Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies

Philip A Hanna, Joseph Jankovic, Angela Vincent

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 50% for frontalis responses whereas the IPA sensitivity was much higher at 84% for clinical (p<0.001), 77% for eyebrow (p=0.111, NS) and 90% for frontalis responses (p<0.02). The IPA specificity was 98% for clinical, 91% 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.

(J Neurol Neurosurg Psychiatry 1999;66:612–616)

Keywords: dystonia; botulinum toxin; antibodies; immunoresistance

An ever increasing number of disorders including dystonia, tremors, tics, hemifacial spasm, spasticity, sphincter dyssynergia, and achalasia are now being treated effectively with botulinum toxin type A (BTX-A).1–10 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).1–11 The reported frequency of such antibodies has ranged from 3% to 57% depending on the assay method used.12–15 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.16 In vitro assays, including the sphere linked immunodiagnostic assay (SLIDA),13 enzyme linked immunosorbent assay (ELISA),15–16 a monoclonal antibody based immunoassay,17 and western blot technique18 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.19 The primary aim of this study was to compare the MPB with a more recent immunoprecipitation assay (IPA) developed by Palace et al20 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 al20 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 injections19 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).22 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.14 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 al6 with slight modifications. After the iodination reaction,19 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 binding sites precipitated/l serum) after subtraction of the mean results (<1000 cpm) from all test values. 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 previously20 due to slight improvements in the assay that reduced non-specific precipitation by control serum samples.

There was a clear correlation between the results of the IPA and MPB assays (fig 2). All serum samples which were Ab+ by MPB were Ab+ by IPA, and all Ab− by 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 921.5): 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-

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 previously20 due to slight improvements in the assay that reduced non-specific precipitation by control serum samples.

There was a clear correlation between the results of the IPA and MPB assays (fig 2). All serum samples which were Ab+ by MPB were Ab+ by IPA, and all Ab− by 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 921.5): 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-

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.
ued to respond to BTX-A despite low, but positive, titres (112–353). Three of these five patients had a reduced, peak effect score 2, response (fig 3).

In a previous report, we showed that lack of response to a test injection into the facial muscles is a more sensitive measure of non-responsiveness than the MPB.18 In the present study, 29 and 19 patients respectively were given eyebrow or frontalis “test” injections, and the IPA titres corresponded well with responses to the facial “test” injections. Four patients showed no response to the eyebrow test injections despite continuing clinical response. However, three of these patients were 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%.
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 proceeding to the next step of using other BTX serotypes, plasma exchange, immunoadsorption, or surgery. Based on the results

### Table 1 Clinical-immunological correlation

<table>
<thead>
<tr>
<th>Response</th>
<th>Mouse bioassay (MPB)</th>
<th>Immunoprecipitation assay (IPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ab+ (n=22)</td>
<td>Ab− (n=67)</td>
</tr>
<tr>
<td>Clinical (n=83 subjects, 89 samples)</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Eyebrow (n=29 subjects)</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Frontalis (n=19 subjects)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total responses</td>
<td>0</td>
<td>30</td>
</tr>
</tbody>
</table>

+ = Responder; − = non-responder.

### Table 2 Mouse bioassay - immunoprecipitation assay comparison

<table>
<thead>
<tr>
<th>Response</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV/NPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV/NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>50</td>
<td>100</td>
<td>100/67</td>
<td>84</td>
<td>89</td>
<td>88/85</td>
</tr>
<tr>
<td>Eyebrow</td>
<td>38</td>
<td>100</td>
<td>100/86</td>
<td>77</td>
<td>81</td>
<td>77/81</td>
</tr>
<tr>
<td>Frontalis</td>
<td>30</td>
<td>100</td>
<td>100/56</td>
<td>90</td>
<td>89</td>
<td>90/89</td>
</tr>
</tbody>
</table>

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

![Figure 5](http://jnnp.bmj.com/ on April 8, 2017 - Published by group.bmj.com)
Hanna, Jankovic, Vincent

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 of 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 correlational 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-respondor, which is supported by our previous finding that all 20 MPB Ab+ patients had no response to BTX-A injections on at least two consecutive treatment sessions. "False negatives" refer to those patients who do not respond to BTX injections despite an Ab− test.

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

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

22 Houser MK, Sheean GL, Lees AJ. Further studies using higher doses of botulinum toxin type F for torticollis resistant to botulinum toxin type A. J Neurol Neurosurg Psychiatry 1998;64:577–80.
Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies
Philip A Hanna, Joseph Jankovic and Angela Vincent

J Neurol Neurosurg Psychiatry 1999 66: 612-616
doi: 10.1136/jnnp.66.5.612

Updated information and services can be found at:
http://jnnp.bmj.com/content/66/5/612

These include:

References
This article cites 19 articles, 10 of which you can access for free at:
http://jnnp.bmj.com/content/66/5/612#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Errata
An erratum has been published regarding this article. Please see next page or:
/content/67/1/133.full.pdf

Topic Collections
Articles on similar topics can be found in the following collections

- Drugs: CNS (not psychiatric) (1945)
- Neuromuscular disease (1311)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
LETTERS TO
THE EDITOR

Cerebral metabolism during vegetative state and after recovery to consciousness

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

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

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

During the vegetative state, average grey matter glucose metabolism was 36% lower than in controls (4.5 ± 7.3 (SD 1.4) mg/100 g/min). CMRGlus was found after recovery (4.7 ± 100 mg/100 g/min). During the vegetative state, significant regional CMRGlus 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 substrate and with PET studies in postanoxic syndrome, in which the parieto-occipital cortex showed the most consistent impairment. 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. Our data point to a critical role for these posterior associative cortices in the emergence of conscious experience.

