Introduction to the diagnosis of dementia

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This chapter will outline general strategies to establish the presence and the differential diagnosis of dementia, and the case studies in this book will allow the reader to explore more in-depth specific causes of dementia across different age groups. We emphasize the diagnosis of dementia in this book, the first step in the management of dementia.

Is dementia present?

A broad interpretation of the current definition of dementia written in the DSM-IV-R is that an intellectual decline involving at least two cognitive domains must be sufficient to interfere with daily life. Thus the clinician must establish through a systematic history with the subject and an informant if there is a decline in memory, language, praxis, gnosis, and/or executive abilities, and if this decline is associated with impairment in activities of daily living (ADL).

Screening questions about changes within the past year in recall for appointments, recent events, or conversations, can be followed immediately and during a follow-up visit with more detailed questions relevant to:

(1) memory: do you look for things in your room; do you need reminders for appointments
(2) language: do you say sometimes "give me the thing there, what do you call it?"
(3) praxis: do you have difficulty using kitchen appliances or tools?
(4) gnosis: do you have difficulties recognizing people?
(5) executive abilities: do you find it harder to plan a meal for the family or friends; do you need help when playing a card game, can you adjust if there is a change of plans?

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Testing for cognitive impairment is usually done using the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). If the MMSE is above 26/30, the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) is usually performed, also giving a total score of 30, but encompassing some executive tests such as the Trail B and the clock. More detailed neuropsychological tests may be required depending on the level of education of the subject, the nature of his complaints (language for instance), and the severity of his decline. Thus, the Severe Impairment Battery is used if the MMSE is below 15/30 (Panisset *et al.*, 1994).

From population studies (Pérès *et al.*, 2007), four ADLs were found to be particularly altered in early dementia:

(1) use of telephone and other means of communication
(2) planning an outing and completing it efficiently
(3) using medications safely
(4) using money appropriately.

These specific ADLs can be asked about for screening purpose, followed immediately or during a follow-up visit with questions on other instrumental (meal preparation, leisure, and housework) and basic (hygiene, dressing, continence, eating) ADLs.

Although surprisingly missing from the current definition of dementia, neuropsychiatric symptoms can precede the onset of cognitive decline and nearly always accompany them. It is thus important to ask about the following common symptoms in a semi-structured way or using an instrument such as the Neuropsychiatric Inventory (NPI; Cummings J, 1997).

(1) apathy
(2) agitation and aggressivity
(3) anxiety and depression
(4) aberrant motor behaviors
(5) delusions and hallucinations
(6) irritability
(7) night-time behaviors

What is the cause of dementia?

It is surprising how a good history addressing the common cognitive, functional (ADL), and behavioral symptoms encountered in dementia will lead to a short differential diagnosis, since the most common causes of dementia have a typical pattern of presentation:

Alzheimer's disease (AD) may be preceded by a prodrome of anxiety, mild depressive mood, irritability, nearly always starts with impaired recent memory,

followed by word-finding difficulties, decreased orientation to time and place. MMSE usually 25/30 or less at time of diagnosis.

Dementia with Lewy Bodies (DLB) nearly always starts with visual hallucinations and fluctuations in cognitive ability. The MMSE may be 22 at times, 26 at other times. Parkinson Disease Dementia (PDD) by definition starts with motoric symptoms of resting tremor, bradykinesia, and/or rigidity, followed at least a year later by visual hallucinations and fluctuations in cognitive ability.

Fronto-temporal dementias (FTD) usually start with language impairment or with social disinhibition. The former can lead to mistakenly low MMSE scores and the latter with mistakenly high MMSE scores. This and other cognitive tests must always be interpreted within the context of cognitive, functional, and behavioral symptoms, and not be used as "a test of dementia."

The common causes of dementia may have atypical presentations, as illustrated in this book. Rare causes of dementia, particular in young subjects (before age 50) require special work-up as demonstrated as well in this book.

What confirmatory tests are required?

