Diagnostic Evaluation of Dementia

3

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Introduction

Dementia is an umbrella term, describing symptoms, consisting of cognitive decline that is severe enough to cause functional deficits. In almost all patients, dementia is associated with behavioral and personality changes. A patient with dementia depends on his or her caregiver to compensate for the functional deficits that affect activities of daily living (ADL). A dementia diagnosis does not imply an etiological diagnosis. Indeed, several brain disorders can cause dementia-like Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), etc. Many patients have mixed causes, like, e.g., AD with cerebrovascular disease or DLB associated with AD co-pathology.

During the past decade, research has significantly improved the accuracy of an etiological dementia diagnosis. As AD is the most frequent cause of dementia, affecting up to 60–70% of dementia cases and exponentially increasing in

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prevalence with age, most research has been performed with regard to improved early and differential diagnosis of AD.

Biomarker-Based Diagnosis of Alzheimer's Disease (AD)

The clinical diagnosis of AD was previously often based on the criteria from the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), originating from 1984 [1]. These criteria are based on the exclusion of other systemic and brain disorders that could account for cognitive deterioration and are confined to the dementia stage, at best resulting in a diagnosis of probable AD. A clinical diagnosis of probable AD achieves an average sensitivity and specificity of 81% and 70%, respectively [2]. A promising tool to increase the diagnostic accuracy of AD is the use of biomarkers that reflect the neuropathology of the disease.

Jack et al. [3] have modeled the biomarker changes across the continuum of AD in 2010. Since then, the model has been adapted several times [4], but its basis remained unchanged (Fig. 3.1). The last curve represents clinical function or activities of daily living. If functional deficits occur, a patient converts from mild cognitive impairment (MCI) to dementia due to AD. It is preceded by cognitive deficits, as objectified by a full neuropsychological examination. Cognitive deficits will appear as from the MCI stage on. Brain structure changes or brain atrophy result from neuronal degeneration and can be quantified by means of a brain magnetic resonance imaging (MRI) scan or a computerized tomography (CT) scan of the brain. Brain atrophy is preceded by functional changes in the brain that can be

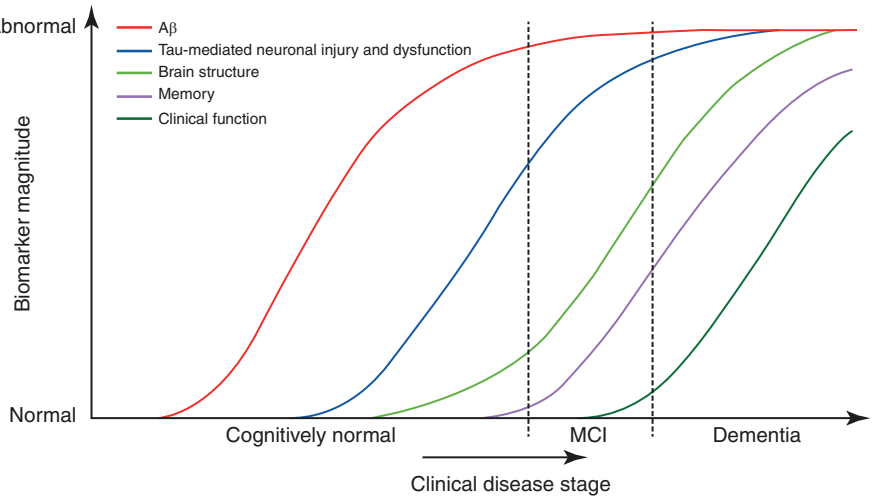

Fig. 3.1 Model of biomarker changes through the AD continuum (after Jack CR et al., Lancet Neurol. 2010;9(1):119–128

visualized through an 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan. Functional changes are linked to neuronal injury and tau pathology, as can be analyzed in the cerebrospinal fluid (CSF). The first biomarker change consists of the abnormal processing of the β-amyloid peptide (Aβ), leading to the formation of amyloid plaques in the brain. The Aβ status can be determined through CSF analyses or by means of a PET scan. As the first amyloid plaques occur 10–20 years before symptom onset, Aβ is the earliest detectable biomarker change. This provides researchers an exceptional window for early diagnosis, future treatment, and prevention strategies.

Biomarker-based diagnosis has been introduced in daily clinical practice [5]. Biomarkers should always be interpreted as a panel, rather than individually, and in the light of the model of biomarker changes (Fig. 3.1). Moreover, biomarker changes should always be interpreted in the clinical context. Whereas hippocampal atrophy on a brain MRI scan is a rather unspecific finding in the elderly, it is suggestive of AD in the case of a patient with amnestic MCI who suffers from episodic memory problems. On the other hand, e.g., in case of differential diagnostic doubt between AD and FTD, the absence of hippocampal atrophy is supportive for ruling out AD [6]. This also implies that a search for (AD) biomarkers without having a clinical context is not done. E.g., analyzing the core AD CSF biomarkers in an asymptomatic individual is not part of daily clinical practice [5].

Timely Diagnosis of Dementia

Although AD and related disorders are still incurable, several treatment options exist [7]. Depending on the symptomatology and the needs of the patient and his/her surroundings, treatments might have beneficial effects on quality of life and can significantly delay nursing home placement, which is a wish of many patients. E.g., psycho-social education and early recognition and (non-)pharmacological treatment of behavioral changes like diurnal rhythm disturbances, depression, or agitation, and aggressiveness can significantly improve the quality of life of both patient and caregiver and thereby delay nursing home placement. Therefore, opting out a diagnostic work-up, will also limit the possible treatment options. Even symptomatic treatment options can have beneficial effects on quality of life, and the currently available treatment options are not solely pharmacological.

