PostScript

CORRESPONDENCE

Evidence for an association between the CSF HVA:5-HIAA ratio and aggressiveness in frontotemporal dementia but not in Alzheimer's disease

In their recent paper, Soderstrom *et al*[1] confirmed their preliminary data suggesting that the CSF HVA:5-HIAA ratio was associated with psychopathic traits and, in particular, violent and aggressive behaviour with childhood onset and adult expression. These findings might indeed reflect changed dopaminergic activity, possibly as a result of serotonergic dysregulation. We hypothesise that their findings might be applicable to other brain disorders characterised by specific behavioural disturbances, including aggression and agitation. Indeed, since several studies have found associations between altered serotonergic neurotransmission and aggression in persons with dementia,[2 3] we could propose that the CSF HVA:5-HIAA ratio might be associated with aggression in persons with dementia as well. To test this hypothesis, we performed an interim analysis on 102 out of 302 patients who were included in a prospective and longitudinal study on neurochemical and genetic correlates of behavioural and psychological signs and symptoms of dementia (BPSD). The data presented further support a general application of the interesting findings of Soderstrom *et al*.[1]

Patients with various neurodegenerative forms of dementia were included in this prospective study, and were followed up by means of a neuropsychological and behavioural assessment every six months. In any case of death, brain autopsy was performed for neurochemical analysis as well as for neuropathological confirmation of the clinical diagnosis. All subjects and their caregivers gave informed consent to participation in the study, which was approved by the local ethics committee.

At baseline, behaviour was assessed by means of a battery of behavioural assessment scales which included the Behavioural Pathology in Alzheimer's Disease Rating Scale (Behave-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). Lumbar puncture was performed between 9 and 10 am following overnight bed rest and fasting. The first 11 ml of CSF were collected in several polypropylene vials that were immediately frozen in liquid nitrogen and stored at −80℃. Neurochemical analysis was carried out on the CSF fraction containing 6–7.5 ml by means of high performance liquid chromatography and electrochemical detection according to a modification of a recently described method.[4] Routine investigation of the CSF included cell count, total protein and glucose analysis, and agar gel electrophoresis of proteins.

For this interim analysis, HVA and 5-HIIA levels were determined in the CSF of 13 participants with frontotemporal lobe dementia (FTD) and 89 participants with probable Alzheimer's disease (AD). Spearman Rank Order was used for correlation analysis between the CSF HVA:5-HIAA ratio and BPSD, applying SigmaStat Software (SPSS Science, Erkrath, Germany).

In the AD patient group, no significant correlations were found between the CSF HVA:5-HIAA ratio and Behave-AD clusters, total and global scores, or CMAI clusters (aggressive, physically non-aggressive, and verbally agitated behaviours) and total scores. In persons with FTD, however, the CSF HVA:5-HIAA ratio correlated significantly with the Behave-AD aggressiveness cluster score ($r = 0.586$; $p = 0.033$) and with the CMAI verbally agitated behaviour cluster score ($r = 0.564$; $p = 0.041$). Despite small sample sizes, effects of treatments were ruled out by comparing the CSF levels of HVA (*t* test: $p = 0.691$), 5-HIAA ($p = 0.370$), and the CSF HVA:5-HIAA ratio ($p = 0.157$) between six untreated subjects with FTD and seven subjects with FTD who were receiving atypical antipsychotics.

Our preliminary results revealed an association between aggression and the CSF HVA:5-HIAA ratio in participants with FTD but not in those with AD. More refined neurochemical analyses, including the determination of all catecholamines and serotonin in an extended population of FTD patients, are scheduled. These will allow further testing of the hypothesis that altered serotonergic modulation of dopaminergic neurotransmission leads to BPSD and in particular to aggression. Meanwhile, our findings suggest that the association between the CSF HVA:5-HIAA ratio and aggression as observed by Soderstrom *et al* [1] is not limited to violent and aggressive behaviour with childhood onset and adult expression, but may indicate an underlying pathophysiological mechanism that may be common to aggressive symptomatology in other brain disorders, such as frontotemporal lobe dementia.

