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Early diagnosis of dementia: neuropsychology

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Abstract Neuropsychology contributes greatly to the diagnosis of dementia. Cognitive deficits can be detected several years before the clinical diagnosis of dementia. The neuropsychological profile may indicate the underlying neuropathology. Neuropsychological assessment at an early stage of dementia has two goals: (a) to determine a memory disorder, not always associated with a memory complaint, and (b) to characterize the memory disorder in light of the cognitive neuropsychology and to assess other cognitive (and noncognitive) functions toward integrating the memory disorder in a syndrome. We review the global tools, the memory tests that describe the memory profile and indicate the underlying pathology, the assessment of other cognitive functions, and the neuropsychological patterns of typical Alzheimer's disease, frontotemporal dementia, primary progressive aphasia, semantic dementia, Lewy body dementia, subcortical dementia, and vascular dementia. These patterns must be interpreted in the light of the history, rate of progression, imaging results, and nature of existing behavioral disturbances. Moreover, there may be overlap between two or more pathologies, which complicates the diagnostic process. Follow-up of patients is necessary to improve diagnostic accuracy.

Key words Dementia · Diagnosis · Neuropsychology · Alzheimer's disease

Introduction

Neuropsychology contributes greatly to the diagnosis of dementia: it documents significant cognitive decline and reveals patterns of cognitive dysfunction that suggest the cause of the dementia. Cognitive deficits can be detected several years before the clinical diagnosis of dementia [49]. Establishing the neuropsychological profile often indicates the underlying neuropathology. Although Alzheimer's disease (AD) is the most frequent disorder, it is not the only cause of dementia in adults. Therefore carrying out the neuropsychological assessment at an early stage of dementia has two goals: (a) revealing memory disorders, which are not always associated with memory complaints (memory impairment is a core feature of dementia, while memory complaints are not always due to a memory disorder, e.g., in anxiety disorders), and (b) characterizing the memory disorder in the context of cognitive neuropsychology, thus allowing other cognitive (and noncognitive) functions to be integrated with the memory disorder into a broader syndrome.

Here we concentrate on the conditions in which dementia is relatively isolated, in the absence of major motor symptoms.

Neuropsychological tools

Global tools: comprehensive assessment of dementia

The multi-item rating scales and batteries of brief cognitive tests evaluate the various cognitive functions that are typically impaired in dementia. Scores on various separate items or tests are summed to provide a total score representing overall cognitive status. These comprehensive assessments are typically used in the diagnosis to confirm the presence of cognitive impairment. The major problem of these cognitive tests in short formats is that their sensitivity is not uniform but varies by age, education, social class, and living situation (e.g., at home, independent of family members, in a geriatric institution, in hospital) [5, 10, 44, 61, 97]. However, they are useful in grading the severity of dementia and assessing the rate of cognitive decline.

One of the simplest and most universal tests is the Mini-Mental State Examination (MMS) [20]. An MMS score of 27 or higher is usually taken as excluding mental impairment [21], while one of 23 or lower generally indicates sufficient cognitive decline for the diagnosis of dementia to be made in epidemiological studies. MMS has disadvantages for the screening of vascular dementia (VaD) [80]: it emphasizes language and verbal memory, it lacks the recognition part of memory, it has no timed elements, and it is not sensitive to impairments in executive functions or mental slowing.

One of the most useful instruments is the Mattis Dementia Rating Scale (DRS) [52]. This was designed as a screening instrument to detect the presence of brain pathology in impaired geriatric patients. It evaluates a broad array of cognitive functions and includes subtests for attention, initiation, perseveration, construction, conceptualization, verbal and nonverbal memory. Thus it is sensitive to frontal and fronto-subcortical dysfunctions. High test-retest reliability has been reported [52], and normative data have been published [89].

Some of the most well-known tests are not designed for diagnosis and are used principally for longitudinal studies. For example, the Alzheimer's Disease Assessment Scale (ADAS) [81] was designed to provide a composite assessment of longitudinal investigations and clinical trials including patients with AD, Also, the Blessed rating instrument does not seem ideal for evaluating the severity of dementia in AD [77].

