a headache and a lingual and circumoral tingling sensation and numbness 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 respiratory distress and cyanosis developed. Her husband remained asymptomatic throughout this time.

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cally within an hour. She could open her eyes and she communicated and answered questions correctly by blinking. Pupillary 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 her symptoms, and caused no clinical evidence of poisoning 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. Except for differences in the predisposing causes, as Bolton et al. reported, it is difficult to distinguish critical illness polyneuropathy from Guillain-Barré syndrome on purely clinical grounds. In both, polyneuropathy runs a monophasic course, the onset being relatively acute but with subsequent improvement in most instances. The clinical features also are similar; evidence of muscle weakness in all four limbs, occasional involvement of facial muscles and frequent involvement of the muscles of respiration, the depression or absence of deep tendon reflexes, and some evidence of distal sensory loss occurs.

The first step by Bolton et al. in determining exact aetiology was to differentiate critical illness polyneuropathy from Guillain-Barré syndrome. In reviewing the patients with critical illness polyneuropathy and Guillain-Barré syndrome who were studied in their EMG laboratory, they found marked differences between the two types of polyneuropathy. Patients with Guillain-Barré syndrome had greater slowing of the speed of impulse conduction, and, in the initial stages, abnormal spontaneous activity in the muscle was absent, indicative of a predominantly demyelinating 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. (including 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 paralytic Guillain-Barré syndrome with acute flaccid paralysis without regard for the underlying physiology or pathology. Classical pathological studies of Guillain-Barré syndrome, however, have identified prominent demyelination and inflammatory infiltrates in the spinal roots and nerves. Guillain-Barré syndrome often has been considered to be synonymous with the pathological designation of acute inflammatory demyelinating polyneuropathy, and physiological abnormalities consistent with demyelination have been taken as supportive evidence for the diagnosis of Guillain-Barré syndrome. Feasby et al. with Bolton's attention to patients who were clinically considered as having Guillain-Barré syndrome, but who were characterised electrophysiologically 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 findings 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 confirmed the existence of the acute motor-sensory axonal neuropathy (AMSAN) pattern of Guillain-Barré syndrome described by Feasby et al.
of acute diarrhoea, commonly precedes the development of Guillain-Barré syndrome. There is a close association between axonal Guillain-Barré syndrome and an antecedent C. jejuni infection. 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 al. confirmed that AMSAN follows C. jejuni infection. Serum samples from patients with axonal Guillain-Barré syndrome subsequent to C. jejuni enteritis often have a higher class autoantibody titer to gangliosides GM1, GM1b, GD1a, or GaNAc-GD1a in the acute phase of the illness, and there is molecular mimicry between these gangliosides and the lipoplysaccharides 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, Hagenesse et al. reported a case of “C. jejuni bacteremia and subsequent Guillain-Barré syndrome” that occurred in a patient with chronic graft versus host disease and required allogeneic marrow 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 diagnoses 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 GaNAc-GD1a could be used as immunological markers for axonal Guillain-Barré syndrome. 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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Replicative 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. In 1994, the use of magnetic stimulation in clinical psychiatry was suggested. Since then, it has been used in the study or treatment of obsessive-compulsive disorder, conversion disorder, schizophrenia, and particularly, depression.

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 have been established in schizophrenia, specifically 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 findings, systemic neurological illness, taking cerebral metabolic activator or vasodilator medications, electroconvulsive therapy within 6 months, and significant abnormal findings on laboratory examinations.

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 effects scale, 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 block design test of the Wechsler adult intelligence scale, the trail making tests A and B, the FAS verbal fluency test, and two subtests of the Wechsler memory scale (the visual memory reproduction and the verbal paired associates subtests).

A brain SPECT study was performed using a rotating dual head gamma camera, fitted with high resolution fanbeam collimators. Two “99mTc-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 dosage of 20 Hz for 2 seconds, once per minute for 20 minutes at 80% motor threshold. The motor threshold was determined by visualisation of finger movement. A butterfly magnetic coil was placed tangential to the orbital area, on the C3 and C4 EEG point.

