MINIREVIEW

An Ideal Biological Marker of Alzheimer’s Disease: Dream or Reality?

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Summary

Senile dementia of Alzheimer’s type (AD) is commonly characterized as a neurodegenerative disorder, which exhibits gradual changes of consciousness, loss of memory, perception and orientation as well as loss of personality and intellect. AD prevalence increases dramatically with age and is the fourth cause of death in Europe and in the USA. Currently, there are no available biological markers, which gives clinicians no other alternative than to rely upon clinical diagnosis by exclusion. There is no assay of objective ante mortem biochemical phenomena that relate to the pathophysiology of this disease. The pathophysiology of AD is connected with alterations in neurotransmission, plaque formation, cytoskeletal abnormalities and disturbances of calcium homeostasis. The search for a test, which is non-invasive, simple, cheap and user-friendly, should be directed at accessible body fluids. Only abnormalities replicated in large series across different laboratories fulfilling the criteria for a biological marker are likely to be of relevance in diagnosing AD. To date, only the combination of cerebrospinal fluid τ and Aβ42 most closely approximate an ideal biomarker of Alzheimer’s disease. A short review on the role of biological markers in AD on the basis of the literature, contemporary knowledge and our own recent findings are presented.

Key words
Alzheimer’s disease • Biological peripheral marker • β-amyloid • Protein τ • Review

Introduction

Alzheimer’s disease (AD) is the most common dementia among older persons. Almost unknown in the first half of the twentieth century, AD appears as a new epidemic threatening of human civilization in the next century. Its incidence, at present, doubles every five years. Social and economic consequences of this disease reach immense dimensions. It is therefore obvious that the pressure of medical and social factors have contributed to the intensive research in the neuropathological changes of the aging brain and to the search for a biological correlation with clinical manifestation of AD. With the public awareness of AD,
more persons go to the doctor complaining of a failing memory. There is no doubt that nearly all people undergo a deterioration of memory late in life. On the basis of a one-year longitudinal study of more than 20,500 adults, standardized to the US census population, 29% met DSM-III-R diagnostic criteria for mental disorders (Regier et al. 1998). It seems difficult even for clinicians to identify dementia and to determine its severity. A decline of memory and logical thinking to an extent that interferes with everyday activities or a change in social behavior lead the clinician to diagnose dementia. The assessment of persons thought to have dementia is an undertaking of crucial importance for them and their families.

Many clinical decisions, especially diagnoses, are made on the basis of probability. Diagnosis of AD fits into this category: "probable AD" is generally used to improve the reliability of clinical diagnoses. Clinicians weigh the accuracy and validity of additional diagnostic tests, such as routine blood examinations, magnetic resonance imaging, computed tomography, functional brain imaging, and neuropsychological tests, to increase the probability of AD by excluding other disorders. Using contemporary diagnostic criteria, the ante mortem diagnosis of probable AD in centers specialized for AD is confirmed in 80% to 90% of the cases. It can not be excluded, however, that diagnostic accuracy is much lower in routine clinical practice outside the centers. Widespread screening using brain imaging is not really feasible since these techniques require highly expensive equipment and technical expertise. Clinicians therefore expect that identification of biological and biochemical markers will soon allow them to make more objective diagnoses.

The hope of proposed diagnostic tests for AD, such as the fingerprint test, the eye drop test, and the fibroblast test, claimed by their authors, and the associated publicity evoked by such claims, seem to be somewhat premature. The early and accurate diagnosis of AD thus falls short of the goal based on a series of subjective diagnostic criteria that rely heavily on the clinician’s experience or on the brain examination post mortem. The development of diagnostic criteria to avoid the misinterpretation and misapplication of various newly introduced tests is urgently needed.

Possible candidates for biological markers in AD

1. Brain imaging techniques in the search for biological markers of Alzheimer’s disease

Structural neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated that rapid progression of atrophy in the temporo-parietal cortex is highly indicative of AD (Jobst et al. 1992). Volumetric measurement of specific brain structures by MRI revealed hippocampal atrophy (Laakso et al. 1995, Jack et al. 1999). However, this information alone is not sufficient to differentiate early AD from normal aging as hippocampal atrophy is commonly seen in normal aging (especially in persons aged over 75 years).