Some interview schedules explore the cognitive functioning of the suspected demented, his/her daily living adaptation, and the presence of psychiatrically relevant symptoms (provided by a close relative or informant). Among the few standardized interview schedules currently available, the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) [82, 83], which contains a cognitive section (CAMCOG), offers high psychometric quality due to its sensitivity to different levels of severity of dementia, rated on the basis of internationally established criteria [65, 66]. In particular, the CAMDEX reliably detects cases of minimal and mild dementia [64] and is independent of cultural factors [15, 36, 48, 63]. However, the generalized employment of CAMDEX in dementia is made difficult by its length (its administration requires 60–90 min). A short version has been designed which requires about 30 min to administer and consists of 106 of the 340 items of the full form [64].

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was developed in the United States to standardize assessment of the presenting neurological manifestations, cognitive impairment, and neuropathological abnormalities in patients with AD [38, 60]. The neuropsychological part may be used to detect and to stage dementia [101]. The normative data of the neuropsychological battery are available [102].

These global tools are useful for documenting dementia but not appropriate for detecting subtle cognitive impairment or discriminating cognitive profiles. The etiological diagnosis of dementia requires a more detailed analysis. Assessing neuropsychological functions should include tests of each major cognitive domain. A qualitative analysis of the errors or types of failures in individual tasks is also required to distinguish between different diseases.

Assessment of memory

In diagnosing the cause of dementia it is important to distinguish between failures of (a) storage (or retention), associated with damage to limbic and especially hippocampal structures, (b) retrieval associated with frontal-subcortical dysfunctions, and (c) short-term memory associated with temporo-parietal lesions:

- Storage disorders are characterized on testing by deficits in both recall and recognition and rapid loss of information at delayed recall. The patient shows little benefit from cues and provision of multiple choice alternatives.
- Retrieval disorders are characterized by a difficulty in accessing information. Free recall is low, perhaps because of lack of active or efficient search strategies, but cues and multiple-choice alternatives enhance performance. Recognition is better than recall, and delayed recall is not impaired.
- Short-term memory disorders are characterized on testing by reduced memory span and rapid loss of information measured by the Brown-Peterson paradigm [68].

The Wechsler Memory Scale-Revised (WMS-R), contains nine subtests and has excellent age norms. It may distinguish amnesic from demented patients [6], but it was not designed for this purpose, and the overall score submerges potential differences in reasons for failure. Moreover, it

does not assess specifically the various components of memory.

The best instrument for assessing memory disorders in early dementia is probably the Free and Cued Selective Reminding Test (FCSRT) [31, 32]. Unlike most clinical memory tests which do not control cognitive processing, this test includes a study procedure in which subjects search for items (e.g., grapes) in response to cues (e.g., fruit) that are later used to elicit recall of items not retrieved by free recall. Including a study procedure is particularly important for identifying early dementia. Other pathological or physiological conditions which limit learning when study conditions are not controlled are otherwise confused with dementia-associated memory impairment in preclinical and early stage disease. Furthermore, cued recall is considered the most useful test among a large neuropsychological battery in making diagnosis decision by neuropsychologists [96]. Performance on the FCSRT distinguishes dementia from normal aging with accuracy. Moreover, the test (immediate recall, free and cued recall, learning slope, recognition, delayed free and cued recall) provides a characterization of the memory impairment which distinguishes AD from subcortical dementia [76] and from frontotemporal dementia (FTD) [69]. This test is sensitive to early neuropathological changes in AD, in comparison to global status tests [33], with a correspondence with the Braak and Braak histological stages.

Short-term memory, assessed by the digit span, is not very sensitive to dementia [18, 49] but may be particularly impaired in progressive aphasia. The Corsi test [92], a spatial span measure, may be more sensitive to dementia. The performance on dual tasks is impaired early in dementia, but the specificity of this impairment according to the required tasks is not yet known.

Assessment of other cognitive functions

Language (production and comprehension), motor/praxis, perceptual and visuospatial, attention and concentration, and "frontal lobe" function must be assessed to integrate the memory impairment into a neuropsychological syndrome. A number of tests are discussed here, but the purpose of this section is not to review psychometric tests in general since each neuropsychologist is accustomed to using his/her own battery. The most important thing in clinical practice is to use pertinent tools to detect and characterize a dysfunction. In addition, the choice of tests depends on the purpose of the study, and, in particular, good tools for early diagnosis are not necessary the best for the follow-up.

