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Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI)

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Abstract

With the increasing life expectancy in developed countries, the incidence of Alzheimer's disease (AD) and thus its socioeconomic impact are growing. Increasing knowledge over the last years about the pathomechanisms involved in AD allow for the development of specific treatment strategies aimed at slowing down or even preventing neuronal death in AD. However, this requires also that (1) AD can be diagnosed with high accuracy, because non-AD dementias would not benefit from an AD-specific treatment; (2) AD can be diagnosed in very early stages when any intervention would be most effective; and (3) treatment efficacy can be reliably and meaningfully monitored. Although there currently is no ideal biomarker that would fulfill all these requirements, there is increasing evidence that a combination of currently existing neuroimaging and cerebrospinal fluid (CSF) and blood biomarkers can provide important complementary information and thus contribute to a more accurate and earlier diagnosis of AD. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is exploring which combinations of these biomarkers are the most powerful for diagnosis of AD and monitoring of treatment effects.

Keywords

Positron-emission tomography; Single photon emission tomography; Magnetic resonance imaging; Biochemical biomarker; Genetic biomarker

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1. Introduction

Age is a major risk factor for neurodegenerative diseases in general but particularly for dementia and its most common form, Alzheimer's disease (AD). More than 4 million people in the United States suffer from dementia, which costs the US economy more than $100 billion per year. Because of the increasing life expectancy, the incidence of dementia is expected to double during the next 20 years [1], and then the cost will well exceed $380 billion per year. This prospect has led to a considerable effort to unravel the pathophysiologic mechanisms of AD and thus allow for the development of an effective treatment against this devastating disease. Over the last years, significant progress in the understanding of some of the pathophysiologic mechanisms involved in AD [2] has been made. Histopathologically, AD is characterized by the accumulation of senile plaques and neurofibrillary tangles. Whereas the senile plaques consist mainly of β-amyloid peptides, the fibrillary tangles consist of abnormal hyperphosphorylated insoluble forms of the τ-protein. Not much is known about how these 2 lesions influence each other, eg, if the hyperphosphorylation of τ-proteins is triggered by the accumulation of β-amyloid oligomers (amyloid cascade hypothesis) or if a defect in the τ-protein leads to an accumulation of β-amyloid (τ and tangle hypothesis). Most of the currently available evidence supports the former hypothesis. Both lesions can exert direct and indirect neurotoxic effects and promote neuronal death by inducing oxidative stress [3,4] and inflammation. While the pathway of the neurofibrillary tangles is very precise, ie, starts in the entorhinal cortex from where it progresses to the hippocampus, the limbic system, and finally to neocortical regions, the amyloid deposition seems to be more heterogeneous and random starting first in neocortical regions before it affects allocortical regions and diencephalic structures [2,5-9]. The analysis of the amino acid sequence of β-amyloid allowed for the identification of the gene encoding its precursor the β-amyloid precursor protein (APP) on chromosome 21 and thus for the identification of the first series of mutations associated with increased amyloid production and AD. However, such mutations account only for a small percentage of AD cases. The majority of AD patients suffer from sporadic AD for which several risk factors in addition to age have been proposed and are currently being explored, eg, apolipoprotein Eε-4 (Apoε-4), hyperhomocysteinemia, hyperlipidemia, and disturbances of the neuronal insulin signal transduction pathway [10]. Although the etiology of AD is still not completely clear, the increasing knowledge about some of most important pathomechanisms in AD allows now for the first time to develop drugs aimed at modifying particular aspects of the AD disease process, eg, antiinflammatory drugs, statins, antioxidants, acetylcholinesterase inhibitors, γ and β secretase inhibitors, β sheet disruptors, immunotherapy, neuro-protective agents, or neuroregenerative treatments (see [2,7,11–13] for more detailed reviews). Some of these compounds showed promising results in animal models and are currently being tested in clinical treatment trials in AD patients.

2. Early diagnosis of AD and monitoring of treatment efficacy

The possibility of an effective treatment against AD in the near future creates new challenges for clinical AD research. Probably the most important challenge is the necessity of an accurate diagnosis of AD during life, because other forms of dementia may not respond well, or not at all, to an AD-specific treatment. The definite diagnosis of AD requires not only the presence of severe cognitive deficits but also autopsy confirmation of the presence of the typical AD histopathologic changes in the brain. In a living person, the diagnosis of possible or probable AD is based on the presence of cognitive deficits in 2 o r more domains severe enough to interfere with normal daily functioning. Although the sensitivity of standardized clinical criteria like the Diagnostic and Statistical Manual of Mental Disorders, and the National Institute of Neurological, Communicative Disorders, and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) definitions is rather high, ie, 81% for probable AD and 93% for possible AD, their specificity is lower, ie, 70% for probable AD and 48% for possible AD.

This low specificity likely reflects the fact that AD shares many clinical features with other forms of dementia [14].