Functional imaging techniques such as positron emission tomography (PET) and single photon emission tomography (SPECT) were expected to play a useful role in the follow up of suspect patients, as being those that would contribute to early diagnosis. SPECT is simple to use and is less expensive than PET, but PET has the advantages of accuracy and depth of information possible. SPECT or PET can provide images of a variety of biochemical functions, such as cerebral blood flow and volume, cerebral glucose and oxygen metabolism, receptor mapping and amino acid incorporation rates into proteins.

Blind clinical PET evaluation indicates that AD patients can be differentiated from other dementias and cognitively intact persons (Powers et al. 1992). The mapping of glucose metabolism using fluoro-deoxyglucose by PET (FDG-PET) also in preclinical stages can differentiate AD from some dementias (for example frontal dementia or Levy-body dementia) and normal aging (Albin et al. 1996). Hypometabolism throughout the neocortical association areas (superior parietal cortex, the inferior parietal, superior temporal and prefrontal cortices) was reported in AD in many studies using PET (for review see Small et al. 1996). The rate of metabolic deficits correlated with the severity of cognitive deficits (Mazziota and Phelps 1986).

On the other hand, temporoparietal hypometabolism characteristic for AD could be seen with bilateral temporoparietal strokes (Foster 1998). Bilateral posterior temporoparietal hypoperfusion found in AD by
SPECT and confirmed by PET has a high specificity (80-95%), but low sensitivity (40-80%) to be able to act as the sole diagnostic marker (Claus et al. 1994, O’Mahony et al. 1994, Powers et al. 1992).

The cost and lack of widespread availability of FDG-PET, the subjectivity of the interpretation of imaging studies and the variability of technical methods are the main obstacles for accepting brain imaging methods as diagnostic tests (Foster 1998).

2. Peripheral biological markers for AD

Recent fundamental research of the pathogenesis of AD has brought evidence that the main histopathological and functional characteristics of this disease are senile plaques and neurofibrillary tangles, alterations in neurotransmission and calcium homeostasis. The main cognitive deficits manifested in patients with AD are connected with the loss of cholinergic neurons resulting in lowered levels of acetylcholine and of choline acetyltransferase, an enzyme necessary for its synthesis. Inflammation and impairment in the action of free oxygen radicals are probably also involved in the pathogenesis of AD. The discovery of genes, which might be involved in the etiology of AD, have introduced new expectations for AD diagnosis.

2.1. β-amyloid

A key component of senile plaques in the brain is β-amyloid which exists in several forms produced from amyloid precursor protein (APP) by a series of proteolytic cleavages. A slightly shorter form Aβ40 is secreted more, but the longer form Aβ42, which is the predominant form of β-amyloid in AD brain, aggregates more readily (Wisniewski et al. 1997). It seems that genes called presenilins affect the production of neurotoxic β-amyloid (Sahara et al. 1996, Haass 1996).

Bush et al. (1990) found APP in blood platelets. It is not known whether Aβ42 is derived from an extracerebral source. It is a well-known fact that APP is an integral membrane glycoprotein encoded by a single gene on chromosome 21. A wide variety of APP-expressing cells have been shown to release β-amyloid (Lustig et al. 1994). Circulating blood platelets can be an important source of APP, which is contained in platelet α granules. The increased content of APP fragments was found in the blood of patients in middle and terminal stages of AD. Platelets could thus be a source of perivascular amyloid deposits (Davies et al. 1997). Any alterations in platelets or the cleavage of APP fragments will lead to a pathological accumulation of this protein. These findings support the hypothesis that changes in APP metabolism may occur in peripheral blood elements.

2.2. Proteins τ

Neurofibrillary tangles in the brains of AD patients contain abnormally phosphorylated protein τ (Mandelkow and Mandelkow 1998, Tolnay and Probst 1999). Proteins τ are microtubule-associated molecules which regulate the dynamics of the microtubule network, especially involved in axonal transport and neuronal plasticity. Proteins τ belong to a family of developmentally regulated isoforms generated by alternative splicing and phosphorylation. This generates several protein τ variants that interact with tubulin and other proteins. Therefore, proteins τ are influenced by many physiological regulations. In AD, all six adult isoforms of proteins τ can become maximally phosphorylated and can, bind to each other, rather than bind to microtubules, thus destabilizing the neuronal cytoskeleton (Khatoo et al. 1995). In addition to the modulation of microtubule stability, proteins τ are likely to play a role in signal transduction. A number of papers demonstrated that proteins τ interact with phospholipase C and phosphatidylinositol bisphosphate (Johnson and Hartigan 1998). There is a growing body of evidence that proteins τ interact with the actin cytoskeleton and thereby play a role in regulating cell shape, motility and microtubule-plasma interactions.

