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Diagnosis and treatment of cognitive impairment

A woman in her 60s presents for a check-up. She plans an active retirement and would like to take any steps possible to stave off "problems with my brain". What advice should she be given?

Cognitive performance decreases with age but a distinction is made between physiological age-associated changes and pathological changes. Dementia is the generic term that describes a clinical syndrome defined by the loss of cognitive functions and everyday life skills and competencies. The main risk factor for the development of dementia is age. In Germany, 1.7 million people currently suffer from dementia [31]. The most common form (in about two thirds of patients) is Alzheimer's disease (AD) and the histopathological characteristics (accumulation of amyloid-beta and tau protein) can be detected decades before onset of symptoms [5, 34]. The older the patients are, the more common are mixed pathologies (neurodegenerative and vascular dementia in patients >80 years). Due to demographic changes, a considerable increase in the prevalence of dementia is expected in the coming decades; however, an unexpected decline in the incidence and/or prevalence has recently been reported in some western countries, suggesting a reduced risk in future generations depending on health and lifestyle factors. These include cardiovascular and cerebrovascular disorders, hypertension and hypercholesterolemia, obesity and diabetes [11] and others, such as depression and social isolation. A Mediterranean diet and education have been recognized as protective factors [18, 24]. Hearing loss has recently been identified as a common treatable risk factor [18]. All these factors together can account for 35% of risk factors for AD [18].

The patient's cardiac risk factors are treated proactively and after a hearing test shows a deficit she obtains a hearing aid. She comes to the clinic with her 75-year-old brother 5 years later. She reports that over the past few years he has been having increasing difficulty remembering appointments and events. She now notices that he is also having trouble finding words, he forgets the date, and he recently got lost trying to return home. He says that he has been having a few problems but that everyone slows down with age. How should he be evaluated?

The word dementia describes a clinical syndrome:

ICD-10 definition. Dementia is a syndrome due to diseases of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior or motivation. This syndrome occurs in AD, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain.

Patients may present at any point on the cognitive impairment-dementia continuum but they are often first diagnosed when the disease is already in an advanced stage despite the fact that neurodegenerative changes can begin decades before the onset of symptoms. The time from first symptoms to the correct diagnosis may take up to 2 years [4]. The reasons for a delayed diagnosis may include the fact that older patients themselves tend to play down their symptoms because they consider them part of "normal" aging, and because of concerns associated with a dementia diagnosis, e.g. fear of limited autonomy, issues with financial management, and need for a caregiver. In clinical practice, medical practitioners may also neglect the diagnosis of dementia because of a misconception of memory problems as normal in persons of advanced age, lack of (neuro)geriatric training, ageism or fear of constraining the patient's independence; however, the recognition and correct diagnostic assessment of dementia are important for enabling targeted treatment and management as well as advance care planning.

For the initial assessment of cognitive deficits, dementia guidelines recommend screening tests to estimate the severity of dementia. Examples are the mini-mental status test (MMST), the DemTect and

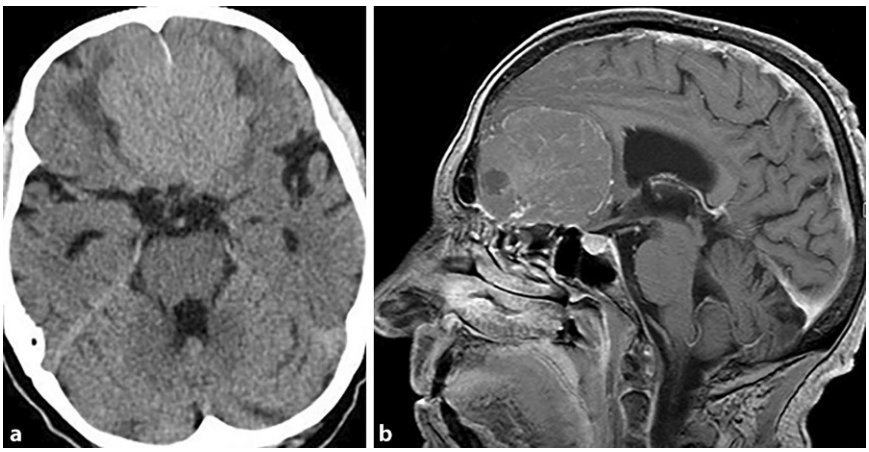

Fig. 1 ▲ Computed tomography (**a**) and MRI (**b**) demonstrating a large frontobasal meningioma in an 82-year-old woman presenting with cognitive decline, spontaneous vomiting in the morning without headache and inability to take care of herself

