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

In a recent report in this Journal Stevens et al described increased titres 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 neuropathy with conduction block and two had overtactive tendon reflexes in limbs, with weak, wasted, twitching muscles, spasticity, Babinski signs and ankle clonus; and (c) three 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 antigangliosides by ELISA (ELISA) according to the method described by Noble-Orazi 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 titres by ELISA, reactivity to gangliosides was confirmed by high performance thin layer chromatography according to the method described by Ilyas et al.4 Total CSF IgM concentration was measured by ELISA.5 Intrathecal production of IgM AGAs was determined by measuring the optical density values per unit weight of IgM in serum and CSF, and expressing results as the ratio CSF values:serum values.6

Increased CSF anti-GM1 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 IgM 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 and anti-GD1b IgM antibodies and were 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-GM1 antibody titres and the degree of blood-brain barrier disruption expressed as the CSF:serum albumin ratio.

The authors report significantly increased antibody titres and evidence of intrathecal production of anti-AGMI (A-GM1) and 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 AGMI, GD1b, and GM1 is specific for these disorders. Although they interpret their data as confirmative for an intrathecal immunological process that is typical of patients with amyotrophic lateral sclerosis, 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-AGMI IgM antibodies do appear in CSF of nine of 35 patients of our previously reported sample. Anti-AGMI 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
Three decades of normal pressure hydrocephalus: are we wiser now?

In his excellent editorial on this subject, Vanneste 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. 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 the pathophysiologic basis of normal pressure hydrocephalus prevalent at the time, was that the test reflected reduced fluid reabsorptive capacity responsible for the syndrome. It would seem now that according to Vanneste’s reference to modern views, the results would have been explained somehow in terms of obstructions, either subarachnoid or intraventricular. The essential predictive value for benefits resulting from shunt diversion was not followed up at that time. Incidentally I think that we owe McHugh credit for the first report describing the clinical normal pressure hydrocephalus syndrome.

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Post-traumatic syringomyelia

The excellent study of Squier and Leht1 reports that post-traumatic syringes based on clinical examination and spinal CT occur with an incidence of between 1-1 and 4-5%; based on MRI studies with an incidence of 12-22%. Their own pathological findings in 20 spinal cords examined between two days 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 summarizes 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>T7</td>
<td>C4-C7</td>
</tr>
<tr>
<td>22 weeks</td>
<td>W2</td>
<td>W2-W12</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, fibroblastic glissis, 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 lower than three, the incidence would be one in 20 (5%), a figure roughly that previously accepted for clinical post-traumatic syringomyelia. This single case may have been an early example of syringomyelia. The advent of modern imaging techniques, their diagnostic and predictive role for the syndrome. It would seem now that according to Vanneste’s reference to modern views, the results would have been explained somehow in terms of obstructions, either subarachnoid or intraventricular. The essential predictive value for benefits resulting from shunt diversion was not followed up at that time. Incidentally I think that we owe McHugh credit for the first report describing the clinical normal pressure hydrocephalus syndrome.

1 Vanneste JAL. Three decades of normal pressure hydrocephalus: are we wiser now? J Neurol Neurosurg Psychiatry 1994;57: 1021-5.

Verbal fluency in cortical and subcortical dementia

In a recent issue Rosser and Hodges1 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 Hodges1 and which they claim to have found, is a differential pattern of change in measures across different measures of fluency between the different patient groups. To confirm what they were seeking in statistical other ways, this form of analysis does not demonstrate a significant interaction between the patient groups and type of measure. In their investigation they have employed four separate groups (including a more control 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 model1 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 group’s × measures interaction.

By contrast what Rosser and Hodges1 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