S Engelborghs, E Vloeberghs, K Maertens, B Marescau, P P De Deyn
Laboratory of Neurochemistry and Behaviour, Born-Bunge Foundation, University of Antwerp, Belgium

S Engelborghs, P P De Deyn
Department of Neurology, Middelheim General Hospital, Antwerp, Belgium

Correspondence to: Professor P P De Deyn; peter.dedeyn@ua.ac.be

References

1 **Soderstrom H**, Blennow K, Sjodin A-K, *et al*. New evidence for an association between the CSF HVA:5-HIAA ratio and psychopathic traits. *J Neurol Neurosurg Psychiatry* 2003;**74**:918–21.
2 **Lai MKP**, Tsang SWY, Francis PT, *et al*. Reduced 5-HT_{1A} receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. *Brain Res* 2003;**974**:82–7.
3 **Sukonick DL**, Pollock BG, Sweet RA, *et al*. The 5-HTTPR*S/*L polymorphism and aggressive behavior in Alzheimer disease. *Arch Neurol* 2001;**58**:1425–8.
4 **Engelborghs S**, Marescau B, De Deyn PP. Amino acids and biogenic amines in cerebrospinal fluid of patients with Parkinson's disease. *Neurochem Res* 2003;**28**:1145–50.

Extensive radiculopathy: another false localising sign in intracranial hypertension

We read with interest the review by Larner[1] on false localising signs. Among the various false localising signs described in patients with intracranial hypertension (ICHT), radiculopathy is an important manifestation which is probably under recognised. Many authors have documented subtle features of radiculopathy in patients with isolated intracranial hypertension (IIH). The usual manifestations of radiculopathy in these cases were acral paraesthesias,[2] and backache and radicular pain.[3 4] Rarely, motor deficits due to radiculopathy caused by ICHT have been described.[5 6]

Obeid *et al* reported two patients with extensive radiculopathy due to ICHT[5]; one individual had IIH and the other had cerebral sinus venous thrombosis. Both persons had papilloedema, marked visual impairment, and flaccid areflexic quadriparesis with normal MRI of brain, brainstem, and cervical spinal cord. The electrophysiological findings were consistent with radiculopathy. Both individuals initially received intravenous immunoglobulin for Guillain–Barré syndrome, without benefit, but they responded well to lumboperitoneal shunting. We also encountered two such cases with angiographically proven cerebral venous sinus thrombosis.[6]

The most likely mechanism at the basis of radiculopathy appears to be similar to that of other cranial neuropathies in ICHT—that is, mechanical compression of nerve roots, due to elevated CSF pressure distending the subarachnoid space. Documented enlargement of spinal subarachnoid space and distended root pouches in a patient with radicular pain and areflexia due to IIH supports this view.[3] Radiculopathy secondary to ICHT has been reported almost exclusively in patients with IIH or cerebral venous sinus thrombosis.

Other causes of ICHT may not induce a diffuse increase in pressure in both intracranial and intraspinal compartments, and are unlikely to manifest as radiculopathy. The constellation of flaccid-areflexic quadriplegia and papilloedema may be misdiagnosed as Guillain–Barré syndrome with papilloedema.[5] Careful analysis of the evolution of symptoms, estimation of CSF pressure, and appropriate vascular imaging should help to correctly identify the cause of ICHT.

A Moosa, M A Joy, A Kumar
Department of Neurology, Amrita Institute of Medical Sciences and Research Center, Cochin, Kerala, India

Correspondence to: Dr N V A Moosa; ahsanmoosa@yahoo.com

References

1 **Larner AJ**. False localising signs. *J Neurol Neurosurg Psychiatry* 2003;**74**:415–18.
2 **Round R**, Keane JR. The minor symptoms of increased intracranial pressure: 101 patients with benign intracranial hypertension. *Neurology* 1988;**38**:1461–4.
3 **Bortoluzzi M**, Di Lauro L, Marini G. Benign intracranial hypertension with spinal and radicular pain. *J Neurosurg* 1982;**57**:833–6.

