Introduction

Alzheimer’s disease (AD) is the main cause of dementia and accounts for two thirds of dementia syndromes in people older than 65 years. Memory impairment, especially impairment of episodic memory, is one of the first symptoms of AD. Due to public awareness of AD, it is often suspected to be the underlying cause of memory problems in elderly patients. Since AD is a progressive neurodegenerative disorder with an untreatable cause and limited therapeutic options, it is highly important to carefully establish the correct diagnosis and be aware of medical conditions that may mimic AD by presenting with memory impairment. In clinical research the correct classification of AD and non-AD is crucial to study disease mechanisms or new treatment possibilities in homogenous study populations. In this article, we aim to describe new aspects of the most common differential diagnoses that may clinically resemble AD, but which have different pathophysiological roots.

Memory function

The term “memory” generally means the ability to reproduce or remember experienced or learned content. There are different types or constructs of memory, and...
the classification of memory categories is still subject to change and discussion. Memory may be classified as implicit or explicit: implicit memory mainly stands for nonverbal habitual memory, such as motor learning (e.g., playing a musical instrument or riding a bicycle); explicit memory contains active or passive recall of facts or impressions (biographical knowledge, chronological sequence of experienced events, speech, etc). Another common distinction is between short-term and long-term memory: short-term memory describes a time span of seconds or minutes (sometimes also referred to as working memory), and long-term memory comprises encoding, consolidation, and recall over or after a long period of time. Memory can also be classified with regard to content: episodic memory, verbal memory, visual memory, or olfactory memory.

Although there are fewer common syndromic variants of AD, one of its main and early features is an impairment of episodic memory—the capacity to remember past events together with details about the context in which they occurred. Episodic memory is an essential cognitive function that supports our ability to form an autobiographical history and helps us to create a concept of the past and the future. The hippocampal network, including the parahippocampal gyrus, hippocampus, and neocortical areas, play a major role in the process of memory consolidation and retrieval. Although its function has not yet fully been understood, the hippocampus seems to be involved in binding features of an event into a mental representation, which is important to form episodic memory. Virtually any neurological, neurodegenerative, toxic, or traumatic damage to brain structures involved in episodic memory generation, especially the hippocampus, may lead to deficits in episodic memory that may resemble or precede AD, especially in the absence of other neurological or neuropsychological symptoms or signs indicative of an alternative cause.

Diagnostic approach and diagnostic criteria

The diagnostic procedure of memory impairment is firstly based on a comprehensive clinical investigation. This should comprise a detailed medical history, medication history, proxy report of the perceived symptoms, neuropsychological memory testing, and a neurological and psychiatric examination. Additional investigations, such as a cranial magnetic resonance imaging (MRI) scan, fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET), cerebrospinal fluid (CSF) examination, and AD biomarkers (β-amyloid42 [Aβ42], total tau protein [t-tau], and tau phosphorylated at position threonine 181 [p-tau]), may further help to establish the correct diagnosis.

A typical clinical picture for AD consists of a slowly progressive memory loss and loss of other neuropsychological functions (e.g., praxis, speech), absence of medical, neurological, or psychiatric condition that may explain the memory loss, brain imaging that is in line with AD, and biomarkers supporting the diagnosis of AD. Atypical symptoms such as early neurological symptoms, mood disorder, visual hallucinations, or an atypical sudden onset may hint at a diagnosis other than AD. Comprehensive information on the clinical diagnosis and management of the most important dementing diseases other than AD (e.g., vascular cognitive impairment, frontotemporal dementia (FTD), Lewy body dementia (LBD), corticobasal syndrome, progressive supranuclear palsy, Parkinson’s disease–related dementia, Huntington’s disease, prion diseases, normal-pressure hydrocephalus, limbic encephalitis and other toxic and metabolic disorders) is provided in the recent EFNS-ENS guidelines (European Federation of Neurological societies–European Neurological Society). For the first time, the recently released revised diagnostic criteria for AD involve biomarkers to support the diagnosis of AD: (i) reduced CSF Aβ42; (ii) raised CSF tau (t-tau and p-tau); (iii) positive PET amyloid imaging;
Non-Alzheimer’s disease–related memory impairment and dementia - Arlt Dialogues in Clinical Neuroscience - Vol 15 - No. 4 - 2013