Although the history is the cornerstone of the diagnosis of dementia, complementary laboratory tests usually include:

(1) basic blood tests (hematologic, endocrine, hepatic, renal function, screening, B12, VDRL, HIV)
(2) brain imaging using Computer Scanning (CT) or Magnetic Resonance Imaging (MRI) studies

Special tests will depend on the suspected cause of dementia and include:

(1) Special blood tests (coeruloplasmin for Wilson's disease, for example)
(2) Special brain imaging such as Positron Emission Tomography (PET) for glucose metabolism (FDG-PET), amyloid load (PIB, for instance)
(3) Electroencephalography (in Creutzfeldt–Jacob disease)
(4) Lumbar puncture (some protein markers in AD, in neurosyphilis)
(5) Immunology work-up for antibody-mediated dementias (paraneoplastia syndromes, Hashimoto's encephalitis)
(6) Genetic and molecular studies (metabolic and inherited diseases).

General advice in dealing with dementia

- It takes time and patience to obtain key elements of history leading to a diagnosis of dementia and its cause; repeated assessments are sometimes

required; additional data may be required from visits at home by occupational therapists or other health professionals.

- Go back to the beginning of the symptoms, since most family members will discuss current problems; the sequence of symptoms is the key to the diagnosis.
- Time tells, e.g. some types of dementia are diagnosed with key physical findings that appear well after the onset of cognitive decline, such as slowing of saccadic eye movements in progressive supra-nuclear palsy.
- There may be more than one cause of dementia, e.g. "mixed-dementia" is more common than a single cause of dementia in elderly subjects (over age 75).
- Psychiatric symptoms may mask a dementia, e.g. depression often co-exists with early AD, and patients with odd personality disorders can have a dementia.
- If the diagnosis is not clear, get advice from colleagues in different disciplines, including neuropsychology, social services, occupational therapy. A consensus approach in difficult cases may be the best way to move forward.

The future

Things will get more complicated as the field in moving towards a diagnosis of common causes of "dementia" in their pre-dementia stages of disease. For instance, an early diagnosis of AD may be possible when only memory is impaired, if at least one biological marker of the disease is found by CSF examination, genetic testing, or neuro-imaging (Dubois *et al.*, 2007). Possibly DLB and PDD will be diagnosed earlier with sleep disturbances such as REM Behavior Disorder associated with an abnormal biological marker (still to be identified). There will be risks (such as a catastrophic reaction), benefits (such as early treatment and arrest or delay of progression), and additional costs (most from neuroimaging procedures) for earlier diagnosis. More to follow on this in the next edition of this book!

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Case 1

Subjective cognitive complaint

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Clinical history – main complaint

A 70-year-old woman consulted for a severe cognitive complaint encompassing numerous domains (i.e. memory, language, calculation…). She described her difficulties as follows:

- "I forget what I did yesterday or even a few hours ago."
- "I am unable to perform mental calculation."
- "I gave an appointment to my daughter and forgot it. When she called me I did not even remember the purpose of this appointment."
- "I did not remember answering my mail."
- "I have trouble finding my words. They are often on the tip of my tongue."
- "I have difficulties remembering my friends' names."
- "I come into a room and do not remember why I entered it."
- "I have trouble finding things in my house."
- "I lose the notion of time so that a recent event feels far gone."
- "I make more and more spelling mistakes."

General history

She is a university educated woman in good general health. She lives with her husband and has two children. She does not have any chronic medical problem and takes no medication. A depression was diagnosed and successfully treated for 6 months with fluoxetine 5 years ago.

Family history

Her father died of myocardial infarct at the age of 75.

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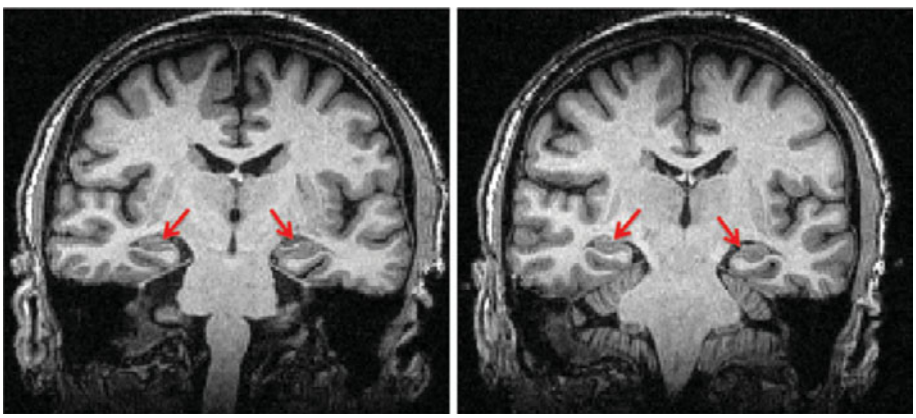

Fig. 1.1. MRI (T1 coronal slices) showing minimal cerebral atrophy especially in the hippocampal regions (arrows).

