Certainly, none of my patients with migraine had any clinical similarity with such a patient. I hope that Wilder-Smith is not suggesting that these patients with migraine have transcranial Doppler sonography to verify the diagnosis.

Further experience and more confidence in clinical diagnosis, obtained through meticulous evaluation of symptoms in classic cases, can lead to hospital lobe epilepsy, as may be needed. This is the main message of my report.

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Antiganglioside antibodies in the CSF of patients with motor neuron diseases and Guillain-Barré syndrome

In a recent report in this Journal Stevens et al described increased titers of antiganglioside antibodies (AGAs) in the CSF of patients with amyotrophic lateral sclerosis.1 They concluded that patients with amyotrophic lateral sclerosis have raised CSF IgM antibodies to all gangliosides except asialo-GM1 (A-GM1), due to a chronic intrathecal immune response. The authors did not, however, evaluate other motor neuron disorders related to amyotrophic lateral sclerosis and with sometimes borderline diagnosis.2 We have studied AGA reactivity in the CSF of 23 patients whose diagnosis included (a) four strictly defined patients with amyotrophic lateral sclerosis; (b) 13 patients with lower motor neuron signs, from which six had a syndrome of multifocal motor neuronopathy with conduction block and two had overactive tendon reflexes in limbs, with weak, wasted, twitching muscles, and Babinski sign or ankle clonus; and (c) six patients with Guillain-Barré syndrome and three patients with chronic inflammatory demyelinating neuropathy. Thirty three subjects were tested as controls, including 28 patients with other neurological disease and 10 people whose CSF was normal and in whom irrelevant diseases, such as migraine or tensional headache, were found after later studies (normal controls).

Serum and CSF were assayed for antibodies to gangliosides GM1, GD1b, GD1a, and A-GM1 by enzyme linked immunosorbent assay (ELISA) according to the method described by Noble-Orraca et al.1 Results were expressed as the mean absorbance obtained from the well coated with ganglioside minus the absorbance obtained from a bovine serum albumin coated well. Results were considered positive when this difference exceeded 0.1. Concentrations of AGA were considered to be increased if this titre was higher than 3 SD from the mean of the results obtained in the 10 normal controls. In patients with high antibody titre by ELISA, reactivity to gangliosides was confirmed by high performance thin layer chromatography according to the method described by Ilyas et al.1 Total CSF IgM concentration was measured by ELISA.1 Intrathecal production of IgM AGAs was determined by measuring intrathecal synthesis values per unit weight of IgM in serum and CSF, and expressing results as the ratio CSF values:serum values.

Increased CSF anti-GMI IgM antibody concentrations, with intrathecal synthesis, were found in six of the 23 patients (two patients with amyotrophic lateral sclerosis, two patients with lower motor neuron signs and hyperreflexia and two patients with Guillain-Barré syndrome). And in one of 28 patients of the group of patients with other neurological diseases (Fisher's test; P = 0.037). Intrathecal synthesis of anti-A-GM1 and anti-GD1b antibodies was also detected in four of these six cases. Two of these patients, one with amyotrophic lateral sclerosis and one with Guillain-Barré syndrome, also had low positive titres of anti-GM1 IgM antibodies. The ratio of CSF values:serum values for the AGAs was significantly higher in the patient group than in the group with other neurological diseases and the control group (table). No intrathecal synthesis of any GM1 anti-bodies was found in CSF of the patients with other neurological diseases and normal controls, even in the cases when such antibodies were present in serum. In patients with Guillain-Barré syndrome there was no correlation between CSF anti-GMI anti-body titres and the degree of blood-brain barrier disruption expressed as the CSF:serum ratio of these indices (figure). In the patients with intrathecal synthesis of anti-GMI antibodies, no abnormalities in cell count, albumin, IgG, IgM, albumin index, IgG index, or IgM index were detected.

Intrathecal synthesis of AGA was not associated with a lower functional status or clinical evolution.