Do we need an early, biomarker-based diagnosis in every patient with cognitive deterioration? As long as no disease-modifying treatment options are available, it remains an option not to refer a patient to a memory clinic for an etiological (biomarker-based) diagnosis. As long as a patient has the intellectual capacity to take decisions, it is her/his right to refuse a diagnostic work-up that might lead to a diagnosis of an incurable disease like AD [8, 9]. In addition, how early a diagnosis should be made (e.g., in the MCI versus dementia stage of AD) primarily depends on the will of the patient. If a patient wants an early diagnosis in the MCI phase of AD in order to be able to take decisions with regard to his or her future (e.g., living will or advanced directives with regard to medical treatments), an early referral to a

memory clinic is needed. On the other hand, if a patient at an advanced age is in a nursing home and has no troublesome symptoms, an etiological diagnosis will probably have no to very little therapeutic consequences.

The primary care physician is best placed to refer a patient with cognitive and/or behavioral signs and symptoms to a memory clinic for a diagnostic work-up, based on the wishes and needs of patient and caregiver and after discussing the possible options [10].

In what follows, the diagnostic steps are described, following a logical stepwise paradigm.

History Taking

Introduction

As the clinical picture of diseases causing cognitive impairment is often dominated by (or even limited to) cognitive decline and changes of behavior and/or personality, careful history taking is the cornerstone of the diagnostic evaluation. The clinician should aim to use clear, practical questions with a limited scope, adjusted to the patient's level of education and social context. General questions such as "How are you doing?" of "What can I do for you?" can obviously serve as polite conversation starters but rarely identify all the aspects involved in cognitive disorders.

The history taking should be driven by the standard clinical diagnostic criteria for dementia (see Chap. 1 for an overview of the most common diagnostic criteria). Corner stone of the history talking based on these diagnostic criteria is that there should be evidence of concern about a change in cognition or behavior, in comparison with the person's previous level [11]. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient. Based on the diagnostic criteria, history taking will as well serve to detect potential mimics or exclusion criteria. E.g., in case of sudden onset, a clinical diagnosis of AD is improbable.

Based on the history taking, the primary care physician can decide (not) to refer a patient to a memory clinic [10]. In the memory clinic, the history taking will result in a differential diagnosis, which will guide the diagnostic process.

General Aspects of History Taking for Dementia Diagnosis

With Whom?

Although the physician's duty is first and foremost directed to his/her patient and symptoms are usually best understood from the patient's perspective, the nature of several cognitive disorders is such that certain symptoms (e.g., memory problems and/or confabulation, delusions that are not frankly absurd, insidious personality change, anosognosia, …) may only be recognized or fully understood through additional information from the patient's caregiver(s). Additionally, lack of insight is a

common occurrence in many patients with dementia, which may mean that patients, even in the early stages, will neglect or under-report symptoms.

Medical History

Various disorders can mimic or even cause cognitive decline, especially in the elderly. These conditions should be ruled out and/or treated adequately before further diagnostic evaluation can be considered. Therefore, medical history taking is very important. Extensive questioning should therefore aim to identify all relevant active and past medical illnesses, hospitalizations, surgery, etc. Especially in the elderly, cognitive tests are highly influenced by active (severe) medical illnesses, a fortiori in the presence of delirium—which may have gone unrecognized. The effects of various prescription and illicit drugs, especially those with sedative or anti-cholinergic side effects, should not be underestimated and carefully evaluated. Ideally, the primary care physician provides the memory clinic staff with a clear overview of the individuals' medical and psychiatric history, which can be double checked with the patient (and his/her caregiver) during the first visit.

Social History and Life Style Habits

As acquired cognitive disorders and dementia are characterized by a change from a previous state of functioning, a general idea of the patient's educational and professional history is required. Furthermore, the selection of neuropsychological tests should be done in light of the patient's capacity to understand these tests (e.g., inability to read and write, language barrier). Formal education and the nature of professional activities should be enquired about.

As already mentioned, a patient with dementia depends on his or her caregiver to compensate for the functional deficits that affect ADL. Furthermore, to differentiate between MCI and dementia, assessment of ADL is required. These include the basic ADL and the instrumental ADL that comprises more complex activities such as using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medications, handling finances. Physicians should enquire whether and how the patient deals and has dealt with the more cognitively complex tasks of everyday life as dementia (as opposed to MCI) is characterized by impairment in one or more of these activities of daily living.

Lifestyle habits should be actively inquired too and should comprise the use of alcohol and recreational drugs, day-night rhythm, sleep quality, and dietary habits too.

Disease Course

The onset and disease course may provide further clues to a diagnosis. Was the onset sudden, e.g., after a stroke, a severe medical condition or surgery, or a psychologically difficult event? Do cognitive symptoms fluctuate more over time than should be expected from the good and bad days we all experience? Is there a progressive cognitive deterioration, or is it perceived as stepwise? How long have symptoms been present? Are there any "attacks," i.e., very sudden changes in behavior or conscience?

Family History

A detailed family history of neurodegenerative and cerebrovascular brain disorders is important in order to judge the risk of an autosomal dominant genetic etiology. The exact diagnosis should be asked for, as well as the age at disease onset as the risk of an autosomal dominant form increases when the age at onset is younger. It is also relevant to enquire about neurological symptoms in family members, as patients may not know the diagnosis of family members, or the family member may not have been diagnosed. Also, the age at and cause of death should be enquired for first and second-degree relatives; if a person died at a young age, before he/she was able to develop symptoms of dementia, it thus might result in a false-negative family history.

Cognitive Symptoms

Cognitive symptoms should be enquired systematically, checking the main cognitive domains. One should always bear in mind that changes to the previous level of functioning are important. Attention should be paid to the presenting symptom and the chronological order of the cognitive domains that were affected next. As most neurodegenerative brain diseases that cause dementia often start with subtle changes, the onset may be underestimated. What caregivers initially often report as disease onset is the moment when symptoms have become very overt, giving an impression of a rapid cognitive decline. Repeated and further questioning helps to identify more subtle cognitive changes.

