LETTERS TO THE EDITOR

Evidence for increased nitric oxide production in multiple sclerosis

Within the CNS two isoforms of nitric oxide synthase (NOS) exist—the constitutive calcium dependent neuronal form and the inducible calcium independent form associated with glial cells. Stimulation of microglia or astrocytes by cytokines in vitro leads to increased nitric oxide (NO) formation as a result of NOS induction and stimulation of the biosynthesis of tetrahydrobiopterin, an essential cofactor for NOS.1

Excessive NO formation has been implicated in the pathogenesis of multiple sclerosis in oligodendrocytes, by contrast with other glial cells, are killed as a result of the induction of microglial NOS in vitro.2 Activation of the immune response is apparent in multiple sclerosis and the demonstration that such patients have increased concentrations of neopterin,3 a precursor of tetrahydrobiopterin, in their CSF supports the notion that increased NO production probably occurs in multiple sclerosis.

Nitric oxide is unstable and is readily converted to nitrate (NO−) and nitrite (NO2−) and recent work has suggested that the concentration of NO− and NO2− in the CSF is a useful indicator of NO production within the CNS. In view of this we have measured4 the total concentration of NO− and NO2− in the CSF from 10 patients with multiple sclerosis and from an appropriate control group. All patients had a clinical picture consistent with multiple sclerosis and had oligoclonal bands in the CSF. The control group comprised 10 patients with non-inflammatory diseases and they were negative for oligoclonal bands. Analysis of our data showed a highly significant increase in NO− and NO2− in the CSF of patients with multiple sclerosis (Table). In part this is surprising as demyelination leads to the specific release of dimethylarginine,5 a known inhibitor of NOS.5 We have shown with tandem mass spectrometry that dimethylarginine does not, however, seem to accumulate in the CSF of patients with multiple sclerosis.

These findings provide, for the first time, evidence for increased NO production in multiple sclerosis. Recently, we showed that induction of NOS in astrocytes leads to mitochondrial damage.1 Such NO mediated damage may therefore contribute to plaque formation and to cell death associated with multiple sclerosis. These results suggest a possible therapeutic role for NOS inhibitors in the management of multiple sclerosis.

**Table:**

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<th>Metabolites in CSF</th>
<th>Controls</th>
<th>Multiple sclerosis</th>
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<tr>
<td>Mean NO− + NO2− (µM) (SEM)</td>
<td>1-53 (0-22)**</td>
<td>2-59 (0-32)**</td>
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<tr>
<td>Mean dimethylarginine (µM)</td>
<td>3-80 (0-41) NS 4-00 (0-49)</td>
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<td><strong>P &lt; 0.01 (Mann-Whitney U test)</strong></td>
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Plasmatic, antinuclear, and anticycardiolipin antibodies, and C3 and C4 complement levels were all within reference ranges.

On the second hospital day she had a brief generalised tonic seizure followed by headache, drowsiness, mild fever (37-2°C), and anorexia. The neurological examination disclosed bilateral papilloedema and non-significant second and third nerve palsy but no visual or sensory inattention. She also had mild bilateral dyspraxia, impaired comprehension and visuospatial perception, verbal paraphasia, dyscalculia, and dysgraphia. The general examination was non-contributory.

A second cranial CT with contrast showed thrombosis of the sagittal and straight sinuses. Magnetic resonance imaging confirmed that it was extensive (figure A) and also identified left parietal cortical venous thrombosis. The EEG comprised irregular generalised delta activity maximal over the left side without epileptiform features.

