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#### Neary 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.<sup>1</sup> 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, psychological, 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,<sup>2</sup> revealing fronto-temporal 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<sup>3,4</sup> 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.<sup>2</sup> 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.

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#### Olivopontocerebellar atrophy with neonatal onset

Sir: I read with interest the article by Harding *et al*<sup>1</sup> on olivopontocerebellar atrophy (OPCA) with neonatal onset combined with systemic purine overproduction. The authors excluded two cases<sup>2,3</sup> presenting in the neonatal period that I had considered as OPCAs.<sup>4</sup> Gross and Kaltenbach'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 pontocerebellar hypoplasia. I would like to comment on this question.

The degree of atrophy of the cerebellar cortex in OPCA varies greatly.<sup>5</sup> It is generally held that the first systems to degenerate in this conditions are nuclei pontis, arcuate nuclei and inferior olives. The cerebellar atrophy, that probably is the result of an anterograde transsynaptic degenerative phenomenon,<sup>6</sup> follows at a later stage and may be minimal at death.<sup>5</sup> In fact, there are well documented adult cases with no lesions at the cerebellar cortex.<sup>7</sup> For these cases the eponym ponto-olivary atrophy<sup>6,7,10</sup> 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.<sup>4</sup> Therefore, the case described by Gross and Kaltenbach<sup>2</sup> should be classified as these authors did, among OPCAs.

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 hilia 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.<sup>3</sup> The authors compared their findings to those exhaustively

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described by Tans<sup>11</sup> in a case of OPCA, concluding that the brain-stem lesions were probably not secondary to the cerebellar anomaly. It is obvious that Norman and Urich's case had not a pure pontoneocerebellar hypoplasia but a neocerebellar hypoplasia with multisystem degeneration that could be included under the general category of OPCA. Similar cases have recently been published.<sup>12-15</sup> Pathogenetically, most authors favour the occurrence of a developmental anomaly producing cerebellar hypoplasia and predisposition of two neuronal systems to abiopathy.<sup>2,3,12-14</sup>

Finally, I agree with the statement that OPCA is a common pathological end point for several clinically and genetically distinct disorders.<sup>1</sup> In fact, olivopontocerebellar lesions have been described in a patient with adrenoleukodystrophy.<sup>16</sup>

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*Harding and Erdohazi reply*

Dr Berciano takes issue with us<sup>1</sup> for disagreeing with his classification<sup>2</sup> of two particular case reports, Case 1 of Norman and Urich<sup>3</sup> and that of Gross and Kaltenbäck<sup>4</sup> as olivopontocerebellar atrophy (OPCA). His letter highlights the particular problems of morphological classification with childhood cerebellar syndromes. There is certainly no unanimity in the literature. Urich<sup>5</sup> classified both cases with pontoneocerebellar hypoplasia (PNCH). Koeppe and Barron<sup>6</sup> also describe Norman and Urich's case as cerebellar hypoplasia, while Friede<sup>7</sup> in his encyclopaedic treatise expresses some difficulty over the interpretation of this case.

The case of Gross and Kaltenbäck would be rather unusual for OPCA in view of the histologically normal cerebellar cortex and severe neuronal loss from the dentate and red nuclei and degeneration of the superior cerebellar peduncles. In a recent review Koeppe and Barron<sup>6</sup> remark that Purkinje cell loss is the outstanding feature in the cerebellum in OPCA, and can be so sweeping that none are found, while deep nuclei and their efferents are generally well preserved. Although its extent can be quite variable cerebellar cortical involvement is found in almost all cases.<sup>6,8</sup> On the other hand dentate involvement is much less frequent, about a third of cases in Berciano's review,<sup>2</sup>

and this is usually only gliosis; the dentate cells and superior cerebellar peduncles are generally well preserved.<sup>8</sup> This is not surprising if one views OPCA, as Berciano suggests, as a linked degeneration commencing in the pontine nuclei with later transsynaptic degeneration of the cerebellar cortex. Dentate degeneration would presumably follow from loss of Purkinje axon activity. Indeed the few well defined reports of OPCA with "normal cerebellar cortex" also have normal dentate nuclei.<sup>9-13</sup>

Berciano is correct in thinking that Norman and Urich's case is a form of cerebellar hypoplasia, although it is not so obvious as he avers (see Friede<sup>7</sup>). But to lump cases of PNCH with OPCA is to confuse fundamentally different processes. In OPCA, pontine and arcuate nuclei and the inferior olives are the prime targets for degeneration. In the rare condition PNCH there is severe hypoplasia of the neocerebellar cortex and pontine nuclei and usually a remarkable malformation of the dentate nuclei which are broken into a series of islands. These classical findings<sup>14,15</sup> are confirmed in recent papers<sup>16-18</sup> and in several personally examined cases. The unexpected finding in our familial cases<sup>1</sup> of cerebellar pathology completely different from PNCH, but quite typical of OPCA and yet occurring in the neonatal period is what prompted our publication. We have examined a third unrelated case with a very similar clinical and pathological picture, which we are preparing for publication. In addition, it has recently come to our attention that two siblings with a very similar clinicopathological picture have been reported by Agamanolis *et al.*<sup>19</sup>

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