Examination

BP: 140/80; pulse: 65 regular. MMSE: 29/30, serial-7s correct but effortful. Five-word test: 10/10. FAB: 17/18. Normal naming, no dysgraphia or dyslexia. Normal neurologic examination. Anxiety and mild depression were also noted (MADRS = 18).

Special studies

MRI showed no focal atrophy especially of the hippocampal regions (see Fig. 1.1).

Neuropsychological tests were normal except for impaired working memory on the digit span test (digit span forward = 6, digit span backward = 3) and a low free recall in the Free and Cued Selective Reminding Test (FCSRT): free recall = 17/48* (significant decrease), total recall = 48/48, delayed total = recall 16/16, no intrusion; Mattis dementia rating scale = 137/144; DO 80 = 78. No apraxia, dyscalculia, Gerstmann syndrome, or visuospatial difficulties.

Diagnosis

The initial diagnostic impression was a subjective cognitive complaint with an attention disorder of probable psychogenic origin.

Follow-up

Fluoxetine was administered. After 6 months, subjective improvement was noted.

Table 1.1. The three mnesic processes one has to assess in case of cognitive complaint

Process	Assessment (with the FCSRT)	Causes
Registration	Immediate recall	Attention deficit due to – Depression – Confusion – Drug therapies
Storage	Retrieval with cue	Hippocampal (or hippocampo–mamillo–thalamic circuit) lesion in – Alzheimer's disease – Korsakoff's syndrome – Limbic encephalitis
Retrieval	Spontaneous retrieval	Executive dysfunction in – Vascular cognitive impairment – Depression – Normal aging – Fronto-temporal dementia

Discussion

Subjective cognitive complaint (SCC) is frequent in normal aging with a prevalence of 50% after 55 years of age (Lowenthal *et al.*, 1967). The problem is that SCC may be the symptomatic expression of several conditions including Alzheimer's disease. To better understand the diagnostic algorithm of SCC, we must have in mind the physiopathology of long-term episodic memory.

Episodic memory is the capacity to recall personal events that can be identified in time or in space. For instance, to recall one's last meal, its taste, smell, the conversation, and state of mind during the meal. To be recalled, the stimulus (whatever it is: a list of words, sentences, stories, images, drawings, smells…) must go through three different and successive stages (See Table 1.1). The three mnesic processes one has to assess in case of cognitive complaint are as follows.

- The first one is registration, which mainly relies on attention resources, which facilitate the capture of information by the perceptual and sensory cortical areas (visual cortex for images, auditory cortex for verbal items…). This stage is impaired in conditions that may interfere with attention processes: depression, anxiety, professional stress, sleep disorders, aging, treatment such as anticholinergic drugs or benzodiazepines… In all these cases, there might be a recall deficit not because of a long-term memory problem, but only because of registration impairment. In all these situations, the information will not be well registered and the recall performance will be decreased in relation to attention disorders.

- The second step is storage, i.e. the transformation of registered perceptual events into memory traces: after the perceptual and identification stages by the sensory cortices and related associative areas, the information is transferred to the hippocampus to be transformed by the hippocampal mamillothalamic circuit into memory traces. In case of hippocampal lesions, such as in Alzheimer's disease, or mamillothalamic lesions, such as in Korsakoff syndrome, the perceived information cannot be stored as memory traces in long-term memory. In such conditions, the information will be lost and cannot be recalled any more: this feature corresponds to a true genuine memory impairment.
- The last stage is retrieval: this stage relies on the ability to activate strategic processes to recollect stored information. This process is directly related to the functioning of the frontal lobes. This is why retrieval abilities are decreased in frontal lesions, fronto-temporal dementias, subcortico-frontal dementias and in functional states such as depression or even normal aging, where the activation of retrieval strategies is decreased and effortful. In these conditions, the recall performance will be decreased in relation with a retrieval deficit.

