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**PROGRESSIVE REGIONAL ATROPHY IN NORMAL ADULTS
WITH A MATERNAL HISTORY OF ALZHEIMER DISEASE**

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NEUROLOGY, 76:822-9, March 1, 2011**

Late-onset Alzheimer disease (AD) is a neurodegenerative disorder caused by complex genetic and environmental mechanisms. Age is the most significant risk factor for developing AD, followed by a family history of AD, with maternal transmission being found significantly more frequently than paternal transmission. In the current longitudinal brain imaging study, the authors attempted to determine whether different patterns of regional gray matter atrophy would be seen in cognitively healthy elderly subjects with and without a family history of late-onset AD.

As part of the University of Kansas Brain Aging Project, cognitively intact individuals who were 60 years of age or older underwent MRI examinations at baseline and at two-year follow-up. The subjects were similar in age, gender, education level, and Mini-Mental State Examination scores and were grouped as follows: 11 with a maternal history of AD, 10 with a paternal history of AD, and 32 with no parental history of AD. *APOE* genotypes were determined by means of restriction enzyme isotyping. While controlling for age, gender, and *APOE4* status, the researchers used a custom voxel-based morphometry processing stream to examine regional differences in atrophy between family-history groups. A secondary analysis was performed to evaluate regional atrophy differences between the 14 subjects who carried an *APOE4* allele and the 39 who did not. Compared with the subjects without a family history of late-onset AD, those with a family history had significantly increased whole-brain gray matter atrophy and CSF expansion. When the subjects with a maternal and paternal family history were considered separately, only maternal family history was found to be associated with longitudinal measures of brain change. Voxel-based analysis also revealed that subjects with a maternal family history had significantly greater atrophy in the precuneus and parahippocampus/hippocampus regions than subjects with a paternal history and those with no family history; this finding was independent of *APOE4* status, gender, and age. Subjects who carried an *APOE4* allele had more regional atrophy in the frontal cortex than those who were noncarriers of the allele.

According to the authors, cognitively normal individuals with a maternal family history of late-onset AD appear to have progressive gray matter volume reductions in select AD-vulnerable brain regions, specifically the precuneus and parahippocampal gyrus. (40 References) EAF

THE SYMPTOM OF LOW MOOD IN THE PRODROMAL STAGE OF MILD COGNITIVE IMPAIRMENT AND DEMENTIA: A COHORT STUDY OF A COMMUNITY DWELLING ELDERLY POPULATION

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J NEUROL NEUROSURG PSYCHIATRY, 82:788-93, July 2011

Subclinical syndromes of depression and isolated depressive symptoms are more common than clinical depression in both mild cognitive impairment (MCI) and dementia. The most prevalent symptom of depression seen in those with MCI is low mood. Taking into account MCI severity, time of assessment, and interaction with other factors, the authors investigated the symptom of low mood as a predictor of MCI and its progression to dementia. Low mood was defined as a report of perceived sadness.

The study sample was composed of 764 cognitively healthy elderly subjects (75 years of age or older) living in the community. The participants were assessed by means of direct interviews to detect low mood. The subjects were then followed for a period of six years to identify those who developed MCI. Those with incident MCI were followed for a further three years to assess progression to dementia. During follow-up, 160 individuals developed MCI; of these, 40 were classified as having amnesic MCI (aMCI) and 120 as having global cognitive impairment (other cognitive impairment no dementia [oCIND]). After adjusting for sociodemographic factors, the researchers found that low mood detected at baseline substantially increased the risk of developing MCI. More specifically, low mood was associated with a 5.8-fold increased risk of aMCI, a 2.2-fold increased risk of oCIND, and a 2.7-fold increased risk of overall MCI. The APOE- ϵ 4 allele interacted with low mood in a synergistic fashion, increasing the risk of aMCI; however, no interaction with psychiatric, vascular, frailty-related, or psychosocial factors was observed. As opposed to low mood co-occurring with MCI, low mood at baseline was found to be associated with a 5.3-fold increased risk of progression to dementia in subjects with aMCI; no such association was found in those with oCIND.