4 **Santinelli R**, Tolone C, Toraldo R, *et al*. Familial idiopathic intracranial hypertension with spinal and radicular pain. *Arch Neurol* 1998;**55**:854–6.
5 **Obeid T**, Awada A, Mousali Y, *et al*. Extensive radiculopathy: a manifestation of intracranial hypertension. *Eur J Neurol* 2000;**7**:549–53.
6 **Moosa A**, Kishore A, Gupta AK, *et al*. Blindness, ophthalmoplegia and extensive radiculopathy- an unusual clinical syndrome in intracranial sinovenous thrombosis. *Neurol India* (in press).

Role of entacapone in later Parkinson's disease not yet established

The study by Brooks and Sagar,[1] along with a number of previous others, demonstrates benefit for the catechol-*O*-methyltransferase (COMT) inhibitor entacapone when compared with placebo in Parkinson's disease (PD). However, this is insufficient evidence to justify the authors' conclusion that ''it appears logical to employ levodopa combined with entacapone routinely''. The important issue is not whether entacapone is more efficacious than placebo, but whether it is more or less clinically effective and cost effective than the other available treatments for patients with PD that is no longer adequately controlled by levodopa alone. Other available agents—including dopamine agonists and monoamine oxidase type B (MAOB) inhibitors—have also shown efficacy when compared with placebo. The paper would have benefited from a balanced discussion of the merits of entacapone compared with these other available treatment options.

Such a discussion is likely to have been inconclusive, however, as there is a dearth of reliable evidence on the best treatment for PD, at any stage of the disease, since very few trials directly comparing active treatments have been undertaken.[2] Companies are reluctant to undertake such trials, as it is not in their commercial interests to risk studies that might show their product to be inferior to that of a competitor. For this reason, independently funded trials—such as the current PD MED trial in the UK[3]—should be supported to provide the reliable evidence on comparative efficacy needed to enable clinicians to make informed treatment decisions. Analysis, presentation and interpretation of the results of independent studies are also likely to be more objective than those of commercial studies. The potential for bias in commercial trials has recently been highlighted by systematic reviews and journal editors—for example ''systematic bias favours products which are made by the company funding the research''[4] and ''scientific studies can be manipulated in many ways to give results favourable to companies''.[5]

There are problems with the trial reported by Brooks and Sagar, and these are common to many PD trials, which are generally of poor methodological quality.[2] In a progressive condition such as PD, it is important to evaluate the long term effects of treatment, and six months follow up is inadequate. The outcome measures used should reflect the impact of treatment on the patients' own perception of their functioning and quality of life, not that of clinicians as with the Unified Parkinson's Disease Rating Scale (UPDRS). It is unclear how well the data obtained from on-off diaries correlates with global quality of life. True intention to treat (ITT) analysis was not performed, since patients who withdrew from treatment were excluded from the analysis—ITT analysis requires such patients to be followed up and included in the analysis according to the arm to which they were allocated even if they have withdrawn from allocated therapy.[6] Nearly 50% more patients (24.1% *v* 16.5%) dropped out of the entacapone arm than from the placebo arm and, in progressive diseases such as PD, dropout bias tends to favour the active treatment.[7] Thus, although COMT inhibitors are welcome additions to the treatment options in PD, large, rigorously conducted comparative trials, assessing the long term impact on patient-rated measures of overall quality of life, are still needed to define their role in routine clinical practice.

K Wheatley, N Ives, R Gray
University of Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK

C Clarke
City Hospital, Birmingham, UK

Correspondence to: Professor K Wheatley, Birmingham Clinical Trials Unit, University of Birmingham, Park Grange, 1 Somerset Road, Edgbaston, Birmingham B15 2RR, UK; k.wheatley@bham.ac.uk

Competing interests: We are investigators in the PD MED trial and thus have a vested interest in obtaining objective evidence on the best treatment for PD. CC has received honoraria for lectures, consultancy fees, and travel expenses from the manufacturers of many of the drugs discussed.

