Demographic data, \([^{[125]I}]\text{IBZM SPECT, and bradykinesia pegboard test in patients with writer’s cramp and controls}

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Duration of disease (y)</th>
<th>([^{[125]I}]\text{IBZM SPECT}</th>
<th>Pegboard (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Writer’s cramp (n = 10)†</td>
<td>51-6 (9-0)</td>
<td>8.6 (3-9)</td>
<td>97 (1-1)</td>
</tr>
<tr>
<td>Controls (n = 12)</td>
<td>51-8 (11-0)</td>
<td>1-56 (0-10)***</td>
<td>9-8 (1-5)</td>
</tr>
<tr>
<td>Controls (n = 46)</td>
<td>55-9 (9-5)</td>
<td>1-88 (0-19)</td>
<td>9-8 (0-9)</td>
</tr>
</tbody>
</table>

Values in parentheses are SD.

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† Four patients had simple writer’s cramp and six had dystonic writer’s cramp.

possible involvement of dopaminergic striatal receptors in dystonia, we measured the availability of striatal D2 receptors in patients with writer’s cramp using \([^{[125]I}]\text{IBZM SPECT}.

Ten consecutive right handed patients (eight male and two female) were classified into four with simple and six with dystonic writer’s cramp depending on whether or not the symptoms appeared only during writing. None of the patients had been treated with neuroleptic, dopaminergic, or anticholinergic drugs for at least two years. Hydrokinetic rigidity, and resting tremor were absent in all patients. Bradykinesia of the hands was assessed with a pegboard test, measuring the time (s) required to invert eight pegs. Pegboard performances of patients were compared with that of 46 age matched controls. Results from \([^{[125]I}]\text{IBZM SPECT} were compared with 12 other age matched controls from our group.

A brain dedicated SPECT system, the Strichman Medical Equipment 810X, was used. Two hours after intravenous injection of approximately 185 MBq \([^{[125]I}]\text{IBZM (Cytopharm, Techno- cal University, Eindhoven), tomographic SPECT studies were performed. A maximum of 12 slices was made, starting at the orbitomeatal line and proceeding parallel to it (300 s/slice; inter-slice distance 1 mm). For analysis of specific striatal \([^{[125]I}]\text{IBZM binding, two slices with the highest striatal activity were summed and a template with fixed regions of interest for the striatum and occipital cortex was placed bilaterally on the summed images.} \) The ratio of the striatal binding divided by the occipital binding quantifies specific binding.

In the table (did not) differ among the three groups (t tests). Left and right \([^{[125]I}]\text{IBZM striatal : occipital ratios were significantly lower in patients than in controls (t test, } P < 0.000). There was no asymmetry between \([^{[125]I}]\text{IBZM ratios for the hemispheres in patients or controls (repeated measures multivariate analysis of variance (MANOVA) tests involving side, group, and group by side: } P > 0.05). The pegboard test did not differ between patients with writer’s cramp and controls in either hand (t tests), showing that the patients with writer’s cramp did not have bradykinesia. There was no correlation between age or duration of disease and \([^{[125]I}]\text{IBZM ratios (Pearson’s correlation coefficients). None of the variables differed between patients with simple and dystonic writer’s cramp.}

Chronic sensory ataxic neuropathy and ophthalmoplegia with oculomotor nerve hypertrophy associated with IgM antibodies against gangliosides containing disialyl groups

Recent studies have shown that serum anti-ganglioside antibodies may be involved in various immunemediated peripheral neuropathies. We report an investigation of anti-ganglioside antibodies in a patient with chronic sensory neuropathy and ophthalmoplegia associated with oculomotor nerve hypertrophy.