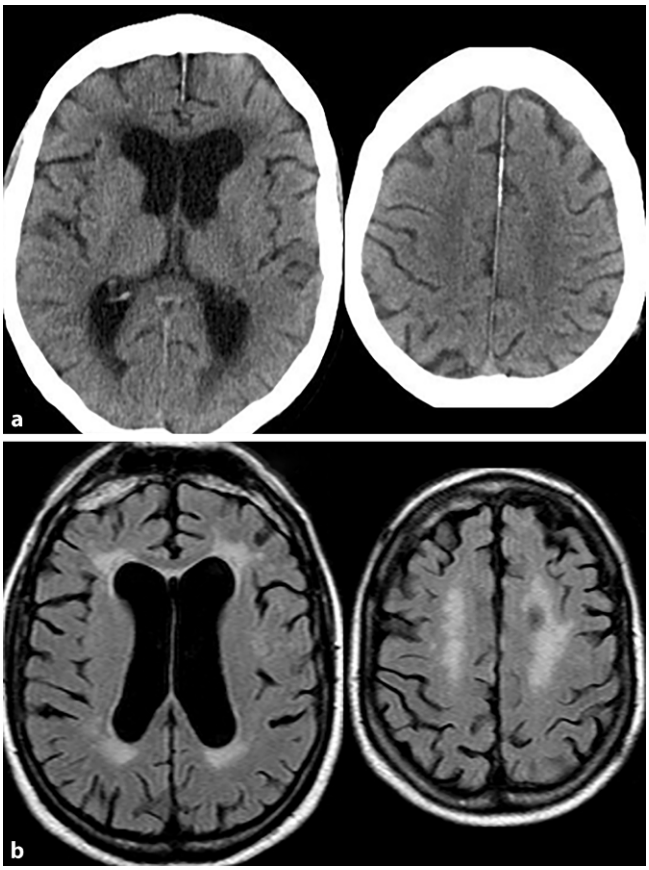

Fig. 2 ◀ Computed tomography (**a**) and MRI (**b**) of an 83-year-old man presenting with gait disturbance for the past two years, cognitive impairment for several months and irregular urinary incontinence. Imaging demonstrates the typical signs of periventricular liquor diapedesis, indicative of normal pressure hydrocephalus. Transversal sections at ventricular level (left image) and supraventricular level (right image)

the Montreal cognitive assessment test (MoCA) [22]. For further assessment, especially of mild cognitive impairment and mild to moderate forms of dementia of unclear etiology, formal neuropsychometric testing is recommended. Generally, the cognitive domains learning and memory, orientation in time and space, attention, practice, language and executive function are assessed. In most German-speaking countries, the consortium to establish a registry of Alzheimer's disease (CERADplus) test battery has become established [10].

A clinical neurologic examination is unremarkable. On psychometric testing, the patient scores 17/30 on the MMSE, and the CERAD indicates that he has deficits in episodic memory, verbal fluency, visuospatial perception, and learning new information. What further assessments would aid in diagnosis?

In the differential diagnosis of cognitive decline in older patients, brain imaging plays an important role. The goals of imaging are:

1. to exclude a potentially treatable disorder, such as a frontobasal meningioma (**Fig. 1**) or a normal pressure hydrocephalus (**Fig. 2**);
2. to detect vascular alterations, such as small vessel disease (**Fig. 3**) with its consequences for secondary prevention;
3. to demonstrate evidence of temporal atrophy indicative of AD or frontal atrophy indicative of frontotemporal dementia (FTD; **Fig. 4**).
4. Most commonly, both atrophic changes and vascular changes are found (**Fig. 4**). This condition is called mixed dementia.

In most patients the imaging diagnosis is based on cranial computed tomography with coronal sections (cCT) (**Figs. 1, 2, 3 and 4a**); however, magnetic resonance imaging (MRI), as suggested by the German guidelines, may be preferred due to higher sensitivity towards vascular changes (**Figs. 1, 2, 3 and 4b**). In coronal MRI sections, hippocampal volumetry can quantify the extent of atrophy in AD (**Fig. 4b**). There are easy to use visual scales for assessing the changes associated with AD and other neurodegenerative diseases [12].

