

SESSION 8B COGNITIVE CHANGE

C66 FRONTOTEMPORAL DEMENTIA AND MOTOR NEURONE DISEASE

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Keywords: frontotemporal lobar degeneration, clinicopathological correlation, behaviour

An association between frontotemporal dementia (FTD) and motor neurone disease (MND) is now well recognised. Nevertheless, the precise nature of the relationship is not yet fully understood. It is not known whether people with FTD/MND are representative of the larger population of patients with forms of frontotemporal lobar degeneration (FTLD) or whether there are clinical, pathological and genetic differences. Similarly, it is unclear whether FTD/MND is a unique syndrome, clinically and aetiologically distinct from classical MND, traditionally thought to be a pure motor disorder, or whether there is a clinical continuum between the two.

In this talk I examine data from a cohort of more than 500 patients with clinical syndromes of frontotemporal lobar degeneration (FTLD) and compare the demographic, clinical and, where available, pathological characteristics of those individuals who develop MND and those who do not. The data reveal similarities between patients with and without MND in terms of age at onset and frequency of family history but highly significant differences in terms of gender ratio and illness duration. There are commonalities between patients with and without MND in cognitive/behavioural presentation, the majority showing the behavioural/executive disorder of FTD and a minority, features of semantic dementia or progressive nonfluent aphasia. However, in contrast to the pathological heterogeneity within FTLD, which encompasses tau and non-tau pathologies, and three sub-types of ubiquitin histopathology, the patients with MND show pathological homogeneity, sharing an identical tau-negative, ubiquitin positive histology. Molecular studies reveal no patient with MND to have mutations in the tau or progranulin gene.

Complementing these data, I describe the findings from a small-scale study of behaviour in MND. The findings point to a spectrum of behavioural change, with some patients exhibiting no behavioural alterations whereas others fulfil behavioural criteria for FTD.

The implications of these data for the “continuum” vs. “phenotypic variant” notion of the relationship between FTD and MND are discussed in the light of advances in molecular biology and genetics.

C67 EARLY VERBAL FLUENCY DEFICITS PREDICT COGNITIVE IMPAIRMENT IN ALS: A POPULATION-BASED LONGITUDINAL STUDY

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Keywords: cognitive, population, longitudinal

Background: Up to 60% of people with ALS have mild cognitive decline; a smaller proportion develop frontotemporal

dementia. The population-based frequency, clinical characteristics and natural history of cognitive decline in ALS are unknown.

Objective: To determine the frequency and natural history of cognitive decline in ALS in a defined population-based cohort, using the latest consensus criteria (1).

Methods: All incident patients with ALS were captured on the Irish ALS Register and were asked to participate in a longitudinal study of cognitive function. Each participant was assessed using an extensive neurological and neuropsychological battery at 3 time intervals over 18 months.

Results: A population-based cohort of 87 patients and matched controls was studied. Clinical characteristics reflect the overall demography of ALS in Ireland. Twenty two (25%) had bulbar-onset disease. A total of 46 (53%) had deficits in verbal fluency on first assessment. Based on consensus criteria of 2 standard deviations below the control mean on two or more cognitive tests, 32.2% of ALS patients had cognitive impairment (ALSci) at time of first assessment. 7 (8%) patients were diagnosed with behavioural impairment (ALSbi+ as per supportive Neary criteria); 20.7% of patients were however behaviourally impaired as measured by a 2-standard deviation (SD) change from premorbid levels on either a FrSBe subscale or FrSBe total score. Apathy was the most marked behavioural change. Total behavioural change in patients predicted caregiver burden and mood.

17 (19%) patients met Neary criteria for FTLD: 12 for behavioural variant FTD, 2 for non-fluent progressive aphasia, and 3 for semantic dementia. Of those who tested within the normal range on the first assessment, only 3 (7%) had evidence of cognitive impairment on subsequent testing. Conversely, those who had verbal fluency deficits on first testing had clear evidence of deteriorating function on subsequent testing.

Conclusions: ALS is associated with a high prevalence of cognitive and behavioural change. Early deficits in verbal fluency predict later cognitive impairment. However, those with normal cognitive function at baseline are unlikely to exhibit any cognitive or behavioural deterioration. These data suggest that ALS with cognitive impairment represent a distinct subpopulation of ALS and not a continuum.