The hyperphosphorylation of τ proteins is catalyzed by various protein kinases. For example protein kinase I identified earlier is identical with β glycogensynthase kinase, protein kinase II has a catalytic subunit identical with cyclin-dependent kinase 5; phosphorylation of τ proteins is also catalyzed by calcium-calmodulin-dependent protein kinase II, phosphatidylinositol 3-kinase, etc. (Xiao et al. 1996, Imahori and Uchida 1997). Hence, it has been postulated that the disturbance in equilibrium between the activity of kinases and phosphatases is the reason for proteins τ hyperphosphorylation with its subsequent pathological consequences. Laboratory studies revealed that the increase in phosphatase activity, which catalyses protein τ dephosphorylation, might stop the neurofibrilar degeneration (Iqbal and Grundke-Iqbal 1996). Munoz-Montano et al. (1997) have proved that lithium, which inhibits the activity of β-glycogensynthase kinase, causes the protein τ dephosphorylation in isolated neurons and rat brains in vivo.

Proteins τ are mostly expressed in the nervous system. The discovery of some novel roles for proteins τ
have revealed new and important roles of cytoskeletal proteins. Their degree of phosphorylation is a good marker of cell integrity. The search for peripheral markers of AD therefore suggests that pathological changes in cytoskeletal proteins may also become manifested in peripheral cells such as the blood elements (Strunecká et al. 2000).

2.3. Could alterations in calcium homeostasis serve as biological markers?

The calcium hypothesis of AD states that long-term slight elevation of cytosolic Ca\(^{2+}\) levels ([Ca\(^{2+}\)]\(_i\)) and/or disturbances in Ca\(^{2+}\) homeostasis are the cellular mechanisms underlying neuronal aging (Khachaturian et al. 1989, Khachaturian 1998). An alteration in calcium homeostasis could affect most of AD-related deficiencies (Řípová and Strunecká 1998). On the other hand, a key element of AD pathology, β-amyloid protein, has been shown to disrupt neuronal Ca\(^{2+}\) homeostasis (Mattson et al. 1993, Fraser et al. 1997).

It is not clear whether changes in [Ca\(^{2+}\)]\(_i\) are the result or the cause of these pathogenic effects (Chen 1999). Although many experimental data have shown alterations of various Ca\(^{2+}\) regulatory mechanisms during aging and AD, the heterogeneity of the types of preparations and experimental techniques does not allow full confirmation of the Ca\(^{2+}\) hypothesis (Verkhratsky and Toescu 1999). Nevertheless, many experimental data have demonstrated alterations in cytosolic Ca\(^{2+}\) levels, calcium superficial binding, and calcium uptake in peripheral cells. Řípová et al. (1999, 2000) reported significant alterations in calcium homeostasis in blood platelets of patients with AD which were not observed during aging. These results further suggest the systemic aspects of AD and support the view that examination of peripheral cells may represent a useful approach in the study of pathological changes in AD. The possibility has not been excluded that disturbances in Ca\(^{2+}\) homeostasis may represent a common denominator for the various pathological hallmarks of AD. Despite the crucial role of the calcium signal in the pathogenesis of AD, the methods used for the study of calcium alterations are not yet accessible for routine clinical use.

2.4. Genetics and biomarkers

It is difficult to understand the genetics of AD, as many of the more recent findings have not been unequivocally confirmed. Until recently, four loci have been identified as contributing to AD. The mutations in the βAPP gene on chromosome 21 (autosomal dominant, four mutations identified so far), and mutations on chromosomes 1 (presenilin 2, autosomal dominant, three mutations) and 14 (presenilin 1, autosomal dominant, 28 mutations), are sufficiently well established to be used as a basis for genetic screening in suspected cases of early-onset familial AD (FAD). These three genes are now known to account for some 30-40 % of early-onset FAD (Wilcock 1999). The theoretical implications of genetic tests in FAD is obvious, but what about subjects with sporadic forms of AD? Only a few cases with genetic mutations in early-onset sporadic AD have been reported (Naruse et al. 1991, Tanahashi et al. 1996) and no missence mutations in these genes have been found in any cases of late-onset sporadic AD (Tanzi et al. 1992, Tsuda et al. 1995).