Although clinical criteria for the diagnosis of AD in the middle to late stages of the disease may not be perfect, its diagnosis in an early or even asymptomatic stage is an even greater challenge. There is now increasing evidence that the molecular pathomechanisms of AD become active several years before neurons start dying and cognitive deficits manifest [15]. During this stage, an effective treatment of AD would have the most impact because the cognitive function might be preserved at the highest level possible. Consequently, there has been considerable interest in recent years to characterize the earliest clinical signs of the degenerative process that is likely to evolve to AD. This effort led to the development of the concept of mild cognitive impairment (MCI), which represents the transitional zone between normal aging and AD. Subjects with MCI are not demented but have significant deficits in one or more cognitive domains and have an increased risk of dementia [16]. Depending on which cognitive domains are most impaired, different subtypes of MCI can be distinguished. The subtype most relevant for AD is amnestic MCI, which is defined by the presence of subjective memory problems and an objective memory impairment relative to the appropriate reference group but otherwise normal general cognitive functions and largely preserved activities of daily living [17]. The annual conversion rate of amnestic MCI t o A D i s about 12% (range, 6% to 25%) per year, which is considerably higher than the conversion rate of 1% to 2% per year observed for age-matched non-MCI subjects. Histopathologic studies have found that MCI subjects, as a group, usually have intermediate levels of AD pathology compared with healthy controls and subjects with probable or possible AD [18]. However, whereas the concept of MCI i s very useful to identify a group of subjects with a high risk of conversion to AD, it includes also a non-negligible number of subjects whose disease never converts to AD or in whom a different form of dementia develops and thus would not benefit from an AD-specific treatment. Therefore, additional measures that might help to more reliably distinguish between these 2 MCI categories are needed.

Finally, given the different pathophysiologic mechanisms active in AD, it is likely that different treatment strategies will be effective at different stages of the disease, and not all treatment strategies will be effective in all patients. Therefore, it will be necessary to find inexpensive ways to monitor the treatment efficacy in individual patients. Currently, neuropsychological tests, eg, the cognitive subscale of the Alzheimer disease assessment scale (ADAS Cog) [19], are used to monitor disease progression or treatment efficacy. However, although these tests unquestionably reflect an important aspect of disease progression, ie, functional impairment, they have also several limitations. One major problem is their relatively poor test–retest reliability (intraclass correlation coefficients circa 0.5 to 0.8) which probably reflects the influence of other factors on cognitive performance, such as the patient's mood, the presence of other illnesses or major life events, side effects of other treatments, and learning effects in repeated tests. The relatively low reliability of these measures reduces their statistical power in clinical trials and complicates the interpretation of cognitive changes in individual patients. Another major limitation of cognitive and functional outcome measures is their inability to distinguish between treatments that modify the disease process in AD and treatments that are purely symptomatic, ie, enhance cognitive performance but do not influence the neurodegenerative process. Finally, it is possible that a treatment modifies the disease progression of AD, but its effects on cognition and functionality may only become apparent after delay and, thus, it might be dismissed wrongly as ineffective.

Because of these limitations of clinical and neuropsychological measures for diagnosis and monitoring of treatment effects, there has been considerable effort recently to identify additional biomarkers that might provide complementary information.

2.1. Characteristics of ideal biomarkers for diagnosis and monitoring of treatment effects in AD

The characteristics of an ideal diagnostic biomarker for AD have been summarized as follows [20]:

1. The biomarker should detect a fundamental feature of the pathophysiologic processes active in AD.
2. The biomarker should be validated in neuropathologically confirmed AD cases.
3. The biomarker has to be precise, ie, able to detect AD early in its course and distinguish it from other dementias.
4. The measurement of the biomarker has to be reliable, minimally invasive, simple to perform, and inexpensive.

All these criteria are also desirable for an ideal prognostic biomarker, ie, a biomarker to monitor disease progression and treatment effects. Such a biomarker should also fulfill the following criteria:

1. The relationship between the biomarker and a disease parameter meaningful to the patient, eg, cognitive function, should be clearly established.
2. The biomarker should be representative of the stage of AD at which the drug is supposed to have its maximal effect, eg, if the drug effect is maximal during the preclinical stage, the outcome measure should reflect the disease process in the preclinical stage.
3. The biomarker should be representative of the supposed mechanism of action of the drug, eg, a measure of amyloid burden if drug is supposed to prevent amyloid accumulation.

2.2. AD biomarkers

In addition to clinical or neuropsychological measures, there are 3 main categories of biomarkers that could provide essential complementary information: genetic biomarkers, biochemical biomarkers, and neuroimaging biomarkers.