It has been shown that hippocampal atrophy can occur up to 3 years before conversion to clinically manifest AD [36]. Further structural changes in the amygdala and nucleus accumbens and changes in cortical thickness in temporal and parahippocampal regions may be prognostically relevant [33]. The MRI-based assessment of disease-related changes in the default network is the subject of intensive research [14]. The term brain frailty has been assigned to white matter hyperintensities as evidence of small vessel disease [27, 35].

Other imaging modalities enable evaluation of molecular alterations by using specific radiopharmaceuticals. Glucose

metabolism visualized by positron emission tomography (PET) can be evaluated to detect pathognomonic reductions in temporoparietal association areas in AD (**Fig. 5**). The PET can also detect other molecular alterations, such as amyloid beta and tau deposits [13, 14] and microglial cells driving neuronal destruction, but should be used only in specialized centers. A diagnostic sequence of MRI and PET in conjunction with other dementia assessment measures has been proposed by Ten Kate et al. ([32]; **Fig. 6**); these imaging parameters are part of a European study on medical information frameworks in AD (EMIF-AD) 90+ [17].

The standard diagnostic work-up also includes laboratory screening to assess treatable comorbidities or primary causes of dementia, in particular, renal and liver dysfunction, vitamin B12 deficiency and hypothyroidism.

Cranial imaging demonstrates temporal and hippocampal atrophy. What other assessments can help confirm the diagnosis?

The currently used McKhann et al. (2011) criteria [21] are depicted in **Fig. 7**. In comparison with the 1984 NINCDS-ADRDA criteria [20], which presented a solely clinicopathological definition, the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria specify assessment of amyloid and neurodegeneration biomarkers in the diagnosis of AD. In parallel, diagnostic criteria for the diagnosis of mild cognitive impairment (MCI) due to AD [1] have been published. Most recently, the 2014 International Working Group (IWG) criteria [9] defined AD as a clinical syndrome in which biomarker levels are already abnormal in MCI (i.e. in the prodromal phase of the illness).

These changes in diagnostic criteria reflect the current paradigm shift from Alzheimer's dementia to Alzheimer's disease. While Alzheimer's dementia was previously considered to be a diagnosis of exclusion, nowadays an etiological classification of Alzheimer's disease is possible even at very early stages on the basis of characteristic pathophysiological changes. Therefore, in 2018 a clinical research framework was postulated in which AD is defined solely by positive biomarkers, regardless of where a patient lies on the clinical spectrum (AD continuum) [13]. There the term Alzheimer disease (AD) refers to pathologic processes and therefore in living persons is defined by biomarkers and harmonized across the disease continuum. Biomarkers are grouped into those of amyloid beta, pathologic tau, and neurodegeneration or neuronal injury. For staging the severity of cognitive symptoms, a syndromal categorical scheme is applied, i.e. cognitively unimpaired, mild cognitive impairment, and dementia. Biomarker staging includes all members of the population, i.e. individuals in the Alzheimer's continuum, with non-AD pathologic changes, and with normal biomarker profiles. Biomarkers are also increasingly being included in the criteria for other types of dementia, e.g. for Lewy body dementia ([19]; **Fig. 8**). Overall, the combined use of cognitive test instruments, MRI and detection of cerebrospinal fluid (CSF) markers increases the diagnostic accuracy for the differentiation of the various forms of dementia from 78% to 97% [6].

Mixed pathology, including AD, vascular alterations (especially cortical microinfarcts) and hippocampal sclerosis

Abstract · Zusammenfassung

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Diagnosis and treatment of cognitive impairment

Abstract

As a result of the aging population dementia is a growing challenge, especially in healthcare. Nevertheless, cognitive disorders are often not systematically evaluated, especially during hospital stays for other reasons; however, cognitive impairment is associated with a number of geriatric syndromes, including falls, delirium, dysphagia and lack of adherence to treatment plans. This article considers the current state of diagnosis and treatment of dementia. Non-pharmacological therapeutic approaches as well as current and future pharmacological treatment options are discussed. The drugs of choice for the symptomatic treatment of cognitive deficits in Alzheimer's disease and Parkinson-associated dementia are cholinesterase inhibitors and memantine; there is no specific pharmacological treatment for other types of dementia. Prevention and treatment of cardiovascular risk factors can potentially retard the progression of possibly all forms of dementia.