Memory

Memory is the ability to receive, store, and retrieve information. The long-term memory is subdivided into several kinds, depending on the nature of the information stored: semantic, episodic (i.e., autobiographic), procedural. In patients with AD, storing new information in the episodic memory progressively gets more difficult and often starts insidiously. This will present as forgetfulness relating to everyday events that require storing new information: grocery shopping, retaining a telephone or bank account number, reiterating the events in a recently watched movie, what one had for dinner the previous day, etc. Repetitive question asking despite clear and repeated instruction suggests short-term memory deficits. These deficits may be masked by confabulations (honestly held erroneous beliefs to fill the amnestic gaps) or frank delusions (e.g., forgetting that one's spouse has gone to the hairdresser and suspecting infidelity). Simple recall tests (e.g., three everyday words) may serve as a quick screening tool. In most degenerative brain diseases, long-term memory is affected much later—especially considering fundamental autobiographical elements (one's date and place of birth, one's name). Sudden (e.g., overnight) and/or prominent loss of these autobiographical elements without affection of other components of memory often suggests psychiatric or functional disturbances. The deflection of simple personal questions towards one's attending spouse or caregiver (the "head turning sign") may be suggestive for memory problems due to neurodegenerative brain disease like AD.

Concentration and Attention

Concentration is generally regarded as the ability to focus one's thought and actions upon a single element or task, which is limited in time, requiring a break. Dividing attention is another aspect of attention (multitasking), which gets more difficult when one grows older. Although attention deficits are often reported by patients as "forgetfulness," these symptoms are not caused by a memory failure, and often the differentiation can be made by careful history taking. Although disorders of attention in (elderly) adults may have a medical cause (as a core symptom of delirium and of dementia), they are often caused by fatigue and sleep disorders, mood disturbances, and other circumstantial factors. Vice-versa, anosognosic patients may wave away their memory disturbances by claiming to be "distracted," "tired," or "absent-minded."

Orientation

Temporal and spatial orientation requires integrating different kinds of information and are often impaired in dementia. The ability to navigate and drive, find one's way in familiar as well as unfamiliar places should be inquired upon. Associated memory problems may contribute to an inability to realize the current day, date, or time of the year—as they may also impair spatial orientation ("how did I get here?").

Language

Language is a core element of everyday life and human interaction. Several cognitive domains are involved in the use of language.

The clinician should at first differentiate between a speech disorder (like dysarthria) and a language disorder. A language disorder (aphasia) can primarily affect speech production (so-called expressive aphasia) or the language comprehension (so-called receptive aphasia), or both. Especially in the case of receptive aphasia, reading or writing abilities will be impaired significantly. The clinician should observe and inquire about symptoms or signs of reduced verbal fluency, word-finding, and the general ability to make conversation. Often, the vocabulary gets reduced, as demonstrated by word-finding difficulties concerning less frequently used words. Secondary languages are affected first, but finally, also the primary language gets affected. Deterioration in reading or writing skills may be indirect clues to deficits of language. During a conversation, the clinician can observe the content and the style of conversation by the patient—speed, volume, articulation, and take note of several types of paraphasias (errors in spoken words). Furthermore, content should be observed for needlessly long explanations of an everyday concept, object, or story, which escapes the patient's memory (i.e., circumlocution).

Executive Disorders

Frontal lobe functions include integrating several mental functions in succession, as is required in planning and organization of complex tasks. Possible questions include asking whether any difficulties are experienced in technical activities or step-by-step endeavors such as cooking. Also in AD, executive functions get progressively impaired.

Behavioural and Psychological Signs and Symptoms of Dementia (BPSD)

The following categories of BPSD should systematically be enquired. In what follows, frequently occurring symptoms per category are described in order to help structuring the history taking.

Mood Disorders and Anxiety

Depressive symptoms are very frequent in patients with dementia [12]. Depression in the elderly can also mimic dementia, as depression in the elderly is more often associated with cognitive symptoms as compared to depressive disorders of earlier adulthood. On the other hand, depressive symptoms may also be the first clinical manifestation of dementia. It has been suggested that depression and dementia share common risk factors and thereby frequently occur together without being causally linked themselves, or those psychological symptoms may occur as a reaction to incipient decline in patients who are aware of their cognitive disturbances. The exact nature of the relationship between depressive symptoms and dementia in the elderly remains inconclusive, with multiple studies supporting both the risk factor and prodromal hypotheses. It seems unlikely that there is no connection at all [12, 13].

A thoughtful inventory of depressive symptoms (depressed mood, anhedonia, vegetative and sleep-related symptoms, suicidal thoughts, etc.) and symptoms of anxiety should be considered in all patients. Screening tools and rating scales may be helpful instruments to systematically enquire about these symptoms [13]. A very common feature of neurodegenerative brain diseases is apathy [14]. Although apathy may be a symptom of depression, further questioning may be helpful to differentiate between apathy as a syndrome versus a symptom that is part of depression. Apathy frequently does not alarm or bother the patient but may prove very stressful to family members and care providers.

Anxiety also frequently occurs and should be systematically enquired. One of the most frequent presentations of anxiety in patients with dementia is the fear of being left alone, which may result in “shadowing” of the main caregiver.

Sleep and Diurnal Rhythm Disturbances

Sleep quality should be systematically assessed as sleep disturbances are very burdensome for the caregiver and as poor sleep quality may have a negative impact on cognitive functioning. Moreover, sleep disturbances can sometimes be improved pharmacologically. When enquiring about sleep quality, signs, and symptoms of REM sleep behavior disorder (acting out dreams, nightmares) should be asked for.

Hallucinations and Delusions

Hallucinations and delusions are both frequent in dementia. Hallucinations should be characterized by the sensory modality they present in—generally visual as opposed to the typical auditory hallucinations of primary psychotic disorders.

Tactile and hallucinations in other sensory modalities may occur too but are very rare in dementia. As patients may or may not be aware of the hallucinatory nature of these events (especially when their content is relatively benign, e.g., a visiting family member or a dog in the garden), these often go unrecognized.

In AD, hallucinations are often not well defined and may be associated with (paranoid) delusions, occurring in the more advanced stages of the disease [15]. Patients with DLB may have well-formed complex hallucinations of people, animals, or objects that can occur in the earliest stages of the disease. Besides complex visual hallucinations, simple visual hallucinations and even visual illusions may occur in DLB, also in the periphery of the visual field. As the latter may as well occur briefly, they are often not perceived as visual hallucinations unless they are specifically asked for. The clinician should moreover be aware that (mild) hallucinations are quite frequent in general and can be provoked by a near endless list of medical conditions and (prescription or illicit) drugs. A frequent cause of visual hallucinations is the Charles-Bonnet syndrome, which is due to loss of visual acuity. As visual impairment is frequent in elderly patients, as is dementia, this is a frequent cause of visual hallucinations in elderly patients with dementia. In the Charles-Bonnet syndrome, patients are often aware of the false nature of these hallucinations, which is often not the case when the hallucinations are linked to dementia syndrome.

