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CLINICAL

A new FRONTIER in dementia differential diagnosis?

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TITLE FRONTIER Executive Screen: a brief executive battery to differentiate frontotemporal dementia and Alzheimer's disease

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SUMMARY

Over the past two decades, John Hodges and his colleagues, working initially in Cambridge, UK, and latterly in Sydney, Australia, have described a number of tests for screening and staging of dementia disorders. These instruments include the Addenbrooke's Cognitive Examination (ACE) and its later iterations (ACE-R, ACE-III, ACEapp, mini-ACE),[1] the Cambridge Behavioural Inventory (CBI),[2] and the Frontotemporal Dementia Rating Scale (FRS).[3] A number of these tests have been developed specifically to diagnose frontotemporal dementias (FTD) and to differentiate them from Alzheimer's disease.[1,2] The recently described FRONTIER Executive Screen (FES),[4] named for the FRONTIER Dementia Clinic at Neuroscience Research Australia, adds to this suite of screening instruments.

The FES uses three relatively simple items to examine the domains of executive function which are typically impaired in behavioural variant FTD (bvFTD), the most common form of FTD. The items assess verbal fluency, verbal inhibitory control, and working memory. Verbal fluency involves generating words beginning with a particular letter (phonological or lexical verbal fluency). Sentence completion tasks require the inhibition of an automatic verbal response to generate the final missing word (e.g. 'The cat sat on the …', where the anticipated final word, 'mat', would be considered an incorrect response due to a failure of inhibition). Working memory requires repetition of strings of letters in the reverse order to which they are given ('letter span task'; hence the response to 'R-K-T' should be 'T-K-R'). These three items are analogous to existing tests of executive function (respectively the Controlled Oral Word Association Test, the Hayling Sentence Completion Test, and the Digit Span Backwards Test). Each FES item generates a score from 0–5, summed to produce a total FES score from 0–15, with higher scores indicating better executive function. The test is brief (5–10 min), relatively easy to score (a scoring guide is provided) and requires no specialist equipment.

In this index study, 14 patients with bvFTD and 14 patients with Alzheimer's disease were tested. The two groups were matched for disease severity (comparable performance on ACE-III). FES demonstrated effective discrimination between the two groups. Total FES score classified 20/28 patients correctly, with area under the receiver operating characteristic curve of 0.842. An FES cut-off score ≤ 8/15 identified bvFTD with sensitivity of 0.86 and specificity of 0.50. Both patient groups scored below age- and education-matched healthy controls (n = 33) on all individual and total FES scores.[4]

OPINION

Dementia is a generic term for acquired cognitive failure sufficient to produce impairments in social and occupational function. There are many potential causes, of which Alzheimer's disease is the most common. An important differential diagnosis is FTD, particularly in younger patients; indeed FTD may be more common than Alzheimer's disease in patients younger than 65.[5]

FTD is a heterogeneous disorder at the clinical, pathological, and genetic levels, encompassing variants presenting with either behavioural or linguistic symptoms,[6] of which the behavioural type, bvFTD, is the most common. The pattern of cognitive deficits in Alzheimer's disease and FTD is different, although often described by patients and collateral sources in terms of 'poor memory'. Typically, patients with Alzheimer's

disease are amnesic (reflecting temporal lobe dysfunction), whereas in bvFTD deficits in executive function predominate. Executive function is a broad term that describes cognitive processes that are supported by the prefrontal cortex, an area that undergoes early pathological change in bvFTD. These functions are potentially amenable to examination at the bedside or in the clinic room with simple tests, as used in the FES.

Although clinicians familiar with these disorders may readily identify archetypal forms, there is considerable clinical overlap which may lead to delayed diagnosis and misdiagnosis.[7] For example, patients with bvFTD may initially be referred to psychiatric services and obtain various psychiatric diagnoses (e.g. depression, mania, obsessive-compulsive disorder) before the correct diagnosis becomes apparent as the disease progresses. This diagnostic difficulty may have significant implications, since FTD and Alzheimer's disease have different prognoses and treatment. Hence, simple instruments that can be used in the clinical setting to differentiate FTD and Alzheimer's disease would be welcome. Existing tests, such as the ACE,[8] may have difficulty in differentiating bvFTD from Alzheimer's disease.

Does the FES fill this gap? These data are encouraging, but preliminary, and will require corroboration in independent patient cohorts before the FES can be widely recommended for use. Caveats include the very small number of patients tested. Moreover, the study design, comparing patients with established diagnoses and using a normal control group, which may be described as a 'proof-of concept' or type II study, may overestimate typical metrics of diagnostic test accuracy (measures of discrimination such as sensitivity and specificity).[9] Studies which more accurately reflect clinical practice, wherein diagnoses are initially unknown and there is no control group (pragmatic or type III studies),[9] will be required to further assess the diagnostic accuracy of the FES. As with all screening instruments, FES is not a diagnostic tool and should not be used as a substitute for more extensive clinical, neuropsychological and neuroradiological evaluations.

One laudable aspect of the current study is that the FES (and its scoring guide) is made freely available by the authors (at either http://dx.doi.org/10.1136/jnnp-2015-311917 or http://www.neura.edu.au/frontier/research). Hence, there are no copyright issues, unlike for one of the very commonly used cognitive screening instruments, the Mini-Mental State Examination. This access should facilitate future studies of the FES, and hence a consensus on whether it does represent a new frontier in dementia differential diagnosis.

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