Keywords

Dementia · Prevention · Alzheimer disease · Antidementia agents · Imaging

Diagnose und Behandlung kognitiver Störungen

Zusammenfassung

Demenzen sind durch die demographische Entwicklung eine wachsende Herausforderung. Trotzdem werden kognitive Störungen oft nicht systematisch evaluiert, insbesondere bei Krankenhausaufenthalten anderer Ursache. Kognitive Beeinträchtigung geht jedoch mit einer Reihe geriatrischer Syndrome, wie z. B. Stürze, Delir, Dysphagie, mangelnder Compliance und Einhaltung von Behandlungsplänen, einher. Dieser Artikel setzt sich mit dem aktuellen Stand von Diagnostik und Therapien bei Demenzen auseinander. Es werden sowohl nichtpharmakologische Therapieansätze als auch derzeitige und zukünftige pharmakologische Behandlungsmöglichkeiten erörtert. Die Wirkstoffe der Wahl zur symptomatischen Behandlung bei der Alzheimer-Demenz und bei Parkinson-assoziierten Demenzen sind Cholinesteraseinhibitoren und Memantin. Eine spezifische pharmakologische Behandlung bei den anderen Demenzformen besteht nicht. Die konsequente Therapie und Einstellung von kardiovaskulären Risikofaktoren dürfte das Fortschreiten von möglicherweise allen Demenzformen verlangsamen.

Schlüsselwörter

Demenz · Prävention · Alzheimer · Antidementiva · Bildgebung

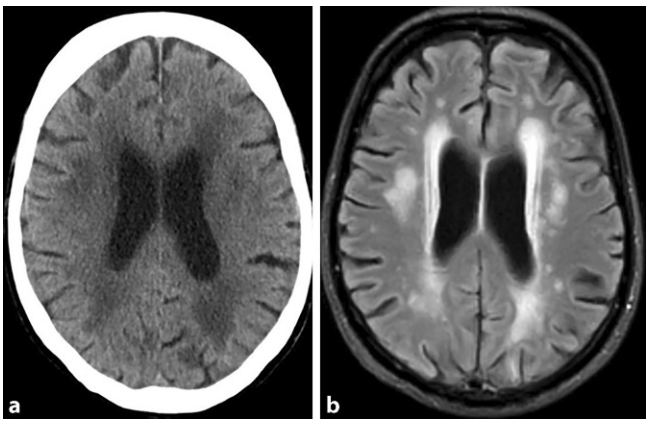

Fig. 3 ◀ Computed tomography (**a**) and MRI (**b**) of a 78-year-old man with memory disturbance for one year and diabetes mellitus for over 10 years. Imaging reveals white matter hypodensities (CT) and white matter signal hyperintensities (MRI) indicating small vessel disease

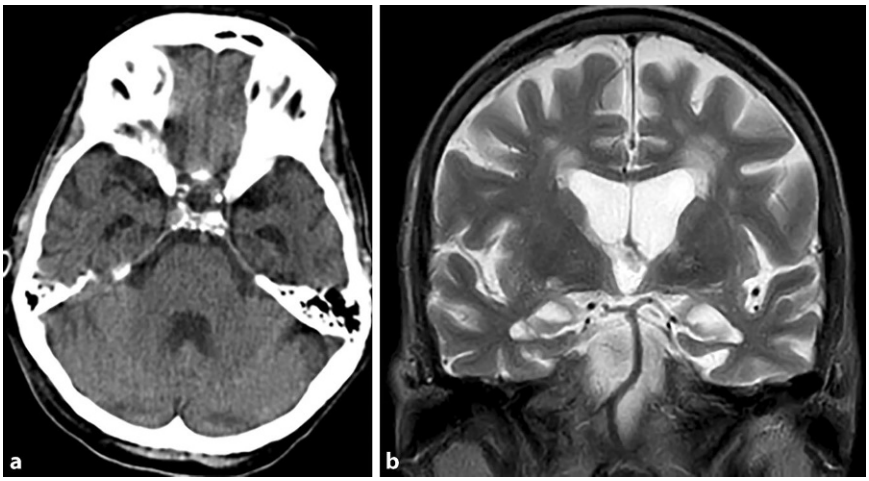

Fig. 4 ▲ Computed tomography (**a**) and MRI (**b**) of an 86-year-old woman with cognitive decline for several years and inability to take care for herself. Imaging demonstrates temporal lobe atrophy (**a**, **b**) and white matter signal hyperintensities (MRI), suggesting mixed dementia