Language

The various components of language may be assessed by confrontation naming: the short version of the Token test [13], reading, writing, and word fluency. Word fluency (letter and category fluency tests) is very sensitive to dementia but is not specific regarding cause. The value of language assessment (type of paraphasia/paragraphia, syntax, phonology, fluency) for differential diagnosis in patients visiting a memory clinic has recently been assessed [93].

Visuospatial ability

Several tests are available for assessing perceptual and particularly visuospatial functions, such as the "embedded" figures tests, the Wechsler Adult Intelligence Scale (WAIS) block design subtests, and the clock drawing test. Disturbances of visual function are not uncommon in AD, and several cases with complex impairment of visuospatial abilities have been described, while these functions are preserved in other dementias.

Apraxia

Constructional praxis (spontaneous drawing, copying geometrical figures) and gestural praxis (imitation and command, uni- and bimanual, object utilization), should be assessed. The nature of the production suggest impairment of the frontal lobe or the subcortical-frontal structures as a difficulty in control and temporal sequencing. It indicates damage of the superior parietal regions as a consequence of spatial dysfunction.

Frontal lobe tests

So-called frontal lobe tests, those evaluating abstraction, planning, and mental flexibility such as the Stroop test [94] and the Trail Making test [78], the Wisconsin card-sorting test, and set-shifting are useful but are not actually specific or sensitive to frontal lobe impairment per se. Divided attention and dual tasks are impaired early in dementia but do not seem to differ between the various types of dementia.

Abstract thinking, concept formation, and problem solving are not the first functions to be impaired in AD [28]. Measures include the WAIS similarities subtest of abstract verbal reasoning, concept formation, and language comprehension. Raven's Progressive Matrices examine problem-solving ability and are frequently used in place of the WAIS to estimate general intelligence in the elderly and to detect cognitive impairment [9].

Neuropsychological profiles of the main dementia syndromes at early stage

The typical AD syndrome is the most common condition. However, patients may present with a different neuropsy-

chological profile. Some of these are likely to be related to AD but others are certainly not. The differential diagnosis between AD and non-AD is of major importance for treatment and research purposes.

Weintraub and Mesulam [99] identified four behaviorally related neuropsychological profiles, based on their experience: (a) progressive amnestic dementia, (b) primary progressive aphasia, (c) progressive visuospatial dysfunction, and (d) progressive comportment dysfunction. Progressive amnestic dementia and progressive visuospatial dysfunction are likely to involve AD [4, 41] while primary progressive aphasia and progressive behavioral disorders are not. In asymmetric cortical degeneration syndromes, neuropathological study usually shows mild nonspecific degenerative changes [8].

We focus on the most frequent syndromes that may pose differential diagnostic problems with AD.

Typical Alzheimer's disease

The first symptom of typical AD [57] is impairment of recent memory: poor learning and retention of information over time. Patients with AD show poor learning over repeated trials and may make intrusion errors [7]. This is a disorder of storage, retrieval, and later of short-term memory. The test for delayed recall has been found to be the best overall discriminatory measure to differentiate patients with early AD from cognitively normal elderly controls with the CERAD battery [100, 101], and this is confirmed by other studies [1, 50]. Patients with AD lose more information after a brief delay than patients with amnesic or dementing disorder. Albert [1] found that the first delayed recall trial from the California verbal learning test, the immediate recall of figures from the Wechsler memory scale, and the time to completion on trail B of the trail making test to be the most significant predictors of progression of cognitive difficulties in subjects followed up for several years. Digit span may be in the normal range at early stages.

Comparison of the relative prevalence of different cognitive deficits indicates that the disorder of lexical-semantic language is second [42], while syntactic and phonological abilities are relatively preserved. Multivariate procedures to determine the efficacy of various measures in distinguishing between early AD and controls have found that the only nonmemory factor that assists delayed recall (the best discriminator) is confrontation naming [101]. The typical pattern of language impairment at an early stage is one resembling anomic aphasia but with few neologistic paraphasia, progressing through patterns resembling transcortical sensory aphasia but with relatively good performance on tasks such as sentence repetition. It is manifested by word-finding pauses in conversational speech. In formal testing, patients are impaired on reading comprehension and verbal reasoning. Verbal fluency tests are impaired in the early stage, especially the category fluency, but this is not specific to AD [73].