An important finding of this study was that RTMS may be given to stable schizophrenic patients without exacerbating their psycho-

<table>
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<th>Table</th>
<th>Neuropsychological tests and PANSS scores</th>
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<tr>
<td>Test</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Block design</td>
<td>Pre 49 (11.95) NS</td>
</tr>
<tr>
<td>Trail making test</td>
<td>Post 50 (8.69) NS</td>
</tr>
<tr>
<td>Trait making test</td>
<td>B</td>
</tr>
<tr>
<td>Immediate visual reproduction</td>
<td>Pre 38.3 (4.5)</td>
</tr>
<tr>
<td>Delayed visual reproduction</td>
<td>Post 41 (10.03)</td>
</tr>
<tr>
<td>Immediate verbal paired associates</td>
<td>Pre 50.5 (4.82) NS</td>
</tr>
<tr>
<td>Delayed verbal paired associates</td>
<td>Post 54.8 (11.2) p&lt;0.05</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 46.18 (23.9)</td>
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<tr>
<td>PANSS-N</td>
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<tr>
<td>PANSS-P</td>
<td>Post 54 (7.46) NS</td>
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<tr>
<td>PANSS-P</td>
<td>Post 59.5 (10.03)</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 8.8 (1.1) NS</td>
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<tr>
<td>PANSS-P</td>
<td>Post 8.8 (1.17)</td>
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<tr>
<td>PANSS-P</td>
<td>Post 37.67 (11.15) NS</td>
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<tr>
<td>PANSS-P</td>
<td>Post 36.5 (11.47)</td>
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<tr>
<td>PANSS-P</td>
<td>Post 31.67 (8.26) p&lt;0.02</td>
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<tr>
<td>PANSS-P</td>
<td>Post 27.83 (8.47)</td>
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<tr>
<td>PANSS-P</td>
<td>Post 16.83 (7.28) NS</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>Post 15.33 (7.55)</td>
</tr>
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</table>

Pre=preatreatment; Post=post-treatment; PANSS=positive and negative scale; GC=general psychopathology scale; NG=negative scale; P=positive scale.

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 working memory. 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 the positive and negative symptoms, all patients tolerated the RTMS well, with minimal side effects (mild headache and dizziness).

Neurological SPECT of one patient was reported to be normal, showing no evidence of hypofrontality. The remainder of the patients showed hypofrontality on the initial neuroimaging. The results after RTMS indicated no change in the hypofrontality.

Negative symptoms showed a general decrease for all patients (table). Significance (p<0.02) was noted on the PANSS negative symptoms subscale. These patients seemed to be more sociable than when originally seen. Nevertheless, clinical effects of the RTMS were subtle and difficult to distinguish from those derived from the supportive environment of the psychiatric ward.

With regard to the neuropsychological battery, we found a general improvement in all post-treatment scores (table), but only delayed visual memory achieved significance (p<0.05). This feature might be basically explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, assigning there are no methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

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hypofrontality after treatment, we are consid-
ering extending the treatment course to 20
sessions, each at 30 Hz for 1 second, at 90% of
motor threshold. It was also suggested that other
positions of the coil and other kinds of coils
might give better results.

The clinical change in our cohort after the
RTMS could be attributed to both the treat-
ment and the supportive environment of the
psychiatric ward, and even to enhance compli-
cance to medication during hospital admission.
We are aware that the small sam-
ple size and lack of controls compel a very
careful interpretation of the results.

Nevertheless, in the light of these, we suggest
further controlled studies to the efficacy of
RTMS in negative symptoms of schizophrenia,
not only as an add on technique but also as
so a sole therapeutic procedure. Research on
RTMS also requires some controlled studies aimed
to the complexity of the methodology (dosage, duration, and localisation), as this
form of intervention may prove to be an eco-
nomical and convenient therapy in treating
several psychiatric disorders.

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Letters, Correspondence, Book reviews, Correction

Sensory alien hand syndrome

The case report by Ay et al of alien hand syn-
drome 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 con-
cerning the intent of the limb. Typically, in
the report of Ay et al, the common belief is
that the limb has deeply malevolent inten-
tions towards the victim.

