Diagnosis of Alzheimer’s disease in Brazil
Supplementary exams

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Abstract – This article presents a review of the recommendations on supplementary exams employed for the clinical diagnosis of Alzheimer’s disease (AD) in Brazil published in 2005. A systematic assessment of the consensus reached in other countries, and of articles on AD diagnosis in Brazil available on the PUBMED and LILACS medical databases, was carried out. Recommended laboratory exams included complete blood count, serum creatinine, thyroid stimulating hormone (TSH), albumin, hepatic enzymes, Vitamin B12, folic acid, calcium, serological reactions for syphilis and serology for HIV in patients aged younger than 60 years with atypical clinical signs or suggestive symptoms. Structural neuroimaging, computed tomography or – preferably – magnetic resonance exams, are indicated for diagnostic investigation of dementia syndrome to rule out secondary etiologies. Functional neuroimaging exams (SPECT and PET), when available, increase diagnostic reliability and assist in the differential diagnosis of other types of dementia. The cerebrospinal fluid exam is indicated in cases of pre-senile onset dementia with atypical clinical presentation or course, for communicant hydrocephaly, and suspected inflammatory, infectious or prion disease of the central nervous system. Routine electroencephalograms aid the differential diagnosis of dementia syndrome with other conditions which impair cognitive functioning. Genotyping of apolipoprotein E or other susceptibility polymorphisms is not recommended for diagnostic purposes or for assessing the risk of developing the disease. Biomarkers related to the molecular alterations in AD are largely limited to use exclusively in research protocols, but when available can contribute to improving the accuracy of diagnosis of the disease.

Key words: consensus, guidelines, diagnosis, supplementary exams, Alzheimer’s disease, Brazil.
Introduction

In recent decades, major advances have been made in research toward diagnosing Alzheimer’s disease (AD), particularly studies on early detection. Consensus and recommendations of societies of medical specialties in the field are generally updated periodically to stay abreast of the impact of new diagnostic methods and instruments for potential introduction into routine clinical practice.

The aim of the present module was to review and update recommendations governing supplementary exams for diagnosing AD in Brazil. The modalities of the exam were grouped into six categories. The critical review of the scientific literature and proposed preliminary recommendations were the responsibility of each of the authors contributing to this module, all of whom are experts in their specific area of knowledge. The recommendations were subsequently debated by the members of the groups to reach the final recommendations. The final recommendations were then presented, discussed and voted on at meetings with all other colleagues involved.

Blood tests

Laboratory blood tests have traditionally been used in the context of the propedueitic on dementia syndrome to exclude possible secondary causes. The American Academy of Neurology (AAN) recommends only the investigation of Vitamin B12 deficiency and of hypothyroidism in the initial propedueitic on patients with clinically suspected dementia. Considering the specificities of the Brazilian population, the preliminary guidelines of the Science Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology (ABN) for diagnosing Alzheimer’s Disease (AD) proposed a significantly more comprehensive list of exams for the assessment of patients with dementia syndrome. This included full blood count, sera levels of urea, creatinine, free thyroxin (T4), Thyroid Stimulating Hormone (TSH), albumin, hepatic enzymes (TGO, TGP, Gama-GT), Vitamin B12, calcium, serological reactions for syphilis, and HIV serology in patients younger than 60 years of age. Closely reflecting these recommendations, the 2010 European Federation of Neurological Societies (EFNS) guidelines also suggest a more extensive list of exams which includes folic acid concentrations.

Over the past two decades however, blood (serum, plasma and blood cells) has also been considered a potential source of biomarkers for diagnosing AD. Ease of obtention of patient blood compared with cerebrospinal fluid (CSF) render plasma and serum biomarkers particularly attractive for use in research and routine clinical practice.

The majority of these studies have focused on investigating single or small series of molecules related to the physiopathologic processes of AD such as amyloid genesis, inflammation and oxidative stress.

The level of tau protein in the blood is extremely low and thus falls below the detection threshold of most tests employed. Studies have explored the potential of the amyloid-β 1-42 and amyloid-β 1-40 peptides as biological marker candidates of AD with conflicting results, showing their ability or otherwise to discriminate AD patients from healthy controls. Some evidence suggests that a steady fall in plasma amyloid-β peptides is associated with progressive cognitive decline in the course of AD but further studies are needed to correlate these findings. Thus, unlike the assessment of tau protein or amyloid-β peptides in CSF, serum or plasma, levels of these molecules appear to have little clinical value.

Regarding the molecules related to inflammatory processes (C-reactive protein, interleukin 6 or IL-6, soluble receptor of tumor necrosis factor alpha or TNF-alpha) oxidative stress (isoprostane), neurotrophic factors (brain derived neurotrophic factor or BDNF) among others, the value of these as reliable biomarkers of AD is not yet clear. This is owing to conflicting evidence and results from studies involving only a small number of patients. In addition, it is noteworthy that these molecules are not exclusively linked to the physiopathology of AD since they can be altered in other diseases such as in the case of inflammatory molecules during infectious conditions.