2.2.1. Genetic AD biomarkers—Studies in twins have shown a heredity of AD of about 60% [21] suggesting that genetic factors play a significant role in the development of the disease. Currently, 3 genes have been identified on which mutations are thought to cause AD: the *APP* gene and the presenilin 1 and 2 genes. Mutations on these genes are associated with an increased β-amyloid production. They are autosomal dominant inherited and have a penetrance of nearly 100% [22,23]. However, although these mutations allowed important insights into the pathophysiologic mechanisms of AD, they account only for about 2% to 5% of all AD cases and are typically associated with its rarest form, familial early onset AD. Most forms of AD are sporadic and cannot be explained by simple Mendelian inheritance. Intensive genetic research has identified several potential susceptibility genes for this form of AD, eg, Apo-ε4, α2-macroglobulin low-density lipoprotein receptor-related protein, insulin degrading enzyme, and glutathione-S-transferase, but, until now, only Apo-ε4 has been established firmly as a susceptibility gene. However, only about 50% of the late-onset AD cases are homo- or heterozygous for Apo-ε4, and thus its use as diagnostic biomarker for AD is limited. Taken together, although there is evidence of an important genetic component in AD, the majority of AD is probably caused by complex interactions between one or more susceptibility genes and different environmental factors. Therefore, it is unlikely that genetic markers can take on a major role as a diagnostic biomarker for AD. However, it can be expected that a better

understanding of the role of susceptibility genes in the AD process will facilitate the early identification of subjects with a high risk for AD in later life.

2.2.2. Biochemical AD biomarkers—Since the identification of some of the key molecules of the AD disease process and thus the possibility to measure them in plasma and CSF, several of these molecules have been investigated regarding their potential use as diagnostic and prognostic biomarkers. Basically, there are 2 main groups: (1) biomarkers specific for the AD disease process, ie, with potential use as diagnostic and prognostic markers, and (2) nonspecific biomarkers, ie, biomarkers that measure an epiphenomenon of the AD process, eg, inflammation or oxidative stress, and could be used to monitor disease progression and treatment response. β-Amyloid protein, which exists in a 40-kD and a more fibrillogenic 42-kD form, which can be determined separately or as total amyloid, belongs in the first group. Elevated plasma and CSF β-amyloid levels have been found in familial AD. However, in sporadic AD, there is a broad overlap with the levels found in controls; thus, it cannot be used as a diagnostic biomarker of AD, and the lack of correlation with cognitive performance makes it unsuited as a prognostic biomarker [24]. τ-Protein is another biomarker that might be considered a specific AD biomarker and is determined either as total τ or as its phosphorylated form. In cross-sectional studies, total τ was found to be increased in AD compared with healthy controls. However, this increase is not specific for AD but is also found in other neurologic diseases associated with axonal damage and neuronal degeneration [25]. Furthermore, despite the increase of τ pathology in brain tissue with progressing AD symptomatology, longitudinal studies have failed to show a consistent, corresponding increase of CSF τ [26]. Therefore, its value as a prognostic biomarker is probably limited. The group of unspecific AD biomarkers contains markers of inflammation, eg, interleukin-1β and -6, tumor necrosis factor, α1 antichymotrypsin , and markers of oxidative stress, eg, F2- or F4-isoprostanes, 3-nitrotyrosine, 4 hydroxynonenal, or markers of cell membrane integrity, eg, sulfatides. Studies assessing inflammation markers as potential prospective biomarkers yielded no conclusive results, ie, there was either no difference between AD and controls, or both decreases and increases were found. To some degree, the inconclusive findings can be explained by the fact that CSF and plasma levels of these markers are low, the detection systems were not very sensitive, and that, particularly in cases of CSF studies, the control group often included patients with other neurological diseases [27]. In contrast, the results of the small number of studies evaluating the potential of markers of oxidative stress, particularly of isoprostanes and 3-nitrotyrosine, have been more encouraging. For example, levels of CSF isoprostanes were found to be correlated to the disease stage and to have a high specificity and sensitivity for discrimination between AD and controls, particularly if combined with a specific biomarker, eg, CSF τ protein [24,27,28]. However, larger studies are needed to validate the use of markers of oxidative stress as prognostic biomarker for AD [27]. Taken together, as of yet, no single ideal diagnostic or prognostic biochemical AD biomarker has been identified. However, with increasing knowledge about how these biochemical markers are influenced by the disease severity as well as concomitant diseases and treatments, it seems likely that a combination of those parameters with a reasonable diagnostic and prognostic specificity and sensitivity can be identified.

2.2.3. Neuroimaging AD biomarkers—Traditionally, imaging, particularly structural imaging, has been used to exclude potentially reversible brain processes mimicking the clinical symptoms of AD, eg, brain tumors or epidural hematomas. However, recently, the potential of neuroimaging, not only to improve the accuracy of the clinical diagnosis of AD but also to monitor disease progression and treatment effects, has been increasingly recognized. There are 2 main categories of neuroimaging: (1) structural imaging, which includes computer-assisted tomography (CT) and magnetic resonance imaging (MRI) and (2) functional imaging, which includes single photon emission tomography (SPECT) and positron-emission tomography (PET). Power analyses for the suitability of these techniques as outcome markers in treatment

trials were done for both modalities and found that both would allow for substantially smaller patient populations and shorter observation times than cognitive or clinical outcome measures currently do, eg, Alexander et al [30] calculated that 36 patients in each group (placebo or drug group) would be needed to detect a 33% treatment response with 80% power in a 1-year PET study and Jack et al [31] determined that 69 patients in each group would be necessary to detect a 25% treatment effect with 90% power in a 1-year MRI study. In comparison, at least 1277 patients in each arm would be necessary to detect a 25% treatment effect with 90% power with a cognitive outcome measure [29–32].