The combination of memory deficits and anosognosia may provoke paranoid delusions. Although not always in and of themselves entirely impossible (e.g., presumed adultery, relatives' financial interests, mislaid items having been stolen by intruders), their sudden prominence in patient's mental life and conversations with strangers may provide clues to their delusional nature. People with dementia may also suffer from the Capgras syndrome, also known as imposter syndrome, which is a delusion (and thus rather a symptom than a syndrome) that someone they know (e.g., spouse) has been replaced by an imposter.

Agitation and Aggressiveness

This category of BPSD becomes more frequent when dementia progresses [16, 17]. The same holds true for aberrant motor activity, which can be very burdensome for caregivers. Severity and frequency should be assessed, as well as provoking circumstances. The latter may help to develop a tailored non-pharmacological treatment strategy. If uncontrollable, these symptoms can be a reason for early nursing home placement.

Personality

Changes in personality is always worrisome and requires neuropsychiatric investigation. The patient should be evaluated for their general impression, grooming, and cleanliness. Is there a tendency towards harsh answers or inappropriate remarks, aggressiveness, impulsivity, and irritability? Even when taking possible marital or familial quarrels into account, caregiver history is often crucial in elucidating these aspects.

Motor Symptoms

Especially parkinsonian symptoms are frequent in neurodegenerative (and cerebrovascular) disorders that cause dementia. Bradykinesia, tremor, rigidity, and gait disturbances are frequent signs and symptoms that should be systematically questioned, the more so as they can also help to differentiate amongst causes of dementia. Given the frequency of the motor and parkinsonian symptoms, it is important to subject each patient to a physical and clinical neurological examination.

Physical Examination

A general physical examination should be performed in every patient in case of a dementia work-up. The general physical exam is needed to detect medical conditions that can cause dementia-like symptoms (e.g., heart failure, malignancy). The clinical neurological examination should focus on parkinsonian symptoms and gait disturbances, signs and symptoms of stroke (lateralization, focal neurological signs). FTD may be associated with amyotrophic lateral sclerosis, so the neurological exam should as well detect amyotrophy, signs of corticospinal tract involvement (paresis, hyperreflexia, …).

Blood Sampling, ECG, EEG

A blood sampling should be performed every time a dementia work-up is carried out. Blood analysis serves to rule out medical conditions that can cause dementia-like symptoms (e.g., renal failure, hepatic failure, hyper- or hypothyroidism, hypovitaminosis B12, folic acid deficiency) and should as well contain complete blood count and blood ionogram. In selected patients, additional serologic testing (HIV, Borrelia, syphilis) should be performed.

Both electrocardiography (ECG) and electro-encephalography (ECG) are worth considering. ECG is useful in selected patients (e.g., cardiovascular risk factors, cardiac comorbidity, bradycardia) before prescribing psychotropic medication. As some forms of epilepsy or a non-convulsive status may mimic some dementia symptoms, an EEG should be considered in selected patients.

Neuropsychological Examination

Introduction

A full neuropsychological examination is the cornerstone of the work-up of patients with dementia and is part of an integrative approach to the (differential) diagnosis of dementia [18]. Brief screening tests can be used to detect patients at risk for dementia [19]. The full neuropsychological examination should be performed by an

experienced neuropsychologist and includes an array of different tests to investigate cognitive functioning. The latter has two major goals: [1] to detect cognitive decline and differentiate between normal aging and cognitive impairment and [2] to help in the differentiation between different causes of dementia. For the interpretation of the test results, the neuropsychologist takes into account the mood and mental status of the patient as well as his/her (neuropsychiatric) history. A neuropsychological evaluation thus as well consists of an expert clinical evaluation, besides the formal testing. As a dementia diagnosis cannot be made in a patient suffering from delirium and should be avoided in a patient suffering from major depressive symptoms, this clinical evaluation is of great importance. Furthermore, a neuropsychological exam can be used to stage the dementia syndrome and to monitor the cognitive decline in patients with dementia.

By use of careful history taking and a full neuropsychological examination, we are able to diagnose neurodegenerative (and cerebrovascular) brain diseases that cause dementia, even before the dementia stage is reached, the so-called MCI stage. Neuropsychological testing is furthermore useful in the differentiation of patients with MCI from those with mild dementia.

No single test is able to differentiate between different types of neurodegenerative and cerebrovascular diseases, which is why a panel of different neuropsychological tests should be used. The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) lists six cognitive domains, which might be affected in neurocognitive disorders, including complex attention, executive functions, learning and memory, language, perceptual motor functions, and social cognition [20]. Deficits in certain domains are more prevalent in different types of dementia [20]:

1. Complex attention includes sustained attention, divided attention, and selective attention.
2. Executive functions include planning, decision-making, working memory, responding to feedback, inhibition, and mental flexibility.
3. Learning and memory include free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, and implicit learning.
4. Language includes object naming, word-finding, fluency, grammar, and syntax.
5. Perceptual motor function includes visual perception, visuoconstructional reasoning, and perceptual motor coordination.
6. Social cognition includes recognition of emotions, theory of mind, insight.

Cognitive Screening Tests

There are several cognitive screening tests used to identify adults at risk for dementia. These tests are also used to obtain a global index of cognitive functioning and in follow-up of patients with dementia. Benefits of these screening tests include being cheap, fast, and non-invasive. Most cognitive screening tests are sensitive to cultural background, premorbid intelligence, and education; results should always be treated with caution. The most commonly used screening test is the Mini-Mental State

Examination (MMSE) [21]. However, there are a lot of other cognitive screening tests available varying in assessment time between less than 5–21 min, including the Memory Impairment Screen [22], the phototest [23], Alzheimer Quick test [24], Quick Mild Cognitive Impairment screen [25], the Cognitive State test [26], Montreal Cognitive Assessment (MoCA) [27], Addenbrooke's Cognitive Examination—Revised [28] and others. These tests cover from one up to seven cognitive domains, including memory, language, orientation, executive functions, praxis, visuospatial abilities, and attention (e.g., MoCA) [19].

