REVIEW ARTICLE

New Developments in the Diagnosis of Dementia

Gerhard W. Eschweiler, Thomas Leyhe, Stefan Klöppel, Michael Hüll

SUMMARY

Background: The terms “dementia” and “Alzheimer’s disease” are often wrongly used as if they were synonyms. Dementia is a clinical syndrome whose main element is memory impairment; it is due to Alzheimer’s disease in more than 75% of cases. Alzheimer’s disease, on the other hand, is a neuropathological entity that is characterized by a protracted preclinical phase followed by the onset of slowly progressive dementia.

Methods: We here review relevant literature that we retrieved by a selective Medline search (2005–2009), paying special attention to the early diagnosis of Alzheimer’s disease, its clinical manifestations, and its relevance in primary care.

Results: The early clinical manifestations of a dementing illness can be detected in primary care through the use of simple screening tests such as the mini mental state examination, clock drawing tests, and DemTect. A diminished concentration of Aβ-peptide and an increase of (phospho)-tau in the cerebrospinal fluid can suggest the presence of Alzheimer’s disease even before the onset of dementia: these substances are components of amyloid plaques and neurofibrillary tangles, which are the characteristic neuropathological lesions of Alzheimer’s disease. New types of morphological magnetic resonance imaging (MRI), and automated analysis of the images obtained, can improve the consistency of radiological assessment over the traditional visual method and thus enable more secure diagnosis.

Conclusion: The early, preclinical phase of Alzheimer’s disease involves what has been termed mild cognitive impairment and may last as long as five years until the onset of dementia. With the aid of the new biomarkers described here, the likelihood of diagnosing Alzheimer’s disease correctly in this phase can be raised above 80%. Early detection of Alzheimer’s disease before the onset of dementia provides an opportunity to study potential approaches for secondary prevention, which are now an object of intense clinical research.

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Alzheimer’s disease is the best-known of all medical eponyms, among physicians and the general public alike. Primary care practitioners today are increasingly likely to see patients in their ninth decade who wish to know, or whose families wish to know, whether an observed decline of memory might be the first sign of Alzheimer’s disease. In Germany, there now live more than one million persons suffering from dementia (1, e1); dementia affects one in twelve persons over age 65, and one in three over age 90. Beyond age 65, the prevalence of dementia doubles for every 5 years of life (e1).

The clinical syndrome called dementia consists, by definition, of an acquired impairment of memory and cognition that diminishes the sufferer’s ability to cope with activities of daily living and that has been present for at least six months (*Box 1*). The ICD-10 criteria for dementia specify that, for a diagnosis of dementia to be made, the presence of an impairment of consciousness (as in delirium or transitional syndrome) or a depressive disorder must be excluded. As the ICD-10 definition of Alzheimer’s dementia (AD) is rather imprecise, its DSM-IV definition still has a useful role in practice: this diagnosis, according to the DSM-IV, requires not just a severe impairment of memory, but at least one other type of cognitive deficit (aphasia, apraxia, agnosia, impairment of executive functions) of insidious onset, as well as the absence of other major cerebral, extracerebral, substance-induced, or psychiatric disease.

A current S3 guideline on dementia has just been issued by the German Society for Psychiatry, Psychotherapy, and Neurology (*Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde*, DGPPN) and the German Society for Neurology (*Deutsche Gesellschaft für Neurologie*, DGN) (e2), in collaboration with the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) and with the acquiescence of other relevant medical societies (e3). Previously, in 2008, a guideline was issued by the German College of General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin*, DEGAM) (e4). The current article is based on a selective review of literature retrieved by a Medline search dating from the years 2005 to 2009, as well as on major older publications and the guidelines of the German-language medical societies.

BOX 1

Alzheimer's dementia (F 00.0/1) as defined by the ICD-10 (WHO)

- Memory impairment
- At least one other cognitive domain impaired
- No delirium
- Resulting impairment of activities of daily living
- Present for at least six months

FIGURE 1

The typical progressive course of Alzheimer's disease, starting with a preclinical phase lasting several years before overt dementia develops. Patients in the preclinical phase often have (amnesic) MCI combined with hyposmia and/or a depressive mood disturbance. Impairment of activities of daily living appears at dementia onset; later on, further cognitive disturbances arise, such as aphasia, agnosia, apraxia, and/or impaired executive function. MCI = mild cognitive impairment

BOX 2

Mild cognitive impairment: criteria for amnesic MCI, according to Petersen 2004 (5)

- Memory impairment described by the patient, relatives, or both
- Cognitive impairment objectified by a neuropsychological test battery
- No impairment of activities of daily living
- Absence of dementia as defined by the DSM-IV criteria

The authors devote particular attention to issues of early diagnosis, screening, clinical manifestations, and the importance of dementia in primary care (key words: dementia, Alzheimer's disease, mild cognitive impairment (MCI), biomarkers in cerebrospinal fluid (CSF), imaging techniques).