STEVEN LAUREYS
CHRISTIAN LEMAIRE
PIERRE MAQUET
Cyclotron Research Centre, University of Liège, Sart Tilman, 4000 Liège, Belgium

CHRISTOPHE PHILLIPS
Institute of Cognitive Neurology, University College London, Alexandra House, 1 Queen Square, London WC1N3AR, England, UK

GEORGE FRANCK
Department of Neurology, CHU Liège Sart Tilman B 33, 4000 Liège, Belgium

Correspondence to: Dr Pierre Maquet, Cyclotron Research Centre (B30), University of Liège, Sart Tilman, 4000 Liège, Belgium Telephone 0032 43 66 36 87; fax 0032 43 66 29 46; email maquet@pet.crc.ac.be


Localisation of voxels in which cerebral glucose metabolism was impaired during vegetative state (in yellow) and after recovery to consciousness (in blue), compared with the control population. SPM(2) threshold was set at voxel level corrected p<0.05 and projected on the patient’s coregistered MRI, normalised to the stereotaxic space of Talairach.
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. In SMA type I (severe; Werdnig-Hoffmann disease), affected persons have onset of symptoms before 6 months of age and are never able to sit without support. Electromyography demonstrates denervation features. In early 1995, the candidate gene, the survival motor neuron (SMN) gene, was identified, making the confirmation of SMA by DNA analysis possible.

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

A 7 week old male infant was born at term. Four fetal movements were noted at 13 weeks of gestation. Chorionic villus sampling at 10 weeks of gestation disclosed normal chromosomal decreases. Decreased fetal movement and polyhydramnios were noted at about 34 weeks of gestation. At delivery, the infant was cyanotic with no respiratory effort and was subsequently intubated. On physical examination, the infant had no spontaneous movements. He opened his eyes with brief fixation but no following. Tongue fasciculations were present. Other cranial nerves seemed intact. Mild flexion contractures of both elbows, knees, and ankles were noted. Tone was flaccid in biceps, brachioradialis, and lower limbs, and there was no movement response to painful stimulus. Deep tendon reflexes were absent.

Brain MRI disclosed mild diffuse cortical atrophy. His EMG was severely abnormal, with widespread fibrillations and absent voluntary motor units except in the genioglossus, where mildly neurogenic motor units with decreased recruitment were seen. Stimulation of the median, ulnar, and peroneal nerves with maximal stimulus resulted in no clinical or electrical response. The biceps brachii and rectus femoris muscles were electrically inexcitable by direct needle stimulation. Median, ulnar, and sural sensory potentials were not obtainable. DNA testing showed a homozygous deletion of exons 7 and 8 of the telomeric SMN gene, all three siblings showed a large deletion in the region that includes all alleles of the multi-copy markers Ag1-CA and C212, localised at the 5' end of the two SMN gene copies. It has been postulated that the severity of disease may be correlated to the extent of a deletion involving the SMN gene and the multicopy markers. The infant in our report with SMA type I showed electrical inexcitability of motor nerves as well as the characteristic alteration of the SMN gene. Although it has been shown for some time from histological studies that sensory systems are involved in SMA, electrophysiological sensory findings have been previously reported only once. Sensory nerve conduction velocity was tested in 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 somatosensory evoked potential potentials” as an exclusion criterion. 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 larger series of patients with SMA have identified cases of SMA variants. These patients were diagnosed as infantile SMA by the presence of proximal weakness and atrophy, hypotonia, and evidence of neuromuscular alterations in EMG and muscle biopsy. In addition, these patients also exhibited one of the exclusion criteria defined by the Consortium—for example, diaphragmatic weakness, involvement of the CNS, or arthrogryposis. Although these patients did not show the typical SMA deletion and were therefore probably not linked to chromosome 5q, they could have had point mutations. The infant in our report showed no respiratory effort after birth, indicating diaphragmatic weakness. He did, however, possess the characteristic SMN gene alterations. This finding suggests that diaphragmatic weakness should be reconsidered as an exclusion criterion by the Consortium.

Review of the literature disclosed no previous reports of electically 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, are often seen in patients with acute denervation and are thought to be caused by perturbation of the sarcolemmal membrane, rendering it unstable. One possibility may be that SMA type I is a result of abnormal function of the membrane to make it electrically inex- citable. Further electrophysiological studies at the cellular level are required to delineate this interesting finding.

ALICE A KUO
Department of Pediatrics
STEFAN-M PULST
DAWN S ELIASIV
CAMERON R ADAMS
Division of Neurophysiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
Correspondence to: Dr Cameron R Adams, Department of Neurophysiology, Cedars-Sinai Medical Center, 8631 West Third Street, Room 1145, East Tower, Los Angeles, CA 90048, USA.

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

Although the effects of a chronic overdosage with levodopa are well known, few cases of acute intoxication have been described. A particular problem in establishing a diagnosis of levodopa overdosage is the relatively short half life in the circulation of levodopa. If there is a delay in bringing an acutely intoxicated patient to hospital, perhaps due to late discovery, the blood concentration of levodopa could already be normal, corresponding to the peak levodopa concentration in Parkinson’s disease therapy) after 6–8 hours. Depending on the extent of the overdosage, the time could be even shorter. This report describes the clinical effects and the plasma concentrations of levodopa and specific metabolites over a period of 135.2 hours after ingestion of 30 tablets of carbidopa/levodopa (50 mg/200 mg tablets).

