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Matters Arising

Combined gaze palsy of horizontal saccades and pursuit contralateral to a midbrain haemorrhage

Sir: Drs Bolling and Lavin[1] report that impairment of both contralateral saccades and smooth pursuit was due to a lesion affecting the ipsilateral midbrain reticular formation. However, damage to one midbrain reticular formation results in loss of all ipsilateral horizontal rapid eye movements, as well as smooth pursuit, preserving vestibular-induced ipsilateral movements.[2,3] In our opinion, the ocular findings in their report would suggest that the supranuclear pathway for voluntary saccades and smooth pursuit (occipito-parieto-pontine pathway) were affected rather than the midbrain reticular formation. Furthermore there is no evidence that these supranuclear pathways have the same location as the reticular formation in the midbrain.

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Dr Lavin replies:

Dr Deleu implicates the midbrain reticular formation in the loss of voluntary ipsilateral horizontal eye movements (pursuit and saccades), citing two studies[1,2] in support. Both these studies describe patients with the "one-and-a-half syndrome" caused by lesions of the paramedium *pontine* reticular formation (PPRF). The subject of the first study, and to a lesser extent patient one in the second study, had some involvement of the lower midbrain; however, the brunt of disease affected the rostral pontine reticular formation in both patients.

That the supranuclear pathways for pursuit travel through the ipsilateral midbrain reticular formation in man[3,4] and monkeys[5] is well documented. Furthermore, thalamic injury has been associated with impaired ipsilateral pursuit in man.[6]

In our patient the lesion involved the rostral midbrain contralateral to the gaze palsy.[7] Without pathological verification one cannot say with absolute certainty that the thalamus was not involved; however, the patient had neither clinical nor radiological (CT and unpublished MRI) evidence of thalamic involvement.

The kernal of our report is that the supranuclear pathways for smooth pursuit eye movements pass through the contralateral midbrain and therefore must decussate twice, at least, in order to innervate the ipsilateral pontine nuclei. The apparent paradox of ipsilateral[3,5] and contralateral[7] pursuit deficits with unilateral midbrain lesions may be explained by the existence of parallel pathways. We stand by our original conclusions.

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Multiple sclerosis: correlation of magnetic resonance imaging with cerebrospinal fluid findings

Sir: Honig *et al*[1] reported that magnetic resonance imaging (MRI) performed by them was normal in 55% of clinically definite multiple sclerosis (CDMS) of less than 2 years duration. In addition they found normal MRI in 26% of CDMS patients with supportive CSF changes. These figures suggest lower sensitivity of MRI than that recorded from other contemporary studies.

One explanation they proposed for their findings is that other studies have looked predominantly at long established disease. However, when MRI was performed during the first presentation of acute idiopathic clinically isolated optic neuritis it was found by us that 64% had multiple brain lesions. This also corresponds well with epidemiological predictions of progression to CDMS, and using combined clinical and imaging evidence for relapse 56% of the same group developed CDMS within one year of follow up.[3]

Another of their proposed explanations was the occurrence of spinal without cerebral lesions. In our study of isolated spinal cord syndromes 75% had brain lesions indistinguishable from those seen in CDMS, also making this explanation unlikely.[4]

The reasons for their low rate of lesion detection possibly lie in their imaging protocol. Firstly 10 mm thick slices are suboptimal as small lesions may not be detected due to partial volume effects (some of our optic neuritis group were, however, scanned with 10 mm slices); MRI with most current systems will image adequately at 4 mm slice thickness and below. Secondly a 0·35T machine will have a lower signal-to-noise ratio than comparable higher field machines, resulting in noisier images and less certainty in lesion detection. Thirdly signal-to-noise can be improved by the design and optimisation of receiver coils and scanning sequences. We have found that inferior images may result from double as opposed to single echo sequences.