It is this aspect of alien hand syndrome that
I suggest also needs incorporating into its
neurological explanations, and which pro-
vides a clue as to why our everyday experience
of being in charge of our bodies, and so initiat-
ing all personal action, itself has a neurological basis. In other words, while the brain is the source of our actions and experi-
ences, there is also a part of our nervous sys-
tem 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.

As a result of conducting 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
precipitated 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 delu-
sion 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 the brain function is 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 specta-
 tors to the actions of their 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 guardians concede the neurological
research indicates that whatever happens
before the brain is roused, must occur below our
conscious awareness.

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 above argument.

If we lose our conscious sense of voluntary
control over our bodies, our minds have to
come up with an explanation for the action of
our movements. We decide that if
ourselves are not in control, then someone or
something else must be; therefore, we no
longer have a sense of the limb belonging to
us.

Because to lose control over our bodies is
one of the most terrifying experiences, our
attempt to explain this finding occurs in the
context of fear. It may be that our apprehen-
sion leads us to misinterpret innocent reflex-
ive acts of our hands, such as scratching or
rubbing, as malevolently inspired. Plus it
could be that our interpretation of spurious
position of our free will in the light of neuropsy-
criticism to act in relations to onset of
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connection syndrome. Schizophr Res 1998;

The authors reply: We appreciate Persaud’s comments regarding the alien hand syndrome, “the perceived
malevolence of the affected limb towards its
victim, and the question of whether with loss
of the conscious sense of voluntary control
over our bodies, our minds… decide that if
ourselves 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—therefore
the term “sensory alien hand syndrome”. As

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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 such. 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 anosognosia 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 they have a pattern of sensory activation that accompanies our own limb movements. When this pattern never reaches specific cortical regions, then the limb is not perceived as self; called "amorphopsynthesis" by Delorme and Patient. Typically stimulation by the centrally deafferented limb in "sensory" or "posterior" alien hand syndrome, or kinaesthetic stimuli due to movement of the limb as in the "anterior" or "motor" alien hand syndrome, is perceived as due to another person or thing without critical questioning. This raises the most interesting question of what brain region is deafferented in the anterior alien hand syndrome where such an illusion is intact.

It is not our clinical nor the conclusions based on published reports that all patients suffering with alien hand syndrome are suffering by the effect of an abnormality in the acute brain or peripheral nervous system suffer from a disturbance of the voluntary movements of the limb. However, the initial syndrome may result in disjoined and terrifying perceptions, it seems that the brain quickly re-establishes its control by presently unknown adaptive capacities. Furthermore, why it almost exclusively involves the left body side in right handed people remains unknown. Studying this syndrome in greater detail may yield additional insights into the pathophysiology of denial and misidentification.

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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 and involuntary limb movements contralateral to haemodynamic failure from severe carotid artery occlusive disease. The authors evoke an "exhausted cerebral vasoreactivity in the hemisphere 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 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 a tic in spiking.

Several episodes of dysarthria, numbness and weakness of the right arm and leg (MRC grade 4/5) were seen, unrelated to posture, of some which occurred when the patient was supine. Most of the seizures were characterised by slight tremulousness and asterioid-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 head regions 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 left internal carotid artery (while the patient was treated with aspirin and phenytoin at a concentration of 16.5 mg/l), the patient was anticoagulated with heparin, but episodes continued. It was only after a left carotid endarterectomy that all episodes were definitively resolved by intravenous movements as well as the sensorimotor deficits, because unilateral asterioid seizures due to subclinical ischemia. Patients with attacks of shaking movements of the limbs have no EEG evidence of epileptic activity, and involuntary movements do not stop after administration of anticonvulsant therapy. (3) Although the patient presented by Kaplan had a 95% stenosis of the left internal carotid artery, it is unclear whether haemodynamic failure was present or not, because no studies evaluating the haemodynamic reserve of the homolateral hemisphere were presented. This is in accordance with the finding that the involuntary movements as well as the sensorimotor deficits of Kaplans patient were not related to parietal TIAs related to involuntary seizures in several ways. (1) They are associated with positive phenomena (limb shaking), and the involuntary movements do not affect the fusiform muscles. Patients with attacks of shaking movements of the limbs have no EEG evidence of epileptic activity, and involuntary movements do not stop after administration of anticonvulsant therapy. (2) The pathogenesis of that condition may be due to disinhibition of subcortical control mechanisms as a result of ischaemia. In our opinion, it is not clear whether the asterioid-like movements of the outstretched right arm of Kaplans patient are due to epileptic seizures, because unilateral asterioid of the outstretched arm has been reported with contralateral vascular lesions affecting almost all cerebral structures involved in subcortical control including ischaemia in the territory of the middle cerebral artery.

