Matters arising


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 T2 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 opthalmoplegia, use of cardiac and respiratory-gated, flow-compensated 3 mm slice 1-3 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 overt cerebral affliction occur in multiple sclerosis as has been established pathologically by Charcot and others.2 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.

References


Dementia of the frontal lobe type

Sir: The manuscript by Dr D Neary and associates1 provides clinical, neuropsychological, and single photon emission tomographic data for seven patients with an unusual form of dementia, termed dementia of the frontal lobe (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 glialosis and microvacuolation 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.1 They 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.

JOHN C MORRIS
Department of Neurology
and Neurological Surgery,
Washington University School of Medicine,
Box 8111, 660 South Euclid Avenue,
St Louis, Missouri 63110, USA

References


Nearly replies:

Dr Morris levels two criticisms of our paper, the one explicit and pathological, the other by implication and clinical. The former arises from his notion that the primary cortical atrophies represent a pathological continuum, with Pick's disease at one end of the spectrum, Alzheimer's disease at the other and non-specific encephalopathies representing an intermediate position, large cortical neuronal loss being the primary fundamental disorder. An implication is that clinical differences in primary cortical atrophy are accidental and non-specific and that pathological diagnosis alone is primary. The argument does not address demographic, genetic and biochemical aspects of cerebral atrophy.

In our study comparison between DFT and proven Alzheimer's disease revealed differences along multiple dimensions: demographic, neurological, pathological, electrophysiological and neuroimaging. Double dissociations in clinical features such as the presence of conduct disorder and absence of spatial disability in DFT contrasting with the absence of conduct disorder and presence of spatial disability in Alzheimer's disease indicate that distinctions are not an artifact of disease severity. Furthermore, longitudinal evaluation shows that distinctions are maintained despite progression of disease. The notion of "controlling for dementia severity" begs the question: it assumes that there is a common dimension of dementia along which patients can be equated.

Dr Morris cites the pathological findings of Brun in defining DFT, revealing frontotemporal cortical neuronal loss, spongiform change and gliosis in the absence of senile plaques and neurofibrillary tangles. He fails to point out that those pathological changes occurred in patients whom Brun and his colleagues in Southern Sweden have identified to be clinically distinct from Alzheimer's disease and who exhibited a syndrome demographically and clinically identical to that of our DFT patients. Of 71 necropsied patients with Alzheimer's disease in Brun's study only two had such a clinical picture and a brunt of pathological change in the frontal lobes.

Since the publication of our paper four brains of patients with DFT have been studied at necropsy. All showed pathological change similar in nature and distribution to that described by Brun. None had evidence of senile plaques or neurofibrillary tangles, or Pick cells.

The relationship between Pick's disease, DFT and focal cerebral atrophies is puzzling and intriguing. However, we see no grounds for accepting them as part of a spectrum with Alzheimer's disease, and consider the notion of a "continuum" to be heuristically sterile since it discourages the search for clinical, physiological, biochemical and genetic distinctions within the cerebral atrophies. It does, however, support the prevailing view that the dementia of the cerebral atrophies is a non-specific intellectual decline, and that distinct neuropsychological syndromes characterising different pathologies do not exist. Such a philosophy has we believe retarded research into dementia.

Dr Morris predicts that patients diagnosed as DFT will prove to have the pathology of Alzheimer's disease. In contrast, we predict that DFT will in the future be increasingly recognised as an entity distinct from Alzheimer's disease and with an incidence far higher than previously supposed.

Matters arising


Olivopontocerebellar atrophy with neonatal onset

Sir: I read with interest the article by Harding et al on olivoponto cerebellar atrophy (OPCA) with neonatal onset combined with systemic purine overproduction. The authors excluded two cases presenting in the neonatal period that I had considered as OPCAs. Gross and Kaltenbäck's case is not classified as OPCA because "the cerebellar cortex was hardly affected whereas the dentate nuclei and red nuclei were severely involved". Norman and Urich's first case is considered more akin to pontocerebel lar hypoplasia. I would like to comment on this question.

The degree of atrophy of the cerebellar cortex in OPCA varies greatly. It is generally held that the first systems to degenerate in this condition are nuclei pontis, arcuate nuclei and inferior olives. The corticopontocerebellar atrophy, that probably is the result of an anterograde transynaptic degenerative phenomenon, follows at a later stage and may be minimal at death. In fact, there are well documented adult cases with no lesions at the cerebellar cortex.

For these cases the eponym ponto-olivary atrophy seems to be more appropriate than OPCA. On the other hand, detailed pathological studies constantly reveal associated lesions with OPCA dentate nuclei degeneration being one of the most frequent of them. Therefore, the case described by Gross and Kaltenbäck should be classified as these authors did, among OPDCas.

Together with neocerebellar hypoplasia, in Norman and Urich's first case there was systemic degeneration (loss of neurons and/or fibrillary gliosis) affecting the following structures: nuclei pontis and transverse fibres, inferior olives and their hilus and capsules, arcuate nuclei and external arcuate fibres, nuclei lateralis medullae, dentate nuclei, central matter of lateral lobes of the cerebellum, thalamus, hypothalamus and other brain-stem nuclei. The authors compared their findings to those exhaustively...
Dementia of the frontal lobe type

John C Morris

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