A 76 year old patient had a pre-existing mild akinetic rigid Parkinson’s syndrome, which had been treated for the past 1.5 years with 3×1 tablets of carbidopa/levodopa (50 mg/200 mg) a day without a substantial response. The weight of the patient was 74 kg. A known chronic obstructive airway disease was treated with a home oxygen appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 30 minutes later, the patient was found unresponsive, 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 EC was carried out before the diagnosis of intoxication had been made; it showed a pronounced subcortical arteriosclerotic encephalopathy with reduced brain volume. The patient was moved to the medical inten-
valse care unit and observed for 24 hours. The ECG showed a P pulmonale, but no other unusual features. Echocardiography showed normal right and left ventricular function with suspicion of right ventricular hypertro-
Distribution into muscles rather than metabolism may largely determine the plasma half life of levodopa and explain why this was only slightly altered with overdose. The measured peak concentration of 66 763 ng/ml is about 30 times higher than the peak concentration to be expected after taking one tablet of carbidopa/levodopa (50 mg/200 mg). It is apparent that the 30 tablets did not interfere with absorption or lead to a gastrointestinal paralysis due to the high dose of levodopa; the relation between amount ingested and plasma concentration seems to be linear, at least in this dose range.

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

H J STUERENBURG  
EG H SCHOSER  
Neurological Department, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Correspondence to: Dr Hans Joerg Stuermen, Neurological Department, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Telephone: 0049 40 4717 4832; fax 0049 40 4717 5086; email stuerenburg@uke.uni-hamburg.de


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

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

Huntington’s disease is a hereditary progressive neurodegenerative disorder. It consists of a triad of symptoms comprising motor, psychological, and cognitive abnormalities. The motor component consists of involuntary choreiform movements and increasing difficulties with voluntary movement. The degree of the involuntary movements is variable but in some patients can be very marked. Progression over time of the movement disorder in Huntington’s disease can be monitored using the quantitative neurological examination (QNE). This measure has three subscales, an eye movement scale, a motor impairment scale (MIS) quantifying voluntary movement, and a checklist scale measuring involuntary movement.1 2

Pharmacological control of the symptoms has been shown to be effective with dopamine antagonists,1 3 but their use is limited because of the side effects. Clinically the most problematic of these are sedation, cognitive slowing, increased mobility problems, and hypotension. The inability of traditional dopamine antagonists to improve functional capacity, despite ameliorating the involuntary movements, is likely due to suppression of voluntary motor activity.4 5 Tardive dyskinesia has occasionally been reported in patients with Huntington’s disease treated with these drugs.6 The atypical antipsychotic clozapine has been shown to be effective in improving the movement disorder. However, in a double blind randomised trial of clozapine which included patients who were already receiving traditional antipsychotic medication,7 a group who had not received drug treatments for their movement disorder, chorea was reduced in those who were antipsychotic naïve only and the authors concluded that clozapine was of little additional benefit in Huntington’s disease.8 Olanzapine is a new atypical antipsychotic drug. It is a thienobenzodiazepine structurally very similar to clozapine. Unlike clozapine it is not associated with the potentially serious side effect of agranulocytosis and therefore frequent blood monitoring is not necessary.

This report describes the progress of a man who has Huntington’s disease. He developed a marked movement disorder and was unable to tolerate both sulpiride and risperidone but had symptomatic improvement when treated with olanzapine. He is a man in his early 50s who had a confirmatory genetic test for Huntington’s disease in 1994, after the development of clinically obvious motor symptoms. It is likely that the onset of symptoms had occurred a few years previously as he had experienced difficulties in concentration and his 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 no early signs of his movement disorder. However there was no known family history of Huntington’s disease which might have led to an earlier diagnosis. By May 1995 his involuntary movements were becoming more noticeable, although control of voluntary movement was good. A trial of sulpiride commencing at 200 mg twice daily and increasing over 1 week to 800 mg daily was undertaken with a subsequent decrease in the frequency and extent of involuntary movement recorded in case notes; unfortunately the QNE was not repeated at this time. However, the patient experienced a subjective slowing of his cognitive processes, concurrently became depressed, and decided to stop the treatment within 3 weeks. Paroxetine, a selective serotonin reuptake inhibitor antidepres- sant, was started at a dose of 20 mg a day, which led to an improvement in his low mood. His involuntary movements continued to cause difficulties in his daily living. He was unable to sit comfortably in a chair and when out felt that he was being followed and was knocking into them. He agreed to a trial of
risperidone. This was started at a dose of 1mg twice daily, increasing to a dose of 1mg four times a day over a period of 2 weeks, stopped after a brief period. He developed hypoten-
sion (blood pressure 100/60 mm Hg), con-
pling 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 sulphird 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 sulphird for 4 weeks with no improvement in his movements, so it was discontinued. The patient continued to experience low mood and after the discon-
tinuation of sulphird, his antidepressant drug was changed to lofepiramine 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 una-
ware of the extent of his movements his eve-
rday life continued to be a problem. He wanted to pur-
chase of his movements his eve-
vryday life continued to be a

neurological basis of chorea in patients with
Huntington’s disease.5 The D2 antagonist
effects of olanzapine may explain its pos-
sible benefits in the improvement of chorea.
Effect of olanzapine may explain its pos-
sible benefits in the improvement of chorea.