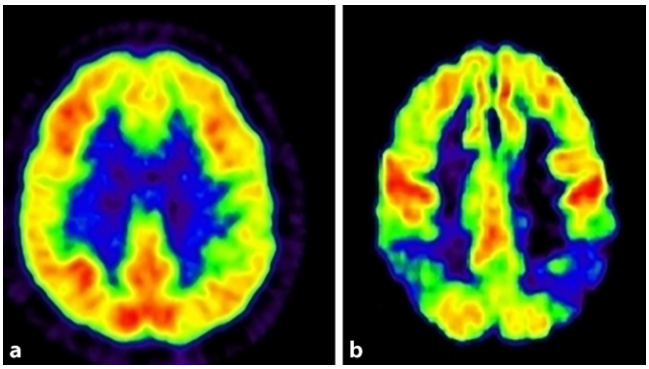

Fig. 5 ◀ Positron emission tomography with 2′-fluoro-2-deoxy-D-glucose (FDG) in a normal control (**a**) and a patient with AD (**b**) and pathognomonic hypometabolic areas in secondary and tertiary temporoparietal association areas

seem to have increasing relevance in old age. In the oldest-old, the presence of multiple pathologies is associated with an increased likelihood and severity of dementia [15]. The use of biomarkers in this age group has not been systemically evaluated; however, existing data suggest a high negative predictive value when dementia biomarkers are absent.

The patient's CSF demonstrates abnormally reduced levels of amyloid beta, indicating that it is accumulating in the brain, and high levels of tau protein as a result of neuronal cell death. Based on the psychometric, imaging, and biomarker results, the patient is diagnosed with mild dementia, most likely due to Alzheimer's disease. How should the patient be treated?

The use of CSF biomarkers is currently a major topic as suggested by the new diagnostic criteria (e.g. IWG-2 [9]; NIA-AA criteria [21]). In AD, the most important markers are amyloid-beta 1-40 and 1-42 and their ratio, tau as well as phosphorylated tau (181P). The classical combination is a reduction of amyloid beta 1-40 and 1-42 and an increase in tau. Recently, the amyloid beta ratio has been shown to be an early marker in AD. It should be noted that up to 20% of patients with signs and symptoms typical of AD may have unremarkable CSF tau and amyloid beta concentrations (**Table 1**).

To date, no drugs can cure dementia; however, approved substances for treatment of mild to moderate Alzheimer's dementia include cholinesterase inhibitors (ChEI, donepezil, galantamine and rivastigmine) that balance a central cholinergic deficit. These medications have comparable efficacy and their effectiveness is dose-dependent. Therefore, ChEI should be maximally dosed except if there are contraindications or side effects (donepezil 10 mg, galantamine 24 mg, rivastigmine p.o. 12 mg or for transdermal application ("patch") 9.5 mg [13.3] mg). The use of ChEIs may stabilize cognitive symptoms and may even lead to slight improvement for a while. They also have a positive influence on activities of daily life and mental and behavioral symptoms [3]. The noncompetitive N-methyl-D-aspartate (NMDA) antagonist memantine is approved in Germany for the treatment of moderate to severe AD. Anti-dementia drugs may delay nursing home placement and reduce mortality [11, 28]. According to the German S3 guidelines on dementia, there is also evidence for the efficacy of *Ginkgo biloba* (EGb 761) on cognition in patients with mild to moderate AD or vascular dementia and with non-psychological or behavioral symptoms [2].

The use of any anti-dementia drugs in multimorbid, geriatric patients with polypharmacy should be discussed and the individual situation of each patient considered. From a clinical perspective, it is not surprising that efficacy data for anti-dementia drugs in typical geriatric patients often do not seem convincing.