The most commonly used test, MMSE, tests patients on several cognitive aspects (attention and orientation, memory, registration, recall, calculation, language, and ability to draw) by use of 30 questions. A score of $\geq$25 is considered normal. However, a meta-analysis has shown that it has a very limited ability to differentiate between patients with MCI and healthy controls. It had the best value for ruling out a diagnosis of dementia in the community and primary care, but for other purposes should be combined with other neuropsychological tests [29]. As said before, early detection of patients with cognitive decline is important, making it a less interesting screening tool, which is why some reviewers suggest to replace the MMSE with more performant alternatives.

Most of the previously mentioned screening tests have been studied for use in a memory clinic setting but have not been validated in a population-based setting. According to recommendations based on a systematic review by De Roeck et al. [19], the MoCA test is the most suitable for overall population-based screening to detect MCI or AD dementia. Although these screening tests are cheap, fast, and non-invasive, clinicians and researchers should bear in mind that no screening test can be used in every setting, for all different neurodegenerative diseases, and for each population.

To conclude, the MoCA, testing seven different cognitive domains, is a promising screening instrument and is validated in a population-based setting, however, specificity to detect early AD is rather low. We should, however, bear in mind that the role of population-based screening for AD is debated. In the absence of disease-modifying drugs, population-based screening cannot be recommended.

A Dementia Diagnosis Requires a Full Neuropsychological Examination

In order to evaluate the extent of cognitive decline and to be able to differentiate between different causes of dementia, batteries of neuropsychological tests are used. Each test separately yields a score indexing the functioning on a certain or on several cognitive domains. This holds true for the MCI and early dementia stages; in more advanced stages of dementia, cognitive deficits tend to be global, which does not allow differentiating between AD and non-AD causes of dementia.

As mentioned before, neuropsychological testing can aid in the differentiation of patients with MCI and the healthy, ageing population. Important to mention is the

fact that the boundaries between age-related cognitive changes and early dementia are more difficult to distinguish in patients aged 80 years or more, due to the fact that many of the structural and functional brain changes in AD overlap with changes observed in normal aging [18].

Different causes of dementia lead to distinguishable neuropsychological profiles (Table 3.1) [18]. In AD, the primary feature includes deficit in episodic memory (recall of experience that is personal to the patient), which is the earliest and most salient sign, with progression to problems with semantic memory (recall of general/lexical facts and impairment of language abilities). Episodic memory can be tested verbally and visually, by asking to remember a list of words (e.g., California Verbal Learning test) [30] or by asking to copy a figure and recall it at a later time (e.g., Visual Reproduction Test) [31] respectively. In a very early stage of AD, patients are particularly impaired on this delayed recall. Furthermore, patients with impairment of episodic memory (e.g., such as in AD) do not benefit from cueing. This is in contrast to patients with deficits of other cognitive domains (e.g., attentional deficits), which may also affect memory ability, and where cueing tends to improve

Table 3.1 Overview of typical cognitive deficits for some of the most common forms of dementia and of commonly used neuropsychological tests, typically used to detect these deficits

Disease	Cognitive impairment	Neuropsychological tests
AD	Episodic memory, semantic memory, language abilities, executive functions, visuospatial abilities	• Episodic memory: California Verbal Learning test, Visual Reproduction Test • Semantic memory, language: Verbal fluency, Boston Naming task • Executive functions: Tower of London, Part B of Trail Making test, Stroop test, Raven Progressive Matrices Task • Visuospatial abilities: Clock Drawing test, complex figure copying, Money Road Map test, segregation of overlapping figures
FTD	Executive functions, language, behavioural, and personality alterations	• Executive functions: Tower of London, Part B of Trail Making test, Stroop test, Raven Progressive Matrices Task, Frontal Assessment Battery • Semantic memory, language: Verbal fluency, Boston Naming task • Behaviour: neuropsychiatric questionnaire
DLB	Visuoperceptual/visuoconstructive functions, executive functions, attention	• Visuospatial: Block Design Test, Clock Drawing Test, complex figure copying, segregation of overlapping figures • Executive functions: Tower of London, Part B of Trail Making test, Stroop test, Raven Progressive Matrices Task, Frontal Assessment Battery • Attention: Digit Span
VaD	Executive functions, visuoconstructional abilities	• Visuospatial: Block Design Test, Clock Drawing Test, complex figure copying, segregation of overlapping figures • Executive functions: Tower of London, Part B of Trail Making test, Stroop test, Raven Progressive Matrices Task, Frontal Assessment Battery

performance. Semantic memory can be tested by use of category fluency in which patients have to generate as much words belonging to a certain category as possible (e.g., category of animals), by use of picture naming tests (e.g., Boston naming task), or by testing the patients´ knowledge of conceptual hierarchies. With disease progression, AD patients also become impaired in executive functions (tested by use of tests like the Tower of London puzzle, Part B of the Trail Making Test, Raven Progressive Matrices Task, and Stroop Test) and visuospatial abilities (including visuoconstructional abilities tested by Clock Drawing test, complex figure copying and visuoperceptual abilities tested by Money Road Map Test) [32].

Episodic memory and visuospatial abilities are typically initially spared in FTD. Problems reported with memory in FTD are more likely linked to inattention, which can be examined with tests like Digit Span. FTD patients, and especially those suffering from semantic dementia or nonfluent primary progressive aphasia, also present with semantic memory impairments. FTD is furthermore characterized by problems with executive functioning, as well as behavioral changes. A commonly used test for detecting frontal dysexecutive phenotype is the Frontal Assessment Battery [33].