Reference:

1. Strong *et al.* Amyotrophic Lateral Sclerosis, 2009; 10(3):131–46

C68 VALIDITY OF A BRIEF COGNITIVE SCREENING EXAM FOR ALS PATIENTS

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Keywords: FTD, screening

Background: Recent investigations suggest that 28–48% of ALS patients possess a spectrum of frontotemporal deficits on neuropsychological measures, and patients with these cognitive and behavioral changes have poorer compliance and reduced survival rates. In this study, a brief screening battery was compared with a thorough neuropsychological evaluation to determine whether a time-efficient,

cost-effective screening exam can be a valid instrument in identifying ALS patients with cognitive and behavioral changes.

Objectives: This 30 minute cognitive screen is predicted to be a valid indicator of the cognitive and behavioral functioning of ALS patients. Specifically, diagnoses based on screening instruments are predicted to correlate with diagnoses based upon separate, standardized measures used in a full two hour neuropsychological battery. The diagnostic categories included ALS, ALS with Cognitive Impairment (ALSci), and ALS with Behavioral Impairment (ALSbi).

Methods: Based upon performance on a thirty minute screening battery, 14 study participants were classified into three diagnostic categories: ALS, ALSci, and ALSbi. Using a separate 2-hour neuropsychological evaluation, independent diagnoses were made. Comparisons were made between screening diagnoses and diagnoses made using standardized, age-matched norms. The screening diagnoses were based upon a cut off score of 12 or below on the ALS-Cognitive Behavioral Screen (ALS-CBS) and a score of 27 or above on the the Frontal Behavioral Inventory (FBI). Full battery diagnoses of ALSci were based on a 5th percentile cut off on two or more measures of functioning. Full battery diagnoses of ALSbi were based on a T score of 65 or above on the Frontal Systems Behavioral Scale.

Results: In 12 of the 14 cases studied for cognitive functioning, matching diagnoses were made using the 30 minute battery. In two cases, the screening tests identified subjects as impaired but when given a full battery and requiring strict cut offs for pathology, they were diagnosed as normal. When measuring behavioral symptoms, 5 of the 7 subjects had matching diagnoses. In both cases, the screening test diagnosed the subject as normal but the full battery identified them as behaviorally impaired.

Discussion and Conclusions: These data suggest that the screening tool may be an effective instrument in identifying ALS patients with cognitive and behavioral changes, particularly when measuring cognitive changes. Behavioral changes may be more accurately measured with the full battery test (the FrSBe) as it was more sensitive than the Frontal Behavioral Inventory.

C69 VALIDATION OF THE PENN STATE BRIEF EXAM OF FRONTAL AND TEMPORAL DYSFUNCTION SYNDROMES IN AMYOTROPHIC LATERAL SCLEROSIS: APPLICATION OF GUILFORD'S STRUCTURE OF INTELLECT THEORY

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Keywords: frontotemporal dementia, assessment, treatment planning

Background: ALS-related cognitive behavioral impairments are estimated to occur in 30–50% of patients, primarily manifested as frontal and temporal dysfunction syndromes, with only a small percentage significant enough to meet the criteria for Frontotemporal Dementia. The Penn State Brief Exam of Frontal and Temporal Dysfunction Syndromes

(PSFTS) is concise enough to be administered during the ALS multidisciplinary clinic visit, while sensitive enough to detect emerging declines in frontal and temporal cognitive behavioral capacities. Cognitive measures were chosen to detect declines in capacities recognized as important for decision making and problem solving. To account for the synergistic role of frontal and temporal cortical processing in decision making, we applied the Structure of Intellect Theory of Guilford during the selection of both brief exam measures and comprehensive neuropsychological measures to which we correlated brief exam findings. In Guilford's Structure of Intellect Theory, intelligence is viewed as comprising distinct Operations, Contents and Products. Operations include Evaluation, Convergent Production, Divergent Production, Memory and Cognition, the latter encompassing basic language skills. The Operation relevant to decision making is Evaluation, while Convergent and Divergent Production are Operations relevant to reasoning and problem solving.

Objectives: This study aimed to validate the PSFTS by correlation of findings to those obtained from a comprehensive neuropsychological battery of measures also constructed from Guilford's Operations, with an emphasis upon decision making and problem solving.

Methods: Thirty-five age, education and ALSFRS-R matched patients with an El Escorial diagnosis of probable ALS participated in the study. Non-parametric Spearman correlations were conducted between the brief exam and comprehensive exam measure findings classified by the Cognition, Evaluation, Convergent Production, and Divergent Production Operations.

