CLINICAL AND NEUROPATHOLOGICAL FINDINGS FROM CERAD

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The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) was established in 1986 to develop standard methods to evaluate persons with Alzheimer’s disease (AD) and to gather clinical, neuropsychological, and neuropathological information about the illness (Morris et al., 1989). Rather than a true registry, CERAD utilized convenience samples from 24 U.S. AD research centers to accomplish its aims of standardizing and testing the reliability of brief assessment instruments for AD and thus provide tools for use in epidemiologic surveys, dementia registries, and AD research protocols, including clinical drug trials. Since the onset of patient recruitment in 1987, CERAD has enrolled 1,281 cases and 472 controls into its longitudinal studies. Analyses of the CERAD database have addressed clinical diagnostic accuracy, neuropsychological staging of dementia severity, rates of cognitive decline, and other issues in the clinico-pathological characterization of AD.

CERAD INSTRUMENTS

The CERAD protocols were designed for ease of administration, brevity, and conventionality to ensure their uniform application across multiple centers. The clinical and neuropsychological protocols are administered annually; annual return rates for CERAD subjects are between 65-75%.

The clinical assessment protocol was designed to provide clinicians with the minimum information necessary to make a confident diagnosis of AD (Morris et al., 1989). It contains semistructured interviews with both the patient and an informant, a general physical and neurological examination of the patient (including a structured assessment for extrapyramidal dysfunction), and brief cognitive scales. Global dementia severity is staged in accordance with the Clinical Dementia Rating (CDR). Diagnostic criteria for AD are adapted from those proposed by the National Institute of Neurological and
Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann et al., 1984).

The *neuropsychological assessment protocol* is administered independently of the clinical protocol (Morris et al., 1989). Measures were chosen to assess the primary cognitive manifestations of AD and to evaluate deficits over much of the course of the disease. Individual measures include Category Fluency, modified Boston Naming Test, Mini-Mental State, Word List Learning, Recall, and Recognition, and Constructional Praxis.

The neuropathology assessment protocol documents gross and microscopic central nervous system abnormalities relevant for dementia (Mirra et al., 1991). Silver (e.g., Bielschowsky) or thioflavine S methods are used to detect senile plaques (SP) and neurofibrillary tangles (NFT) in five anatomic regions: middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, hippocampus and entorhinal cortex, and midbrain. Diagnostic criteria for AD are based on semiquantitative assessment of neuritic neocortical SP (i.e., those with thickened silver-positive neurites) in the most severely affected regions. An age-adjusted plaque score is integrated with clinical information about the presence or absence of dementia to determine the level of certainty for the diagnosis of AD.

Coronal T1-weighted spin echo sequences from magnetic resonance images (MRI) of the brain are used in the MRI assessment protocol to rate atrophy (focal and global), white matter abnormalities, and areas of cerebral infarction or hemorrhage (Davis et al., 1992). The family history assessment protocol collects demographic and cognitive information on family members of probands by means of a structured telephone interview by trained family historians (Silverman et al., 1994). The Behavior Rating Scale for Dementia samples the psychopathology encountered in demented patients, including mood disorders, agitation, aggression, and psychotic symptoms (Tariot et al., 1995), and is administered to an informant by a trained interviewer. Items are scaled by frequency of occurrence within the previous month.

**STANDARDIZATION AND RELIABILITY**

Instruction manuals have been developed for all CERAD protocols. The individual guidebooks, the training methods, and data management procedures are contained in the CERAD Manual of Operations.

Clinical and neuropsychological protocol standardization is accomplished in part through videotaped demonstrations. Each center is certified for use of the protocols after demonstrating standard administration and scoring procedures. Uniformity and completeness are maintained by monthly random review of subject protocols and regular communication with each center. Interrater agreement on the quantitative CERAD tests is high, with intraclass correlation coefficients ranging from 0.92 (Constructional Praxis) to 1.0