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, 5H2A, 5H2C, 5HT3, a-1-
adrenergic, histamine H1, and 5 muscarinic
receptors. This binding profile is similar to
clozapine, another atypical antipsychotic
drug, but substantially different to the
conventional antipsychotic haloperidol.1 Preferential loss of D2 projection neurons which are involved in a feedback loop normally active in the suppression of involun-
tary movements is thought to be the patho-
ophysiological basis of chorea in patients with
Huntington’s disease.3 The D2 antagonist
properties of olanzapine may explain its pos-
sible 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 Hunt-
ington’s disease, therefore the D4/D2 ratio of
activity may also be relevant. Differences in
binding profile across a range of receptors
effect may explain clinical differences in outcome when comparing different antipsychotic
drugs.
Case report indicates that olanzapine may be a useful addition to the treatments for
movement disorder, for some patients, and
trolled trials of its use in Huntington’s
disease would be welcome.

**Patient characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at surgery</th>
<th>Sex</th>
<th>Years with PD</th>
<th>H and Y*</th>
<th>MIS</th>
<th>Chorea</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>F</td>
<td>7</td>
<td>2/2.5</td>
<td>22/7</td>
<td>L</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>15</td>
<td>2/1.5</td>
<td>55/15</td>
<td>L</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>12</td>
<td>2/2</td>
<td>45/22</td>
<td>L</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>14</td>
<td>2.5/4</td>
<td>69/36</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>13</td>
<td>2.5/3</td>
<td>48/27</td>
<td>L</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>F</td>
<td>15</td>
<td>2.5/4</td>
<td>55/NP</td>
<td>R</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 antipar-
kinson medication; ‡NP=not performed.

**Quantitative neurological examination scores showing the progress of the movement disorder.**

<table>
<thead>
<tr>
<th>Score</th>
<th>06/95</th>
<th>09/95</th>
<th>09/96</th>
<th>09/97</th>
<th>03/98</th>
<th>04/97</th>
<th>04/98</th>
<th>06/98</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chorea</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

HEATHER C DIPPLE
Department of Psychiatry, Leicester Royal Medical
Health Services Trust, Huntington’s Disease Service,
Mill Lodge, Mill Lane, Kegworth, Derby DE74 2EF;
UK. Telephone 0044 1509 670774.

1 Foltstein SE, Bender B, Leigh RJ, et al. The measurement of abnormal movements: meth-
ods developed for Huntington’s disease. Neu-
2 Foltstein S. Huntington’s disease: a disorder of
families. Baltimore: Johns Hopkins University
3 Quinn N, Marsden CD. A double blind trial of sulphird in Huntington’s disease and tardive
dyskinesias. J Neurol Neurosurg Psychiatry 1984;
neuroleptic treatment on involuntary move-
ments and motor performance in Huntington’s
Disease. J Neurol Neurosurg Psychiatry 1984;
47:848–52.
5 Schou J. Care of patients and families with
Huntington’s disease. In: Marsden CD, Fahn,
eds. Movement disorders. London: Butterworth,
6 Schott K, Reid S, Stevens I, et al. Neurolepti-
cally induced dystonia in Huntington’s disease: a
7 Bymaster FP, Caligari DO, Falcone JF, et al. Radiode-
ceptor binding profile of the antipsychotic
8 van Vliet JP, Sieling S, Vergeer M, et al. Clozap-
ine versus placebo in Huntington’s disease: a
double blind study. J Neurol Neurosurg Psychiatry
1997;63:35–9.

**Transient hiccups after posteroventral
pallidotomy for Parkinson’s disease**

Hiccup is defined as an abrupt intermittent,
involuntary, contraction of the diaphragmatic
and external (inspiratory) intercostal mus-
cles, with inhibition of expiratory intercostal
activity. This results in a sudden inspiration,
abruptly opposed by closure of the glottis.1 Hiccup may result from various structural or
functional disorders of the medulla, the affer-
ent or efferent nerves to the respiratory mus-
cles, and the gastrointestinal tract.2,3 Newson
Davis performed a study of hiccup with elec-
trophysiological techniques and concluded
that hiccup is served by a supraspinal mech-
nism 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 particu-
larly associated with structural lesions of the
medulla oblongata.

Since 1994 we have performed 66 palli-
dotomies 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 post-
eroventral globus pallidus at the border of the
medial and lateral segments are 2–3 mm
anterior to the midcommissural point, 5 mm
below the intercommissural line and 22 mm
lateral to the midline of the third ventricle.
Ventriculography was performed for target

1 Pallidotomies performed. No postoperative
hiccups were recorded.

**Letters, Correspondence, Book reviews, Correction**
localisation. Patients started with a short schedule of corticosteroids (5 days) the night before surgery. The hiccups started immediately after the operation or the next day, were intermittent, and the bouts of hiccup of six patients, with a duration of hours, resolved within 3 days after the procedure. One patient complained of yawning more often and frequent bouts of hiccup for 6 months.

Five patients were men. All patients were right handed. The mean age at surgery was 54 years and the mean duration of Parkinson’s disease was 12 years. All patients were taking levodopa. In four patients the hiccups appeared after a left sided pallidotomy. Patient 2 had a right sided thalamotomy 4 years before the pallidotomy. Patient 5 underwent a left sided pallidotomy 10 months before the right sided pallidotomy which caused the hiccups. The pallidotomies improved parkinsonism in the “off” state (table), contralateral dyskinesias, and pain accompanying Parkinson’s disease. Six patients had transient adverse events: four patients had a transient facial paresis postoperatively and two a slight transient dysarthria (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.¹

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 the GPe and putamen. In patient 5 the lesions were located in the posterior commissure and (B) 6 mm more ventral.