2.3. Structural neuroimaging

CT and MRI have been used for structural imaging in AD. Both modalities provide theoretically similar information, ie, the loss of synapses and neurons associated with the AD disease process leads to tissue atrophy, which can be detected by structural imaging. However, MRI has several advantages compared with CT: higher resolution, optimal angulation of the imaging plane, no bone hardening artifacts in the temporal lobe region, excellent gray–white matter discrimination, and identification of additional vascular lesions, particular small lacunes and white matter lesions. All of these factors probably contribute to the higher sensitivity and specificity of MRI (sensitivity, 80% to 94%; specificity, 60% to 100%) for the diagnosis of AD compared with CT (sensitivity, 63% to 88%; specificity, 81%) [33]. In contrast, CT has the advantage of shorter acquisition times, ie, it is less prone to motion artifacts, and its use is not restricted by metal implants or claustrophobia. Several studies have found a good correlation between degree of atrophy on structural imaging and histopathologically confirmed neuron loss and AD pathology [26,34,35] and between progression of cognitive impairment and atrophy rate [31,36]. Mirroring the progression of the tangle pathology, atrophic changes detected by structural imaging affect primarily the entorhinal cortex and hippocampus in the stage of MCI, progress to temporal and parietal lobes in AD, and finally involve the frontal lobes in late stages of AD [26,31,37–39]. Unfortunately, neuron loss and atrophy are not specific for AD but are also found in normal aging or other neurodegenerative diseases. However, large cross-sectional and longitudinal studies have shown that there are substantial qualitative and quantitative differences in pattern and rate of atrophy in aging and AD, which allow a differentiation of these 2 processes. For example, in normal aging, rates of global atrophy typically increase from 0.2% per year at age 30 to 50 to 0.3% to 0.5% per year at age 70 to 80 and affect frontal and parietal gray matter more than occipital and temporal gray matter, whereas changes in white matter are more diffuse [40]. In AD, brain atrophy rates are significantly higher, ie, up to 2% to 3 % per year [41,42] and so are atrophy rates of hippocampus (controls, 1.0% to 1.2% per year; AD, 3.0% to 5.9% per year) and in entorhinal cortex (controls, 1.4% to 2.9% per year; AD, 7.1% to 8.4% per year [31,37], ie, structures known to be affected early in AD. Although there is some overlap between the brain regions with the most pronounced atrophy in AD and atrophied brain in other types of dementia, degree of atrophy and pattern of involved brain areas seem to be sufficiently different to allow for a differentiation between various forms of dementia, eg, Lewy Body Disease, Parkinson's disease with dementia, fronto-temporal lobe dementia [43–50].

Changes in structural images are assessed by either qualitative visual assessment or by quantitative volumetric measurements of the entire brain or a structure of interest, ie, medial temporal lobe or hippocampus. Visual assessments use a scaling system, eg, no hippocampal atrophy, questionable atrophy, mild atrophy, and severe atrophy, to describe the degree of atrophy. Although this type of assessment has the advantage of being fast, it is also very subjective and is highly dependent on the rater experience. Quantitative volumetric measurements use either a single measure, eg, radial width of the temporal horn [51], or manually outline the whole structure of interest, eg, entorhinal cortex. However, particularly the latter method requires some expertise and is time consuming. Therefore, semiautomated

and automated computer-based methods, eg, tissue segmentation, global boundary shift integral method, voxel-based morphometry, or tensor-based morphometry, which in addition have the advantage to assess the entire brain and are not restricted to a single region of interest, are being used increasingly for volumetric studies.

