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Unit 10.3: Assessment of Cognitive Impairments in the Diagnosis of Alzheimer's Disease"

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Abstract

Alzheimer's disease (AD) is the most common form of dementia in older adults. It represents a significant public health concern because of its associated personal, social, and economic burden. As such, AD is the focus of considerable research world wide. This unit reviews the major cognitive and behavioral impairments associated with AD, and the practical application of current neuropsychological procedures used to assess these deficits.

Keywords

Neuropsychological Assessment; Alzheimer's disease; dementia

I. Introduction

Alzheimer's disease (AD) is the most common type of dementia in the elderly and is becoming a major public health issue as the population ages. As such, it is the focus of significant research. AD is a slowly progressive neurodegenerative disorder that affects cognitive abilities, activities of daily living, and is also associated with a variety of neuropsychiatric symptoms and behavioral disturbances. AD is associated with a characteristic pattern of progressive neuropathological changes (i.e., early medial temporal lobe involvement) that results in a fairly consistent pattern of progressive cognitive deficits with memory impairment as an early symptom. There are several different sets of diagnostic criteria used to diagnose Alzheimer's dementia. The most commonly used diagnostic criteria include those set forth by the National Institute of Neurologic, Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association (NINCDS-ADRDA; McKahnn et al. 1984) and the Diagnostic and Statistical Manual (DSM; 3rd and 4th Editions) (American Psychiatric Association, 1987 and 1994, respectively).

According to the NINCDS-ADRDA criteria a diagnosis of AD is stratified as definite, probable or possible according to the certainty of diagnosis based on the available information. Definite AD requires histopathological confirmation via autopsy or biopsy. Probable AD requires the presence of multiple cognitive impairments which are progressive in nature, there is no disturbance in consciousness (i.e. a delirium), the disease begins between the ages of 40 and 90. and there is no systemic or other brain disorder that could account for the deficits. Possible"AD is reserved for those cases which present with an atypical onset, presentation or progression.

Both the DSM-III R and the NINCDS-ADRDA diagnostic criteria for AD demonstrated good reliability and validity (Blacker et al. 1994; Jobst et al., 1998;).

Because the definitive diagnosis of AD requires histopathological evidence, practically speaking the diagnosis of AD is a clinical one. The clinical evaluation for AD includes a physical and neurological evaluation, appropriate lab work, and typically also includes structural neuroimaging to help rule out other causes of cognitive deterioration. Quantification of which cognitive domains are impaired and the degree of impairment is accomplished through a neuropsychological evaluation and the protocols used to establish specific cognitive impairments in the diagnosis of AD is the focus of this unit. “Impairment” of cognitive functions is defined in various ways but is often discussed in terms of standard deviation units below some normative reference group. By convention, performance falling 1.5 to 2 standard deviations below the mean of a normative group is widely considered to be impaired. A cutoff of 2 standard deviations represents a level of performance which, on a normally distributed measure, has less than 2.5% change of being representative of the normative group. The choice of which normative group to use as a comparison is a source of heated debate. Most typically, age-corrected norms are used; however, age and education-corrected norms are becoming more commonly used and are particularly important for individuals falling at either end of the education spectrum (i.e., having very low or very high levels of education).

II. The general course of cognitive and behavioral disturbances in AD

Before proceeding to a discussion of the neuropsychological protocols used in the diagnosis of AD, a brief description of the course of cognitive and behavioral decline in AD is instructive. The onset is usually slow and insidious and the duration of each stage may differ markedly. The cognitive deficits of AD relate to the neuroanatomical features that are affected in the disease process. The first stages of AD are usually characterized by memory impairment (Albert et al., 2001). The patient usually presents with difficulty remembering recent conversations and events. As such, the patient will often repeat themselves and misplace items. The neuroanatomic correlates to the beginning stages of AD are cell loss in the hippocampus, entorhinal cortex, and other regions of the temporal lobe (Strange, 1992; Zola and Squire, 2000).