When it comes to cognitive domains affected, DLB is best delineated from AD by disproportionately severe visuospatial and visuoconstructive deficits in the former. This can be elucidated by tests for visuoperception (e.g., Money Road Map Test, segregation of overlapping figures), for visual search (parallel search tasks), and visuoconstructional abilities (e.g., drawing complex figures). They are often also more impaired in executive functions and attention than patients with AD [32].

VaD is characterized by greater deficits in executive functions and visuoconstruction, rather than memory and language. However, patients with vascular dementia exhibit a variable cognitive profile, which is a reflection of the extent and spatial location of the underlying pathology. They are usually less impaired regarding episodic memory.

Differential Diagnosis: Role of the Neuropsychological Examination

Next to the above-mentioned causes of dementia, some other causes might lead to cognitive impairment, e.g., depression or other psychiatric conditions, alcohol abuse, sleeping problems (e.g., obstructive sleep apnoea syndrome), multiple sclerosis, normal pressure hydrocephalus, and tumors. These conditions should be screened for during history taking (see above) and by use of supplementary investigations (see below), but screening for some of these conditions also takes part in the neuropsychological examination. Patients with multiple sclerosis have a slowing down of processing speed but might also get impaired on episodic memory, attention, or executive functions. Normal pressure hydrocephalus is characterized by executive dysfunction, psychomotor slowing, inattention, and mood symptoms, especially apathy.

Structural Imaging: Magnetic Resonance Imaging (MRI)

From Exclusion of Other Causes to Automated Volumetry

Structural imaging of the central nervous system has made incredible progress over the last 50 years and is indispensable in today's neurology practice. Computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in the differential diagnosis of degenerative versus structural causes of cognitive impairment. Guidelines propose to perform structural imaging in all patients presenting with cognitive decline [34]. It enables exclusion of brain lesions such as brain neoplasms, strategic infarcts, subdural hematoma, and normal pressure hydrocephalus. These structural etiologies account for 2–5% of dementia cases and can be present in patients without suggestive history or without abnormalities on the clinical neurological examination [35].

To visualize the brain in detail, MRI is the preferred imaging modality because of its superior contrast of gray and white matter. Moreover, MRI is more performant to detect vascular pathology than CT scan, allows automated volumetry, which can be a helpful tool to detect (hippocampal) atrophy. In case of normal pressure hydrocephalus, prominent aqueductal flow void due to increased CSF velocity across the aqueduct is often seen on a specific sequences of a brain MRI scan. Certain patients will not be able to undergo an MRI, due to incompatible metal implants, claustrophobia, or the inability to lay still during the examination. If a patient is unable to undergo an MRI, CT can be sufficient for cognitive impairment work-up [36].

Different neurodegenerative disorders have characteristic signatures of brain atrophy that can be detected by structural imaging. Brain atrophy in AD generally follows the classic pattern described by Braak and Braak, with the hippocampus and entorhinal cortex affected first [37]. Scheltens and colleagues proposed a 5-point scale for visual assessment of medial temporal atrophy (MTA) on MRI [38]. The score is based on the coronal hippocampal height and width of the adjacent fissures. Hippocampal volume is lower compared to age-matched healthy controls in both dementia due to AD (20–30%) and MCI due to AD (15%) and a lower hippocampal volume in patients with MCI increases the risk to progress to the dementia stage [39]. With the increased availability of MRI, serial imaging to quantify the speed of volume loss over time in different brain regions seems interesting. Hippocampal volume reduces with age, but this reduction is twice as fast in AD compared to age-matched healthy controls and is even a predictor of evolution to the dementia stage in MCI [40]. With advancing computing power and MRI image quality (semi)automated volumetry of the hippocampus became feasible. Intuitively, the volumetric approach seems to have several advantages over visual MTA evaluation: lower to no interobserver variability, detection of more subtle changes, and a scale that is not limited to 5 discrete values. Automated extracted hippocampal volumes can differentiate between clinical diagnostic groups and may be a useful tool for characterizing and diagnosing AD, also in its prodromal stage [41]. Validation and harmonization exercises have been and are being performed [41, 42].

Limited Sensitivity and Specificity of Structural Imaging Biomarkers

Hippocampal atrophy is neither sensitive nor specific for AD. About one in ten AD patients has an atypical form of AD, with relatively preserved memory but impairment in other cognitive domains. These patients have a different pattern of brain atrophy, with relative sparing of the hippocampus and more prominent neocortical atrophy. The occipito-parietal cortex is most attained in posterior cortical atrophy, the left posterior temporal cortex in primary progressive aphasia, and the frontal lobes in the behavioral variant of AD [43]. The rate of hippocampal atrophy is not equal over the disease course of AD, but is inversely related to MMSE, with little volume loss earlier in the disease [44]. MCI may have a completely normal MRI for their age.

Specificity of hippocampal atrophy is also limited, since other non-AD neurodegenerative disorder causing dementia such as frontotemporal lobe degeneration, hippocampal sclerosis and the new entity limbic-predominant age-related TDP-43 encephalopathy are all associated with hippocampal atrophy [45–48].

PET Imaging

Introduction

Positron emission tomography (PET) is a nuclear imaging technique, using positron-emitting radionucleotides. These radionucleotides are fused with a molecule of choice and injected intravenously, after which they are transported through the bloodstream to specific organs or cells. Here they will decay and emit a positron that will almost immediately fuse with an electron, thereby emitting two photons in opposing directions that will be detected by cameras. These cameras attain a spatial resolution of 3–5 mm. PET allows the visualization of various molecular processes occurring in the body. The main disadvantages of the technique are the limited availability due to costs of hardware and the short half-life of relevant radionucleotides (The longest frequently used radionucleotide is fluorine-18 (F-18), with a half-life of 110 min) and thus the necessity to make them at the facility, or be in close proximity to a commercial dealer. As a PET scan involves radioactive tracers, there is exposure to radiation, albeit minimal. Altogether, PET imaging will not serve as a screening tool for dementia, but is a powerful diagnostic tool in selected subjects.