2.4. Functional neuroimaging

Structural imaging detects AD at a stage at which the disease process is so far progressed that neurons are already irreversibly lost. Ideally, it should be possible to diagnose AD earlier, ie, at a stage at which neurons are impaired by the disease process but not yet irreversibly damaged and thus can be potentially salvaged [52]. Functional neuroimaging modalities, eg, perfusion measurements by hexamethylpropyleneamine oxime SPECT or measurements of brain glucose metabolism by 18F-fluorodeoxyglucose PET (FDG-PET), might be better suited to detect such an early stage, because neuronal function is tightly coupled with neuronal energy metabolism, which, again—at least under normal circumstances—is tightly coupled with brain perfusion. Despite using different radiopharmaceutical agents and instrumentation, SPECT and PET should, in theory, depict the same functional processes, ie, reduced neuronal function either caused by impaired neuronal functionality or by a reduced neuronal density. However, spatial resolution is typically poorer in SPECT than in PET (3 to 5 m m for PET, 7 t o 8 m m for SPECT), and SPECT might be more sensitive to concomitant cerebrovascular disease than PET [53,54]. Studies comparing both modalities in the same study population found that metabolic abnormalities in PET were more pronounced and widespread and correlated better with degree of dementia than the perfusion abnormalities in SPECT. Accordingly, they also provided a better distinction between controls and AD [55–57] (PET: sensitivity, 94%; specificity, 73% to 78% [58,59]; SPECT: sensitivity, 70% to 89%; specificity, 80% [60–62]. Studies correlating metabolic abnormalities to the histopathologic hallmarks of AD found a good correlation between regions with reduced regional metabolism and regional amyloid burden, except for the temporal lobes, but a poor correlation with neurofibrillary tangle staining [63,64]. However, some discrepancy between metabolic–perfusion abnormalities and histopathology has to be expected. The death of neurons in primarily affected regions, eg, entorhinal cortex, leads to loss of efferent and afferent connections with histopathologically normal regions and results in functional impairment of those regions [65,66]. Therefore, functional deficits are probably more widespread than structural deficits, particularly in the early stages of the disease [67]. The most prominent and consistent metabolic–perfusion abnormalities in MCI and early AD are found in the parieto-temporal areas and posterior cingulate, and in later disease stages also involve the frontal areas, whereas primary motor and visual areas and cerebellum, basal ganglia, and thalamus are relatively spared. Although there is a certain overlap of the hypometabolic regions found in AD with those found in other forms of dementia, the patterns of metabolic abnormalities are sufficiently different to distinguish AD from other dementias [53]. In contrast to structural studies, only a small number of PET studies [67–70] found hippocampal abnormalities in AD, which might be explained by the absence of MRI–PET coregistration, use of axial scan acquisition used by most PET studies, and a lower resolution in older PET cameras [53]. As can be expected, PET and SPECT correlate well with the degree and the progression of cognitive impairment in AD patients [30,71]. In this context, however, it is interesting to note that metabolic abnormalities similar to those observed in AD, ie, in parietotemporal, posterior cingulate were found in elderly but also young cognitively normal Apo-ε4 heterozygote subjects [32,72,73]. Structural studies showed corresponding findings in Apo-ε4 carriers, ie, volume reductions in structures typically affected early in AD, eg, hippocampus and temporal lobe [74,75]. This raises the question as to what degree those findings in Apo-ε4 carriers just represent a developmental abnormality associated with this genotype or are the earliest expression of the beginning AD disease process.

2.5. Other potential neuroimaging biomarkers

Recently, a variety of other imaging techniques, in addition to the conventional structural and functional imaging techniques, have been evaluated regarding their usefulness as diagnostic or prognostic biomarkers in AD. Some of these new techniques have shown very promising results in small studies. However, further studies allowing for rigorous assessment of test–retest reliability, power calculations, and cost effectiveness compared with the established techniques are necessary, before any of these new techniques can be accepted as complementary or eventually even superior to the currently established neuroimaging markers.

The application of MR techniques in AD has not been restricted to structural imaging. Other MR modalities like MR spectroscopy, perfusion MRI, and diffusion weighted–diffusion tensor imaging have also been evaluated regarding their usefulness as diagnostic or prognostic biomarkers. Diffusion-weighted imaging (DWI) is sensitive to the degree of microscopic motion of water molecules. In tissues, this motion is hindered by the physical boundaries of the 3-dimensional tissue microstructure and thus occurs preferentially perpendicular to those boundaries. In highly structured tissues, eg, white matter, the motion of the water molecules becomes anisotropic. Damage to the tissue microstructure results in a loss of anisotropy, which can be detected by DWI. Diffusion tensor imaging (DTI) is a more sophisticated application of the same principle that additionally provides information about the directionality of the water motion. Because DWI and DTI are relatively new techniques, the number of studies in AD is restricted. DTI and DWI abnormalities in AD were found in the corpus callosum; white matter of the parietal, temporal, and occipital lobes; posterior cingulate; and hippocampus [76–79]. An increased water diffusivity in the hippocampus was found to be useful not only for discrimination between AD and healthy controls but also for discrimination between MCI and healthy controls and prediction of cognitive decline in MCI [78,80].

MR spectroscopy (MRS) measures several brain metabolites. Probably the most important metabolite for AD is N-acetyl aspartate (NAA), a marker of neuronal viability and function, which is decreased in AD. Furthermore, an increase of myoinositol (MI), a glial marker and marker of secondary messenger metabolism, has also been shown to be useful for the differentiation between AD and healthy controls. An increased choline signal, a marker for membrane integrity, has also been described in AD patients, but is not found consistently [81]. Significant NAA reductions were found in the hippocampus, posterior cingulate, and gray matter of the temporal, parietal, and sometimes the occipital and frontal lobes [82–89]. The degree of cognitive impairment was found to be well correlated with the degree of NAA decrease [90]. In addition, several studies found MRS also useful in differentiating AD from other forms of dementia, eg, vascular dementia, fronto-temporal lobe dementia [85,86,91–93].