In the intermediate stage, the patient continues to have memory impairment, but other domains such as language, attention, spatial orientation, and executive functions are also affected. The memory impairment increases in severity and involves a pattern of rapid forgetting of information (i.e., within a few minutes). In regard to changes with language, verbal output remains generally fluent but marked by word-finding difficulty. Attentional changes can often interfere with the patient’s ability to track conversations and maintain a coherent stream of thought. Changes to spatial orientation can often result in occasions of becoming lost or disoriented, or general geographic disorientation. Executive dysfunction can affect the ability to multi-task, plan, organize, and reason. By the intermediate stage, patients typically have lost most higher-level instrumental activities of daily living (i.e., driving, managing finances, cooking, cleaning, shopping, medication management). The neuroanatomic correlates as the disease progresses involve more extensive regions of the

temporal lobe and other neocortical areas such as the parietal and frontal regions (Terry et al., 1991). Subcortical structures such as brainstem nuclei are also affected (Terry and Katzman, 1983; Mann et al., 1984; Yamamoto and Hirano, 1985).

In the final stage of the disease the patient usually has an inability to recognize family members and become dependent even in basic activities of daily living (i.e., washing, dressing, grooming, mobility, feeding, toileting). There is extensive cortical involvement. Near the end of the disease the patient may develop motor difficulties, sensory abnormalities, gait disturbances, seizures and psychosis, and is eventually bedridden.

III. Cognitive Assessment

A. General Screening Instruments

Several screening tests for dementia have been devised. These tests consist of a set of 20 to 30 questions which assess basic cognitive functions. Most assessments require the individual to give basic personal information (i.e., name, address, etc.), answer simple questions based on common knowledge (i.e., president of the USA), and remember simple items of information such as a list of three words or name and address to recall later. The most extensively used of the screening tests is the Mini-Mental State Examination (MMSE) of Folstein et al. (1975). A score below 24 (out of 30) is usually considered abnormal but the cutoff scores vary by age, education, and race. Other examples of similar scales are the Blessed Scale (Blessed et al., 1968), and the 7-min neurocognitive screening battery of Solomon et al. (1998). Screening tests can be helpful, but there are limitations, specifically in regards to missing many cases of mild dementia (e.g., poor sensitivity to mild AD).

B. Assessment of Memory

Neuropsychological tests of memory are often the most useful in discriminating those with AD from those without, particularly in the early stages (Albert et al., 2001). In particular AD is associated with poor learning and rapid forgetting of newly acquired information. This pattern reflects neuropathological changes in the entorhinal cortex, hippocampus, and other regions of the temporal lobe (Zola and Squire, 2000). Memory can be assessed using a variety of different paradigms. Two common paradigms used to assess verbal memory include story memory tasks and verbal list-learning tests. It is also important to evaluate an individual’s memory for nonverbal information.

Using a narrative format, the examinee is read 1 or 2 stories and asked to immediately recall them. After a delay of about 20–30 minutes the individual is asked to recall the stories from memory. Alternatively, list learning tasks assess memory for discrete bits of information (i.e., a list of words) presented over multiple learning trials. A supra-span word list is used (typically 10–16 words) and often the list is made up of words falling into several categories (tools, animals, colors, etc.). Typically there are five learning trials after which there is a short delay filled by a distraction task (sometimes a second list of words), followed by a test of how much the person has retained by asking them to recall the words once again. A similar procedure is also repeated after a longer delay of about 20–30 min. Some tests also incorporate delayed recall trials in which semantic cues are given (i.e. “Which tools were on the list?”). A recognition trial is also very helpful wherein the individual is read a long list of

words and has to discriminate which of the words was from the original list, and which are foils. See Table 1 for a list of commonly used verbal memory tests.