The neuropathology of Alzheimer's disease

60% of demented patients manifest the typical pathological findings of Alzheimer's disease—amyloid deposits and neurofibrillary tangles—, without any other abnormalities in the brain, while a further 15% have these findings accompanied by brain damage of vascular origin. Dementia due to vascular lesions alone is rarer, accounting for fewer than 15% of cases (e2). Lewy-body dementia (usually accompanied by parkinsonism and marked fluctuations of consciousness) and frontotemporal lobar degeneration (FTLD) each account for about 5% of cases of dementia. According to epidemiological data, dementia is secondary to another disease in fewer than 5% of cases; causes in this category include endocrine disorders such as hypothyroidism and hyperparathyroidism (e2, e3).

Amyloid plaques and neurofibrillary tangles are the two lesions of Alzheimer's disease that can be seen under the light microscope; they were first described by Alois Alzheimer in a lecture in Tübingen, Germany, in 1906 (2). Amyloid plaques consist of a pathologically processed amyloid protein, the amyloid beta peptide (Abeta). Neurofibrillary tangles are formed by the aggregation of hyperphosphorylated tau proteins into paired helical filaments (PHF). Both of these processes are associated with loss of synapses and, ultimately, with death of neurons. Activated microglia (already described by Alzheimer as "small glial cells") are found in and around the amyloid plaques. Microglia, like the macrophages of other organs, are derived from the myeloid cell line. They may play a mixed role in dementia (3). On the one hand, they can be neurotoxic; on the other hand, they can also remove Abeta from the brain (3).

The progressive deposition of neurofibrillary tangles has been divided into six stages by Braak and Braak (4). The clinical diagnosis of Alzheimer's disease is usually made when the neuropathological changes have reached stage III to VI. In the transentorhinal stage (Braak stages I and II), the deposition is still restricted to the entorhinal cortex and the parahippocampal cortex, which play a role in the formation of memories and the identification of odors. Disturbed function in these areas probably underlies early clinical changes of Alzheimer's disease, including delayed memory recall and odor identification (e5).

Mild cognitive impairment (MCI)

The identification of Alzheimer's disease before Alzheimer's dementia arises would be a precondition for the development of (as yet nonexistent) interventions to prevent, or at least delay, progression of the disease to dementia. The appearance of overt dementia is

TABLE

Clinical aspects of age-associated cognitive decline, depression, mild cognitive impairment (MCI), and dementia

	Age-associated cognitive decline	Depression	Mild cognitive impairment	Dementia
Subjective worry about forgetfulness	common	very common	usual	possible in early stage
Worry among other family members	absent	worry about lack of motivation and mood disturbance	common	always present
Objectifiable memory impairment	semantic memory preserved, long-term memory impaired	common	obligatory according to the definition of 2004 for the amnesic subtype	marked
Disturbances in other cognitive domains	impaired attention and speed of cognitive performance	generalized complaint of inadequate performance ability	depending on the subtype, deficits of language, of planning, and of spatial perception	marked, with impairment in activities of daily living
Sensory disturbances	often mild visual and auditory impairment	age-associated	often, impaired identification of odors	usually, impaired identification of odors
Functional impairment	none	always present in severe depression	no impairment in activities of daily living	always present
Behavioral abnormalities	none	often inhibition or agitation	often, brooding and/or depressed mood	usually agitation, depressed mood, anxiety, apathy
Structural abnormalities	age-associated; often, white-matter lesions	age-associated; often, white-matter lesions	mild mesial temporal atrophy, white-matter lesions	commonly, atrophy and/or marked white-matter lesions
Typical chief complaints	Everything was better before.	I just can't do anything anymore.	I have become more forgetful lately.	He/she can't cope any more. (Statement of relative)

modified and extended from Ellisson, JAMA 2008 (25)

preceded for several years by a stage of mild cognitive impairment (MCI), which is defined by the criteria of Petersen (5). Further clinical abnormalities (depressive episodes and impaired identification of odors) may help the clinician detect preclinical Alzheimer's disease (Figure 1).