More recently, strategies not aimed at target molecules such as the simultaneous analysis of multiple molecules and proteomic analysis have been employed with promising results. Two studies in this area are worthy of men-
Cognitively normal subjects and a slightly lower sensitivity and specificity in differentiating individuals with AD from others contributed to the identification of frontotemporal dementia. When its use is contra-indicated, MR plays a central diagnostic role for some dementia types such as subdural hematoma, tumors or normal pressure hydrocephaly. However, the metabolic alterations outlined above are non-specific. Thus, correlation with clinical data and preferential analysis of early or typical sites of early impairment may serve to increase the accuracy of the method. The posterior cingulate is one such region commonly targeted in many studies and is technically easier to evaluate and reproduce than the hippocampus.

Proton magnetic resonance spectroscopy (MRS) is an MR application enabling non-invasive in vivo assessment of metabolites. It is considered a functional neuroimaging method but is discussed under this section together with the other parameters and data obtained for MR. The most frequent findings of MRS studies in AD are reductions in N-acetyl-L-aspartate (Naa) and its ratios (Naa/creatine (Cr) and Naa/water) and increases in myoinositol (mI) and its ratios (mI/Cr and mI/water), with increased mI and ratios being an earlier finding. The mI/Naa ratio, which combines two of the most significant metabolic alterations in AD, is considered important in detecting the disease.

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MRS has less validation as a marker of AD than temporal medial atrophy, even in research studies, and although its findings allow accurate discrimination between AD patients and controls, and contribute to disease staging, broad normalization of normal values is needed for individual application in routine clinical practice. However, when hallmark features are detected in individuals with cognitive decline, MRS findings can serve to corroborate the clinical diagnosis.
Other MR volumetric techniques such as diffusion weighted MRI (DWI), tractography by diffusion tensor MRI (DTI), magnetization transfer, brain perfusion MRI, arterial spin labeling (ASL) and functional MRI are markers with a lesser degree of validation in research protocols and have no established role in clinical practice.\textsuperscript{41,42}

**Recommendations** – (1) Structural neuroimaging exams, CT or preferably MR, are indicated for diagnostic investigation of dementia syndrome to rule out secondary causes (Standard). (2) The identification of temporal mesial atrophy on MRI scans, by visual analysis and manual or automated volumetry, contribute to the diagnosis of AD in clinical practice (Practice Option), although it is of greater value for use in group comparisons within research protocols. (3) MRS can be recommended for research protocols.

### Molecular and functional neuroimaging

**Markers**

Currently, the diagnosis of neurodegenerative conditions can be based on two main classes of biomarkers: (1) “pathologic signature” biomarkers; and (2) biomarkers of neuronal degeneration and synaptic dysfunction.

Pathologic signature markers constitute markers of amyloid-\(\beta\) plaque deposits in neural tissue on positron emission tomography (PET). The presence of \(\beta\)-amyloid deposits are known to precede the emergence of clinically-confirmed AD by years or even decades.\textsuperscript{43} Results of antemortem studies in patients with MCI and even populations diagnosed with AD, correlated with those of necropsy studies, have confirmed a strong association of the \textit{in vivo} presence of this biomarker with the clinical disease or evolution/conversion to AD.\textsuperscript{44,45}

The markers of progressive neuronal degeneration are based essentially on determination of synaptic dysfunctions and functional disconnections by detection of regional perfusion and metabolism deficits in bilateral posterior temporo-parietal cortex and precuneus/posterior cingulate gyrus, respectively, by single-photon emission computed tomography (SPECT) and PET. Studies on correlation with necropsy findings are available, showing high diagnostic accuracy of these biomarkers when correlated with the characteristic anatomopathological substrates involved in AD.\textsuperscript{46}

**Clinical applications of biomarkers: limitations and indications**

**“PATHOLOGICAL SIGNATURE” BIOMARKERS**

Despite evidence of a correlation between the \textit{in vivo} presence of the amyloid-\(\beta\) protein on PET and the diagnosis of AD in the dementia, MCI or even pre-clinical states,\textsuperscript{47} the role of these biomarkers as a tool for early detection of the disease in routine clinical practice remains unclear.\textsuperscript{48} Several factors limit the routine use of these biomarkers, namely:

- Availability and cost in Brazil.
- Absence of standardized qualitative and quantitative criteria for accurately differentiating among high, low and intermediate probability diagnoses.
- Definition of its value as a prognostic indicator of future conversion to dementia. Additionally, the typical time interval which elapses between detection and development of dementia is not yet known.
- Many studies use matched group analyses in which transposition to individual-based analyses is not yet well defined.
- Absence of a proven therapeutic arsenal enabling reversal of, or control of evolution to, the dementia stage of AD, especially in pre-clinical or MCI phases.