(iv) typical patterns in 18F-FDG-PET; and (v) disproportional atrophy involving medial, basal, and lateral temporal lobes and medial and lateral parietal cortices.5,7
If available, these biomarkers may be helpful in the distinction between AD and non-AD memory impairment. However, some alterations and biomarker constellations thought to be typical for AD may also be found in other neurodegenerative disorders, possibly hampering the discrimination between AD and non-AD etiology of memory impairment. For example, CSF Aβ42 values have been found to be decreased in AD as well as in LBD patients, and CNS amyloid accumulation can be observed in patients with AD and LBD using amyloid imaging.11 Hippocampal atrophy, as seen in many AD patients, is also found in patients with frontotemporal dementia (FTD), possibly due to hippocampal sclerosis related to this disease.12

Neuropsychological testing

During the diagnostic process for memory complaints, it is essential to objectively assess memory impairment, and the impact on activities of daily living, in order to discriminate between subjective memory impairment (SMI), mild cognitive impairment (MCI), and dementia (mild, moderate, or severe). Memory impairment may objectively be quantified on the basis of neuropsychological tests using age-specific standard values. Neuropsychological testing allows the differentiation of memory impairment with regard to age and education-specific normal values, eg, using the Wechsler Memory scale or the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) test. However, a normal score on such tests does not exclude memory impairment, since SMI has been revealed as a strong predictor of dementia and brain atrophy associated with dementia.13-17 In cases with SMI, or doubtful cases, repeated longitudinal testing to assess the course of the memory impairment is recommended.

Amyloid imaging

In 2004, a significant step towards an improvement of the ante-mortem diagnosis of AD and estimating the brain amyloid burden was made through the development of cerebral amyloid imaging using Pittsburgh compound B (PiB).18 Cerebral amyloid was not only detected in AD patients, but also in patients with LBD, which is in line with neuropathological findings of increased amyloid pathology in LBD.19 In MCI patients an AD-like binding pattern of PiB was found in 60% of the patients20 and in longitudinal studies MCI patients who were PiB-positive had a higher risk of developing AD than patients with PiB-negative MCI.21 In cognitively healthy elderly patients, amyloid load was related to hippocampal atrophy and cognitive function, possibly indicative of preclinical AD.20 Recently AD and Parkinson’s disease–related dementia could successfully be distinguished due to different patterns of PiB binding.22 Since amyloid PET methodology is still under development, and the interpretation of results may be difficult in a single subject, criteria on the appropriate use of amyloid PET have been recently defined.23 In a recent study of a cohort of 64 clinically diagnosed AD patients, 14 of which were PiB-negative, CSF, MRI, and 18F-FDG-PET biomarkers were used to review the diagnosis.24 The results suggested argyrophilic grain disease in three cases, FTD in three cases, neurofibrillary tangle-predominant dementia in one case, and AD in two cases; however, there were no identified cases of LBD. From these findings it may be concluded that the use of single biomarkers may be misleading in the distinction between AD and non-AD, and the use of multiple biomarkers may reveal a clearer pattern that links to a specific underlying pathology.

The distinction of AD and non-AD pathology using amyloid PET still seems to be limited with respect to single-subject analyses for clinical use; however, amyloid PET is a valuable research tool to study brain amyloid burden in vivo.