Visuospatial skills are often impaired relatively early in the disease. Patients with AD suffer from disorientation and are unable to copy three-dimensional figures accurately [11]. On the WAIS they obtain their lowest scores on Block Design and have difficulty copying the designs of the Benton visual retention test [67]. Facial recognition is generally impaired early in AD, with deficit attributable to both perceptual and memory dysfunction.

Frontotemporal dementia

Most of the patients with FTD meet the criteria for AD. Standard tests and many tasks traditionally thought to be sensitive to frontal dysfunction are ineffective in discriminating between AD and FTD [30]. Nevertheless, the diagnosis of FTD is clinically possible on the basis of history (personality and behavioral changes precede and remain prominent during the course of the disease), the nature of the behavioral disorder, normality on EEG, predominance of frontal or anterior temporal abnormalities on brain imaging, and neuropsychology [17, 69, 91].

At the beginning of the disease, scores on global scales such as the WAIS may be within the normal range. There is no systematic dissociation between verbal and performance IQ, in contrast to AD [59], although it is sometimes observed [45]. It highlights the dissociation between the profound alteration in personality and behavior and breakdown in social competence, and relative preservation of cognitive skills [91]. It contributes to the misdiagnosis of FTD. The MMS score may remain high for a long time [19]. Counting backwards may be the most sensitive subtest in FTD. Thus this tool does not seem suitable as a screening tool for differentiating FTD from AD. The Mattis DRS [52] is more reliable, as it is in subcortical dementia [86].

At early stages, patients are typically oriented in time and place and provide correct current autobiographical information. Family members notice a memory impairment but considers it less important than the behavioral disorder [69] and regard it as due to the behavioral difficulties [34]. Some memory tests are normal [43]. Patients may obtain normal scores on the logical memory subtest of the Wechsler Memory Scale with disjoined account [69]. Thus the choice of the test is important for showing the memory deficit. On the FCSRT [31, 32], free recall is as poor as in AD at the same degree of severity of dementia, but recall performance is more enhanced by the use of specific, directed questions rather than open-ended questions and by the use of cues and provision of multiple-choice alternative responses in FTD than in AD [62, 69, 91]. Table 1 compares AD and FTD on cognitive testing.

The pattern of memory breakdown is consistent with a "frontal-type" amnesia, with memory failures arising sec-

Table 1 Major differences between AD and FTD on cognitive testing (from [73])

	FTD vs AD
Short-term memory	
Digit span	=
Brown-Petterson paradigm	
Verbal	=
Visuospatial	>
Verbal explicit long-term memory	
Immediate recall	>
Free recall	=
Benefit of cueing	>
Recognition	>
Delayed cued recall	>
Implicit memory	
Verbal priming	>
Perceptual priming	>
Verbal fluency	=
Attention	
Selective attention (cancellation task)	
False alarms	>
Sustained attention	>
Alert	<
Stroop test	
Time	<
Errors	=
Trail Making Test (part B)	
Time	<
Errors	>

ondary to failures of attentional, retrieval strategies, organizational, and regulatory factors rather than a primary impairment of storage. The variability and unpredictability of memory performance support this hypothesis.

Spontaneous speech is usually reduced. Language utterances are typically grammatically correct without paraphasias and are sometimes of the semantic type [62, 69, 91]. There may be stereotyped remarks. Comprehension typically remains well preserved except for complex syntactic sentences which requires mental manipulation and sequencing of information. Naming skills are usually well preserved, although responses of the "don't know" variety are not rare. Reading aloud is preserved. Verbal fluency is impaired early [59, 73].

Patients have no difficulties in the perceptual recognition of objects and the appropriate use of objects. The main feature is that spatial skills are notably preserved [69, 91]. Although during the early part of the disease patients may perform poorly on constructional tasks such as drawing and block constructions, qualitative examination of the pattern of impaired performance suggests that this does not have a primarily spatial basis but arises secondary to organizational failure. This feature distinguishes FTD from AD. Upon testing, gestural praxis may be more easily evoked by imitation than by verbal command, and long remain normal, which is also a differential trait from AD.

