

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-

cal, and may have been as much due to the release of neurotrophic factors from the transplant and host sprouting as well as breaching of the blood brain barrier by the non fenestrated endothelium and better delivery of L-dopa to the brain, as to dopamine replacement by the transplant itself. Furthermore significant morbidity and mortality was attached to the procedure and so by the early 1990's the procedure fell out of favour. In this short report, Kompoliti et al report on the post mortem findings of an adrenal medullary transplant 16 years after it was performed in a patient who died after a 38 year-history of Parkinson's disease. The patient had significant benefit from the transplant for 4 years but subsequently declined and developed dementia and drug related psychosis. At post mortem some surviving chromaffin cells were found although none stained positive for tyrosine hydroxylase, the rate limiting enzyme that is used as a marker of catecholamine including dopaminergic cells. Thus the transplant failed to survive in a functionally useful state as the clinical course indicated. This is an important paper, because often the long term consequences and outcome of these experimental procedures are forgotten, as the initial enthusiasm for the therapy wanes to be replaced by uninterested scepticism. It is therefore good to see that follow up of the patient was continued in this case to the point of death and pathological examination of the brain. – RAB

Kompoliti K, Chu Y, Shannon KM and Kordower JH.

Neuropathological study 16 years after autologous adrenal medullary transplantation in a Parkinson's disease patient.

MOVEMENT DISORDERS

2007;22(11):1630-3.

SCHIZOPHRENIA: What is the problem?

Schizophrenia is a common disorder that affects a significant proportion of the population and the causes and treatment of it have been argued about for years. For many years now schizophrenia has been considered a neurodevelopmental disorder involving dopaminergic systems and in part this relates to the efficacy of dopamine receptor blockers as treatment for this condition and the non progressive changes that can be seen on imaging studies. However new ideas are always emerging in this field and more recently issues relating to neurogenesis and glutamatergic systems have been raised. Two recent papers provide further evidence in support of this. In the first of these, Patil et al have shown that metabotropic glutamate receptor 2 and 3 agonists are effective in schizophrenia possibly by reducing glutamate release without any effect directly on dopaminergic networks. This implies that manipulation of glutamate release could be important in the treatment of schizophrenia although this does not exclude some downstream action of such transmitter changes on dopamine networks. In another study Duan et al report that abnormalities in DISC 1 (Disrupted-In-Schizophrenia) alters neurogenesis during development and adulthood especially in the hippocampus in the latter case. How such alterations relate to the clinical features of schizophrenia are as yet unclear but again point the focus away from the dopaminergic synapse. Thus both of these new findings are interesting and may even be linked given the recent interest in neuro transmitter modulation of neurogenesis. Whatever the ultimate significance of this work both studies have suggested new ideas in the genesis of this devastating neuropsychiatric disorder. – RAB

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Nezmanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA, Schoepp DD.

Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial.

NATURE MEDICINE

2007;13(9):1102-7.

Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu XB, Yang CH, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng HJ, Ming GL, Lu B, Song H.

Disrupted-In-Schizophrenia 1 Regulates Integration of Newly Generated Neurons in the Adult Brain.

CELL

2007;130(6):1146-58.

HEADACHE: Topiramate treatment for chronic headache

*** RECOMMENDED

This randomised, double-blind, placebo-controlled trial of topiramate in chronic headache found a significant reduction in monthly migraine days on topiramate compared to placebo. Adults with more than 15 monthly days

were called chronic headache and of those, 78% met the criteria for acute medicine overuse at baseline. During the study, other migraine prophylactics, apart from antiepileptic drugs, were continued. Study completion rates were 75% in the topiramate group, and only 52% in the control group. The mean reduction in monthly migraine days was 3.5 compared to -0.2 in controls, and this was significant statistically. Data from quality of life questionnaires was conflicting, with improvement in the MIDAS rating (a migraine disability scale), but no change in the HIT-6 (Headache impact scale). Adverse events were high in both groups, with 73% in the topiramate group and 37% in the control group (who were taking a variety of medicines). In the topiramate group, the most common side effect was paraesthesiae (53%). Disturbance in attention in this trial was 6%, similar to other studies, and does not appear dose related so if it occurs, usually means the medication needs to be stopped. This study shows efficacy of topiramate in this headache group, who are often resistant to treatment. It is important that the treatment worked in patients overusing analgesics, as we need more good treatment options in this group in particular. – HAL

Diener H-C, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, on behalf of the TOPMAT-MIG-201 (TOP-CHROME) Study Group.

Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.

CEPHALALGIA

2007;27:814-23.

STROKE: Training stroke patients' arm movements

Task specific practice is recommended for improving motor function after stroke, but the best way to provide feedback in training is not known. Many therapists use manual guidance, using their hands to focus on the pattern of movement produced. Others focus on the achievement of goals and set up the position of targets to encourage the desired movements, for example to reach further or higher. Most give encouragement during the movement, after it or both. There is a lack of evidence to inform the most effective information to give as feedback and when to give it. The motor learning literature, which has been driven by sports science, distinguishes between two types of feedback: 1. Knowledge of Performance (KP) - on line feedback about performance as it occurs. 2. Knowledge of Results (KR) - information about the result of the movement when it is completed. In practice then KR may allow the person to know whether they were successful in picking up an object or placing it in the desired position, while KP could inform the person about the trajectory of the movement and the temporal relationships of joint motion as it happens. Cirstea and Levin have reported an interesting experiment to compare the effectiveness of KP and KR in stroke patients learning a pointing task. Twenty-eight stroke patients, who were at least three months post stroke, were randomly allocated to two groups. Both groups practiced reaching, with the affected arm, to a target for 75 pointing trials a day, for ten days. The target was positioned just out of reach, but the participants were asked to point to the target as quickly and accurately as possible in a single uncorrected movement. After a few initial trials with the eyes open, the participants were asked to practice with eyes closed to allow greater distinction between feedback regimes. One group was given concurrent verbal information about arm joint movements while they performed the pointing movements (KP), the other group were allowed to open the eyes at the end of the movements and correct their terminal position (KR). Statistically significant increases in joint range, better inter-joint coordination and generalisation of these gains to pointing to a target positioned in a different place were observed only in the group who received KP. In sports training for individuals without impairments the use of KP has been questioned. It has been argued that because motor planning is most likely to be done in terms of hand or foot space, it is better not to focus attention onto the performance of joints through the movement. It seems that this advice should not apply to training patients with stroke. These results go a little way to helping the therapist to direct feedback effectively. Many questions remain though. Would the difference in arm movement have been apparent if the patients had been allowed to use vision as well? Is it helpful to use manual guidance as feedback or is it better to use verbal feedback? Answers to these questions will help not only therapists in clinical practice but also the development of robots and virtual reality games for rehabilitation in the future. – AJT

Cirstea MC, Levin MF.

Improvement of arm movements patterns and endpoint control depends on type of feedback during practice in stroke survivors.

NEUROREHABILITATION AND NEURAL REPAIR

2007;21:398-411.