Other imaging and cerebrospinal fluid biomarkers

Other biomarkers that may help distinguish AD from non-AD related memory impairment include the CSF biomarkers Aβ42, t-tau, and p-tau, as well as imaging biomarkers such as MRI volumetry and 18F-FDG-PET. In patients with MCI, these core AD biomarkers have been shown to be helpful in the prediction of the later development of AD especially in cases with biomarker alterations typical for AD, while atypical biomarker constellations, possibly related to non-AD MCI, did not allow a clear prediction of the course of MCI.25

Hippocampal atrophy is one of the early signs of AD, and atrophy patterns including the hippocampus have
been proposed as a biomarker. Automated hippocampus volumetry may facilitate the use of the hippocampal volume as a clinical biomarker, since the value of MRI volumetry as a diagnostic marker seems to be highly dependent on the technical accuracy and standardization of the procedure. Although decreased CSF Aβ42 and increased t-tau and p-tau have been described as reliable biomarkers to distinguish AD from normal controls or patients without neurodegenerative disease, diagnostic accuracy may not be sufficient, as CSF biomarker constellations typical of AD have also been found in LBD, depression, and FTD. New biomarkers such as CSF proteomic patterns are under investigation to improve the distinction of AD and non-AD neurodegeneration.

Neurodegenerative diseases

In light of the common biomarker featured in AD and non-AD dementia, a recent neuropathological study looked at patients diagnosed with clinical AD according to the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association). In a substantial number of cases (119 out of 533) the underlying neuropathological diagnosis did not meet neuropathological criteria for AD. The main AD “mimics” were: LBD, neurologically insufficient AD, vascular disease, FTD, and hippocampal sclerosis. Neuropathological features of more than one neurodegenerative disease are frequently found in dementia patients, eg, mixed dementia (vascular lesions and AD pathology) or AD pathology with cerebral Lewy bodies. In a large population-based neuropathological study on elderly patients without dementia nearly all subjects exhibited AD pathology; 75% had cerebral amyloidosis, 13% had Lewy bodies, and 46% had cerebral micro- or macro-infarctions.

Lewy body dementia

LBD, after AD, is the second most common neurodegenerative cause of dementia. Although there are clear clinical symptoms in the advanced stages of LBD that make it relatively easy to distinguish from AD (Parkinson’s syndrome, fluctuating alertness, optical hallucinations), it may be difficult to discriminate AD from LBD in the early stages. The core neuropathological finding is the abundance of intracellular Lewy bodies consisting of α-synuclein in the affected brain regions. Atrophy, affecting especially the cornu ammonis (CA) 1 region of the hippocampus and the subiculum, could be observed in patients with mild LBD using MRI volumetry, although this was less pronounced than in AD of the same stage. These findings may explain deficits of declarative memory often found in LBD. Entorhinal cortex atrophy typical of AD has also been described in LBD, although has been found to be less pronounced in the latter. In later stages of the disease a clearer pattern of atrophy distinct from AD could be observed, with more pronounced atrophy of temporal lobe structures in AD than in LBD. The posterior cingulum island sign in the 18F-FDG-PET seems to be an exclusive feature of LBD and may help in the distinction from AD if present. Clinically, neurological signs of Parkinsonism may be absent in the early stages of the disease. In a community-based longitudinal neuropathological study, as described above, Lewy bodies were found in 13% of the elderly population, even without dementia. Cognitive decline, including episodic memory decline, was related to cortical Lewy body pathology independent of coexisting AD pathology in a large neuropathological study.

Vascular dementia

Vascular cognitive impairment, or vascular dementia, due to vascular brain lesions may also lead to an amnestic syndrome resembling AD, and may clinically mimic AD. Neuropathologically confirmed vascular lesions have been found to be related to episodic memory impairment in elderly individuals without dementia. In addition to multiple lesions that may be seen in multi-infarct dementia, single strategic lesions, eg, in the hippocampal network or thalamus, may lead to specific neuropsychological deficits. Vascular lesions may cause cognitive deficits by themselves or contribute to other neurodegenerative processes. It is under discussion as to whether vascular lesions and white matter hyperintensities may foster AD pathology and accelerate the course of AD.

Frontotemporal dementia

FTD, or frontotemporal lobar degeneration, comprises a group of degenerative diseases: behavioral variant of FTD (bvFTD), primary progressive aphasia, and semantic...
The abundance of AD variants in elderly patients with Huntington’s disease may also account for different patterns of impairment of neuronal networks, including the frontal and anterior temporal lobes in FTD patients. The abundance of AD variants (e.g., frontotemporal variants) and AD-typical patterns of biomarkers found in one fifth of FTD patients makes the differentiation between FTD and AD even more difficult. A recent study showed that hippocampal volume measurement was not a sufficient biomarker to distinguish bvFTD from AD, and found similarly reduced hippocampal volumes in bvFTD and AD. Hippocampal volume reduction may be due to hippocampal sclerosis observed in a large proportion of bvFTD patients.