FDG-PET

^{18}-fluorodeoxyglucose (FDG) PET uses F-18 coupled to a 2-deoxy-glucose molecule as radiopharmaceutical. FDG has a similar uptake and metabolism as glucose. Glucose is the main energy source of the neuron and its uptake correlates well with

synaptic activity. Most synapses in the brain are glumatergic, and FDG-PET is thus a proxy for local glutamatergic synaptic function. In neurodegenerative disorders, synaptic dysfunction is an upstream event of neuronal death, which enables earlier detection than techniques measuring atrophy [49]. A brain FDG-PET scan should be combined with structural imaging (mostly brain CT scan) in order to correct for brain atrophy and cerebrovascular disease

With aging, glucose metabolism of the brain decreases mainly in motor, parietal and anterior and middle cingulate cortex decreases in a symmetrical manner. The typical AD dementia pattern of hypometabolism in FDG-PET is early (possibly asymmetric) hypometabolism of the precuneus, posterior cingulate cortex (PCC), and temporoparietal cortex with sparing of the primary motor and sensory cortex. The hypometabolism may extend to frontal or occipital regions but is not more pronounced in these regions than in the PCC [49]. Atypical AD forms, with relatively preserved memory, have a different pattern with hypometabolism in occipital (PCA variant); left-sided posterior parietotemporal (logopenic variant); prefrontal, dorsolateral prefrontal and orbitofrontal (behavioral variant) or superior parietal cortex, contralateral to the most affected limbs (corticobasal syndrome due to AD) [50]. A meta-analysis of 119 studies in 2011 revealed a pooled sensitivity of 91% and specificity of 86% at differentiating AD dementia from healthy controls with FDG-PET [51]. Automated FDG-PET analysis seemed even more potent to answer this question, with a sensitivity of 99% and a specificity of 98% [52]. Only two studies used autopsy-confirmed cases and showed a pooled sensitivity of 89% and a specificity of 74% for discerning AD from healthy controls [53, 54]. In MCI due to AD, PCC seems to be most frequently affected, with other regions of the AD signature variably affected, but to a lesser extent than in AD dementia. The severity of hypometabolism is correlated with cognitive impairment in both MCI and dementia due to AD.

An important clinical question is whether FDG-PET can differentiate neurodegenerative disorders underlying dementia. DLB typically has lower metabolism in the occipital cortex, especially the primary visual and visual association cortex, while preserving regions commonly affected in AD, especially the PCC (known as "posterior cingulate island sign") [55]. The FDG-PET signature of frontotemporal lobar degeneration (FTLD) depends on the clinical variant: behavioral variant FTD has the involvement of frontal and anterior temporal lobes, semantic variant presents as bilateral but asymmetrical involvement of anterior temporal lobe, progressive nonfluent aphasia shows hypometabolism of the frontal opercular and temporal, insular cortex of the dominant hemisphere [56]. Patients with VaD typically show subcortical or focal cortical hypometabolism, corresponding to infarcted zones on structural imaging [56].

FDG-PET has found its way into the diagnostic criteria for AD, FTD, and DLB. Certain drawbacks exist for FDG-PET. High blood glucose levels in patients with uncontrolled diabetes mellitus mimic an AD signature in FDG-PET. Psychotropics and benzodiazepines, as well as alcohol, reduce overall glucose uptake, but without region-specific pattern [57].

Amyloid PET

Amyloid PET allows in vivo detection of one of the pathological hallmarks of AD: extracellular amyloid plaques. The first tracer was ^{11}C Pittsburgh-compound B (PiB), a thioflavin-T analog that at the concentrations used for PET only binds to the beta-sheets of amyloid plaques. The short half-life of ^{11}C led to the development of three approved equivalent ^{18}F tracers: florbetapir, flutemetamol, florbetaben that are, however, not all three available worldwide.

Since amyloid PET gives non-invasive in vivo information on one of the key players in AD, it is a useful diagnostic tool for AD. In autopsy-confirmed cases, amyloid PET imaging carried out on average 3 years before autopsy had a sensitivity of 91% and a specificity of 92% at differentiating AD from non-AD dementia [58]. The typical AD amyloid PET sequence shows uptake in the orbitofrontal and inferior temporal cortex, cingulate gyrus, and precuneus first, followed by prefrontal, lateral temporal, and parietal cortex [59]. In contrast to other imaging markers, atypical forms of AD present with a similar pattern. As holds true for all biomarkers, amyloid PET should only be used in the correct clinical context, especially given the high number of asymptomatic amyloid positive elderly. This makes amyloid PET an excellent instrument to rule out AD in individual subjects and to diagnose AD amongst individual younger patients. However, its positive predictive value might be less strong in individual elderly subjects due to the high number of asymptomatic amyloid positive subjects.

Amyloid PET is excellent at differentiating AD from a pure tauopathy as FTLD, with an accuracy of over 90% [60]. In DLB, however, up to 60% of patients have amyloid deposition following a similar pattern as AD, with a total amyloid load that is generally lower than patients with dementia due to AD. It was not thought possible to discriminate between both diseases based on amyloid PET, but a study published in 2020 on 39 autopsy-confirmed DLB and AD patients showed that a cut-off with 93% accuracy could be established in amyloid PET [61]. A meta-analysis concluded that patients with VaD have a similar percentage of amyloid positive scans as age-matched controls [62].

Defining amyloid positivity can be done in a qualitative or quantitative way. Standard uptake value (SUV) is a widely used quantifier to assess the activity of radioligand, corrected for weight and injected dose. For amyloid PET, an SUV ratio (SUVR) is calculated between regions with frequent amyloid deposition in AD and the cerebellum, where no amyloid deposition occurs. This value depends on the used tracer, pre- and postprocessing of images, and is difficult to generalize between centers. This problem is tackled by the "centiloid" measure, that corrects for these parameters by according a value to every scan, where 0 is no amyloid pathology, and 100 equals amyloid load in patients with mild dementia due to AD [63]. This enables to correctly interpret data from different centers within one study or to make shared databases easily interpretable.