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Honig et al reply:

Kermode *et al* raise important issues concerning the multiple sclerosis patients in our population who displayed normal brain MRI studies. This small subgroup is notable, since in this nascent era of MRI, many clinicians view areas of increased T_2 signal in the brain as sine qua non for diagnosis of multiple sclerosis. The group from Queen Square suggest technical reasons may explain in part the reported results. Indeed, employment of what is now relatively thick 10 mm sections, and low 0·35T MRI field strength were likely factors in the failure to detect some small lesions, due to partial volume averaging and suboptimal contrast. Yet even state-of-the-art MRI does not reveal the pontine lesion in many patients with clinically obvious internuclear ophthalmoplegia, use of cardiac and respiratory-gated, flow-compensated 3 mm slice 1·5 T single echo sequences notwithstanding.

Despite the technical limitations of our earlier studies, the major thrust of the report remains: there is a progressive increase of brain lesions with duration of multiple sclerosis. Some of those cases without brain MRI lesions, noted in almost all studies, plausibly have plaques too small or subtle to be detected, while likely others simply do not have cerebral lesions. The valuable studies of Miller *et al* reveal 36% of optic neuritis patients have normal brain MRI, some of whom probably will ultimately represent early multiple sclerosis. Their group also has shown that most patients with spinal disease have brain MRI lesions; our data (79%) are in accord, but among patients *without* MRI discernible brain disease 38% display abnormal cord signal.[1] Spinal cord plaques without cerebral affliction occur in multiple sclerosis as has been established pathologically by Charcot and others.[2,3] Furthermore, anatomical patterns of involvement by demyelinating disease may vary in frequency from one geographic location to another, as with the comparatively high prevalence of neuromyelitis optica in Japan.

Despite the use of up-to-date MRI protocols and 0·5 and 1·5 T MRI machines, we continue to find normal brain images in some patients who meet diagnostic criteria for multiple sclerosis, just as we encounter patients with white matter lesions who have no clinical history of that disease. Useful as they are, radiological studies have neither 100% specificity nor 100% sensitivity.

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Dementia of the frontal lobe type

Sir: The manuscript by Dr D Neary and associates[1] provides clinical, neuropsychological, and single photon emission tomographic data for seven patients with an unusual form of dementia, termed dementia of the frontal lobe type (DFT); the authors are to be commended for their thorough evaluation of this interesting case material. Their premise, however, that the cases are clearly distinguishable from Alzheimer's disease is open to question. Virtually all of the clinical features deemed characteristic for DFT have been observed in Alzheimer's disease, including early personality change,[2] family history of dementia,[3] primitive reflexes,[4] apathy and indifference,[5] mutism,[6] and variable memory loss;[7] the reported neuropsychological differences between DFT and Alzheimer's disease are confounded by the failure to control for dementia severity, a factor which notably influences psychometric performance.[8] That Alzheimer's disease can produce the frontal lobe manifestations used to define DFT is not surprising, given its inherent clinical heterogeneity and occasional predilection for pronounced frontal gyral atrophy.[9–11] It is possible, therefore, that postmortem examination may show Alzheimer's disease to be the underlying process for many purported cases of DFT.

DFT was originally defined as a pathological syndrome in which cerebral cortical neuronal loss with associated gliosis and microcavitation of the neuropil occurred without the histological hallmarks of Alzheimer's disease or Pick's disease; a frontal lobe emphasis was noted, although other cerebral regions were involved as well.[12] These changes are not unique to DFT but are also common in Alzheimer's disease and Pick's disease, in which neurofibrillary tangles and neuritic plaques or Pick bodies serve as distinctive markers of disease. In addition, the pathological features of DFT closely resemble those of the "non-specific" dementias,[13–16] a small but well-established group of disorders which, like Pick's disease, often are clinically indistinguishable from Alzheimer's disease. Indeed, the clinical and pathological overlap among Alzheimer's disease, the "non-specific" dementias, and Pick's disease suggests that these disorders form a spectrum of cerebral degenerative disease in which cortical neuronal loss is the fundamental lesion.[17] The reported features of histologically verified cases of DFT indicate that this syndrome may occupy a point along the same continuum.

Dr Neary and colleagues acknowledge the possibility that DFT may be a subtype of Pick's disease. Extending these diagnostic considerations to include, rather than exclude, Alzheimer's disease and its variants would more properly clarify the position of DFT within the broad spectrum of cerebral cortical degenerative disorders.

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