**Hippocampal sclerosis**

Hippocampal sclerosis is a common neuropathological finding in the elderly, has been shown to be present in one fourth of elderly autopsy cases, and is the leading neuropathological diagnosis in nearly 2% of cases previously diagnosed as having AD. Hippocampal atrophy is even more pronounced in hippocampal sclerosis than in AD. The pathophysiology of hippocampal sclerosis has not entirely been understood, but it is common in patients with temporal lobe epilepsy and may present clinically as memory impairment. Hippocampal volume loss, as well as reduction of other brain regions, is present in patients with temporal lobe epilepsy and is related to epilepsy chronicity. Hippocampal sclerosis may also accompany transactive response DNA binding protein 43 kDa (TDP-43) associated FTD, which may account for a hippocampal volume loss. Elderly patients with hippocampal sclerosis may be misdiagnosed as having AD, since the clinical features of memory loss may be identical to memory loss in AD.

**Memory impairment due to other neurological diseases**

Impairment of episodic memory and other cognitive functions is a common feature in a range of neurological disorders such as Parkinson’s disease, Huntington’s disease, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, or limbic encephalitis. In most of these diseases, clinical investigation and brain imaging will lead to the correct diagnosis of non-AD memory impairment, and the syndromal overlap with AD is usually smaller than in other neurodegenerative disorders.

Awareness of cognitive symptoms in Parkinson’s disease is growing. Approximately one fourth of nondemented patients with Parkinson’s disease were identified as suffering from MCI, with the majority suffering from the amnestic subtype. In a recent MRI study on hippocampal volume and microstructural alterations using diffusion tensor imaging analyses, declarative memory impairment was associated with microstructural alterations, but not hippocampal total volume in nondemented Parkinson’s disease patients.

In patients with epilepsy, hippocampal atrophy has been described in patients with transient amnesia and hippocampal sclerosis associated with epilepsy may also lead to an amnestic syndrome possibly resembling AD in elderly patients. Atrophy observed in patients with epilepsy may be partly reversible. Limbic encephalitis is a rare but treatable neurological, autoimmune, often paraneoplastic, disorder that mainly presents with memory impairment, temporal lobe seizures, or affective symptoms. Damage of the medial temporal lobe is common in limbic encephalitis; typical hyperintensities of the temporal lobes are seen in the cranial MRI and may cause severe reduction of memory function.

**Memory impairment due to general medical conditions**

Apart from neurodegenerative or neurological diseases, general medical diseases may also lead to an impairment of memory, e.g., diabetes mellitus, obstructive sleep apnea (OSA), pregnancy, or menopause among others (for an overview see ref 6). Brain atrophy, particularly microstructural hippocampal alterations seen using diffusion tensor imaging, has been associated with diabetes, independent of vascular lesions. Hypoglycemia due to insulin therapy may also lead to structural brain damage and memory impairments in patients with type 1 diabetes. The possible relationship between pathologial glucose tolerance and AD has been under investigation. Recently, no association has been found between amyloid plaque load and pathological glucose tolerance in a large prospective longitudinal neuropathological study. Fatigue and memory problems are often reported in patients with OSA. Neuropsychological testing may...
reveal a retrieval deficit of episodic memory with normal intact maintenance, recognition, and forgetfulness, as well as a decreased overall performance in procedural memory, and impairment of specific working memory capabilities despite normal short-term memory. Hippocampal volume may also be reduced in OSA. Continuous positive airway pressure (CPAP) treatment has been shown to improve cognitive function in OSA. Memory function may also be influenced by hormonal alterations, e.g., during pregnancy and menopause. Pregnant women were found to have mild memory alterations in regard to immediate and delayed verbal episodic memory tasks compared with non-pregnant women. In menopausal women, both estradiol and testosterone levels were related to semantic and verbal episodic memory performance. In both pregnancy and menopause, the impairment of memory performance is normally mild and does not meet the criteria for mild cognitive impairment or dementia.