On both the story recall and list learning tasks individuals with AD show deficits in acquisition and retention of information. Rapid forgetting characterizes Alzheimer's patients after they demonstrated acquisition of material during the learning trials (Larrabee et al., 1993). In particular, On either the word list learning or story recall tasks this is observed when after even a short delay patients are able to recall little to none of the information (Brandt et al., 1988). When given cues, individuals with AD often make intrusion errors (i.e., producing information that was not part of the initial word list or story). Additionally, even when given a yes/no recognition format, the Alzheimer's patient performs poorly, demonstrating that it is not a deficit in retrieval per se but rather one of complete loss of the information. In particular a characteristic feature of AD is the production of a high number of false-positive errors (i.e., endorsing items that were not in the initial learning trials), demonstrating poor discriminability (Deweer et al., 1993).

A common approach to measuring recall of nonverbal material is to show individuals one or more visual designs (e.g., simple geometric figures) and then have them subsequently draw the designs from memory. Several available tests that use this approach are listed in Table 1.

C. Assessment of Language

Impairment in expressive language abilities occur fairly early in the course of AD (Bayles, 1988; Bschor et al., 2001; Hebert et al., 2000). Verbal output becomes progressively devoid of meaning due to both word retrieval deficits and degradation of semantic knowledge (i.e., long-established general knowledge about objects and facts no linked to a specific event) Commonly encountered language impairments on formal testing in AD include confrontational naming and semantic verbal fluency (Bowles et al., 1987; LaBarge et al., 1992; Thompson-Schill et al., 1999).

A commonly employed test of confrontation naming is the Boston Naming Test (Goodglass and Kaplan, 2000). It is comprised of 60 line drawings of objects of increasing difficulty, ranging from simple high frequency vocabulary words (i.e., comb) to low frequency words (i.e., abacus). The examinee is given credit if the item is named correctly within 20 sec. If the drawing is misperceived the examinee is given feedback that the picture represents something else and is given a stimulus cue. A phonemic cue (e.g., "The word begins with the sound…") is given after failure to respond correctly, whether spontaneously or after a stimulus cue. The most frequent type of errors on confrontation naming tests include circumlocutional errors in which the patient describes rather than names the object (i.e. an escalator is called a moving staircase, as well as paraphasic errors (primarily of a semantic nature, for example calling a pen a pencil) (Constantinidis et al. 1978).

Semantic verbal fluency tasks require patients to name as many exemplars as possible that belong to a given semantic category within a 60-sec period. Common categories used include animals, fruits and vegetables.

Aside from prominent anomia (difficulty with word finding), other classic aphasia syndromes are rare in AD. Thus, although there are a variety of other language measures, including batteries specifically designed to determine aphasia type, these are generally not highly useful in the diagnostic assessment of AD, with the exception that those types of tests can help to determine whether AD may be less likely and other forms of dementia (frontotemporal dementia) may be more likely. However, some individuals with AD can have more extensive and prominent language changes.

D. Assessment of Executive Functions and Working Memory

Simple attention remains relatively preserved in early AD, while more complex forms of attention are affected early in the course. Executive functions encompass a broad range of high-level processing abilities related to reasoning, planning, mental flexibility, response inhibition, and abstract concept formation, among others. These abilities are generally thought to be highly dependent on frontal lobe functioning, but ultimately involve a very broad cerebral network.

There are a variety of tests commonly used to assess aspect of executive functioning in older adult populations. The Trail Making Test (Part B) measures mental flexibility, divided attention, and the ability to quickly sequence items. This is a timed task that requires the subject to alternate between two sequences (counting and reciting the alphabet).. The Wisconsin Card Sorting test is another very commonly used test to asses a variety of executive functions related to abstract concept formation, problem solving, and the ability to utilize feedback to flexibly modify behavior. The Controlled Oral Word Association Test measures response generation, working memory, and speed. Individuals are asked to name as many words beginning with a specified letter as possible within 60 seconds (i.e., words beginning with ‘S’). Finally, the Digit Span backward subtest of the WMS-III assesses working memory. During this task the patient is read a string of numbers and asked to repeat the numbers backward. When the examinee repeats a number sequence correctly, the examiner reads a longer number sequence. This task continues until the examinee fails a pair of sequences or repeats the highest sequence correctly. Table 2 includes a list of these and other measures of executive functioning that can be useful in the evaluation of AD.