According to the authors, the current findings revealed that low mood was more strongly associated with amnesic MCI than with global cognitive impairment. Progression toward dementia was predicted only by low mood that was manifest in the prodromal stage of MCI. The researchers conclude that low mood appears to be particularly prominent in the very early stages of cognitive decline. (41 References)

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COGNITIVE DECLINE IN PRODROMAL ALZHEIMER DISEASE AND MILD COGNITIVE IMPAIRMENT

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David A. Bennett, MD ARCH NEUROL, 68:351-6, March 2011**

By definition, dementia due to Alzheimer disease (AD) is preceded by a minimum of six months of cognitive decline. However, there have been relatively few studies of this prodromal phase of the disease, and estimates of its duration range from approximately one year to more than 10 years. In the present investigation, the authors examined changes in cognitive function during the prodromal phase of AD and before the onset of mild cognitive impairment (MCI).

The sample was drawn from two longitudinal cohort studies (the Religious Orders Study and the Rush Memory and Aging Project). For up to 16 years, more than 2,000 older individuals underwent annual clinical evaluations that included detailed testing of cognitive function and clinical classification of MCI, dementia, and AD. At baseline, there were 2,071 persons without dementia and 1,511 without cognitive impairment. During follow-up, 462 individuals developed AD; 20 persons with dementia solely due to another condition were excluded from the analyses. Those who developed AD were older than those who did not (81.3 years vs. 76.3 years), but the groups were similar in years of education (16.4 vs. 16.2 years) and sex distribution (72.7% female vs. 71.9% male). The data revealed that five to six years before diagnosis, the rate of global cognitive decline accelerated more than 15-fold. The acceleration in cognitive decline occurred slightly earlier for semantic memory (76 months before diagnosis) and working memory (75 months before diagnosis) than for other cognitive functions. MCI was also preceded by years of cognitive decline that began earlier (80 months before diagnosis) and proceeded more rapidly (annual loss of 0.102 unit) in the amnestic than in the nonamnestic (62 months, 0.072 unit) subtype.

According to the authors, the findings of the present investigation indicate that dementia due to AD is preceded by approximately five to six years of accelerated decline in multiple domains of cognitive functioning. By the time that individuals meet clinical criteria for a diagnosis of AD, they have already experienced many years of progressive cognitive decline. On the other hand, however, little cognitive decline is evident in those individuals who do not develop AD. (*38 References*)

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**IMPACT OF IMPAIRMENT IN INSTRUMENTAL ACTIVITIES
OF DAILY LIVING AND MILD COGNITIVE IMPAIRMENT
ON TIME TO INCIDENT DEMENTIA: RESULTS OF
THE LEIPZIG LONGITUDINAL STUDY OF THE AGED**

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PSYCHOL MED, 41:1087-97, May 2011**

Mild cognitive impairment (MCI) has been found to be associated with a high risk for the development of dementia. In addition, some studies have shown that impairments in cognitively demanding instrumental activities of daily living (IADL) may serve as early indicators for the development of dementia. The aim of the current investigation was to determine the impact of MCI and IADL impairment on the time to incident dementia diagnosis in a large population-based sample of subjects who were 75 years of age or older.

The data were derived from the Leipzig Longitudinal Study of the Aged. The study covered a period of eight years and included a baseline assessment and five follow-up assessments, conducted on an average of every 1.4 years. Kaplan-Meier survival analysis was used to determine time to incident dementia. Cox proportional hazards models were applied to determine the impact of MCI and IADL impairment on the time to incident dementia. In all, 180 (22%) of 819 initially dementia-free subjects had developed dementia by the end of the study. The mean time to incident dementia was 6.7 years. A significant association was found between MCI and IADL impairment. The presence of MCI in combination with impaired IADL was associated with a higher conversion rate to dementia, a shorter time to clinically manifested diagnosis, and a lower chance of reversibility to cognitively normal functioning. The highest conversion rate and the shortest time to incident dementia was found in those subjects with both the amnesic subtype of MCI and impaired IADL.