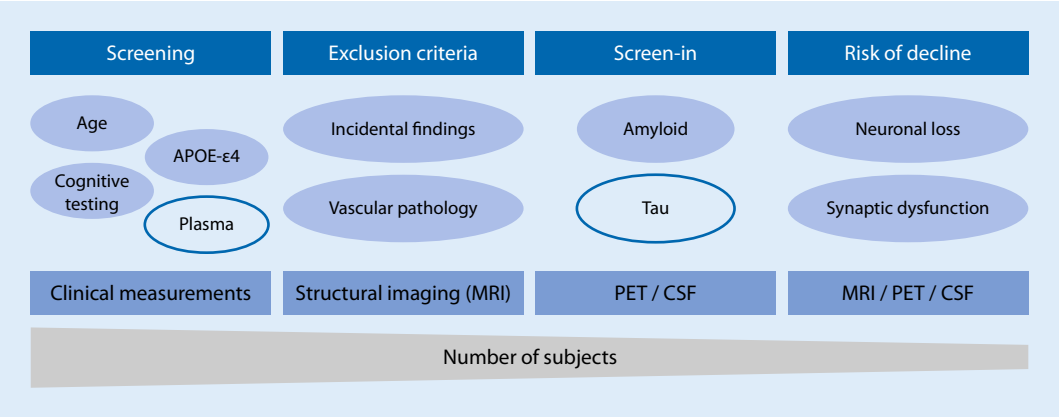

Fig. 6 ◀ Diagnostic set of images of patients with cognitive decline at various disease stages and ages (from Ten Kate et al. [32]). *APOE-ε4* apolipoprotein E 4, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *CSF* cerebrospinal fluid

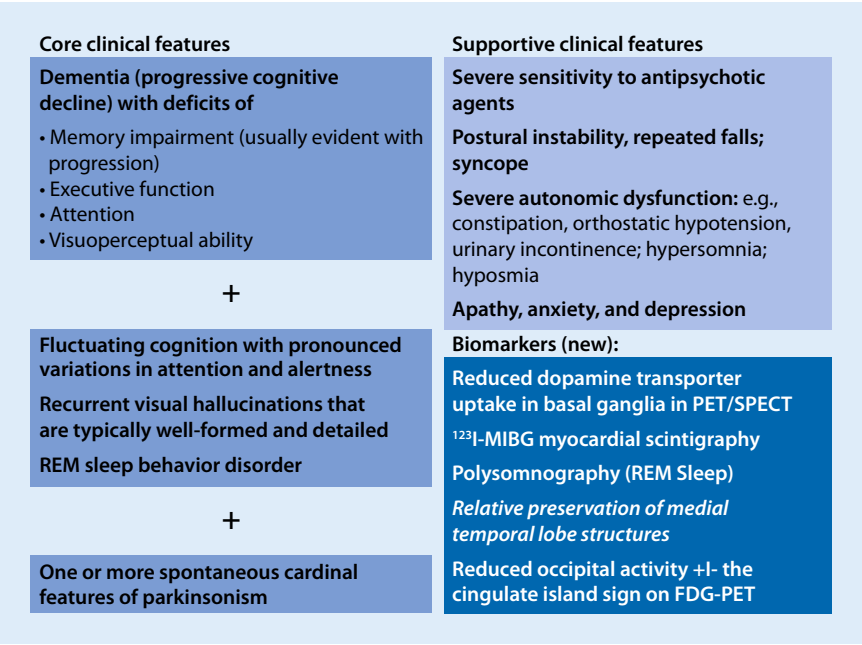

Fig. 7 ▲ McKhann et al. criteria according to the diagnostic guidelines for Alzheimer's disease of the National Institute on Aging-Alzheimer's Association workgroups (compiled from [21]). ^{123}*I*-MIBG radioactive isotope of iodine, *MIBG* metaiodobenzylguanidine, *FDG* 18F-fluorodeoxyglucose, *PET* positron emission tomography, *REM* rapid eye movement, *SPECT* single photon emission computed tomography

Anti-dementia drugs were tested in randomized controlled trials that typically excluded older multimorbid patients; however, in everyday situations, these are exactly the patients who would most profit from anti-dementia treatment. The impact of therapeutic interventions on dementia in old, multimorbid patients urgently requires research.

