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 AGA titres 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.1 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 hereditary tendon reflexes in limbs, with weak, wasted, twitching muscles, and Babinski sign or 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 antibodies to gangliosides GM1, GD1b, GD1a, and A-GM1 by enzyme linked immuno- sorbent assay (ELISA) according to the method described by Nabielek et al. 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. Total CSF IgM concentration was measured by ELISA.1 Intrathecal production of IgM AGA 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.

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 hypertreflexia and two patients with Guillain-Barré syndrome). One of these patients was 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 IgM in serum. 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 anti-GM1 IgM antibody 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-GM1 antibody titres and the degree of blood-brain barrier disruption expressed as the CSF:serum ratio of anti-GM1 antibodies, in the patients with intrathecal synthesis of anti-GM1 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 anti-ganglioside reactivity is present in 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. It seems highly specific for these neurological disorders, excluding the acute demyelinating inflammatory polyneuropathies, the clinical pattern of which is easy to differentiate from motor neuron diseases. The reactivity against GM1, GD1b, and A-GM1 suggest that Galβ1,3(Nac)Gal is the common reactive epitope. It is still necessary to clarify if cases of amyotrophic lateral sclerosis and lower 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.

Stevens et al reply: The authors report significantly increased antibody titres and evidence of intrathecal synthesis of anti-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 supportive for an intrathecal immunological process that is typically raised in this disease, 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 the anti-AGM1 IgM antibody 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