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.¹

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 the GPe and putamen. In patient 5 the lesions were located in the posterior commissure and (B) 6 mm more ventral.

Five months after left sided pallidotomy, MRI of patient 6: (A) transversal slice at the level of the anterior commissure and (B) 6 mm more ventral.

References:

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

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

None the less, many patients with emotionalism describe their crying as provoked by emotionally congruent experiences, which makes the tearfulness seem understandable.¹ In two previous studies ² 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;² a widely used measure of intrusive thoughts of the sort encountered in post-traumatic stress disorder—the impact of events rating scale;³ 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.⁴ All the measures are self-report questionnaires.

A total of 177 stroke patients were screened, of whom 112 were excluded. The 65 participants (29 men, 36 women) had a mean age of 71.8 years (range 43 to 88 years). Nineteen (29.2%) patients met our criterion for emotionalism,¹ a rate similar to that found in other studies. Their scores on the study measures are compared with the scores of patients without emotionalism in the table. It might be that these associations with emotionalism were accounted for by the greater general levels of distress experienced by those with emotionalism. We therefore undertook analysis of covariance with GHQ-12 and presence of emotionalism as the covariates, and each of the other test items in turn as the independent variable. The results showed an association, after adjustment for GHQ-12 score, between emotionalism and the impact of events subscales intrusion
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 intrusion subscale** Impact of events scale avoidance subscale* MASS1 Sense of lack of personal control over crying MASS Avoidance subscale* MASS Helplessness/hopelessness subscale** (n=118, p=0.001); the mental adjustment to stroke scale subscales helplessness/ hopelessness (n=11.71, p=0.001) and anxious preoccupation (n=8.05, p=0.006). The associations with emotionalism (F=14.79, p=0.052) and avoidance (F=6.06, p=0.05) 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 high 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 illness in a pattern similar to those reported by people with post-traumatic stress disorder. This unpleasant remembering is probably responsible for their higher ratings on anxious preoccupation. It is compatible with our finding in a previous study1 that irritability is associated with emotionalism; as irritability is a common response to threatening intrusive memories of the sort encountered in post-traumatic stress disorder. It may not be that emotionalism is a direct manifestation of post-traumatic stress disorder, although that condition has been described after stroke,2 but the analogy raises the possibility that an abnormal stress response is important. The mental adjustment to stroke scale subscales helplessness/hopelessness or anxious preoccupation may place them at risk of this disorder.

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

STEVEN ECCLES ALLAN HOUSE Division of Psychiatry and Behavioural Sciences in Relation to Medicine, University of Leeds, Leeds, UK

PETER KNAPP Stroke Outcome Study, Research School of Medicine, Leeds, UK

Correspondence to: Dr Allan House, Division of Psychiatry and Behavioural Sciences in Relation to Medicine, University of Leeds, 15 Hyde Terrace, Leeds LS2 9LT, UK.


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, Bencze2 reported on 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 electrophysiologi-cal features. By contrast, another report described two patients with stiff limb syndrome who tested positive for anti-GAD antibody.3 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 neoplasia. We present a patient clinically consistent with the stiff limb syndrome who was found to have autoimmune-3 body 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 ankle 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 fibre density and terminal axonal swelling distally, consistent with a small fibre sensory neuropathy.4 The patient would not tolerate EMG. Magnetic reso-nance images of the brain and the entire spinal cord were normal. Fine needle aspiration of a soft tissue right axillary mass showed 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 spontaneous extension of hallucis longus. The patient died 18 months after symptom onset. Gross necropsy attributed the cause of death to aspiration pneumonia. Neuropathological evaluation showed a grossly normal and spine. 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 recog-nised as a heterogeneous disorder.5 Other case reports have documented patients with “focal” disease involving either lower or upper extremity posturing,6 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 abnormal CSF. Our patient is only the second reported with criteria for classic SMS and malignancy.

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 molecule is a manifestation of involvement of small fibres.

The search for an occult primary 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 abnormal CSF. Our patient is only the second reported with criteria for classic SMS and malignancy. 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 molecule is a manifestation of involvement of small fibres.

Changes in the symptoms of poisoning in relation to each course of haemodialysis. Scales in the vertical axis represent the arbitrary measurements of severity of each symptom; the numbers indicating day(s) after onset; ↓ = haemodialysis).
ally within an hour. She could open her eyes and she communicated and answered questions correctly by blinking. Pupillary reflex recovered and voluntary eye movements were limited only at the extreme lateral gaze. Muscle power was grade 3 and 4 in the proximal and distal muscles of the four limbs. Tendon reflexes were still absent. She was taken off mechanical ventilation the next day. Her clinical condition continued to improve and her symptoms subsided in a stepwise pattern, in response to each course of haemodialysis (figure). When recalling, she could remember certain events such as the recording of the EEG, but was “too weak to move” at that time. She regained her initial strength by the time she was discharged on day 16.