According to these results CSF antiganglioside reactivity is present in some patients with specific motor neuron disorders—namely, amyotrophic lateral sclerosis and lower motor neuron signs with hyperreflexia—but not in other forms of lower motor neuron signs. This seems highly specific for these neurological disorders, excluding the acute demyelinating inflammatory polyneuropathies, the clinical pattern of which is easy to differentiate from other motor neurone disorders. The reactivity against GM1, GD1b, and A-GM1 suggest that Gal[β1,3]NacGal is the common reactive epitope. It is still necessary to clarify if cases of amyotrophic lateral sclerosis and other motor neuron disorders when CSF antiganglioside reactivity is negative, represent a different pathogenetic mechanism, a failure of detection of intrathecal AGA reactivity due to a change in antibody profile during the evolution of the disease, or an imprecise detection method.

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Sexton et al reply:
The authors report significantly increased antibody titres and evidence of intrathecal production of anti-GM1 antibodies to ganglioside-GM1 (AGM1), GD1b, and GM1 in the CSF of patients with amyotrophic lateral sclerosis and lower motor neuron disease, as well as from Guillain-Barré syndrome. They conclude that CSF immunoreactivity to AGM1, GD1b, and GM1 is specific for these disorders. Although they interpret their data as affirmative for an intrathecal immunological process in motor neuron disease,1 they report antibody spectra differing from those in our sample of patients with amyotrophic lateral sclerosis. On closer scrutiny, this seems not to be the case, as anti-AGM1 IgM antibodies do appear in CSF of nine of 35 patients of our previously reported sample. Anti-AGM1 antibodies are not, however, part of the panel of antibodies that are typically raised in this disease.

Although the comparative approach of Iniguez et al is up to date, due to the small sample size the results are difficult to interpret in terms of specificity and sensitivity—for example, the CSF-IgM and the IgG index of their patients are raised (which was not the case in our study) but are not reported as significant due to large within-group variation. The results within the three

<table>
<thead>
<tr>
<th>Mean (SD) blood and CSF variables measured in patients and control groups</th>
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<tbody>
<tr>
<td><strong>Normal control group</strong></td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Albumin index</td>
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<tr>
<td>IgG index</td>
</tr>
<tr>
<td>GM1 index</td>
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<tr>
<td>CSF: serum ratio (GM1)</td>
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<tr>
<td>CSF: serum ratio (GD1b)</td>
</tr>
<tr>
<td>CSF: serum ratio (AGM1)</td>
</tr>
</tbody>
</table>

*Analysis of variance.
diagnostic groups are heterogeneous, with only six of 23 patients (combined group, with amyotrophic lateral sclerosis, lower motor neuron disease, and Guillain-Barré syndrome) showing raised titres against GM1 and only four of 23 (one of four patients with amyotrophic lateral sclerosis) against AGM1 and GM1. As in our sample, this may reflect heterogeneity of disease processes in motor neuron disease. Already these findings argue against a specific pathogenetic role of antganglioside antibodies. As was pointed out in our study, there is no characteristic antibody pattern (in 75% of our sample of 35 patients with amyotrophic lateral sclerosis); however, we warn against considering them specific.

There is a similar debate about the role of serum antibodies in motor neuron disease and especially of antibodies to GM1: raised titres of anti-GM1 antibodies are not specific for motor neuron disease, but when there are motor neuron symptoms, they can also be found in lower motor neuron disease type.2,3 Whereas the first studies claimed an association of GM1 antibodies and amyotrophic lateral sclerosis, Willison et al4 found in their 1993 casecontrol study a lack of association of amyotrophic lateral sclerosis and antibodies to GM1. These data support our earlier findings, that GM1 may not be specific for motor neuron disease or amyotrophic lateral sclerosis (in our sample only four of 35 patients with amyotrophic lateral sclerosis had serum IgM anti-GM1 serum antibodies). Thus to establish a possible pathogenitic or diagnostic role for these antibodies, studies with large sample size and tests for reactivity to multiple antigens are needed.1


Three decades of normal pressure hydrocephalus: are we wiser now?