Results: Statistically significant relationships were evidenced for all four Operations evaluated. Evaluation (decision making) relationships were evidenced for the brief exam task of Judgment and battery tasks of Consequences Obvious ($p < 0.014$) and Consequences Remote ($p = 0.054$). Problem Solving relationships included significance between 1) a brief exam task of Convergent Production (Similarities) and a battery task of Convergent Production (Missing Cartoons) ($p < 0.007$), as well as a battery task of Divergent Production (Alternate Uses), and 2) brief exam task of Divergent Production (letter fluency) and a battery task of Divergent Production (Alternate Uses) ($p < 0.0001$).

Discussion: Accounting for the synergistic role of frontal and temporal cortical processing in decision making by applying Guilford's Structure of Intellect Theory, we developed a brief exam applicable to the ALS multidisciplinary clinic, able to detect emerging declines in problem solving ability. Currently, we validated this brief exam by demonstrating the high degree of concordance between findings generated by 35 ALS subjects who completed both the brief exam and a comprehensive neuropsychological assessment, also selected by applying Guilford's Structure of Intellect Theory.

Conclusions: The PSFTS is a valid approach to early detection of frontal and temporal dysfunction syndromes by brief exam. The ability to identify emerging difficulties with decision making and problem solving in the ALS multidisciplinary clinic is of vital importance for optimal treatment planning.

C70 ANTI-SACCADE PARADIGM IN THE COGNITIVE FRONTAL ASSESSMENT OF AMYOTROPHIC LATERAL SCLEROSIS

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Keywords: anti-saccade paradigm, neuropsychological assessment, eye-movements

Background: Eye movement abnormalities are sensitive markers of neurological diseases and have been studied in a variety of neurological conditions (1–3). The analysis of saccadic eye movements may provide a useful tool for investigating neurological or psychiatric disorders in which the frontal lobe is impaired. Frontal alterations in Amyotrophic Lateral Sclerosis (ALS) have been variously described and assessed in literature (4). Involvement of frontal function has recently been studied exploring ocular fixation with the aid of eye-tracking technology, thus revealing the importance of detecting the whole spectrum of frontal involvement characterizing motor neurone disease’s cognitive pattern (5). Anti-saccade paradigm is ideal in exploring frontal cognitive functions (6). In the anti-saccade paradigm subjects are instructed not to make a reflexive saccade to an appearing lateral target but to make an intentional saccade to the opposite side. This ability depends on the integrity of the dorsolateral prefrontal cortex (DLPFC) (7).

Objectives: The purpose of this study was to analyze frontal cognitive functioning of ALS patients with cognitive computerized measures and the anti-saccade paradigm.

Methods: Fifteen patients fulfilling El Escorial Criteria (8) for ALS and fifteen controls underwent an extensive neuropsychological and psychodiagnostic assessment. Patients received the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS_r). Different cognitive domains were investigated with both traditional cognitive tools as well as computerized tests: reaction time, attention, eye-movements, executive functions, cognitive flexibility, language, problem solving. This battery included: computerized measures of reaction time and eye-movements (PVA test-Visuo-Attentional Performance Evaluation), Frontal Assessment Battery (FAB), Stroop Colour-Word Test, Symbol digit modalities test, Trail Making Test, Mini Mental State Examination (MMSE), Raven’s Coloured Progressive Matrices (CPM). Eye-movements were measured using a 1750 Tobii eye-tracker. Clinical tools for assessing psychological and emotional status included: MOS 36-Item Short-Form Health Survey (SF-36), Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory-Y (STAI-Y).

Results: Our data show quantitative and qualitative differences in cognitive performance between patients and controls, with higher difficulties in the anti-saccade task for the former and better scores in neuropsychological traditional tools for the latter. Significant differences and paradigmatic patterns of data emerge on different eye-movements/reaction times measures, while a general cognitive slowness characterized patient’s performances. Patients displayed lower performances on frontal measures of cognitive functioning. Subjects differed significantly for the presence of depressive/anxious symptoms.

Discussion and Conclusions: Neuropsychological assessment reveals specific cognitive and psychological patterns, as well as peculiar alterations of eye-movements patterns. Computerized neuropsychological assessment seem more sensitive in detecting small ‘frontal’ cognitive changes frequently observed at the onset of the disease. Moreover this assessment seems to be an ideal tool in assessing ALS longitudinally. These data suggest that oculomotor assessment and the anti-saccade paradigm may be useful in this kind of diagnosis.