The fourth gene, which had been identified and well established as contributing to AD, is on chromosome 19. Although this gene itself does not cause AD, it is considered a risk factor, which does not inevitably lead to the disease. Three common polymorphisms of apolipoprotein E gene known as alleles ε2, ε3 and ε4 (ε1 is very rare), are associated with late-onset familial and sporadic AD. The number of ApoE4 allele copies not only correlates with an earlier age of onset but also with an increased density of senile plaques in late-onset AD. ApoE4 genotype is clinically important although the ApoE genotype is not sufficiently reliable to be used as a diagnostic test. Carriers with the ApoE4 allele have a 1.5-3-fold increased risk of developing AD compared to the general population; inheritance of two copies of the ApoE4 allele further increases this risk. However, it must be pointed out that the majority of ApoE4 individuals reach age 80 without evident cognitive impairment (Giacobini 1996, Hyman et al. 1996). ApoE status testing is not currently recommended as a means of predicting future risk of AD in asymptotic individuals, but this genotyping may be useful in improving the diagnosis in symptomatic subjects.

In conclusion, the actual genetic testing cannot fulfill the criteria of a biological marker (low sensitivity and specificity). At the clinical level, it may be important for some members of affected families and it may be useful for clinicians to confirm AD diagnosis. However, these new possibilities introduce numerous ethical, psychological and social problems.
2.5. Other possible biomarkers

The use of biomarkers in diagnosis presents a challenge. There is a huge and a still growing body of evidence from various research areas suggesting new AD biomarkers that are closely associated with the pathophysiology of the disease. These include oxidative stress and inflammation markers, neurotransmitters and related proteins (acetylcholine and enzymes of the cholinergic system; neuropeptides – somatostatin and neuropeptide Y; aminoacids – glutamate, aspartate, alanine, methionine), markers related to synaptic function (synaptophysin, synaptotagmin, chromatogranin A), destruction or synaptic degeneration markers (neuron-specific enolase, neuromodulin, growth-associated protein GAP-43), blood-brain barrier damage markers (CSF/serum albumin ratio), etc. (for review see Bancher et al. 1997). Phospholipid and fatty acid abnormalities were reported by other authors (Cuenod et al. 1995, Řípová et al. 1997, Kyle et al. 1999). The specificity and selectivity of all the above mentioned markers for AD remain open and will have to be investigated further. Some of the most interesting potential markers are outlined here.

Inflammation markers: Two major observations led scientists to study the role of inflammation in the development of AD: neurodegenerative changes in AD are accompanied by an inflammation reaction (on the other hand immunological reactions in the brain may play a role in neurodegenerative processes), and the risk of AD is reduced among users of antiinflammatory non-steroidal drugs. An acute phase response was observed in AD brain (increase in cytokine level – IL1 and IL6, expression of tumor necrosis factor, upregulation of the complement system). In the cerebrospinal fluid (CSF) more conflicting data have been reported (for review see Bancher et al. 1998). To date, no available data have supported the usefulness of these proteins in searching for biomarkers of AD.

Melanotransferrin (the iron-binding protein p97) has recently been proposed as a possible diagnostic marker of AD. It originates in the reactive microglia associated with dense senile plaques (Yamada et al. 1999) and was found elevated in the CSF and serum of AD patients (Kemnard et al. 1996). This marker awaits validation on large numbers of patients in a multicenter study.

Glycosylation of acetylcholinesterase (AChE) as a diagnostic marker for AD was suggested (Saez-Valero et al. 1997). AChE activity was lower in the CSF of AD patients post mortem as compared to age-matched controls and other cases of dementia. There was a large overlap (40 %) between the groups. However, these authors demonstrated that glycosylated AChE was significantly elevated in AD. Thus lectin-binding analysis of CSF AChE could provide a diagnostic test which is 80 % sensitive and 97 % specific. This marker has to be replicated ante mortem and on a large sample of patients.

Tropicamide eye drop response was referred as a simple, fast, inexpensive and non-invasive neurobiological test for AD (Scinto et al. 1994). Marked hypersensitivity in the pupilar dilatation response to the cholinergic antagonist tropicamide has been proposed to demonstrate a central cholinergic deficit present in AD. However, these results were not confirmed by other authors who concluded that the papillary response is not a reliable and specific diagnostic test for AD (Growdon et al. 1997).

Biological markers of Alzheimer’s disease in clinical practice

What is a meaning of biomarker for clinical use?