Recently, the importance of non-drug therapies in dementia has been examined and is emphasized in the current S3 guidelines. Recommendations were made despite limited evidence levels due to methodological reasons. Non-drug interventions are a central and necessary therapy component because of their focus on approaches and goals relevant to daily life. Cognitive training/cognitive stimulation is often recommended when cognitive performance is only mildly impaired. Reality orientation and reminiscence are recommended in all phases of dementia. Other reasonable options include physical activity, occupational therapy, and music therapy, as well as sensory stimulation such as aroma therapy and *Snoezelen* in advanced stages.

Throughout the course of dementia, neuropsychological and behavioral changes can occur. Addressing these issues is important because they affect the patient's quality of life, the caregiver burden, and result in early institutionalization and related healthcare costs. Patients should be screened for depressive symptoms, as depression, dementia, and Parkinsonism are common comorbidities in geriatric patients [25]. For targeted diagnostics, appropriate instruments (nursing observation scale for geriatric patients, NOSGER, neuropsychiatric inventory, NPI [8]) are available. Such questionnaires can be helpful, as patients and caregivers may not spontaneously report many symptoms as a result of shame or fear.

Psychological and behavioral disorders should be treated primarily with anti-dementia drugs and non-drug interventions. In agitation, aggression, delusion and hallucinations, neuroleptics such as risperidone can be used. Haloperidol is relatively contraindicated due to its unfavorable side effect profile. In Parkinson's dementia or Lewy body dementia, standard neuroleptics are contraindicated and quetiapine is used. A well-structured daily routine has proven particularly effective in day-night reversals and sleep disorders.

To date, disease-modifying drug therapies for AD have been tested in clinical trials only. Drug substances have been tried against amyloid-beta, tau and other pathways (for example inflammation). Anti-amyloid approaches interfering with the metabolism of amyloid or its precursor protein have not been successful. Studies with gantenerumab, a fully human IgG1 antibody designed to bind

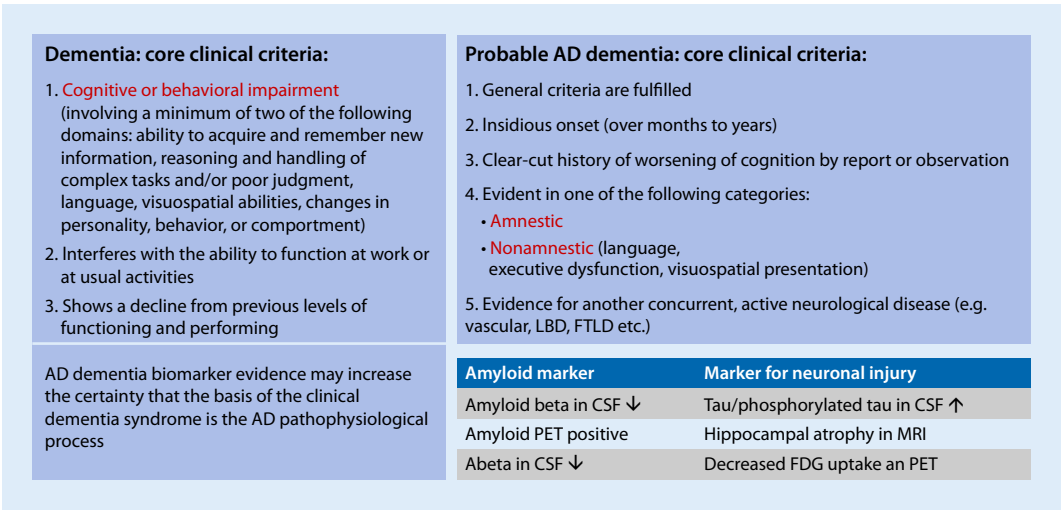

Fig. 8 ◀ Diagnostic criteria for dementia with Lewy bodies according to McKeith et al. (compiled from tables and text in [19]). *AD* Alzheimer's dementia, *CSF* cerebrospinal fluid, *FDG* 18F-fluorodeoxyglucose, *FTLD* frontotemporal lobar degeneration, *LBD* Lewy body dementia, *MRI* magnetic resonance imaging, *PET* positron emission tomography

Table 1 Concentrations of biomarkers in the CSF by neurodegenerative diseases (adapted from [23])