There is current debate over the significance that ought to be attached to patients' own complaints of impaired memory as a potential predictor of incipient dementia (e6). Persons aged 50 to 70 with subjective memory impairment often have normal findings, even on highly refined neuropsychological tests. Such persons often complain of stress and show more somatoform and depressive symptoms than other persons, yet they do not develop dementia after multiple years of observation (6). On the other hand, some persons over age 70 without symptoms of stress or subclinical depression, who possess a good capacity for self-observation, and who report a loss of memory despite normal findings on screening tests, may indeed go on to develop dementia in the ensuing years (7).

If the patient or a third party report impaired memory, then psychological testing should be performed to obtain objective and quantitative findings that can be compared with those of normal individuals of the same

age and educational status. Poor test performance in the absence of other explanatory factors, e.g., an attention deficit iatrogenically induced by the use of antihistaminic or anticholinergic drugs, is taken as evidence of an amnesic MCI, as defined by the Petersen criteria of 2004 (Box 2; for differential diagnosis, see the Table). There are, however, other definitions of MCI and its subtypes that are currently in use (5, 8, e2).

The risk that MCI will progress to dementia within one year is approximately 10% to 15%, and even higher—up to 25%—if other conditions such as depression, sleep disorders, and damaging use of benzodiazepines or alcohol can be rigorously excluded (8, 9). Clinical studies reveal that progression to dementia usually occurs within a few years of the diagnosis of MCI, yet half of persons with MCI do not go on to develop dementia even over the long term (10 years), especially when MCI is diagnosed before age 70 (e7). The prevalence of MCI among patients over age 75 in a general medical practice is 15% to 20% (10). The strongest predictors for MCI progression are the extent of cognitive impairment revealed by more extensive testing (e8) and the findings of CSF examination and positron emission tomography (PET). The most important genetic factor for late-onset Alzheimer's disease is the

Typical clock drawings by patients with early Alzheimer's dementia. The patients were asked to draw the face of a clock showing ten minutes past eleven o'clock within a pre-drawn circle. The minute hand can no longer be correctly placed (15); reproduced with the kind permission of the publisher, SAGE

FIGURE 2

apo-E epsilon-4 allele (11), which is carried by about half of all demented patients. Nonetheless, genotyping to detect this allele is not currently performed in clinical practice, as the result would have (as yet) no therapeutic implications. Only 0.5% of patients with Alzheimer's dementia suffer from familial Alzheimer's dementia (FAD), a disorder that becomes clinically manifest before age 60 and can be caused by a number of single-gene mutations (11).

Diagnostic evaluation for (amnesic) MCI requires psychological testing and is, therefore, time-consuming. It is best performed in a specialized memory clinic where follow-up testing can also be performed. Many such clinics offer patients the opportunity to participate in trials of interventions, both pharmacological and non-pharmacological, that might delay the progression of MCI to dementia.

The practical approach to diagnostic evaluation

A two-step approach to the diagnostic evaluation of dementia has proved useful in both general and neuropsychiatric practice (12, e2–e4). First, it is determined whether the patient has the dementia syndrome, as defined by the ICD criteria (*Box 1*). Second, the etiology is narrowed down. The initial diagnostic step is the systematic collection of all relevant medical historical and clinical data (12):

- the patient's own description of the symptoms and past history
- the history obtained from third party sources
- the findings of the neurological and general medical examination
- the findings of the psychiatric examination
- screening tests of cognitive function
- laboratory tests
- imaging studies of the brain
- neuropsychological tests

The Mini-Mental State Examination (MMSE)

The MMSE (e9) tests various types of cognitive performance and takes 10 to 15 minutes to complete. One of its elements is a list of only three words, which the subject is asked to recall a few minutes later. Nonetheless, the MMSE is widely used to label the severity of dementia of Alzheimer's type (mild, 20 to 26 points; moderate, 10 to 19 points; severe, 9 points or less) (e3). When used in general practice, the MMSE has been found to have 78% sensitivity, 88% specificity, a positive predictive value of 54%, and a negative predictive value of 96%. When used in specialized settings and memory clinics, it has 80% sensitivity, 81% specificity, a positive predictive value of 86%, and a negative predictive value of 73% (13). Thus, the main usefulness of the MMSE in general practice is as a test for the exclusion of dementia. Its use as a single measure in specialized settings is not justifiable, in view of the high prevalence of mild dementia of various types. The MMSE cannot be used to diagnose MCI.

DemTect

The DemTect™ contains a ten-word list for later recollection (thus, a much longer list than the MMSE) and avoids direct questions regarding place and time. It takes 8 to 12 minutes to complete and is thus moderately time-consuming; it does not contain a drawing task. Its sensitivity is good: a validation study revealed 85% sensitivity (with a cutoff of 13 points) for mild cognitive impairment, and 83% sensitivity (with a cutoff of 11 points) for Alzheimer's dementia (14). This test is now well established in Germany, but is hardly used in other countries (e10).