In the last few years, different MR techniques to measure different aspects of brain perfusion and thus, indirectly, brain metabolism have been developed. Dynamic susceptibility weighted (DSW) MRI is based on the principle that the passage of an exogenous paramagnetic contrast material through the tissue microvasculature results in signal intensity changes in T_2-weighted images. Arterial spin labeling methods (ASL) are based on the same principle but use an endogenous tracer, ie, blood water molecules in arteries providing the blood flow to the brain are “magnetically tagged.” These tagged water molecules then diffuse across the blood–brain barrier into the brain and alter the local magnetization state of the brain tissue in proportion to the inflow of saturated protons. DSW and ASL imaging are mostly used for resting state perfusion measurements. Like PET and SPECT, both perfusion modalities have shown regions of hypoperfusion in the temporo-parietal lobes and in the posterior cingulate in AD and MCI [94–96]. One study found that these perfusion deficits had a 95% sensitivity and 74% specificity in AD patients and a 88% sensitivity and 50% specificity in MCI [97]. ASL and DSW have the advantage of not needing radioactive tracers and are thus not only less expensive

but also safer than FDG-PET and SPECT. Therefore, these MR perfusion techniques have the potential to replace SPECT and PET, particularly if repetitive studies are necessary to assess treatment effects. The third method, blood oxygenation level–dependent (BOLD) MRI, is used mostly for activation studies. The BOLD signal results from a decrease of the deoxyhemoglobin concentration relative to an increase of the cerebral blood flow during neuronal activity. Currently, functional MRI (fMRI) activation studies are mostly used to gain a better understanding of the neuronal networks involved in specific tasks in the healthy human brain. Only a minority addresses the question of how these networks are altered in subjects at risk for AD or subjects with AD. Depending on the disease stage and the task used, decreased as well as increased activity has been described in these subjects [98–104]. Whereas such studies unquestionably give interesting insights into functional deficits and compensatory mechanisms in AD, they might be less suited as diagnostic or prognostic biomarkers because contain similar problems as cognitive measures, ie, the results depend very much on the compliance of the subject.

Recently, several interesting new PET–SPECT tracers have been developed. Two of them seem to be particularly promising for AD. The first group encompasses carbon 11–labeled acetylcholine analogues, which allow for an in vivo measurement of the activity of the acetylcholine degrading enzyme acetylcholine esterase (ACHE). AD is associated with loss of cholinergic neurons in the basal fore-brain and, thus, with decreased levels of acetylcholine and the enzymes responsible for its synthesis and degradation in this region and connected cortical regions. In accordance with this, several PET studies have found a reduction of the cortical ACHE activity in AD compared with controls, particularly in the hippocampus and parieto-temporal regions [105–107]. The degree of the ACHE reduction was found to be well correlated with the degree of the cognitive impairment [108]. Furthermore, treatment with ACHE inhibitors resulted in a measurable decrease of the remaining ACHE activity and was well correlated with improvements of the cognitive measures [109–111]. Therefore, this technique seems to be quite promising not only as a diagnostic biomarker but also as a prognostic biomarker. The second group of interesting new PET tracers are carbon 11–labeled compounds that bind with high affinity to fibrillar amyloid plaques and thus allow for the first time for an in vivo quantification of the amyloid burden [112,113]. As with the kinds of ACHE analogues, this new tracer class has not only the potential to improve the accuracy of the diagnosis of AD but also allows study of the effects of various kinds of treatments on one of the histologic hallmarks of the disease.

2.6. Summary

Over the last years, a number of genetic, biochemical, and imaging measures have been explored regarding potential to improve the accuracy of the clinical diagnosis of AD or to monitor disease progression and treatment effects. As of yet, none of them has emerged as an ideal diagnostic or prognostic biomarker for AD. Considering the complexity of the AD disease process, it seems also rather unlikely that such a single ideal diagnostic or prognostic AD biomarker even exists. However, as these markers assess slightly different aspects of the disease process, a combination of 2 o r 3 of them might be much more powerful [26] than each of them alone. Therefore, one of the currently most important issues of clinical AD research is to identify the combination of the already-established biomarkers with the highest diagnostic and prognostic power. To address this question, a new mutlicenter AD research project, called the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) was launched in October 2004. This initiative is, to date, one of the most comprehensive efforts to identify neuroimaging measures and biomarkers associated with cognitive and functional changes in healthy elderly, MCI, and AD subjects and encompasses clinical sites in the United States and Canada.

3. Alzheimer's Disease Neuroimaging Initiative

The ADNI is funded by the National Institute on Aging (NIA) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH), several pharmaceutical companies (Pfizer, Wyeth, Eli Lilly, Merck, GlaxoSmithKline, AstraZeneca, Novartis, Eisai, Elan, Forest Laboratories, Bristol Meyers Squibb), and foundations (Alzheimer's Association, Institute for Study of Aging) in conjunction with the NIH Foundation. The overall goals of the ADNI are:

1. Development of optimized methods and uniform standards for the acquisition of longitudinal, multicenter MRI and FDG-PET data on patients with AD and MCI a s well as healthy elderly controls.
2. Implementation of these optimized methods and acquisition of longitudinal structural and metabolic imaging data in a large cohort of healthy elderly, MCI, and AD patients and validation of these imaging surrogates with parallel acquired biomarkers and clinical and cognitive measures.
3. Identification of those neuroimaging measures, cognitive measures, and biomarkers, which provide the maximum power for the diagnosis of MCI and AD and for the assessment of treatment effects in trials involving healthy elderly, MCI, and AD.
4. Creation of a generally accessible imaging and clinical data repository, which describe longitudinal changes in brain structure and metabolism, cognitive function, and biomarkers in healthy elderly, MCI, and AD patients.