E. Assessment of Visual Spatial Abilities

Visuospatial abilities become affected relatively early in the course of AD and reflect parietal lobe dysfunction to large degree. Visuospatial functions make up a fairly wide range of abilities and hence there are a number of approaches to testing them. A common approach to measuring visuospatial functions in AD is to have an individual either spontaneously draw various objects, or have them copy line drawings. For example, an individual may be asked to draw the face of a clock. A number of formal scoring criteria have been developed to help interpret the results and one must also be mindful that, in fact, many cognitive abilities including, but not limited to, visuospatial abilities must be intact to perform the task. Individuals can also be asked to copy different designs such as a three-dimensional house, or cube. More complex line drawings are also available (Rey Complex Figure), but, again, other abilities such as executive functions (i.e., planning) also come into play when copying these types of designs. Another common approach to measuring visuospatial

functions is to have an individual reproduce block designs (i.e., Block Design subtest of the WAIS-III). Using this type of paradigm the individual is shown a visual design and then given blocks to reproduce the design. Tests that assess the functions described above are listed in Table 3.

F. Neuropsychological Batteries Used to Evaluate Dementia

There are several brief neuropsychological batteries which have been developed specifically to assess cognitive abilities in Alzheimer's disease. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al., 1989) is probably the best known of the dementia batteries. This battery includes verbal fluency, confrontational naming, a Mini-Mental Status examination, a word list memory test, and constructional designs. This battery has been used as both a diagnostic tool and to follow the patient's course. The CERAD total score is highly accurate in differentiating normal controls, mild cognitive impairment, and Alzheimer's dementia patients, and had excellent test-retest reliability across samples that were highly correlated with the Mini-Mental Status Examination and the Clinical Dementia Rating Scale in mixed Alzheimer's dementia and normal control samples, and with the Blessed Dementia Rating Scale in an Alzheimer's dementia sample (Chandler et al., 2005).

The Mattis Dementia Rating Scale (Mattis, 1988) examines five areas that are particularly sensitive to behavioral changes in AD. The areas are attention, initiation and perseveration (executive functions), construction, conceptual abstraction, and memory.

The ADAS-Cognitive subscale was developed specifically to measure the principal features of cognitive dysfunction in AD. Items cover language ability (naming, comprehension, expressive language, word finding); memory (recall of instructions, word list recall and recognition); praxis (ideomotor apraxia, the inability to perform gestures on command, is common in the moderate to late stages of AD) (constructional and ideational); and orientation (Rosen, 1984).

IV. The assessment of everyday function

In addition to impairments in multiple cognitive domains, both the DSM criteria and the NINCDS-ADRDA criteria require that there be concomitant loss in daily function. That is, the cognitive impairments have significant ramifications with regard to one's ability to function in daily life. While there are fairly well established definitions of what constitutes *cognitive* impairment (i.e., 1.5 standard deviations below age-adjusted normative values), there are essentially no similar guidelines to establish what constitutes functional impairment. The assessment of everyday functioning in older adults typically focuses on an individual's ability to carry out activities of daily living (ADLs). Basic ADLs (BADLs) include tasks such as eating, bathing, grooming, and toileting, while instrumental ADLs (IADLs) involve more complex behaviors including managing finances, handling medications, driving, cooking, and housekeeping. IADLs are affected relatively early in the course of dementia. Assessment of ADLs in large-scale studies is usually conducted through informant report. This method of ADL assessment has the advantage of asking family members or caregivers who are familiar with the individual's performance in real-world environments to rate their level of functioning, and is also highly time- and cost-efficient.

Performance-based assessment of ADLs, in contrast, allows a trained rater to directly observe behavior in well-defined functional tasks. The advantage of this method relates to the reduced influence of rater bias. However, this method may not accurately reflect true abilities insofar as the assessment is conducted in a structured environment with prompts to carry out desired tasks. Furthermore, performance-based scales are time-consuming and therefore less practical for use in large-scale research studies. Table 4 provides examples of some of the available instruments to assess everyday function, both informant- and performance-based instruments are included.