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Baumgartner and Baumgartner reply: We are grateful for the response of Kaplan to our short report. We agree that somatic inhibitory seizures may mimic transient ischaemic attacks (TIAs). Such TIAs are associated with negative somatomotor sensation, reflective sensory motor deficits and difficulty with speaking, EEG evidence of seizure activity, and cessation of the TIAs after the administration of an anticonvulsant drug. 1, 2, 3, 4, 5, 6 Limb shaking TIAs, however, differ from TIAs related to inhibitory seizures in several ways. (1) They are associated with positive phenomena (limb shaking), and the involuntary movements do not affect the fusiform muscles. Patients with attacks of shaking movements of the limbs have no EEG evidence of epileptic activity, and involuntary movements do not stop after administration of anticonvulsant therapy. (2) The pathogenesis of that condition may be due to disinhibition of subcortical control mechanisms as a result of ischaemia. In our opinion, it is not clear whether the asterioid-like movements of the outstretched right arm of Kaplans patient are due to epileptic seizures, because unilateral asterioid of the outstretched arm has been reported with contralateral vascular lesions affecting almost all cerebral structures involved in subcortical control including ischaemia in the territory of the middle cerebral artery. 1
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 lesion.” 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-craniac, and acute haemorrhagic encephalomyelitis. There is, however, a tendency for the discussion after each question to be rather brief. A fuller explanation, with more allowance 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 characteristic EEG of Creutzfeld-Jakob disease I surely hope not. Finally, the slide tests are disappointing. If anything, neurology lends itself best to this section of the written examination but it is let down by the poor quality of some of the images in this book. This is especially 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 same section are remarkably impressive. The of some of the images in this book. 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.

NEIL ROBERTSON


This monograph is the latest to be produced by the American Association of Neurological Surgeons as part of their Neurosurgical Topics series. It begins by tracing the history of calvarial reconstruction from ancient times. There follows a discussion of the different autologous donor sites and synthetic materials currently available. In view of the calvarial and facial defects. The merits, disadvantages, and contraindications of each are considered. Dural substitutes are then dealt with in similar fashion. Specific problems, such as scalp reconstruction, the management of comminuted frontal sinus fractures, and reconstruction of the anterior skull base are the subject of separate chapters. The final part of the book is devoted to craniomaxillofacial. A review of current knowledge on pathology 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 multisuture involvement, but the chapter provides well chosen references for further reading.

The reconstruction of traumatic and post-surgical calvarial defects is 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 bewildering variety of autologous, synthetic, and xenograft materials which are available when vascularised periosteal tissue is not an option.

Craniosynostosis is a topic which is covered very well in standard paediatric neurosurgical 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.

ROBERT MACFARLANE


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 illustrated 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.

PETER MARTIN


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 neurophysiologists. 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 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 patients are referred to 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 untaught (our fault, not theirs). The chapter on depression illness will be fed 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 the 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 an 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.

Dr 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 current practice as well as the wide range of conditions affecting the cord that are outside the field of surgery”. While I agree that educating surgeons is an admirable aim, I think that the authors rather undersell themselves and that this book’s main strength, as I have said above, is that it will appeal to all disciplines that deal with spinal cord disease, bringing together neurological, rheumatological, and surgical disease that is often covered in separate textbooks.

GILLIAN HALL


This is the second time that I have been asked to review a book on this topic. The first time I approached the task with some scepticism were neurological diseases in women really so different from those in men that they warranted their own text book? But I rapidly became a convert to the cause, being reminded that there are issues specific to females that influence both disease, investigation, and treatment (pregnancy, breast feeding, menopause, to name the most obvious) and that not all neurological diseases attack 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 Issues 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 with in 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 beatings, 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.