Diagnosis	Total tau	Phosphotau	$A\beta_{1-42}$	$A\beta_{1-40}$	$A\beta_{1-38}$	S-100 CSF	S-100 serum	H-FABP CSF	H-FABP serum	14-3-3 WB
AD	↑↑	↑↑	↓	↔↓	↔	–	–	↔	↔	(+) rare
DLK	↑	↑	↔↓	–	↔	–	–	↑	↑↑	–
FTD	↑	↑	↔	–	↔↓	↑	–	–	–	–
MSA	↑	↑	↔↓	↔↓	–	–	–	–	–	–
CJD	↑↑↑	↑	↔↓	↔↓	↔	↑↑↑	↑↑	↑↑	↑	+
vCJD	↑↑	–	–	–	–	↑↑	–	–	–	(+) rare

AD Alzheimer's dementia, *DLK* dementia with Lewy bodies, *FTD* frontotemporal dementia, *MSA* multiple system atrophy, *CJD* Creutzfeldt-Jakob disease, *vCJD* new variant, *H-FABP* heart fatty acid-binding protein, *CSF* cerebrospinal fluid, *Aβ* beta-Amyloid, S-100, *14-3-3 WB* 14-3-3 Western blot, *Phospho-tau* CSF phophorylated tau
↑ increased in comparison to normal values, ↓ reduced, ↔ unchanged, — immunoblot negative, + immunoblot positive, – insufficient data available

with subnanomolar affinity to a conformational epitope on amyloid beta fibrils and BAN2401, an anti-amyloid beta protofibril antibody, are ongoing [30], although hopes for success have dimmed with the failure of other anti-amyloid antibodies, where phase III trials have been recently discontinued due to futility analyses (crenezumab, aducanumab) [29]. Anti-tau approaches promising in preclinical models include passive immunization (phase 2 studies) as well as innovative approaches using antisense oligonucleotides [16] but the results are not yet available.

The patient requires hospitalization for treatment of other health issues. How can his inpatient care be optimized?

Unfortunately, studies show that cognitive impairment has not been systematically addressed for inpatients, although it is a major risk factor for the development of a geriatric syndrome [21], including falls, delirium, and dysphagia. Particularly relevant in the inpatient geriatric setting is the distinction between dementia and an acute cognitive deterioration due to delirium. The history of the patient is crucial to help distinguish between these diagnoses. It is particularly challenging to recognize delirium in a patient with pre-existing dementia.

Since cognitive impairment and dementia are very common in geriatric wards, some geriatric departments have designed special care units (SCUs) for cognitively impaired patients who are unable to adapt to the normal hospital routine. A recent national survey found that 44 German geriatric departments operated SCUs in 2017 [37]. Although size, characteristics, and treated patient groups were heterogeneous, all SCUs followed most of the recommendations in the position paper of the German Geriatric Society (Deutsche Geriatrische Gesellschaft, DGG) on SCUs for patients with dementia [7]. Regardless of whether an SCU is available, a key feature of high-quality geriatric medicine is the development of multimodal treatment plans that address multimorbidity and additional rehabilitative, psychological, and social needs of individual patients and their families. Clearly, cognitive status significantly affects the feasibility and meaningfulness of diagnostic and therapeutic interventions as well as prognosis and must be integrated into a successful treatment plan.

Practical conclusion

The detection and treatment of dementia is a major challenge; dementia is still often underdiagnosed and undertreated in older people, including in nursing home residents and inpatients. Currently available treatment options are only symptomatic and have been tested on patients who are significantly different from those given anti-demen-

tia drugs in real life. In parallel with ever-improving methods of early detection, which allow for early counselling and non-medical care, new drugs are being tested in the hope of being able to modify the course of the disease. Prevention and treatment of cardiovascular risk factors can also decrease the incidence of dementia.

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Compliance with ethical guidelines

Conflict of interest C.A.F. von Arnim received honoraria from serving on the scientific advisory board of Nutricia GmbH (2014) and Honkong University Research Council (2014) and has received funding for travel and speaker honoraria from Nutricia GmbH (2014–15), Lilly Deutschland GmbH (2013–2016), Desitin Arzneimittel GmbH (2014), Biogen (2016–2018), Roche (2017–2018) and Dr. Willmar Schwabe GmbH &Co. KG (2014–2015). T. Bartsch, A.H. Jacobs, J. Holbrook, P. Bergmann, T. Zieschang, M.C. Polidori and R. Dodel declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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