When analysing the remains of the cooked fish (identified as \textit{Onychostomus unicolor}), tetrodotoxin was demonstrated by thin layer chromatography, high performance liquid chromatography, and cellulose acetate membrane electrophoresis. Toxicity was assayed by using Institute of Cancer Research strain adult male mice and the toxicity score was 25 mouse units (MU)/g in fish muscle (1 MU = 0.178 µg in the ICR strain mouse).1 Tetrodotoxin exerts its effect through binding with and blocking the voltage dependent sodium channel.7 The voltage clamp experiments showed that tetrodotoxin diminished the sodium inward current responsible for the depolarization of excitation membrane. The gating properties of the sodium channel, such as the activation and inactivation mechanism, are not altered—that is, the sodium channel is not permanently damaged and its function recovers when the bound toxin is released. In uraemia, ion conductance through the sodium channel is also impaired. Sodium permeability through excitatory membranes is reduced and small inward sodium current and reduced action potential amplitudes are noted in experimental uraemic neuropathy.8 By contrast with the effects of tetrodotoxin, uraemia changes the basic property of the sodium channel by an increased inactivation and an impaired activation mechanism. The excitability of peripheral nerves will be more significantly depressed when these two conditions combine. The synergistic effect of uraemia and tetrodotoxin is obvious in this incident in which the patient and her husband ingested roughly an equal amount of tetrodotoxin (about 200 µg, calculated from toxic score times the weight of ingested fish). The amount is about 10% of the estimated lethal dose in humans—2200 µg/60 kg body weight9 (body weights of the patient and her husband were 54.5 and 62 kg respectively)—and caused no clinical evidence of poisoning in the healthy person. It was of interest that the CNS was relatively spared from the toxicity as the EEG showed a posterior dominant, promptly reactive alpha rhythm and the patient retained consciousness when the symptoms were at their most severe.

One of the most striking clinical features in our patient was the response to haemodialysis. Despite the small amount of toxin ingested, the dramatic improvement of her clinical condition was most likely attributed to the rapid elimination of absorbed toxin in the course of haemodialysis, rather than spontaneous recovery. The physical and chemical properties of tetrodotoxin are also supportive to this hypothesis.10 It has a low molecular weight (C$_{11}$H$_{17}$N$_{3}$O$_{8}$), is water soluble, and not significantly bound to protein—all these features are often found in toxins amenable to haemodialysis. Traditionally, the management of tetrodotoxin intoxication is mainly supportive, such as gastric lavage to remove unabsorbed toxin and machine assisted ventilation when respiration is severely affected. We suggest that haemodialysis may be an effective method in the treatment of tetrodotoxin intoxication.

MIN-YU LAN
SHUNG-LON LAI
SHUN-SHENG CHEN
Department of Neurology, Kaohsiung Medical College, Kaohsiung City, Taiwan
DENG-FU WU HANG
Department of Food Science, National Taiwan Ocean University, Keelung City, Taiwan

Correspondence to: Dr Shun-Sheng Chen, Department of Neurology, Kaohsiung Medical College Hospital, 100 Shih-Chung 1st Road, Kaohsiung City 807, Taiwan. Telephone 00886 7 3232437; email sheng@mail.nsysu.edu.tw

4 Tam I. Toxicological studies of puffers in Japan. Tokohoku-Ishin (Tokyo) 1945;103.

Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome

The clinical entity critical illness polyneuropathy occurs almost exclusively in patients in critical care units and has been characterised as a complication of sepsis and multiple organ failure.1 Critical illness polyneuropathy may be a common cause of the difficulty in weaning patients from the ventilator, particularly those who show intractable ventilator dependence. All the measures used to prevent or treat respiratory failure are the main methods now used to deal with critical illness polyneuropathy. Knowledge of this type of polyneuropathy is of help in making the appropriate decision on ventilator techniques, nursing care, prognosis, and overall management. Moreover, recognition of critical illness polyneuropathy indicates the need for physiotherapy, rehabilitation, and other supportive measures as the patient recovers. Bolton et al.2 have made an important positive contribution to the care of patients with critical illness polyneuropathy. The actual aetiology, however, has yet to be determined. The pathogenesis needs to be clarified to treat patients more effectively.

Critical illness polyneuropathy invariably occurs at the peak of critical illness and sepsis, but in Guillain–Barré syndrome there is a brief period of recovery after a relatively minor illness or inoculation. 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 infantile paralysis. 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 notably 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 biopsy 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.10 Zochodne et al. (excluding Bolton) therefore concluded that the two types of polyneuropathies most probably are separate entities.

Guillain and colleagues enumerated the clinical and spinal fluid features of patients with acute flaccid paralysis without regard for the underlying pathology or physiology. Classic 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 electromechanical abnormalities consistent with demyelination have been taken as support for the diagnosis of Guillain–Barré syndrome. Feasby et al.4 focused in particular 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 made a slow recovery, probably reflecting the need to regenerate axons rather than remyelinate. 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.4 confirmed the existence of the acute motor-sensory axonal neuropathy (AMSAN) pattern of Guillain–Barré syndrome described by Feasby et al.4

Infection caused by the gram negative bacterium \textit{Campylobacter jejuni}, a leading cause
of acute diarrhoea, commonly precedes the development of Guillain–Barré syndrome.1 There is a close association between axonal Guillain–Barré syndrome and antecedent C jejuni infection.3 The antecedent infectious symptom was diarrhoea in three of five patients with axonal Guillain–Barré syndrome described by Feasby et al.1 Observations by Griffin et al2 confirmed that AMSAN follows C jejuni infection. Serum samples from patients with axonal Guillain–Barré syndrome subsequent to C jejuni enteritis often have high class autoantibodies to gangliosides GM1, GM1b, GD1a, or GaINAc–GD1a in the acute phase of the illness,4 and there is molecular mimicry between these gangliosides and the lipopolysaccharides of C jejuni isolates from patients with Guillain–Barré syndrome.5 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, Hagenes et al4 reported a case of “C jejuni bacteremia and subsequent Guillain–Barré syndrome” that occurred in a patient with chronic graft versus host disease and chronic graft versus host disease 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 GaINAc–GD1a could be used as immunological markers for axonal Guillain–Barré syndrome.6 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.