In his excellent editorial on this subject, Vanneste5 refers to the place of CSF removal and pressure monitoring tests in the diagnosis of normal pressure hydrocephalus, and their possible predictive role for the success of shunt procedures. With regard to lumbar CSF infusion methods, he regards their invasiveness and the need for technical expertise, as making them unsuitable for widespread clinical use. In the early days of recognition of the syndrome, and well before the advent of modern imaging techniques, we described a simple bedside CSF manometric procedure.2 This involved CSF pressure readings after withdrawal of fluid into a syringe and its reinjection after the pressure returned to its previous level. The immediate resulting pressure rise lasted for only a few minutes in cases where normal pressure hydrocephalus was not present, but for a long period in those patients in whom the diagnosis of normal pressure hydrocephalus was considered acceptable. The assumption, in view of current knowledge of the physio-pathological basis of normal pressure hydrocephalus prevalent at the time, was that the test reflected reduced fluid reabsorptive capacity necessary for the syndrome. It would seem now that according to Vanneste’s reference to modern views, the results would have to be explained somehow in terms of obstructions, either subarachnoid or intraventricular. The essential advantages of this method were of course the absence of risks associated with the introduction of any material other than the patient’s own CSF, together with its technical simplicity. The possible predictive value for benefits resulting from shunt diversion was not followed up at that time.

Incidentally I think that we owe McHugh’s credit for the first report describing the clinical normal pressure hydrocephalus syndrome.

Post-traumatic syringomyelia

The excellent study of Squier and Leh1 reports that post-traumatic syringes based on clinical examination and spinal CT occur with an incidence of 1-4% per annum. Based on MRI studies with an incidence of 12-22%. Their own pathological findings in 30 spinal cords examined between two years and 43 years after severe spinal injury yielded four cases (20%) with cysts extending at least two segments from the site of original trauma. The table summarises the positive results.

<table>
<thead>
<tr>
<th>Time after injury</th>
<th>Level of initial cord lesion</th>
<th>Extent of pathological syrinx</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>T5</td>
<td>T5-T8</td>
</tr>
<tr>
<td>12 weeks</td>
<td>T5</td>
<td>C4-C6</td>
</tr>
<tr>
<td>22 years</td>
<td>Wy2</td>
<td>C6-T12</td>
</tr>
<tr>
<td>34 years</td>
<td>L3</td>
<td>C8-L3</td>
</tr>
</tbody>
</table>

Before we accept the important inferences suggested by these data, we should examine the defining criteria. The authors do not provide clinical data to establish to what extent, if any, their four patients had clinical signs of a syrinx. A mixture of myelomalacia, fibrillary gliosis, and often cystic change is found at the level of injury in all cases after the first few months, and extends locally, rostrally, and/or caudally in relation to the severity and extent of the softening, infarction, and atrophic damage. Any persisting bone fragments or malalignment may increase the size of the cord damage and cyst formation.

The criterion of a cystic cavity extending for at least two segments is, I suggest, arbitrary. For if we took the defining limit as two segments, then the incidence would be one in 20 (5%), a figure roughly that previously accepted for clinical posttraumatic syringomyelia. This single case survived 34 years from an injury of the age of 25. It may be that many patients with an extensive syrinx shown at MRI have no clinical signs, and we do not know how long it takes for the MR image of a syrinx to become symptomatic; indeed in some such injuries in middle aged and elderly people it is likely that the syrinx may never cause appreciable symptoms or deterioration of neurological function. The medicolegal implications are self-evident.

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Verbal fluency in cortical and subcortical dementia

In a recent issue Rosser and Hodges5 have presented some potentially interesting data relating to measures of verbal fluency in patients with Alzheimer type dementia, Huntington’s disease, and progressive supranuclear palsy. Their main finding is unfortunately dubious in view of an inappropriate statistical analysis.

The effect being sought by Rosser and Hodges5 and which they claim to have found, is a differential pattern of performance across different measures of fluency between the different patient groups. To confirm what they were seeking in statistical terms, we set out to see whether the median the demonstration of a significant interaction between the patient groups and type of measure. In their investigation they have employed four separate groups (including a normal group as well as the three patient groups already mentioned) with patients in each of these being tested on three separate fluency measures. This corresponds to what is commonly described as a split plot analysis of variance model5 having both within subject and between subject effects. Data obtained in accordance with this model and subjected to an appropriate analysis do enable the computation of a groups × measures interaction.

By contrast what Rosser and Hodges’ report for their statistical analyses are three one way analyses of variance carried out on each of the three measures with these followed by post hoc comparisons of particular pairs of groups. Apart from possibly being unsuitable in other ways, this form of analysis does not permit the computation of interaction terms. It is also possible for the effects described as emerging from these analyses to appear and yet to find that the more appropriate analysis fails to achieve the
MATTERS ARISING: Antiganglioside antibodies in the CSF of patients with motor neuron diseases and Guillain-Barré syndrome

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