Memory deficits due to mental disorders

Cognitive symptoms are associated with a number of mental diseases, e.g., depression, post-traumatic stress disorder, or schizophrenia. Mild psychiatric symptoms and subjective memory complaints require neuropsychological tests to objectively assess the amount of impairment. Mood disorders in the elderly are often accompanied by cognitive deficits independent of AD; however, depression may accompany AD as an early symptom, possibly complicating the diagnosis. In a recent study, deficits in a broad range of cognitive domains, including semantic and episodic memory, were related to depression in elderly patients. Depressive patients also suffer from structural abnormalities such as reduced hippocampus volume, which may be reversible during remission. The AD biomarker CSF Aβ42 has also been found to be decreased in elderly patients diagnosed with a depressive disorder, pointing to an overlap of depression and AD that has not been fully elucidated.

Traumatic or toxic causes of memory impairment

Traumatic or toxic causes of memory impairment comprise traumatic brain injury (TBI), cerebral hypoxia, e.g., due to cardiac arrest, and impairment related to alcohol or drugs. TBI survivors often suffer from long-term memory impairment as a consequence of the insult. Mild TBI leads to an impairment in declarative memory, compared with controls, in the post-acute phase within 6 weeks after the trauma; memory function was related to medial temporal lobe activation in a functional MRI paradigm. Even 1 year after mild TBI, cognitive deficits and memory problems may be found in affected persons as a long-term consequence. Another possible consequence of single or repeated TBI may be the development of a chronic traumatic encephalopathy, which may also lead to dementia. Neuropathological findings after TBI share similarities with findings in AD, and TBI may lead to a pathophysiological cascade including axonal damage, increase of Aβ42 production, and decrease of long-term potentiation. In mild TBI, a pattern of change in white matter integrity similar to that found in AD was recently found. Biomarker studies revealed that AD CSF biomarkers may also be altered in TBI, e.g., increase of CSF tau and Aβ peptides early after severe TBI, while their diagnostic and prognostic value is still uncertain. Cardiac arrest may lead to gray matter reductions in the cingulate cortex, precuneus, insular cortex, posterior hippocampus, and dorsomedial thalamus, which account for a broad range of neuropsychological impairment in these patients, notably amnestic syndromes. Cerebral accumulation of Aβ42 was seen in short-term survivors of cardiac arrest as well as animal models, leading to the conclusion that brain hypoxemia after cardiac arrest may foster cerebral Aβ42 accumulation and AD pathology. However, it is unclear, if this finding further adds to the cognitive impairment seen in patients after cardiac arrest and cerebral hypoxemia. Alcohol-related cognitive impairment may resemble AD and hippocampal atrophy may be present. CSF biomarkers Aβ42 and tau may be helpful in the distinction of alcohol-related memory decline and AD in unclear cases. There is a broad range of medication that may cause or increase memory impairment, including benzodiazepines, psychotropics, opioids, antiepileptics, glucocorticoids, and anticholinergics. A recent study using data from the French pharmacovigilance database found a significant relationship between “memory loss” and benzodiazepines, benzodiazepine-like hypnotics, some antidepressants, analgescics, anticonvulsants, antipsychotics, and other drugs, pointing to the importance of a detailed drug history in patients who complain of memory deficits.
Conclusion

With the use of new imaging techniques and biomarkers of dementing diseases, knowledge is further growing on the pathophysiology of AD and non-AD memory impairment. Biomarkers that are recommended in current diagnostic guidelines will not only lead to a higher diagnostic accuracy, but also reveal overlapping pathologies between different neurodegenerative diseases, helping us to develop new concepts on AD and non-AD memory impairment. Although it is evident that mixed pathological entities of neurodegenerative and mental diseases are common, it is important to utilize existing diagnostic possibilities to aim to correctly identify the leading underlying cause of memory impairment and to take suitable therapeutic measures.

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