Nobuhiro Yuki
Koichi Hirata
Department of Neurology,
Dokkyo University School of Medicine,
Japan

Correspondence to: Dr Nobuhiro Yuki, Department of Neurology, Dokkyo University School of Medicine, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi 321-0293, Japan.


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

Recently, a new technology known as repetitive transcranial magnetic stimulation (RTMS) has been developed.7 In 1994, the use of magnetic stimulation in clinical psychiatry was suggested.8 Since then, it has been used in the study or treatment of obsessive-compulsive disorder, conversion disorder, schizophrenia, and particularly, depression.9

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,10 specially under conditions of task activation.

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

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

All patients were admitted to hospital. Inpatients underwent the UKU side effects scale,11 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 subtest 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-
Sensory alien hand syndrome

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

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

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

Research conducted in the 1980s has found that the same electrical brain wave changes that characteristically precede all limb movements, occur several 100 ms before we seem to consciously decide to move a limb. If our conscious decision to act is preceded by brain changes that anticipate action, then our “decision” to choose how to behave or “freedom”, as in free will, is in fact illusory. Our choices have in a sense been decided beforehand by our brains. Spence asserts that evidence such as this, combined with phenomena such as alien hand syndrome, means that philosophers have to reconsider whether we have free will. He argues that these data suggest that our sense of agency is illusory and it follows that most of us share in common the useful delusion that we have free will. Patients with alien hand syndrome have lost this experience in relation to a particular limb. There is a sense then that those who experience the syndrome are closer to the reality of how much we are responsible for our actions than the rest of us. This is because they lose the function of the part of the brain that normally works to make us think that we have conscious freedom of will. They develop the experience, therefore, of becoming mere remote spectors to the actions of the body.

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 assumption that we lose our conscious sense of voluntary control over our bodies, our minds have to come up with an explanation for the location of 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 apprehension leads us to misinterpret inherent reflexive acts of our hands, such as scratching or rubbing, as malevolently inspired. Plus it could be that our interpretation of spurious possession in turn inspires the patient, only this is beyond our conscious awareness.

It may therefore be that we need to believe in our own free will and personal control over our actions, because if we did not, the experience of our bodies acting as if we merely came along for the ride, too frightening. Also, we may no longer believe that our bodies or its relevant parts belong to us. All neurologists who have reported alien hand syndrome remark on how psychologically disturbing the symptom is for the patient. Psychiatrists would be interested in the parallels between alien hand syndrome and the empathy phenomenon. So the fact that every case, plus the fact that the two diseases may share corpus callosum pathology, could go some way to explaining why schizophrenic symptoms are frightening to the patient. So it seems we know that our limbs belong to us because they obey us. When they seem to stop responding to our wills, we conclude that our limbs are no longer our own, and try to fend them off. Hence it would seem that one of the prices we had to pay for conscious awareness of ourselves to evolve as a function of the brain, is the delusion that we are responsible for all our actions. If we had conscious awareness of ourselves, but no sense of free will, our bodies would feel alien to us.

The philosophical importance of alien hand syndrome is that it shows emphatically via neurology that it is possible to drive a wedge between consciousness and the experience of free will. The brain had to develop the sensation of free will after developing consciousness, because being without the sensation of free will produces extremely negative emotional experiences. So the fact that every case, so far reported of alien hand syndrome imputes negative intent to the alien limb might not be an incidental finding, but a core aspect of the disorder.

R PERSAUD
The Maudsley Hospital, Croydon Mental Health Services, Westways Rehabilitation Unit, 49 St James’s Road, West Croydon, Surrey CR9 2RB, UK. Telephone 0044 181 700 8512; fax 0044 181 700 8504; email rajiendra@btinternet.com


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
opposed to the idea that “we know our limbs belong to us because they obey us”, we know that our limbs belong to us because they provide us with sensory input that is recognised as self. Many patients with movement disorders or paralysis lose control of their limbs but still have no difficulty in realising them as self. Indeed even in “phantom limb” there is sense of self due to central processes in the absence of a limb. Our patient, as do others with paresis 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 of the pattern of sensory ownership that accompanies our own limb movements. When this pattern never reaches specific cortical regions, then the limb is not perceived as self; called “amorphogenesis” by Denny-Brown and Banker. Sensation 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 whose processing is intact.

It is not our clinical experience nor the conclusions based on published reports that all patients suffering with alien hand syndrome are tetraparetic by the affected limb. In one author’s experience (BHP), two patients with alien hand syndrome and related intermanual conflict were irritated by but not terrified by their opposing limbs simultane-ouslyague valve that the other patient was amused but rather indifferent to his affected left side. The most terrifying situation we have heard is when the patient identified his affected left side as belonging to his mother. We have treated a patient reported by Heilman’s group with persistent alien hand syndrome referred to it as “my little sister”. Similar to our experience, they suggest that a particular symptomatology type may be necessary given that most patients with collosal infarcts or tumours do not emphasise this complaint.