Despite dexamethasone and heparin anti-coagulation she became stuporous with bilateral chemosis and extensor plantar responses. Local dural venous sinus thrombosis was performed through a right sphenoidal sinus catheter (Target Therapeutics) with multiple side holes in the distal 6 cm. The catheter was advanced through the right sigmoid and transversed the superior sagittal sinus to the left transverse sinus with the side holes bridging the torcula (figure B). Urokinase (20 000 U) was pulse injected into the thrombus over one hour, followed by a continuous infusion of 100 000 U over four hours. There was little improvement so continuous infusion with streptokinase (10 000 U/hour) was commenced for the next 11 hours with considerable thrombolysis and the thrombus showed no signs of being patent, and transit of the catheter was noted. The catheter was advanced further into the left transverse sinus and streptokinase (5000 U/hour) was continued for 12 hours. Final angiography at 28 hours (figure D) showed rapid flow in the transverse sinus. In parallel there was a pronounced reduction in papilloedema, improvement in consciousness, and resolution of headache. In view of the inherent risks of prolonged thrombolysis and the dramatic clinical improvement, the procedure was terminated without advancement of the catheter up the sagittal sinus. Two weeks later her vision and repetition were intact and she was able to obey complex commands. At this time MRI showed patency of the torcula and transverse sinuses and further clearance of the sagittal sinus.

Despite adequate anticoagulation with warfarin (INR = 3-5) over the next month she developed signs of deep and superficial venous thrombophlebitis of both legs and one arm. Colonoscopy revealed mild proctitis, more severe at the rectosigmoid junction. There was no active inflammation proximal to 25 cm, and no evidence of malignancy. Three months later her neuro-logical examination was normal apart from residual floating point dyscalsia.

In this patient the local infusion of streptokinase was effective in treating fulminating dural sinus thrombosis, but heparin had failed to arrest progression. The procedure was well tolerated and no relevant complications occurred. The use of transcranial sonography and/or ultrasonography in the diagnosis and management of venous sinus thrombosis is a cost effective and non-invasive tool which can be performed with good sensitivity and specificity. The patient was fortunate to survive without serious neurological sequelae given the
Cervical dystonia as an isolated sign of a basal ganglia tumour

We report a patient who had cervical dystonia for two years before a tumour involving the basal ganglia and surrounding white matter was detected. This case indicates that symptomatic focal dystonia may be the only early sign of a basal ganglia tumour. This male patient with an unremarkable medical history felt pain in his right neck and shoulder at the age of 40. When referred to a neurologist some months later, a laterocollis with inclination of the head to the right side was diagnosed. Trihexyphenidyl (50 mg daily) was effective in reducing the feeling of muscle tension. At that time the neurological state was otherwise normal.

One month later, the patient developed a headache and numbness in the right temporal region. There was hypaesthesia in the first right branch of the trigeminal nerve. Brain MRI showed an extended tumour involving the right basal ganglia and frontoparietal white matter with a large surround oedema. A stereotactic brain biopsy gave evidence of an anaplastic glioma consisting mainly of glial fibrillary acidic protein-negative tumour cells. As the tumour was too extensive to be surgically removed, radiotherapy and steroid medication were started. In the course of the next nine months, a left hemiparesis developed, whereas the laterocollis almost disappeared. The patient died from a pulmonary embolism less than three years after the first appearance of cervical dystonia. A mixed grade III glioma was confirmed at necropsy. Aside from this case describing a glioma involving the basal ganglia associated with laterocollis, cervical dystonia has been reported as a consequence of arteriovenous malformations located at the head of the caudate nucleus in two cases, of infratentorial tumours, and of traumatic lesions.

Cases of symptomatic contralateral hemidystonia have been described after basal ganglia infarction and after trauma. Although there was no family history of dystonia in our patient, a single case cannot rule out the possibility that his dystonia was idiopathic and unrelated to the tumour. If, however, the tumour is not merely coincidental with laterocollis, the question arises as to whether brain imaging should be performed also in patients presenting with cervical dystonia to exclude a structural pathology.

Laterocollis in this case improved in parallel with tumour growth and almost disappeared when hemiparesis developed. After infarcts and head trauma, dystonia may develop when hemiparesis improves. This clinical finding as well as pathological investigations have led to the hypothesis that dystonia may arise when striatal lesions leave the pyramidal tract relatively intact. In the case reported here, tumour growth may have presented as cervical dystonia only when basal ganglia began to be involved. With tumour extension into the internal capsule and white matter surrounding the basal ganglia, dystonia improved and paresis developed. The reversed