A 40 year old man had been in good health when he developed subacute diplopia in 1987. At the age of 45, he developed a moderately rapid gait after an infection of the upper respiratory tract. The ocular symptoms gradually worsened and he was unable to run at the age of 46. At the age of 48, he was admitted to hospital because of progressive numbness in all limbs and difficulty in performing fine motor movements. Treatment
included high dose intravenous steroid and immune absorption plasmapheresis. Because he did not improve, he was transferred to our hospital. There was no family history of neuropathy or other systemic diseases. On admission, he had anisocoria (right 2-5 mm, left 3-5 mm), and light reflexes were absent on both sides. Ocular movement was impaired in all directions. The other cranial nerves were normal. Finger strength in the limbs was normal and there was no muscular atrophy. All deep tendon reflexes and Babinski’s sign were absent. Touch, cold, and pinprick sensations were slightly impaired in his hands and feet, but not in his face and trunk. There was profound loss of position and vibration senses in all limbs. The patient had pseudohypotonia of the upper limbs. A finger-nose test showed dysmetria with terminal tremor in both sides. He could not sit up in bed due to severe truncal ataxia. Autonomic functions were intact. Routine laboratory tests and concentrations of IgM and other immunoglobulins were normal. Serum immunoelectrophoresis did not show monoclonal gammapathy. The titre of cold agglutinin was not raised. There was no CSF pleocytosis and CSF protein content was 275 mg/dl (IgG 11-9%, normal: 2-5%). Brain MRI showed hypertrophy of both oculomotor nerves with no gadolinium enhancement (figure). The EEG was normal. Motor nerve conduction studies showed a prolonged F wave latency (39.6 ms, control 25.4 ms) with reduced amplitude of compound muscle action potentials (2.3 mV, control 9.5 SD 3.2 mV) in the right median nerve and prolonged (60 mV, control 44.4 ms (SD 3.4 ms) with reduced motor conduction velocity (36 m/s, control 49 (SD 3 ms) in the right tibial nerve. Sensory nerve conduction studies in the right median and sural nerves showed decreased amplitude of sensory nerve action potentials (SNAPs) and reduced conduction velocities (median nerve; SCV 24 m/s, SNAP 0-9 mV, sural nerve; SCV 38 m/s, SNAP 0-9 mV). An EMG showed mild chronic partial denervation in all limbs. Sural nerve biopsy showed a decreased density of large myelinated fibres (density of myelinated fibres: total 8721/mm³, 5 μm ≥ 138/mm³, 5 μm ≤ 8563/mm³, control; total 8500 (SD 650)/mm³, 5 μm ≥ 3080 (SD 462)/mm³, 5 μm ≤ 5412 (SD 332)/mm³, associated with several thinly myelinated axons. Some fibres showed myelin ovoid degeneration. A few onion bulb formations were noted. There was subperineurial oedema in some fascicles. In teased fibre preparations, the frequency of fibres with segmental demyelin- nation with remyelination was 6%, with axonal degeneration in 20%, and remyelina- tion without demyelination in 10%. The severe truncal ataxia and ophthalmoplegia improved after double filtration plasmapheresis. However, his symptoms gradually worsened three months later with increases in several antiganglioside antibodies. A combi- nation of prednisolone and azathioprine treatment was not effective. Antiglycolipid antibodies were investigated by enzyme linked immunostaining as previously described.1 Antigens used in enzyme linked immunosorbent assay (ELISA) were GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, galactocerebroside (Gal-C), and asialo GM1. ELISA showed IgM antibody activities against GD1b, GD3, GT1b, and GQ1b in the patient’s serum, but not IgG antibody activities against any of the gangliosides. The reactivity was also detected by thin layer chromatography and immunostaining. Although the antibody titres decreased after plasmapheresis, the titres rose again at the time of exacerbation, three months after plasmapheresis. This unusual case has features of both chronic sensory axatic neuropathy and ophthalmoplegia. Considering the effectiveness of plasmapheresis, the pathophysiologi- cal mechanism may be immune mediated. IgM M proteins binding to several gangliosides with disialyl residues, such as GD1b, GD3, GT1b, and GQ1b, have been detected specifically in serum samples from patients with sensory axatic neuropathy.1 The present patient had serum IgM antibody with reactivities to GD1b and other gangliosides with disialyl residues, although no IgM M protein was detected. Preliminary incubation with GD1b, GD3, and GT1b, performed as previously described1 reduced the antibody activities against all four gangliosides (data not shown). It suggests that the same IgM anti- body, which may recognise the disialyl residue, binds to all four gangliosides. This antibody reactivity may play an important part in chronic sensory axatic neuropathy in this patient. The most interesting feature of this patient is ophthalmoplegia with oculomotor nerve hypotrophy. Although focal cranial nerve involvement has been shown in chronic immune mediated neuropathy, ocu- lomotor nerve hypotrophy has not been previously reported. There was no gadinodin- um enhancement of either oculomotor nerve, suggesting that the appearance on MRI is likely related to increased connective tissue elements and Schwann cell proliferation as a consequence of chronic inflam- mation. Recently, Chiba et al found that IgG antibody against GQ1b was specifically raised in acute phase serum samples from patients with Miller Fisher syndrome5 and Guillain-Barré syndrome with ophthalmo- plegia.6 Anti-GQ1b antibody is therefore considered to be specifically associated with ophthalmoplegia in both diseases. Because GQ1b is rich in the paranodal regions of oculomotor, trochlear, and abducens nerves,4 anti-GQ1b antibody might be involved in the pathogenic mechanism of ophthalmoplegia by binding to these regions. Although IgM M protein binding to gangliosides with disialyl residues such as GQ1b has been reported, the patients usually did not have ophthalmoplegia. This may be due to the difference in the class and specificity of the antibody; anti-GQ1b anti- body in Miller Fisher syndrome and Guillain Barré syndrome with ophthalmoplegia is of the IgG class and cross reactions with gangliosides such as GD1b, GD3, and GT1b are rare. There is one reported patient with IgM paraproteinemia sensory axatic neu- ropathy with transient ophthalmoplegia.7 IgM M protein of that patient bound to gangliosides with a disialyl residue but the reactivity with GQ1b was not examined. In the present patient, we confirmed IgM reactivity with GQ1b, which might account for the ophthalmoplegia, oculomotor nerve hypotrophy. We thank Dr Raymond L. Rosales for critical reading of the manuscript.