Frontal lobe tests may be impaired, but surprisingly not always, at early stages of the disease.

FTD is associated with a primary degeneration of the frontal and anterior temporal lobes that may correspond with several histological syndromes, including Pick's disease and nonspecific degeneration, but not with AD. It is not yet possible to distinguish Pick's disease neuropsychologically from nonspecific frontal lobe degeneration.

Primary progressive aphasia

If the language disorder remains isolated for more than 2 years without behavioral abnormalities, the syndrome of "primary progressive aphasia" should be considered [91, 99]. It is characterized by difficult speech output, phonemic paraphasias, and relative preservation of comprehension, different from the pattern of AD. Calculation disorders may be contemporary, as well as some orofacial dyspraxia. Nonlanguage tasks are performed well, although praxic difficulties may be present on testing [58, 91, 99].

It is unlikely to find Alzheimer pathology at autopsy of patients with this syndrome. Nonspecific frontotemporal lobe degeneration or Lewy body disease and even corticobasal degeneration are more likely.

Semantic dementia

Some patients present with a progressive fluent aphasia on testing, in which the "aphasia" appears to reflect a severe loss of the semantic components of language with a preservation of other linguistic abilities. This syndrome is termed "semantic dementia" [90] (see below). It is characterized by profound loss of meaning for both words and objects. The loss of knowledge in semantic dementia is not confined to tests for understanding word meaning and word production. They are also grossly impaired on nonverbally based tasks requiring the matching of semantically related pictures of objects. This is in contrast to well-preserved memory for day-to-day events, such as remembering recent personal events and appointments [29, 39, 40, 90, 98]. Patients perform visuospatial and praxis tasks normally, and memory is not impaired at an early stage.

Relatively few patients with semantic dementia undergo postmortem histological study, but all show either classic Pick's disease or nonspecific temporal more than frontal degeneration [29, 40, 91].

Lewy body dementia

There are still only few neuropsychological data available on patients with Lewy body dementia. This dementia is characterized by cortical and subcortical-frontal dysfunctions [54–56]. In a retrospective study, Salmon et al. [87] compared patients with Lewy body disease with equally demented patients with "pure" AD and found that they have severe deficits in visuospatial and visuoconstructive abilities. Differences in the impairment of visual memory and attention have been described between patients with Lewy body disease and those with AD [84, 88]. Studies have demonstrated that Lewy body dementia without concomitant AD can produce a global dementia characterized by particularly pronounced deficits in memory (i.e., retrieval), attention, visuospatial abilities, and psychomotor speed [85]. A recent study has shown severe but similar degrees of impaired performances in tests of attention/short-term memory (digit span) frontal lobe function (verbal fluency, category, and Nelson card-sort test) and motor sequencing in both Lewy body dementia and AD groups as in Parkinson's disease patients and controls [26]. In the clock face test improved performance was noted in the "copy" compared to "draw" part of the test in controls, patients with AD and those with Parkinson's disease but not in the patients with Lewy body dementia, who achieved equally poor scores in both part of the test. This feature could help to distinguish between patients with Lewy body dementia and patients with AD. The clock face test assesses executive and visuospatial functioning, which may be greatly impaired in Lewy body dementia [26]. Fluctuations in performance from one testing to another is a striking feature in Lewy body disease [53].

Subcortical dementia

The clinical concept of subcortical dementia was introduced by Albert et al. [2] to describe the mental deterioration in Huntington's disease and progressive supranuclear palsy. This concept has been extended to other extrapyramidal syndromes. Its cardinal features are: forgetfulness, i.e., difficulty in retrieving learned material; slowing of mental and motor processes; intellectual deterioration characterized by impaired ability to manipulate acquired knowledge to generate problem solving; impairment of arousal, attention, and motivation and affective changes (depression); and impairment of set-shifting [12]. Freedman and Albert [22] have suggested that the term frontotemporal system dementia would be more accurate since it is better correlated with anatomical and functional disturbances of the frontal lobe and the deep white matter.