### BIOMARKERS OF NEURONAL DEGENERATION

There is currently a body of evidence, including correlation with necropsy findings, that demonstrates high accuracy in diagnosing AD by means of determination of metabolic and perfusion deficits in bilateral association cortex, including the precuneus and posterior cingulate.\textsuperscript{49} Patients with MCI presenting with these functional deficits on functional neuroimaging as an indirect indicator of neuronal degeneration and principally, synaptic dysfunction, shall be categorized as converters in contrast to patient groups which have no deficit in regional blood flow on SPECT (rCBF) or regional glucose consumption deficit on PET.\textsuperscript{50} The progressive cognitive decline seen in AD is strongly associated with the presence of synaptic dysfunction which in turn is directly correlated with PET/SPECT findings.\textsuperscript{51} However, these findings are not strictly specific and may be observed in association with other neurological conditions (such as Parkinson’s disease and vascular dementia). Therefore, indication of these techniques should invariably be made as a supplement to clinical diagnosis, which remains the gold standard for AD diagnosis.

Another controversial aspect is the choice between PET and SPECT, given that the former offers 15 to 20% greater accuracy but is significantly more costly and with limited availability in Brazil. Therefore, supplementary indication remains conditioned on clinical judgement, taking into account the availability of the technique and the socio-economic situation.

**Recommendations** – (1) When available, “pathologic signature” biomarkers can be employed in investigation protocols or in clinical therapy trials. In clinical practice, their use can contribute to greater
accuracy diagnosing AD in both dementia and MCI phases (Rule). (2) Biomarkers of neuronal degeneration (SPECT and PET) when available, increase diagnostic reliability in clinically well-defined cases of AD and also assist in the differential diagnosis of other types of dementia (Rule).

Cerebrospinal fluid exam (CSF)

The CSF exam comprises the supplementary propedeutic on the diagnosis of various causes of dementia. It is extremely useful for identifying infectious dementia conditions affecting the central nervous system such as neurosyphilis, neurocysticercosis, neuro-Aids (dementia-Aids complex), herpetic meningoencephalitis, chronic meningitis, Creutzfeldt-Jakob disease; in dementia conditions of neoplastic, paraneoplastic and lymphoproliferative diseases; in dementia conditions of inflammatory and auto-immune diseases; as well as in hydrocephalus especially normal pressure hydrocephalus with application of the "tap-test".

In AD, there are biomarkers appearing in CSF that determine a "pathological signature" of the disease. This entails the measures of two alterations: (1) reduction in amyloid-β 1-42 protein, the main component of neuritic plaques; (2) increase in tau and phosphorylated tau proteins, due to neuronal degeneration associated to intracellular accumulation of neurofibrillary tangles. Reduction in amyloid-β 1-42 protein and increase in tau and phosphorylated tau have a sensitivity and specificity ranging from 85% to 90% for diagnosing AD.

Temporally, pre-clinical and pre-dementia phases of AD can be observed by reduced amyloid-β 1-42 protein levels in CSF. In a later phase, albeit still clinically asymptomatic, the neuronal degeneration markers tau and phosphorylated tau protein can also be detected. Similarly, these markers are also changed in patients with MCI evolving to AD.

Interpretation of these biomarkers in CSF should be done carefully and set against the clinical condition of the patient. This is important since the classic profile of alterations across all CSF biomarkers is often lacking. Future multicentric studies are needed before implementation of the exam in routine clinical practice.

Recommendations – (1) The CSF is indicated in the investigation of pre-senile onset dementia (before 65 years of age) in cases with atypical clinical presentation or course, communicant hydrocephaly and the presence of any evidence or suspicion of inflammatory, infectious or prion disease of the central nervous system (Standard). (2) Levels of amyloid-β 1-42 peptide and tau and phosphorylated tau proteins in CSF can be employed in research protocols or clinical therapy trials. In clinical practice, its use can contribute to greater accuracy diagnosing AD in both dementia and MCI phases (Rule).

