LETTERS TO THE EDITOR

Evidence for increased nitric oxide production in multiple sclerosis

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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 as 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_3^-) and nitrite (NO_2^-) and recent work has suggested that the concentration of NO_3^- and NO_2^- in the CSF is a useful indicator of NO production within the CNS. In view of this we have measured[4] the total concentration of NO_3^- and NO_2^- 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_3^- and NO_2^- 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.[6] 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 the cell death associated with multiple sclerosis. These results suggest a possible therapeutic role for NOS inhibitors in the management of multiple sclerosis.

Metabolites in CSF

	Controls	*Multiple sclerosis*
Mean NO_3^- + NO_2^- (μM (SEM))	1·53 (0·22)**	2·59 (0·32)
Mean dimethylarginine (μM (SEM))	3·80 (0·41)	NS 4·00 (0·49)

**P < 0·01 (Mann-Whitney *U* test).

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4 Kuiper MA, Visser JJ, Bergmans PLM, Scheltens P, Wolters EC. Decreased cerebrospinal fluid nitrate levels in Parkinson's disease, Alzheimer's disease and multiple system atrophy patients. *J Neurol Sci* 1994;121:46–9.
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Progressive dural venous sinus thrombosis treated with local streptokinase infusion

Dural venous sinus thrombosis is an uncommon condition, which, if extensive, may lead to fulminant neurological dysfunction and death.[1,2] Treatment is usually supportive with management of raised intracranial pressure, seizures, and underlying predisposing factors. Treatment with systemic anticoagulation may be used although there is a risk of promoting intracerebral haemorrhage.[2] Some case reports have been published advocating treatment with local thrombolysis,[3–5] often combined with local thrombectomy.[4] We describe a case of extensive dural venous sinus thrombosis progressing despite heparinisation in a patient with ulcerative colitis. The thrombosis was successfully treated by local infusion of streptokinase without complications.

A 49 year old woman was admitted to hospital after a three day history of gradually increasing headache and vomiting. Examination was said to be normal. She had had ulcerative colitis for 14 years but at the time of admission the disease was relatively quiescent on olsalazine (250 mg four times a day) and prednisolone (25 mg each morning). Two years earlier during a flare of the ulcerative colitis she had developed venous thromboembolism.

Non-contrast cranial CT was normal. Analysis of CSF showed 1 white blood cell μl^{-1}, protein 0·50 gl^{-1}, and glucose 4·9 $mmol^{-1}$. Coagulation profile, Protein C and S, antithrombin III, full blood count, erythrocyte sedimentation rate (2 mm hr^{-1}), routine biochemistry, aspartate aminotransferase, alkaline phosphatase, bilirubin, albumin, serum electrophoresis, and thyroid function were normal. Antineutrophil cytoplasmic, antinuclear, and anticardiolipin 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-selective saccadic pursuit eye movements, 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 vein thrombosis. The EEG comprised irregular generalised delta activity maximal over the left side without epileptiform features.

Despite dexamethasone and heparin anticoagulation she became stuporous with bilateral chemosis and extensor plantar responses. Local dural venous sinus thrombolysis was performed with a Tracker-25 catheter (Target Therapeutics) with multiple side holes in the distal 6 cm. The catheter was advanced through the right sigmoid and transverse sinuses, past the torcula into 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 (figure C). 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 after admission, naming 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 showed 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 neurological examination was normal apart from residual floating point dyscalculia.

In this patient the local infusion of streptokinase was effective in treating fulminant dural sinus thrombosis where systemic heparin had failed to arrest progression. The procedure was well tolerated and no relevant complications occurred. The use of transvenous catheters obviated the need for craniectomy and direct thrombectomy. The patient was fortunate to survive without serious neurological sequelae given the