This syndrome is encountered in VaD and in extrapyramidal diseases (progressive supranuclear palsy, Huntington's disease, and Parkinson's disease (for review see [16]). It obviously has common features with FTD, but motor and mental slowing (in absence of adverse medications such as neuroleptics) is very late in FTD and suggests a dysfunction of basal ganglia, as well as an apathetic state; magnetic resonance imaging is thus needed to detect lacunae in the thalamus caudate or lenticular nuclei [72, 74].

Corticobasal degeneration

This is characterized by a severe asymmetric apraxia, which may or may not be accompanied by spatial dysfunction. It may also be associated with a mild subcortical dementia [51].

Vascular dementia

A wide variety of neuropsychological changes may be observed in VaD. Clinical features depend on the location, number, size, and cause of vascular lesions [80]. Among neuropsychological deficits, the presence of cognitive and behavioral disorders resembling those in patients with lesions of the prefrontal cortex is frequently underlined [27]. The first description of qualitative neuropsychological aspects in the subcortical type of VaD (small vessels, in contrast to the cortical form due to large vessel disease) was published by Cummings and Benson [11]. This form of VaD may lack an abrupt onset and show a progressive course; it is therefore sometimes confused with AD. The neuropsychological profile is of subcortical dementia with mental slowing and problems in retrieval more than of storage.

The MMS has disadvantages for VaD screening [80]. The Mattis DRS is preferable. However, no specific pattern has been found to distinguish between VaD and AD, except for a greater impairment of conceptualization in Bingswanger's disease than in AD [3]. A list is available of the tests that are sensitive to the disturbances in VaD [71, 79, 95].

Differences between AD and VaD have been reported in executive and motor functions, language, speech, attention, fluency, and episodic memory. VaD patients are better at naming and commit fewer intrusion errors than AD patients in confrontation naming. Lexical-semantic abilities are better preserved, but syntax and motor aspects of speech are more impaired [42]. The motor speech abnormalities include dysarthria, reduced rate, and disruption of melody and pitch. There is a slight difference in favor of AD for executive functions, in agreement with studies emphasizing the importance of frontal lobe dysfunction in VaD. Moreover, patients with VaD are more helped by semantic cues in retrieving information than are patients with AD [14], again in agreement with a frontal-subcortical dysfunction rather than a hippocampal impairment. Some patterns of behavior, such as the closing-in phe-

Table 2 Suggested neuropsychological assessment of dementia at early stage (from [74])

Cognitive function assessed	Suggested tests
Overall severity of dementia	Mattis Dementia Rating Scale [52]
Short-term memory	Digit span (Wechsler Memory Scale) Block tapping test [92]
Verbal long-term memory	FCSRT [32, 33]
Organized information (+/–)	Logical memory (Wechsler Memory Scale)
Visual long-term memory	Subtest of the Wechsler Memory Scale revised
Intelligence	Subtest of the WAIS
Frontal lobe test	Stroop test [94] Digit Cancellation test [92] Go–No Go test
Motor speed	Finger tapping
Constructional abilities	
Spontaneous speech	
Confrontation naming	
Comprehension	Token test, short version [13]
Verbal fluency	
Behavioral changes	Questionnaire de dyscontrole comportemental [46] Frontotemporal behavioral scale [47]

nomenon and the tendency to globalistic and odd responses on the Raven's Colored Matrices are considered to be a better indicator of a degenerative than for a vascular form of dementia [24]. VaD patients are helped by the cueing of geometrical figures if they fail to draw it, in contrast to AD patients [23].

Conclusion

There are qualitative differences in the cognitive impairment of patients with AD and patients with other types of dementia that contribute to the clinical differential diagnosis between neurodegenerative dementias. Neuropsychological assessment is of help for the early diagnosis of dementia to determine a profile that suggests its cause. We suggest a set of tests to assess dementia at early stage (Table 2). However, the results must be interpreted in the light of the patient's history, rate of progression, imaging, and nature of any behavioral disturbances. There may be some overlap between two or more pathologies such as AD plus vascular changes [37, 70] or AD plus Lewy bodies [35] that complicates the diagnostic processing. Follow-up of patients is necessary to improve diagnostic accuracy.

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