The authors conclude that subject with both MCI and IADL impairment constitute a high-risk population for future dementia. The consideration of IADL impairment, in addition to MCI, could help to improve the prediction of dementia, especially with regard to an estimation of the time to clinical manifestation. IADL impairment in particular could aid in improving the prediction of dementia, because it reflects the development of dementia in real situations of daily life and can be assessed by less extensive methods than biological markers. (33 References) EAF

**FUNCTIONAL IMPAIRMENT IN ELDERLY PATIENTS WITH
MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER DISEASE**

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ARCH GEN PSYCHIATRY, 68:617-26, June 2011**

The term mild cognitive impairment (MCI) is used to identify a stage of impairment that demonstrates considerable heterogeneity, with MCI being displayed by individuals at high risk for conversion to dementia. While original MCI criteria excluded substantial functional deficits, recent research reports have suggested otherwise. Identifying the extent, severity, type, and correlates of functional deficits that occur in MCI and mild Alzheimer disease (AD) may aid in the early detection of incipient dementia and may help in the identification of potential mechanistic pathways to disrupted instrumental activities of daily living (IADLs). Using baseline data from the Alzheimer's Disease Neuroimaging Initiative, the authors examined the number, type, and severity of functional impairments and attempted to identify the clinical characteristics associated with functional impairment in patients with amnesic MCI (aMCI) and in patients with mild AD.

The study sample was composed of 394 patients with aMCI, 193 patients with mild AD, and 229 healthy, cognitively intact individuals (control group). The 10-item Pfeffer Functional Activities Questionnaire (FAQ) was used to assess functioning. Self-reports of functional deficits were collected for the control group, but informant reports were collected for the aMCI and AD groups. Informant-reported FAQ deficits were common in patients with aMCI (72.3%) and AD (97.4%), but were rarely self-reported by control subjects (7.9%). The average severity per FAQ deficit did not differ between patients with aMCI and controls; both were less impaired than patients with AD. Two FAQ items (remembering appointments, family occasions, holidays, and medications; and assembling tax records, business affairs, or other papers) were specific in terms of differentiating the control group from the combined aMCI and AD groups; only 34% of patients with aMCI and 3.6% of those with AD had no difficulty with these two items. The severity of FAQ deficits in the combined aMCI and AD group was associated with poorer Trail Making Test, Part A scores and with smaller hippocampal volumes.

The authors conclude that mild deficits in IADLs appear to be common in individuals with aMCI and should be incorporated into MCI criteria. (53
References)

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CLINICAL FEATURES AND APOE GENOTYPE OF PATHOLOGICALLY PROVEN EARLY-ONSET ALZHEIMER DISEASE

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NEUROLOGY, 76:1720-5, May 17, 2011

Alzheimer Disease (AD) is the most frequent cause of degenerative dementia in developed countries. The typical clinical pattern starts with episodic memory dysfunction and then progresses to other cognitive domains. The diagnosis of early-onset AD (EOAD) presents a challenge because it frequently presents with atypical clinical manifestations such as visual, executive, behavioral, or language impairments. The purpose of the present study was to describe the clinical features of a group of patients with pathologically confirmed EOAD (onset before age 60), investigate the frequency of nonmemory presentations in EOAD, and identify features that led to misdiagnoses.

The authors conducted a retrospective review of clinical data (age at onset, family history, clinical presentation, diagnostic delay, diagnosis) and *APOE* genotype for 40 cases (25 male, 15 female) with neuropathologically confirmed EOAD. The mean age at onset was 54.5 years (range, 46-60). The mean disease duration was 11 years, with a mean diagnostic delay of 3.1 years. Twenty-five patients (62.5%) presented with typical episodic memory dysfunction as the first symptom, while the other 15 patients (37.5%) had an atypical presentation. Behavioral/executive dysfunction was the most prevalent atypical presentation. Incorrect initial clinical diagnoses were common (53%) in patients with atypical presentations, but were rare when anterograde amnesia was the presenting symptom (4%). Incorrect initial clinical diagnoses were as follows: behavioral variant frontotemporal lobar degeneration (N=2), normal pressure hydrocephalus (N=2), semantic dementia (N=1), primary progressive aphasia (N=1), corticobasal degeneration (N=1), pseudodementia with depression (N=1), and unclassifiable dementia (N=1). The *APOE* genotype was $\epsilon 3/\epsilon 3$ in 59%, with no significant differences between typical and atypical presentations. *APOE* $\epsilon 4$ was found 3.3 times more frequently in subjects with a family history of AD. In all, 97.5% of the cases presented with advanced neurofibrillary pathology.

