

EDITOR'S CHOICE

ALZHEIMER'S DISEASE: New research diagnostic criteria for Alzheimer's Disease

The current NINCDS-ADRDA diagnostic criteria for Alzheimer's disease (AD) date back almost a quarter of a century (Neurology 1984;34:939-44), a time when the molecular nature of amyloid was only just being characterised, the molecular structure of neurofibrillary tangles was unknown, MRI was still in its infancy, and deterministic genetic mutations were yet to be defined. All these factors have prompted this (self-appointed) group to suggest new diagnostic criteria for AD. The old criteria required a 2-step process: 1. Is there dementia? 2. Is it AD? Possible, probable and definite categories of AD were defined. The recognition of mild cognitive impairment (MCI) as a possible prodrome of AD implies that disease may be present without the clinical correlate of dementia (as may also be true in other 'dementias' such as DLB, FTD, prion disease). The new criteria, although still probabilistic, aim to bypass this 'binary outcome' by taking a biological approach to disease definition, eliminating the categories of MCI and possible AD.

Core and supportive criteria are proposed. Core (criterion A) relates to cognition: gradual and progressive memory change, with objective impairment of episodic memory which may or may not be an isolated finding. Contrary to DSM-IV-TR, dementia diagnosis does not require presence of a functional disability (in agreement with studies which do not find ADL scales useful as a diagnostic test). Supportive criteria relate to imaging (B: presence of medial temporal lobe atrophy on MRI; D: specific pattern on functional imaging with PET, not SPECT), CSF (C: abnormal CSF biomarker), and genetics (E: proven autosomal dominant mutation within the immediate family). Diagnosis requires A + 1 or more of B-E. There are also exclusion criteria, similar to those of NINCDS-ADRDA.

Although still to be validated, undoubtedly some such revision of AD diagnostic criteria will be of value in the research and clinical trials settings. But what are their implications for day-to-day practice outside major research centres, particularly in light of UK NICE/SCIE guidance which envisages all dementia care as led by old age psychiatrists? Access to quality imaging (MRI, PET), specialised CSF markers, and neurogenetics is restricted or non-existent in much of the UK. Here presumably the old criteria will prevail: certainly the authors foresee "technically less demanding criteria for clinical settings". Some of the exclusion criteria may also be objected to, sometimes being transgressed in AD cases (e.g. sudden onset, early seizures). The proof of the pudding will be whether the criteria permit earlier AD diagnosis and, hopefully, meaningful disease-modifying interventions. – *AJL*

Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P.

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria.

LANCET NEUROLOGY

2007;6(8):734-46.

EPILEPSY: Valproate and phenytoin for status epilepticus

*** RECOMMENDED

The use of antiepileptic drugs in status epilepticus is limited by logistical factors such as availability as an IV preparation and ability to give a large initial dose without gradual dose titration. Valproate has been available for a long time and has been looked at in a number of small and uncontrolled studies and this to my knowledge is the largest study to assess it. The authors used a definition of status as seizures lasting more than five minutes, which has been previously suggested but not universally adopted. Also their definition of ongoing status, in which patients had ceased to seize but had not yet woken up after 30 minutes, will have meant the inclusion of some patients with a milder problem than in other studies. Forty per cent had an associated illness, most commonly infective, especially septicaemia (14%) and 'viral fever' (8%). The commonest reason for status was drug withdrawal, whether accidental or through non-compliance. The study appears to have been only of patients with tonic-clonic status, but it is not entirely clear. They split 100

patients, who had not responded to an initial benzodiazepine into two groups, one receiving phenytoin and the other valproate. About half in each group had seizures which had lasted more than two hours. Overall response rates were 88% to IV valproate and 84% to IV phenytoin. When these were broken down according to duration of status, the response to valproate was 100% for those under two hour's duration and 70% for those over two hours. Comparable figures for phenytoin were 96% and 71%. One patient in each group left the study early, because of the cost of treatment. I assume, that unless their relatives withdrew them, that they had recovered. Mortality was 8% in either group and adverse events were similar. So this study gives further support to the use of valproate in status, although there are some differences in the patients being treated, both in terms of causes of status and severity from other studies and from common clinical practice in Western countries. – *MRAM*

Agarwal P, Kumar N, Chandra R, Gupta G, Arun R, Garg N.

Randomized study of intravenous valproate and phenytoin in status epilepticus.

SEIZURE

2007;16:527-12.

BRAIN INJURY Two neurons to rub together? – Applicability of neural reserve theory in mild traumatic brain injury

*** RECOMMENDED

One of the great challenges in predicting the longer term consequences of mild brain injury is that there is often little correlation between the severity of the injury and the eventual outcome. Two individuals may be unfortunate enough to have very similar accidents, producing identical physical brain damage and yet make completely different progress in recovery. The authors of this study suggest that a possible reason for the different outcomes lies in an individual's neural reserve. Put simply, the more brain you've got, the more you can lose before adverse effects kick in. While this theory has been used in models of different neurodegenerative diseases, there have only been two studies, to date, applying this model to brain injury. There is, apparently, a very good correlation between levels of education, IQ, and neural reserve (measured by brain volume, neuronal size and level of branching). This somewhat contentious proposal was used by the authors as a basis for assessing the effects of moderate brain injury, in terms of the duration of post traumatic amnesia, in people with different "neural reserves". Apart from educational attainment and IQ, alcohol use, marijuana consumption, age and previous neurological damage were also assessed as were levels of depression, anxiety and stress. A total cohort of 59 patients were identified and screened retrospectively for the measures in question. Unfortunately, post traumatic amnesia, which was being used as a marker of severity of injury, was assessed by asking patients to describe the point at which they developed continuous memories following the initial accident. This seems like rather a flawed process, but has been utilised in other research. Somewhat surprisingly, no correlation was found between duration of post traumatic amnesia and previous neurological injury, alcohol or marijuana use. There were, however, significant relationships between IQ, duration of education and the duration of post traumatic amnesia indicating that greater neural reserves may have a protective effect. While this is an interesting study, which addresses an important area in the field of brain injury, some of the methodological problems (retrospective data analysis, the use of subjective quantification of post traumatic amnesia and the assumption that IQ correlates with "neural reserve") mean that it is difficult to draw conclusions from it that would be helpful in the clinical context. – *LB*

Dawson KS, Batchelor J, Mears S, Chapman J, Marosszeky JE.

Applicability of neural reserve theory in mild traumatic brain injury.

BRAIN INJURY

2007;21(9):943-9.

PARKINSON'S DISEASE: adrenal transplants 16 years on

*** RECOMMENDED

In the 1980s following the paper by Madrazo et al in the New England Journal of Medicine, adrenal medullary transplants became an attractive experimental treatment for Parkinson's disease. The rationale was simple, the adrenal medulla produces catecholamines including dopamine albeit at low levels, and thus transplanting it from its normal site to the head of the caudate nucleus should produce clinical improvement from local dopamine release within this structure. However, with time the results proved equivo-