The clock drawing test

The clock drawing test is often used as an additional screening instrument for patients suspected of having Alzheimer's disease (*Figure 2*). In order to draw a

Figure 3: Morphological MRI scans subjected to automated image analysis. Color coding is used to indicate the brain areas that are particularly informative for the computer program with regard to the differential diagnosis of Alzheimer's disease from normal aging. The blue and green areas are mainly in the hippocampus and are reduced in size in the patients with Alzheimer's disease; modified from Reference 20, Diagram 2; reproduction rights belong to the author, S. Klöppel

clock properly, an individual needs intact semantic memory, spatial perception, visuoconstructive skills, and executive functions (e11). When used in specialized outpatient clinics, the clock drawing test has 90% sensitivity, 56% specificity, a positive predictive value of 84%, and a negative predictive value of 69% (e12). It is probably not useful for differentiating between mild cognitive impairment and Alzheimer's dementia (AD) (e13, e14).

Many different scoring systems focus on the integrity of the clock face, the presence of two hands for the hours and minutes, practical problems in drawing, and conceptual problems. A detailed analysis of faulty placement of the hands is generally not performed (e15). A neuropsychological study carried out by the authors (15) revealed differences between patients with early AD and normal control persons, particularly involving deficient drawing and placement of the minute hand (Figure 2). Only patients with progressed AD have problems drawing the clock face, as well as problems with the drawing, placement and reading of the hour hand (15). The usefulness of this "minute-hand phenomenon" has not yet been validated in other types of dementia.

Identification of odors

In a number of prospective studies, impairment of odor identification has been found to predict a decline of memory (e16, e17), both among healthy elderly persons and among patients with MCI. The test involves holding an odor stick (16) or rub-off card containing an artificially produced odor under the subject's nose (brief smell identification test, BSIT) (e16, e17). The test is simple and fast, can be delegated, and finds ready acceptance among patients, as most of the odors tested are pleasant ones. Elderly persons with hyposmia (i.e., performance in the 10th percentile or below) were found to suffer twice as much deterioration of semantic memory in four years as comparably aged persons with excellent olfactory identification (90th percentile or

above) (e16). A test of persons with MCI involving a total of 137 subjects revealed that their risk of developing AD within two years quadrupled, from 15% to 60%, if they could identify fewer than seven of ten proffered odors correctly (17). An autopsy study (e5) revealed a significant association between olfactory deficits and the frequency of neurofibrillary tangles in the entorhinal cortex and hippocampal CA1 region, but not elsewhere in the cerebral cortex.

History of depression

Moreover, a meta-analysis (18) revealed that persons with a history of major depression had approximately twice the risk of becoming demented. The pooled risk factor was 2.0 (95% confidence interval, 1.7–2.4) in case-control studies and 1.9 (95% confidence interval, 1.6–2.3) in cohort studies (18).

Extended neuropsychological testing with the CERAD battery

The CERAD-Plus battery (produced by the Consortium to Establish a Registry for Alzheimer's disease) is the standard neuropsychological testing battery that is used in memory clinics. It consists of all of the individual test components of the CERAD battery, with the addition of a phonemic fluency test (S-words) and the Trail-Making Test (A, B). It is an economical and highly valid means of assessing performance in various cognitive domains (e18). The main advantage of this multidimensional test battery is that it can distinguish among different types of MCI (8). A noteworthy aspect of the CERAD is that persons with amnesic MCI perform poorly in the delayed recall of words from a list (5) (Box 2). Patients with amnesic MCI are at the highest risk of progression to Alzheimer's dementia. Amnesic MCI, however, can also appear as a manifestation of severe major depression, or as a transient stage of vascular dementia. Non-amnesic MCI, without any other cognitive deficits, can be found as an early stage of frontotemporal dementia (8).

Imaging techniques

Once the cognitive deficits have been objectively demonstrated, brain imaging should be performed. Although computerized tomography (CT) of the head does enable judgments of the pattern of brain atrophy and of vascular changes, magnetic resonance imaging (MRI) affords markedly higher resolution without exposing the patient to ionizing radiation. According to the guidelines of the DGN and DGPPN (e2, e3), MRI should be used in younger patients, in preference to CT.