Unlike our case of limited duration, the persistence of alien hand syndrome is dependent on mesial frontal dysfunction. These patients rarely deny that the affected limb belongs to them. Instead, they understand it in terms of their “anarchic hand”. Hence, although the initial syndrome may result in disjunctive and terrifying perceptions, it seems that the brain quickly re-establishes its control by presently unknown adaptive capacities. Furthermore, why it almost exclus-ively 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.

HAKAN AY FERDINANDO S BUONANNO DEAN A LE WALTER J KOROSHEZT Department of Neurology, Stroke Service, Massachusetts General Hospital, Harvard Medical School, 32 Fruit Street, Boston MA 02114, USA

BRUCE H PRICE Department of Neurology, McLean Hospital, 115 Mill Street, Belmont MA 02178–9106, USA

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 whether an involuntary limb movements contralateral to haemody-namic failure from severe carotid artery occlusive disease. The authors evoke an “exhausted cerebral vasoreactivity in the hemispheres opposite the involuntary limb movements”. In their report, involuntary movements affected only the limbs, and displayed no tonic contraction, tonic-clonic jerking, or Jacksonian march and no epileptic activity during attacks. These findings led the authors to strongly argue against seizures as the cause of limb shaking in these transient ischaemic events.

In contradistinction, a 72-year-old right handed man was admitted to our hospital with a 3 month history of episodic weakness and numbness of the right arm. The patient then had six discrete stereotypic episodes of right arm weakness and clumsiness that were also associated with involuntary speech in a foreign language. Several episodes of dysarthria, numbness and weakness of the right arm and leg (MRc grade 4/5) were seen, unrelated to posture, some of which occurred when the patient was supine. Movements were characterised by slight tremulousness and asterixis-like move-ments 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 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 disappeared, tremulousness, and EEG epileptiform activity stopped. They have not recurred over the past 5 years.

The literature includes several cases of focal motor inhibitory seizures causing weakness. Although it is impossible to prove a negative, it could be argued that although no epileptiform or other evidence of seizure activity is present in a particular case, the abolition of ongoing clinical and EEG evidence of inhibitory motor activity by intravenous diazepam argues in favour, at least in part, of an ictal contribution. The fact that in virtually all reported cases, abnormal movements are more definitively resolved by carotid endarterectomy, argues for an under-lying ischaemic aetiologies that induces focal seizures. There are few reports that clearly delineate the interaction and association of inhibitory focal motor seizures and transient ischaemic attacks, as there are few sequential trials of antiseizure drugs or anticoagulation (under EEG monitoring) and finally carotid endarterectomy. Several authors support the concept of an inhibition of motor function in parietal and secondary somatosensory re-gions by seizure activity which then inter-rupts the sensory feedback loop to motor integration with inhibition of subcortical and cortical areas.

PETER W KAPLAN Department of Neurology, University Hospital of Zurich, Switzerland

Letters, Correspondence, Book reviews, Correction


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 symptoms such as sensorimotor deficits and difficulty with speaking, EEG evidence of seizure activity, and cessation of the TIAs after the administration of an anticonvulsant drug. 1. 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 face or muscles. Patients with attacks of shaking movements of the limbs have no EEG evidence of epilep-tic activity, and involuntary movements do not stop after administration of anticonvul-sive therapy. (2) Although the patient pre-sented 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 involun-tary movements as well as the sensorimotor deficits of Kaplan’s patient were not related to paresis. (4) The pathogenesis of the attacks is due to disinhibition of subcortical control mechanisms as a result of ischaemia.

In our opinion, it is not clear whether the asterixis-like movements of the outstretched right arm of Kaplan’s patient are due to epi-leptic seizures, because unilateral asterixis of the outstretched arm has been reported with contralateral vascular lesions affecting almost all cerebral structures involved in visceral control including ischaemia in the territory of the middle cerebral artery.

RALF W BAUMGARTNER

Department of Neurology, University Hospital of Bern, Switzerland

IRIS BAUMGARTNER

Division of Angiology, University Hospital of Zurich, Switzerland

Correspondence to: Dr Ralf W Baumgartner, Neurologische Klinik, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland. Telephone: +41 1 4441 804; fax 0041 1 255 43 80; email Strub@neur Bal.unizh.ch


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 meningitis, and acute haemorrhagic encephalitis. 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 Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recognise the characteristic EEG of Creutzfeldt-Jakob disease? I surely hope not. Finally, the slide tests are a little too well; would an MRCP candidate really be expected to recogn
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 occipital rhizotomy in spinal cord injury.

This is an ambitious attempt at being comprehensive. The editors themselves worry that the emphasis favours surgical conditions. Although this might be the case, many surgical terms in the text may be unfamiliar to many readers. 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 for particularly practical, and a must for both doctors dealing with spinal disease and for patients themselves who are often uninformed (our fault, not theirs). The chapter on depression illness will be food for thought for many doctors who enjoy recreational diving, for although studies have not yet shown adverse affects on the quality of life in those who dive frequently but without incident, 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 a intramedullary arteriovenous malformation). In addition to imaging many of the chapters also make good use of schematic diagrams and line drawings to enhance the text.

Drs Engler, Cole, and Merton end their preface by commenting that “Our main hope, however, is that the chapters will read as a series of views on the spinal cord and its disease, so that a surgeon may learn about 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 socio-economic 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 within the context of their lifestyles and women’s health and its relation with the law. This chapter considers issues such as coercive approaches to preventing foetal harm, those relating to informed consent to medical treatment, and difficult choices with neurological implications. The law and the case examples are exclusively American but the issues are universal. This opening section leaves no doubt that this is a book that has taken female issues extremely seriously.

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

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.