In the current study, one third of patients with pathologically confirmed EOAD presented with atypical symptoms. The authors conclude that EOAD patients with nonamnestic presentations often receive incorrect clinical diagnoses. (32 References)

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**INTERPERSONAL TRAITS CHANGE AS A FUNCTION OF DISEASE
TYPE AND SEVERITY IN DEGENERATIVE BRAIN DISEASES**

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J NEUROL NEUROSURG PSYCHIATRY, 82:732-9, July 2011**

Personality (an individual's habitual pattern of cognition, emotion, and behavior) may change dramatically in people with traumatic brain injuries or degenerative brain diseases. Different degenerative brain diseases result in distinct personality changes because of divergent patterns of brain damage; however, little is known about the natural history of these personality changes throughout the course of each disease. The aim of the present study was to determine how interpersonal traits change as a function of degenerative brain disease type and severity.

Using the Interpersonal Adjective Scales, the authors collected annually for one to four years informant ratings of retrospective premorbid and current scores for dominance, extraversion, warmth, and ingenuousness on the following: 188 patients (67 with behavioral variant frontotemporal dementia [bvFTD], 40 with semantic dementia [SemD], 81 with Alzheimer's disease [AD]) and 65 older healthy controls. Through the use of random coefficient models, interpersonal behavior scores at very mild, mild, or moderate-to-severe disease states were compared within and between patient groups. The results showed that bvFTD, SemD, and AD patients demonstrated changes in specific personality traits at a very mild stage of disease, and these traits changed with disease progression. For example, bvFTD and SemD patients could be differentiated from AD patients on the basis of their progressively decreasing levels of extraversion, warmth, and ingenuousness (i.e., interpersonal traits associated with emotional affiliation) and their increasing interpersonal rigidity. Among these behaviors, lack of warmth best differentiated bvFTD and SemD patients from AD patients at all disease stages.

The authors conclude that interpersonal trait changes in bvFTD, SemD, and AD patients occur as a function of disease type and severity, thereby providing further evidence of direct brain-behavior relationships for some aspects of personality. While patients in all three disease categories experienced loss of social dominance early, only bvFTD and SemD patients showed progressive alterations in their capacity for affiliative social behavior, which is consistent with the severity of damage known to occur in the emotion-related frontoinsula and anterior frontal cortex. (42 References)

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PREDICTING SURVIVAL IN FRONTOTEMPORAL DEMENTIA WITH MOTOR NEURON DISEASE

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NEUROLOGY, 76:1886-93, May 31, 2011**

Frontotemporal dementia (FTD) encompasses clinical syndromes characterized by progressive and insidious behavioral changes and language deficits. Clinical symptoms of motor neuron disease (MND) can develop in patients with FTD, and patients with MND may manifest behavioral or language symptoms over the course of the disease. In the present study, the authors attempted to determine whether clinical and demographic features are associated with prognosis in patients with both FTD and MND, i.e., FTD-MND.

A database search of the Mayo Clinic electronic medical record system was used to identify all patients diagnosed with both dementia and MND between January 2000 and July 2010. Those with FTD-MND were classified according to the existence of behavioral- or language-dominant symptoms at presentation and throughout the course of illness. Demographic, clinical, imaging, and survival data were analyzed with respect to dominant FTD-MND type. Voxel-based morphometry was used to assess and compare regional patterns of atrophy in behavioral- and language-dominant FTD-MND types. Of 56 patients identified with FTD-MND, 31 had dominant behavioral symptoms, and 25 had dominant language symptoms; 53 patients had died. A survival difference was found between types; patients with behavioral-dominant symptoms survived 506 days longer than patients with language-dominant symptoms (mean, 1,397 days vs. 891 days; $p = 0.002$). There was also a difference between groups in time from diagnosis to death. Patients with language-dominant disease were more likely to have bulbar-onset than limb-onset MND. There was a similar pattern of frontal and temporal lobe atrophy in both types, although there was some evidence indicating that patients with the behavioral type had more frontal atrophy, while those with the language type had more left temporal atrophy.