Automated techniques for the analysis of magnetic resonance images ("support vector machines") have been developed in specialized centers and will shortly be available in MRI scanners of the types used for routine patient care. Such techniques involve computer programs that learn how to distinguish among different entities, e.g., Alzheimer's disease, frontotemporal dementia, and normal aging, on a morphological basis alone (Figure 3) (19, 20). The procedure is entirely automatic, but the intergroup differences must first be "learned" on the basis of a large, well-defined data set. Programs of this type can be integrated into already existing software packages for image visualization and could easily be made available outside of specialized centers. Data from multiple centers have already been successfully combined in a number of studies (20, 21, e19). The use of such techniques for prognosis of conversion would also be of clinical interest: for example, among patients with MCI, a positive predictive value of 80% has been found for the differentiation of converters and non-converters to Alzheimer's dementia (21).

Furthermore, the techniques of single photon emission computerized tomography (SPECT) and positron emission tomography (PET) can be used to display glucose metabolism directly, and thus to provide an indication of synaptic function or of amyloid deposition (e20, e21). These techniques will continue to be available only in specialized centers because of the costs involved and the need for a cyclotron nearby for the generation of unstable radioactive isotopes.

Laboratory testing of cerebrospinal fluid and blood serum

Laboratory testing of the cerebrospinal fluid (CSF) has been found to be a reliable way of obtaining additional supportive evidence for a diagnosis of Alzheimer's disease. Particular attention must be paid to the use of proper materials for the pre-analytic handling of CSF specimens, because many types of surface will strongly absorb Abeta peptide. The determination of the quotient of Abeta 42 to Abeta 40, and the finding of an elevated level of overall tau protein or of phospho-tau, have been found to have more than 85% sensitivity and specificity (e21–e25). Furthermore, a Swedish group (22) has been able to show that MCI patients with low Abeta and high phospho-tau are 17 times as likely to progress to AD as are MCI patients without this CSF profile. A combination of structural abnormalities that are visible by MRI with CSF abnormalities of this type

raises the "likelihood quotient" to as high as 19.2 (23). This is the first study documenting the ability to diagnose Alzheimer's disease before the onset of dementia with clinically acceptable sensitivity and specificity (greater than 80%). Thus, it is already possible to characterize a high-risk group in the preclinical stage of Alzheimer's disease.

Future prospects

In a groundbreaking publication (24), new diagnostic criteria for Alzheimer's disease have been proposed for incorporation into future editions of the DSM and ICD (DSM-V and ICD-11), requiring not only an insidiously progressive impairment of episodic memory, but also supporting evidence from a biomarker of some type (atrophy visible by MRI, hypometabolism revealed by PET, low Abeta and/or high phospho-tau levels in the CSF, or a strongly positive family history). This type of categorization makes scientific sense, but it would lead to a marked elevation of costs for diagnostic testing in the clinical setting.

Alzheimer's disease is present in the individual patient for a number of years before dementia arises. Advances in early diagnosis (CSF analysis, neuropsychological testing, imaging studies) now make it possible, for some persons with mild cognitive impairment (MCI), to detect the presence of Alzheimer's disease before dementia becomes manifest. This type of early diagnosis creates an ethical dilemma by identifying a disease for which there is, as yet, no treatment, but it is also a prerequisite for the study of treatments that might modify the course of the disease. Over the next few decades, research in this area will center on the development and evaluation of potentially useful therapeutic interventions.

Conflict of interest statement

Dr. Klöppel states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

KEY MESSAGES

- Patients'—and third parties'—complaints of forgetfulness should be taken seriously.
- A number of different psychological tests, with varying degrees of comprehensiveness, can be used to obtain objective data that permit a judgment whether dementia is probably present or probably absent.
- The diagnosis of mild cognitive impairment (MCI) can only be made after extensive testing, which is available in specialized memory clinics.
- In patients with MCI who have a certain pattern of findings on ancillary tests (CSF tests and imaging studies), dementia can be predicted to develop within a few years with a probability greater than 80%. Thus, it is already possible to speak of persons with Alzheimer's disease who have not yet developed overt dementia.

Prof. Eschweiler conducts clinical studies on Alzheimer's dementia for the ACI-Immune and Janssen-Alzheimer-Immunotherapy companies.

PD Dr. Leyhe has received lecture honoraria from the Novartis and Merz Pharmaceuticals companies, as well as fees for translating rating scales from Astra Zeneca, sponsoring of phase II and III drug trials from GlaxoSmithKline and Astra Zeneca, and reimbursement of travel expenses from Merz Pharmaceuticals. He belongs to an Expert Forum on Alzheimer's Disease sponsored by Merz Pharmaceuticals and receives reimbursement of expenses incurred in this capacity.

Prof. Hüll has received outside support from Wyeth/Pfizer and Medivation for drug-approval studies, as well as lecture honoraria from Wyeth/Pfizer and Merz.

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