3.1. Study outline

There are several ADNI Cores:

1. A clinical coordination center (Principal Investigators (PI) Drs L. Thal, University of California, San Diego and R. Peterson, Mayo Clinic, Rochester, MN), responsible for subject recruitment and maintenance, uniform collection and quality control of clinical and neuropsychological data, deposition of the processed clinical data in a common database, and testing the clinical hypotheses.
2. Two neuroimaging cores: (1) MRI Core (PI Dr. C. Jack, Mayo Clinic Rochester, MN) and (2) PET Core (PI Dr. W. Jagust, University of California, Berkeley) responsible for determining the optimal imaging parameters, ensuring uniform collection and quality control of the neuroimaging data and testing of the imaging hypotheses.
3. A biomarker core (PIs Drs. J. Trojanowski and L. Shaw, University of Pennsylvania) responsible for collection and storage of blood, urine, and CSF specimens; development of immortalized cell lines for genetic analyses and all standard clinical laboratory tests; and measurements of selected AD biomarkers (APOE genotype, isoprostanes, τ, β-amyloid, sulfatides, homocysteine).
4. An informatics core (PI Dr. A Toga, University of California, Los Angeles) responsible for management and storage of all raw and processed MRI and PET images in a generally accessible data repository.
5. A biostatistics core (PI Dr. L. Beckett, University of California, Davis) responsible for the development of statistical tools and all statistical analyses.

The total duration of the ADNI is 5 years. This time is divided into 2 main phases: the preparation phase of 6 months followed by the execution phase of 54 months. During the preparation phase, the clinical core establishes a network of clinical sites and develops a plan for the recruitment and retention of subjects. The neuroimaging core uses the preparation phase

for the development of the final imaging protocols for MRI and PET acquisitions and the procedures necessary for control of data quality and scan consistency between the different sites. During the first 12 months of the execution phase, 800 subjects, including 200 healthy elderly subjects, 400 MCI, and 200 mild AD subjects will be recruited. The participants will be followed up over a period of 2 (AD) to 3 (healthy elderly, MCI) years. Clinical–cognitive assessments and 1.5 T structural MRI examinations will be performed at regular intervals. Approximately 50% of each group will additionally undergo FDG-PET scans at the same time intervals, and 25% of each group (who do not undergo PET) will have additional 3 Tesla MRI examinations. Biomarkers in blood and urine will be regularly collected from all participants, in 25%, biomarkers will also be determined in CSF. All clinical data and results of the laboratory tests obtained during the execution phase will be transmitted to the clinical core and regularly entered into the clinical database of the initiative. After removal of all identifying information, the entire clinical data base will be placed on a public Website so that it can be accessed by the initiative investigators, the pharmaceutical industry and the public. Similarly, all imaging data will be sent to the central imaging data repository and made available to the public. At about 2 1/2 years into the project, all imaging data acquired so far will be analyzed by a variety of state-of-the-art automated processing applications available at the participating centers (MRI: boundary shift imaging, volumetric measurement of entorhinal cortex and hippocampus, tensor-based morphometry, voxel-based segmentation–brain parcelation, T_1/T_2 relaxometry, voxel-based morphometry, cortical time-lapse maps, cortical thinning, parametric 3-dimensional surface mesh modeling of subcortical structures, and 4-dimensional tensor maps; PET: statistical parametric mapping, stereotactic surface projections, and volume of interest analyses). This allows for a comparison of these methods regarding their immunity to artifacts and cerebrovascular disease, their ability to detect the expected changes cross-sectionally and longitudinally, and their processing speed and cost efficiency.

3.2. Current state of the ADNI

At the time of this writing, (May 2005), the clinical core has already recruited a network of clinical study sites, and the final imaging sequences/procedures have been selected. By June 2005, approximately 20 performance sites will have IRB approval and will be able to begin enrollment. By September 2005, the reminder of the selected sites should have Institutional Review Board approval and start with enrollment.