According to the authors, the results of the current study suggest that patients with behavioral-dominant FTD-MND but without bulbar onset have the best survival rates, whereas those with language-onset FTD-MND and bulbar onset have the poorest survival rates. It appears that patients with FTD-MND can be categorized according to behavioral or language dominance through the use of clinical features outlined in the consensus criteria and that this categorization has implications for survival in counseling patients and their families. (34 References)

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**DISEASE-MODIFYING PROPERTIES OF LONG-TERM LITHIUM TREATMENT
FOR AMNESTIC MILD COGNITIVE IMPAIRMENT:
RANDOMISED CONTROLLED TRIAL**

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The findings of two recent clinical studies support the feasibility of conducting trials aimed at evaluating the disease-modifying properties of lithium in Alzheimer's disease, although no benefits were found with regard to short-term treatment. In the present single-center, double-blind, placebo-controlled study, the authors attempted to evaluate the effects of long-term, low-dose lithium treatment on cognitive and biological outcomes in a group of community-dwelling outpatients with amnesic mild cognitive impairment (aMCI).

To be enrolled in the trial, subjects had to be 60 years of age or older; have a diagnosis of aMCI according to Mayo Clinic criteria; and have no evidence of ongoing psychiatric disorders. Forty-five participants with aMCI were randomly assigned to receive lithium (N=24) or placebo (N=21) for a period of 12 months. The primary outcome measures were modifications in cognitive and functional test scores and concentrations of cerebrospinal fluid (CSF) biomarkers (amyloid-beta peptide, total tau, and phosphorylated-tau). Forty-one participants (91% of the total sample) completed one year of follow-up (21 in the lithium group and 20 in the placebo group). Eleven participants (24% of the total sample) progressed to Alzheimer's disease after 12 months of follow-up. Long-term lithium treatment was associated with a significant decrease in CSF concentrations of phosphorylated-tau as well as better performances on attention tasks and on the cognitive subscale of the Alzheimer's Disease Assessment Scale. In general, tolerability to lithium was good, and the adherence rate was 91%.

According to the authors, the findings of the current investigation reinforce the notion that in an individual at risk for Alzheimer's disease, lithium treatment may have a protective effect with regard to the progression from cognitive impairment to dementia. In the researchers' opinion, this is probably a consequence of the effect of lithium on glycogen synthase kinase 3 beta and possibly on other pivotal cascades involved in the pathophysiology of Alzheimer's disease. (27 References)

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IMPROVED LANGUAGE PERFORMANCE IN ALZHEIMER DISEASE FOLLOWING BRAIN STIMULATION

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J NEUROL NEUROSURG PSYCHIATRY, 82:794-7, July 2011**

Alzheimer disease (AD) is a progressive disorder that impacts memory, language, and several other cognitive functions. Given the limited effectiveness of pharmacological treatments for AD, non-pharmacological interventions have gained attention in recent years, and there are currently many different approaches under investigation, ranging from multistrategy interventions to cognitive training. For example, repetitive transcranial magnetic stimulation (rTMS) has been proposed as a possible treatment for the cognitive deficits associated with AD. The aim of the present study was to assess the long-term effects (on cognitive performance) of rTMS applied to the left dorsolateral prefrontal cortex ((DLPFC) in patients with AD.

The study sample was composed of ten outpatients who met diagnostic criteria for probable moderate AD. A multiple-baseline design was used, and the patients were randomly assigned to one of two groups. The first group underwent a four-week real rTMS stimulation protocol, while the second group underwent two weeks of placebo treatment, followed by two weeks of real rTMS stimulation. Each session consisted of the application of rhythmic high-frequency rTMS over the DLPFC for 25 minutes. Sessions were conducted once a day, five days a week. The main outcome measure was the change in cognitive test performance at two and four weeks after rTMS treatment initiation, with follow-up performed eight weeks after the end of rTMS (compared with baseline performance). A significant difference was found between groups over sessions in terms of the percentage of correct responses on auditory sentence comprehension. Only real treatment induced an improvement in performance with respect to baseline or placebo. Moreover, both groups exhibited a lasting effect on the improved performance eight weeks after the end of treatment.

According to the authors, the results of the present study provide initial evidence for the persistent beneficial effects of rTMS on sentence comprehension in patients with AD. The current findings may reflect an rTMS-induced modulation of short- and/or long-range cortical synaptic efficacy and connectivity that potentiates the system within the language network, leading to more effective processing. Rhythmic rTMS, in conjunction with other therapeutic interventions, may represent a novel approach to the treatment of language dysfunction in patients with AD. (15 References) EAF