There are numerous reports supporting the possibility that protein τ or β-amyloid 42 in CSF are the most promising biomarkers for clinical use to aid in the diagnosis. However, lumbar puncture to obtain CSF samples is too invasive for use as a fully routine procedure. The search for a test which is non-invasive, simple, cheap and user-friendly should be directed at accessible body fluids. The finding of a biological peripheral marker for AD, even one based on an isolated pathological pathway, and not indicative of the basic etiology of AD, would be a significant progress.

The biochemical approach is based on the hypothesis that the causative disorder of AD may lurk at the level of cell physiology, altering various brain functions, such as recognition, memory, language and visuospatial skills. The identification of a biological peripheral marker would not only validate the presumptive clinical diagnosis but should also help to determine whether AD is a systemic disease or whether it is limited to the brain. According to the Consensus Report of the Working Group on "Molecular and Biochemical Markers of Alzheimer’s Disease" (1998), sponsored by the Reagan Research Institute of the Alzheimer’s Association and the National Institute on Aging, five different purposes of biomarker predictive testing were identified, namely improving and confirming diagnosis, monitoring disease progression (over time and/or after
pharmacological intervention), studying brain-behavior correlations and epidemiological screening.

An ideal biomarker for clinical use should fulfil the following criteria:

1. **To have a high specificity** (to be able to distinguish AD from other dementias, normal aging and other causes of cognitive impairment), specificity should exceed 80 %, the higher specificity the better to avoid false labeling of normal subjects;

2. **To be very sensitive** (enabling the identification of nearly every AD patient, with no false positive or negative results);

3. **To be able to detect AD early** in its course (or presymptomatically);

4. **To be useful in monitoring the progression** of the disease and pharmacological treatment;

5. **To be non-invasive or to be based on well accessible body fluids** (blood, urine, saliva); CSF tapping is not a simple routine procedure;

6. **To be inexpensive and simple to perform** as a routine procedure.

**1. Protein ϩ and Аβ42: the most promising biomarkers for clinical use?**

**1.1. Protein ϩ**

Since proteins ϩ is normally an intracellular axonal protein, it is likely that increased CSF-τ level is associated with neurodegeneration. An increase of total CSF-τ level in AD was reported in numerous studies (for review see Vanmechelen 1998). The sensitivity of CSF-τ to identify AD is over 70-80 % and its specificity is also relatively high, although elevated CSF-τ level was detected in some studies in patients with frontal lobe dementia and vascular dementia (Blennow et al. 1995, Arai et al. 1997). Most follow-up studies in AD patients have revealed that protein ϩ level does not change during the course of the disease (Andreasen et al. 1998) and a clear correlation between CSF-τ level and the severity of dementia has not been well established (Munroe et al. 1995). The recent study of Blennow (2000) on a large sample of patients with mild cognitive impairment, who later progressed to AD (n = 480) has indicated that increased CSF-τ level might be an early marker. In this study, when CSF-τ measurement is combined with that of CSF-Aβ42, the sensitivity for the prediction of AD was 90 %, while its specificity was 80 %. The determination of CSF-τ level could also potentially serve for monitoring the effect of treatment. Although under treatment with galantamin and Aricept the level of CSF-τ did not change (as these drugs are symptomatological), treatment with GM1 ganglioside (Augustinsson et al. 1997) lowered the levels of CSF-τ in all patients.

The measurement of hyperphosphorylated protein τ (PHF-τ) in the CSF would theoretically reflect the formation of neurofibrillary tangles in the brain. A sandwich enzyme immunoassay has revealed that phosphorylated CSF-τ was higher in AD patients than in non-AD controls (Ishiguro et al. 1999). Discrimination between the two groups was clearer in PHF-τ than in total CSF-τ level. However, this method is not a routine procedure and there are some problems with overlapping. Consequently, this type of assay has to be developed further.

**1.2. β-amyloid**

β-amyloid in the CSF should reflect cerebral β-amyloid turnover. In AD patients, no differences in total β-amyloid were found in the CSF as compared to the controls (Wisniewski et al. 1989). Using an ELISA assay able to recognize the 42 amino acid form of β-amyloid (Aβ42) it was established that Aβ42 is decreased in the CSF of AD patients in many clinical trials (Motter et al. 1995, Tamaoka et al. 1997, Andreasen et al. 1999a). However, the sensitivity and the specificity of Aβ42 in CSF for the diagnosis of AD differ in many studies and are much lower than in the case of protein τ. Moreover, Lannsfelt et al. (2000) reported an increased Aβ42 in the early course of AD, which tends to decrease with the progression of the disease. The authors explain the discrepancies of some findings as being due to methodological differences. The β-amyloid signals could be reduced by albumin in CSF.