To summarize, memory disorders in everyday life can result from attention disorders, retrieval difficulties as well as genuine memory deficit due to Alzheimer's disease. The best way to disentangle the diagnostic problem is to assess memory by objective tests that may control for attention and that can facilitate the retrieval. This is the case of the Free and Cued Selected Recall Test (FCSRT) (Grober *et al.*, 1988). The FCSRT has been recommended in the new diagnostic criteria of AD for the assessment of episodic long-term memory (Dubois *et al.*, 2007). Semantic cues are used to control for an effective encoding of the 16 items just after their presentation and to maximize retrieval (in case of a dysexecutive syndrome) after a 30-minute delay. Therefore, low total recall, despite the facilitation procedures, indicates the existence of an amnestic syndrome of the hippocample type, mostly in relation to an Alzheimer's disease.

The FCSRT

Sixteen words have to be learned following a standardized procedure. The 16 items to be learned are presented on four successive cards of four items each. These items are presented in quadrants on a sheet of paper as a word (e.g. grapes) which goes with a unique category cue (e.g. fruit). The subject is asked to point to and name aloud each item (e.g. grapes) after hearing the appropriate cue (e.g. fruit). After all four items were identified correctly, the card is removed, and *immediate cued recall* of the four items is tested by giving the cues again in order to control for encoding.

Once a group of four items had been successfully encoded (evidenced by complete immediate recall), the next set of four items is presented. **This first phase of the test is done to control the *registration* process and provides a score called *immediate recall*.** By this way, the examiner knows that the subject has registered all the items. Unfortunately, only a few memory tests control that the information – used to study long-term memory – has been truly registered. Then, three successive recall trials are performed, each consisting of two parts. First, a free recall of as many items as possible and second, a cued recall in response to orally presented semantic category for those items that were not spontaneously retrieved by the patient. This provides a *free recall score* and a *total recall score*, (the latter being the sum of free and cued recall). As semantic cueing, in normal controls, normalizes the performance of recall by facilitating the retrieval of stored information, the total score is expected to be higher than 44/48.

To evaluate the efficacy of semantic cues used to facilitate retrieval from stored information, an *Index of Sensitivity of Cueing* (*ISC*) was defined, which is determined as: (total recall – free recall)/(48 – free recall). **A low index reflects a *storage* deficit** (because free and cued recalls do not differ to a great extent). **Conversely, a high index, points toward *retrieval* difficulties** (because cues are frequently needed to recall the information). After a 30-minute delay, filled by other non-verbal tests, a delayed recall task is proposed with the same procedure of free and cued recall, providing a score for *delayed free recall* and a score for *delayed total recall* (*DTR = maximal score of 16*). During the test, the number of *intrusions* (i.e. words absent from the list and falsely "recalled") is recorded.

In conclusion, SCC can be observed in many circumstances and has varied causes, the first of which being an attention disorder. This disorder is frequent in anxiety (Craik *et al.*, 1995; Ganguli *et al.*, 2004), depression (McGlone *et al.*, 1990; Tierney *et al.*, 1996; Schmand *et al.*, 1997), and drug therapies (benzodiazepines, anticholinergics…) or even in normal aging. An attention disorder is a handicap in daily life when dual tasks are required or working memory is needed. By contrast, neuropsychological tests are frequently normal in these conditions because the examiner avoids eliciting divided attention.

However, subjective cognitive complaint can also be caused by an organic cerebral affection such as Alzheimer's disease (AD). In this case, the storage of information is impaired and controlling the efficacy of the registration process is no longer enough to allow its normal recall (Hodges, 1998; Dubois and Albert, 2004). This justifies a complete neuropsychological assessment if any doubt about a neurodegenerative process remains after the initial neurological consult. Perceptions of patients' symptoms from an informant or proxy may be more significant as they are more strongly related to objective memory performance (McGlone *et al.*, 1990) and are predictive of conversion to AD (Tierney *et al.*,