V. The Assessment of Neuropsychiatric symptoms

Neuropsychiatric symptoms, although not required for the diagnosis of AD as are cognitive and functional impairments, are common to the disease and are often a focus of research studies. Behavioral disorders that fall under this category include depression, anxiety, apathy, agitation, and a variety of psychotic symptoms including delusions such as paranoia, and hallucinations (visual and auditory). By far the most common instrument used to assess neuropsychiatric symptoms in dementia is the Neuropsychiatric Inventory (NPI; Cummings et al. 1994). The NPI assesses 10 behavioral disorders including delusions, hallucinations, depression, apathy, agitation, irritability, aberrant motor function, euphoria, and disinhibition on the basis of caregiver/informant ratings. Each domain is rated in terms of the frequency and the severity of the behavior.

Since depression is the most common neuropsychiatric symptom in early AD, there are a number of scales that specifically focus on depression. The Geriatric Depression Scale (Yesavage et al. 1983) is one such instrument and is particularly useful in the AD population as it includes fairly simple questions and requires only a yes/no response (rather than a Likert scale used in other depression screening instruments). Alternatively, the Hamilton Depression Scale (Hamilton, 1960) is based on informant- or clinician-based ratings of depression and can be useful for very impaired individuals or those that are not able to directly participate for other reasons.

Summary

Neuropsychological assessment is an important component of the diagnostic evaluation of AD. Due the characteristic distribution of neuropathological changes associated with AD, there is a common set of cognitive impairments that develop and progress throughout the disease. The goals of this unit were to help characterize the types of cognitive deficits that arise in association with AD and describe the practical methods by which these deficits are measured. Using well established criteria for AD, which includes establishing a specific pattern of cognitive deficits, the diagnosis of AD has been shown to be highly reliable. However, it is important to keep in mind that there is considerable individual variability in the nature and course of cognitive impairments associated with AD it is sometimes very difficult to distinguish AD from other causes of late life dementia.

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Table 1

Tests of Memory

Name of Test	References
Verbal Memory	
Logical Memory (WMS-III)	Wechsler, 1997
Learning and Memory Battery	Tombaugh and Schmidt, 1992
California Verbal Learning Test-II	Delis et al. 2000
Hopkins Verbal Learning Test-Revised	Benedict et al., 1998
CERAD Word List Memory	Rosen, Mohs, & Davis 1984
Nonverbal Memory	
Visual Reproductions (WMS-III)	Wechsler, 1997
Rey Complex Figure (delayed recall)	Meyers & Meyers, 1995
Benton Visual Retention Test	Sivan, 1992

Table 2

Tests of Executive Functions.

Name of Test	References
Trail Making Test (Parts A & B)	Reitan, 1955
Wisconsin Card Sorting Test	Grant & Berg, 1948
Stroop Color and Word Test	Golden, 1978
Controlled Oral Word Association	Spreen & Strauss, 1998
Similarities (WAIS-III)	Wechsler, 1997
Digit Span (WMS-III)	Wechsler, 1997

Table 3

Tests of Visuospatial Functions.

Name of Test	References
Block Design (WAIS-III)	Wechsler, 1997
Clock Drawing	Mendez et al. 1992
Judgment of Line Orientation	Benton et al. 1994
Rey-Osterrieth Complex Figure Test	Meyers and Meyers 1995

Table 4

Instruments used to assess everyday function.

Scale	Reference
Informant-based rating scales	
Physical Self-maintenance and Instrumental Activities of Daily Living Scales	Lawton & Brody, 1969
Disability Assessment for Dementia (DAD)	Gelinas et al. 1998
ADCS – Activities of Daily Living Inventory	Galasko et al., 1997
IQCODE	Jorm et al. 1994
ECog	Tomaszewski Farias et al. (2008).
Performance-based measures	
Direct Assessment of Functional Status (DAFS)	Loewenstein et al. 1989
UCSD Performance-Based Skills Assessment (UPSA)	Patterson et al. 2001
Structured Assessment of Independent Living Skills (SAILS)	Mahurin et al. 1991