References

1 **Brooks DJ**, Sagar H, the UK-Irish Entacapone Study Group. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind six month study. *J Neurol Neurosurg Psychiatry* 2003;**74**:1071–9.
2 **Wheatley K**, Stowe RL, Clarke CE, *et al*. Evaluating drug treatments for Parkinson's disease: how good are the trials? *BMJ* 2002;**324**:1508–11.
3 **PD MED: A phase III Parkinson's disease trial**. www.pdmed.bham.ac.uk (accessed 17 March 2004).
4 **Lexchin J**, Bero LA, Djulbegovic B, *et al*. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;**326**:1167–70.
5 **Smith R**. Medical journals and pharmaceutical companies: uneasy bedfellows. *BMJ* 2003;**326**:1202–5.
6 **Collins R**, Peto R, Gray R, *et al*. Large-scale randomized evidence: trials and overviews. In: Weatherall D, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine, Volume 1*. London: Oxford University Press, 1996:21–32.
7 **Gray R**, Stowe RL, Hills RK, *et al*. Non-random drop-out bias: intention to treat or intention to cheat? [Abstract] *Control Clin Trials* 2001;**22**:38S–39S.

Portal-systemic shunts, manganese, and parkinsonism

I read with interest the article by Yoshikawa and colleagues.[1] The authors reported the case of a 44 year old woman with hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease) involving the liver, who had raised serum concentrations of manganese, hyperintense areas in the basal ganglia on T1 weighted magnetic resonance images, and levodopa unresponsive parkinsonism. Naturally, I agree that the parkinsonism in this case is most probably related to portal-systemic (portal-venous) shunts. There are, however, two points that deserve clarification.

First, it is not entirely clear whether their fig 2 (left panel) shows portal-systemic or arteriovenous shunts. The authors say that the figure shows a selective angiogram of the superior mesenteric artery. If that were the case, there should not be a ''feeding artery'' involved in the intrahepatic shunts (as they state in the legend to fig 2). Instead, the figure would show the portal vein and portal-systemic shunts (that is, portal phase of the angiogram). If, on the other hand, the catheter were in the coeliac artery (as they mention in the text), then the figure would probably correspond to the arterial phase of the angiogram and show a feeding artery (the hepatic artery) and arteriovenous (not portal-systemic) shunts. Interestingly, there is evidence to suggest that both types of shunt may be necessary for the development of neurological complications in the presence of an intact (or mostly preserved) hepatic parenchyma.[2] Thus excessive quantities of potentially toxic substances (for example, ammonia, manganese) passing directly from the gut to the systemic circulation through portal-systemic shunts could be rapidly cleared by a normal liver as long as the hepatic arterial blood flow is adequate.

Second, Yoshikawa and colleagues claim that the parkinsonism of their patient was induced by manganese. While this is a reasonable working hypothesis, the authors provide no direct evidence supporting such a statement. The fact that serum manganese was raised does not necessarily imply that manganese played a key role in the pathogenesis of parkinsonism. Indeed, their patient lacked various clinical features often seen in cases of manganese induced parkinsonism[3] (for example, cock walk and propensity to fall backwards).

Levodopa unresponsive parkinsonism is a well known manifestation of chronic non-Wilsonian hepatocerebral degeneration.[4] Although blood concentrations of ammonia were within the normal range in the case reported by Yoshikawa and colleagues, the possibility of transient abnormal increases of ammonia occurring particularly after meals was not investigated.

R de la Fuente-Fernández
Division of Neurology, Hospital A Marcide, Estrada San Pedro-Catabois s/n, 15405 Ferrol, A Coruña, Spain

Correspondence to: Dr Raúl de la Fuente-Fernández, rfuente@medynet.com

References

1 **Yoshikawa K**, Matsumoto M, Hamanaka M, *et al*. A case of manganese induced parkinsonism in hereditary haemorrhagic telangiectasia. *J Neurol Neurosurg Psychiatry* 2003;**74**:1312–14.
2 **Yilmaz S**, Kirimlioglu V, Katz D, *et al*. An attempt to decrease ammonia levels after portacaval anastomosis in dogs: hepatic periarterial neurectomy. *Dig Dis Sci* 2002;**47**:1943–52.
3 **Calne DB**, Chu NS, Huang CC, *et al*. Manganism and idiopathic parkinsonism: similarities and differences. *Neurology* 1994;**44**:1583–6.
4 **Adams RD**, Victor M, Ropper AH. *Principles of neurology*, 6th ed. New York: McGraw-Hill, 1997.

Authors' reply

We are pleased to have an opportunity to comment on the important issues raised by Dr de la Fuente-Fernández regarding a case of hereditary haemorrhagic telangiectasia