It is somewhat difficult to understand why the Aβ42 level is low in CSF of AD patients, while Aβ42 is high in the brain. It is possible that amyloid plaques in the brain act as a "black hole" and absorb extracellular Aβ42 in the brain, so that Aβ42 cannot reach the cerebrospinal fluid.

**2. Improved discrimination of AD patients using a combination of markers in clinical practice**

In a longitudinal study (Kanai et al. 1998), CSF examinations of AD patients revealed that such parameters as protein τ, Aβ42 and the ratio Aβ40/42, when estimated alone, did not meet all criteria for a biomarker (where specificity was high, sensitivity was
low and vice versa). Other authors (Andreasen et al. 1998, Hesse et al. 1998) confirmed these results. A combination of estimations of protein τ and Aβ42 may provide greater diagnostic accuracy than each individually. This was well documented by Hulstaert et al. (1999) in a large multicenter study in which eight European and two US university centers participated. Sandwich ELISA tests were used on site for measuring protein τ and Aβ42. Levels of Aβ42 in CSF were significantly lower in AD (n = 150) than in the controls (n = 100) and other neurological disorders (n = 84). Discrimination of AD from the controls and patients with other neurological disorders by the combined assessment of protein τ and Aβ42 was significantly improved. At 85% sensitivity, specificity of the combined test was 86% compared with 55% for Aβ42 alone and 65% for protein τ alone. This combined test at 85% sensitivity was 58% specific for non-Alzheimer types of dementia (n=79). The authors concluded that the combined measurement of protein τ and Aβ42 meets the requirements for clinical use in discriminating Alzheimer’s disease from normal aging and specific neurological disorders. The use of these combined tests as predictors of AD development was reported by Andreasen et al. (1999b) in 16 patients with mild cognitive impairment (MCI) who had progressed to Alzheimer’s disease 6-27 months later. At the beginning 14 out of 16 MCI patients had high CSF-τ and/or low CSF-Aβ42 levels. This indicates that these cerebrospinal fluid markers are abnormal before the onset of clinical signs of AD dementia. However, no other types of dementia and other neurological disorders in their preclinical stages were investigated in this study.

The discriminant power of combined CSF-τ and of the soluble interleukin-6 receptor complex (putative markers of neuroregulatory and inflammatory processes in the brain) in the diagnosis of AD was assayed on a group of 25 patients with mild and moderate AD and on a group of 19 age-matched healthy controls. The sensitivity was 92% and specificity 90% (Hampel et al. 1999). These data suggest that multivariate discriminant analysis of combined CSF-τ and soluble interleukin-6 receptor complex may add more certainty to the diagnosis of Alzheimer’s disease. However, the method will need to be extended to a larger group of subjects to assess its reliability. Moreover, the discriminant function of this method has to be validated by including other dementia disorders and confirmed by at least one other independent study.

Conclusions

Alzheimer’s disease is a heterogeneous disease from a clinical, genetic and pathological aspect. At present, it seems that more than one biological marker is needed to aid in the diagnosis of AD. In the context of the above mentioned six points on the definition of an ideal biological marker, at present a combination of CSF τ and Aβ42 most closely corresponds to an ideal biomarker of AD. A potential biological diagnostic marker has to be understood in the context of the basic clinical question. However, the complex of clinical, cognitive and behavioral impairment of AD patients is so varied, wide-ranging and subtle in early stages of the disease that some authors consider the expectation of ideal diagnostic biological markers to be an unachievable and unrealistic goal (Foster 1998). Nevertheless, the search for diagnostic markers could help in the therapeutic strategy of Alzheimer’s disease. Experience from AD therapy does not support the expectation that a “magic pill” will be found. AD provides an example demonstrating a failure of the highest levels of integration in the human brain. The pharmacological attempts to modify the failure of cognitive functions in AD patients have not been found to be fully effective.

In spite of this, the huge amount of laboratory and clinical observations should help in understanding the multifactorial aspects of the etiology and pathogenesis of AD in providing a better chance of preventing this most devastating neurodegenerative disease in man and in revealing new pathways for its treatment.

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