CSF Biomarkers

Introduction

The CSF offers a window to the brain as the brain's metabolism and pathology is reflected in the CSF. To collect CSF, a lumbar puncture (LP) is needed, which is a safe and well-tolerated procedure. If performed correctly, LP has a low complication rate and a high diagnostic yield. While structural brain imaging studies may sometimes eliminate the need for a diagnostic LP, indications for diagnostic LP still remain, especially in cases of suspected infectious or immune-mediated inflammatory disorders of the nervous system. Moreover, diagnostic LP may be indicated in AD and other neurodegenerative disorders, Creutzfeldt-Jakob disease, normal pressure hydrocephalus. For the latter condition, evacuating LP is indicated.

As AD is the most frequent cause of dementia, most biomarker research focused on AD, resulting in several CSF biomarkers that increase the diagnostic accuracy of AD. Biomarkers that reflect the pathology of AD already show abnormal concentrations in the preclinical stage of AD, thus allowing early AD diagnosis. Although no CSF biomarkers for non-AD dementias are available for daily clinical practice yet, the core AD CSF biomarkers have an added diagnostic value for differential dementia diagnosis too.

Lumbar Puncture (LP)

An LP can be safely performed with a high acceptance rate and a high diagnostic yield. The most common complications of LP consist of post-LP back pain and post-LP headache (PLPH). Very rare (prevalence of <0.01%), but potential serious complications consist of post-LP infections, spinal and subdural cerebral hematoma, and cerebral venous thrombosis.

Although a substantial proportion (31%) of patients reported post-LP complaints in an international, multicenter LP feasibility study, these were mostly mild and transient [64]. Back pain, headache, and typical PLPH were reported by 17%, 19%, and 9% of subjects, respectively. Only 0.3% of the subjects needed a blood patch for PLPH, and in 0.7%, a hospitalization was required. The most important risk factors for post-LP complaints were related to patient characteristics: history of headache and fear of complications. A cutting bevel needle-type appeared to be the only procedure-related risk factor for typical PLPH. The number of LP attempts was related to post-LP back pain. A large needle diameter was a risk factor for severe headaches.

Based on the results of this international, multicenter LP feasibility study, as well as a literature review, consensus guidelines and recommendations for the LP procedure in adults were formulated [65]. These recommendations should minimize post-LP complications, the most frequent being PLPH and post-LP back pain.

Core AD CSF Biomarkers

The core AD CSF biomarkers are related to the three main pathological changes: amyloid-β deposition into extracellular amyloid plaques, intracellular neurofibrillary tangles formation, and neuronal loss. The β-amyloid peptide composed of 42 amino acids ($A\beta_{1–42}$) results from the cleavage of the transmembrane amyloid precursor protein. $A\beta_{1–42}$ is insoluble and aggregates into extracellular amyloid plaques, detected as decreased CSF $A\beta_{1–42}$ concentrations. Tau proteins are present in the cytosol of neurons, where they stabilize microtubules. In AD, a hyperphosphorylation of tau occurs, leading to the formation of neurofibrillary tangles. During the neurodegenerative process, tau and phosphorylated tau proteins are released into the extracellular space, resulting in increased CSF tau concentrations.

The first amyloid plaques occur at least 10 years, and probably 20–30 years before the first symptoms [3]; CSF $A\beta_{1–42}$ therefore is a very early marker of AD. CSF tau biomarkers change later in the pathophysiological process compared, and CSF tau is stronger correlated to cognitive decline than $A\beta_{1–42}$. CSF biomarkers give a complete overview of AD pathophysiology, and in addition, an LP is highly accessible with a low cost price, in contrast to the imaging-based markers used in AD diagnosis.

Core AD CSF Biomarkers for Early Diagnosis

The core AD CSF biomarkers $A\beta_{1–42}$, total protein tau (T-tau), and tau phosphorylated at threonine 181 ($P\text{-}tau_{181}$) are strongly associated with future development of AD dementia amongst patients with MCI, which was proven in a several prospective, longitudinal studies [5]. The core AD CSF biomarkers can in fact identify those MCI patients who have prodromal AD. In the study of Hansson et al., The combination of CSF $A\beta_{1–42}$ and T-tau at baseline yielded sensitivity and specificity levels of 95% and 83% for diagnosing prodromal AD in a heterogeneous MCI cohort [66].

Core AD CSF Biomarker for Differential Dementia Diagnosis

The core AD CSF biomarkers $A\beta_{1–42}$, T-tau, and $P\text{-}tau_{181}$ can discriminate between AD and non-AD dementias, but they cannot be used to confirm another type of dementia [5]. Several other brain diseases can lead to changes of these CSF biomarker levels, causing possible misinterpretation of the biomarker results in the absence of clinical information. A marked increase in T-tau is also detected after stroke and in Creutzfeldt-Jakob's disease. For this reason,, $P\text{-}tau_{181}$ is a very helpful marker for differential dementia diagnosis as it is a more specific marker for AD. Indeed, CSF levels of $A\beta_{1–42}$ and T-tau are often intermediate between normal control and abnormal AD values in non-AD patients, especially in DLB but also in FTD, VaD.

The addition of the most abundant Aβ isoform, $A\beta_{1–40}$ into an $A\beta_{1–42}/A\beta_{1–40}$ ratio diminishes inter-patient variability (to control for high or low $A\beta_{1–42}$ production, irrespective of AD pathology) and also improves differential dementia diagnosis in patients with intermediate P-tau_{181} levels [67]. Increased concordance between amyloid markers (amyloid PET scan and CSF Aβ) was found in two studies when the $A\beta_{1–42}/A\beta_{1–40}$ ratio was applied compared to a CSF $A\beta_{1–42}$ concentration alone [68]. Therefore, the $A\beta_{1–42}/A\beta_{1–40}$ ratio has become part of the core AD CSF biomarkers.

Other CSF biomarkers are under development and may, following validation and standardization, be used in daily clinical practice, like neurofilament light to diagnose FTD.

Conclusions

In the past, the diagnosis of AD could only be suggested when the dementia stage was reached. Due to major advances in biomarker-based research, it is now possible to detect AD-related changes at the first clinical symptoms.

If a timely diagnosis is desirable, history taking and a full neuropsychological examination are the cornerstone of a dementia diagnosis. Specific biomarkers can be applied to increase the early and differential diagnostic accuracy.

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