4. Future challenges

Nearly 100 years have passed since Alois Alzheimer first described his index patient Auguste D and the pathologic changes found in her brain in the postmortem examination. Since then, intensive research has allowed us to unravel some of the key mechanisms of AD and to identify a number of promising potential biomarkers for its diagnosis and prognosis. Although the search for new and better biomarkers needs to be continued, the full potential of the existing biomarkers needs to be explored in large prediction trials. However, for such trials to produce meaningful and generally applicable results, a further standardization, not only of the criteria for diagnosis but also of the measurement techniques of surrogate biomarkers, will be necessary. Most studies already use standardized criteria for the diagnosis of AD, eg, the NINCDS-ADRDA criteria. In contrast, the definitions of early stages or presymptomatic stages of AD or even healthy control subjects are less rigorous. The terms *mild cognitive impairment* or *cognitively impaired nondemented*, for example, have been used with varying definitions, and efforts to define standardized criteria have only recently been made [16]. The same is true for the definition of *healthy elderly controls*, ie, the term needs to be defined—if normal means healthy in every aspect or only absence of cognitive impairment or neurologic disease but otherwise allowing for the entire range of diseases frequently found in the elderly population. In addition to standardization of diagnostic criteria, it is also necessary to identify

and then strictly apply optimized measurement parameters of the already-existing biochemical and neuroim-aging biomarkers. The ADNI will be a first important step toward this goal.

An important issue for trials searching for the most powerful combination of diagnostic and prognostic biomarkers is also the identification and, if possible, correction of factors that increase measurement variability. Generally, there are 2 sources of measurement variability: variability owing to limitations of the measurement technique and variability owing to subject-related factors. The former can be best addressed by the development of optimized and standardized measurement protocols. Subject-related measurement variability is more difficult to account for because it is usually multifactorial. Factors contributing to subject-related measurement variability can, for example, be genetic, eg, Apo-ε4 carrier status or environmental, eg, exposure to putative neurotoxins or dietary deficiencies, concomitant diseases and their treatment, eg, cerebrovascular disease or diabetes mellitus. In addition to these common sources of subject-related measurement variability, there are 2 sources that are also of potentially diagnostic and prognostic importance. The first is effects of AD treatments. Although there is currently no definite proof that any of these drugs could prevent AD or at least significantly slow down its progression, more and more patients with possible AD or even amnestic MCI are treated with cholinesterase inhibitors, or high doses of α-tocopherol, and even healthy subjects take antioxidants or vitamin preparations as protection against AD. It might even be possible that some of the drugs originally developed for the treatment of AD enhance cognitive performance in healthy subjects and are thus taken for this purpose only by otherwise completely healthy people. Therefore, it will become increasingly difficult in the future to observe the natural course of AD, and it is possible that such treatments influence the expression of some biomarkers and render them useless for diagnostic or prognostic purposes. Finally, the probably most important source of measurement variability is the variability caused by the disease itself. The fact that despite the intensive research efforts the etiology of AD is still elusive suggests that the disease processes in AD are either very complex or AD is just the common expression of several different etiologic processes. If the latter is true, it is very well possible that the different forms also vary in the expression of AD biomarkers.

Ultimately, the goal is diagnosis and treatment in the earliest possible stage of AD. For this purpose, it is also necessary to differentiate early AD from early manifestations of other dementias. Therefore, it will be necessary to test those biomarkers found to be useful for diagnosis and prognosis in AD and MCI patients also in other risk groups, eg, cognitively nonimpaired patients or young Apo-ε4 carriers, asymptomatic subjects with strong family history for AD, subjects with cognitive impairment in non-memory domains, or subjects suffering from other neurodegenerative diseases, eg, vascular dementia or Lewy body disease. However, although expanding the study population is essential to explore the full potential of a biomarker, ethical questions are also raised, particularly in subjects that are included because they already belong to a group with a higher risk for AD, eg, Apo-ε4 carriers. Some of these subjects will be found to be positive for the biomarker in question, and thus their risk for AD or the risk that they may already be in a very early stage of AD might be even higher than previously assumed. This raises the question if these subjects should be informed about their increased risk and if they should even be offered treatment with one of the currently available AD drugs or treatment in a study protocol. A similar problem occurs in subjects recruited as healthy controls who are positive for a single biomarker or a combination of different biomarkers that have been found to be highly predictive for the development of AD.

Although the currently available surrogate biomarkers need to be further explored, the search for new biomarkers and for less-invasive, safer, and, for the patient, more acceptable alternative measurement techniques needs to be continued. PET, for example, seems to be one of the most sensitive imaging markers for AD in the very early or even presymptomatic stage, particularly if the new tracers for amyloid imaging are as reliable as promised. Efforts to develop MR

techniques allowing for the measurement of brain amyloid concentrations are under way, but none of them have progressed far enough to be tested in patients [114–118]. Functional MRI techniques such as perfusion MRI o r BOLD fMRI may also be useful. The diagnostic and prognostic potential of other already-existing imaging modalities, eg, DTI, MRS o r PET with acetylcholine analogues needs to be explored further particularly regarding their usefulness to detect very early disease manifestations or contraindications for some forms of treatment, eg, risk of bleeding after amyloid vaccination. Finally, the knowledge about the earliest molecular pathomechanisms gained from studies in animal models of AD needs to be translated in new biochemical and neuroimaging biomarkers to allow the detection of the disease in its presymptomatic stage.

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