Electroencephalogram (EEG) and evoked potentials

Visual analysis of routine EEG is a useful method to aid differential diagnosis of dementia types, distinguishing between dementia syndrome, cognitive complaints and psychiatric disorders. EEG can also aid diagnosis of Creutzfeldt-Jakob disease, suggest the possibility of toxic-metabolic disorder or transient epileptic amnesia. The most common findings in AD are slowed background frequency with increased delta and theta bands, and reduction or abolition of the alpha frequency band. However, these changes are generally only visible on EEG in moderate and advanced stages of AD. There is an inverse correlation between degree of cognitive impairment and strength of electrical activity at high frequencies (alpha and beta) on EEG. A reduction in the alpha band and increase in theta, plus lower mid-range frequencies, are characteristic electroencephalographic findings of patients with AD, but EEGs can be normal at early stages of the disease in up to 14% of cases. The accuracy of electroencephalographic diagnosis of AD patients versus healthy controls with similar demographics reported by different studies varies widely. EEG revealing patterns of diffuse abnormalities alone are more frequently associated to AD whereas those showing diffuse and focal alterations suggest AD and/or other forms of dementia.

Since the very first quantitative EEG studies, both spectral and statistical analyses have been applied to the method. Lower alpha and beta activity has been observed in a number of studies conducted over the last few decades. In addition, the alpha rhythm could serve as a potential diagnostic marker, since there is a reduction in alpha frequency to 6.0-8.0 Hz in patients with mild AD. Another highly sensitive aspect in EEG is the base spectral analysis which is associated with the clinical diagnosis of AD. The sensitivity of spectral analysis has been found to range from 71% to 81% in various studies and correlates significantly with neuropsychological tests.

Another feature offered by EEG is coherence analysis (Coh) which assesses the level of covariance among spectral measurements obtained by a pair of electrodes. High Coh has been taken as evidence of structural and functional connections among cortical regions.

In guidelines produced by the Brazilian Medical Association (AMB) and the Brazilian Society of Clinical Neurophysiology (SBNC), EEG is recognized as an established method for assessing dementias. In addition, frequency
analysis represents a valuable tool for improving the detection of slow waves. This analysis can show increased theta wave activity and reduced alpha and beta waves in AD patients compared with healthy individuals.\textsuperscript{78} Frequency analysis is also a predictor of the development of cognitive impairment, independently of clinical parameters.\textsuperscript{79} Moreover, there is a strong correlation between EEG activity and cognitive brain functions quantified by specific assessment scales.\textsuperscript{79} The use of a combination of these EEG parameters with cognitive assessment instruments is recommended to improve dementia detection.

With regard to evoked potentials, delayed P300 latency is considered the best parameter for electrophysiological diagnosis of cognitive decline and dementia. However, the wide inter-individual variation (approximately 50 milliseconds) limits its diagnostic reliability in initial phases of AD, since this changes can also occur in depression, schizophrenia and other dementia types.\textsuperscript{2,63}

**Recommendations** – (1) The use of routine EEG is an established supplementary method for differential diagnosis of dementia syndrome from other conditions impairing cognitive functioning such as epilepsy, toxic-metabolic and infectious encephalopathies (Standard). EEG is an important tool for diagnosing Creutzfeldt-Jakob disease (Standard). (2) EEG is not helpful for early diagnosis of AD (Standard). (3) Event-related evoked potentials (example P300, N400) are recommended for use in the research setting only.

**Genetic study**

On the genetic front, rare dominant autosomal mutations indicating early onset of AD (before 65 years of age) with complete penetrance is associated to three genes: amyloid precursor protein (APP),\textsuperscript{80} presenilin 1 (PSEN1),\textsuperscript{81} and presenilin 2 (PSEN2) genes.\textsuperscript{82} Mutations of the APP gene located at chromosome 21 are found within or adjacent to areas which codify the amyloid-\beta peptide and account for less than 5% of familial AD cases.\textsuperscript{83} Mutations in PSEN1 and PSEN2 genes located at chromosome 14 and 1, respectively, codify the proteins of highly conserved membrane needed for activity of the \(\gamma\)-secretase enzyme which cleaves the APP protein. Mutations in PSEN1 are responsible for the majority of cases of familial AD whereas mutations in PSEN2 are less frequent.\textsuperscript{84}

The e4 allele of apolipoprotein E (APOE), a susceptibility variant with common and incomplete penetrance, significantly increases the risk of developing late-onset AD (after 65 years of age).\textsuperscript{85,87} The APOE gene, located at chromosome 21, has three common allelic forms: e2 (occurs in 8% of the white population), e4 (in 15%) and e3 (in 75%).

The presence of the e4 allele triples the risk of developing the disease and individuals homozygous for e4 have a 12-fold greater chance of developing AS than e3 individuals. The presence of the e2 allele however, is a protective factor against AD.\textsuperscript{87} Similar allelic and genotypic distribution, besides association of the presence of the e4 allele with AD diagnosis, were also found in population-based and case-control studies in Brazil.\textsuperscript{88,92} APOE is involved in cholesterol transport and formation of the amyloid-\beta by as yet unknown mechanisms.\textsuperscript{87} Approximately 42% of individuals with AD do not carry the e4 allele of the APOE gene.\textsuperscript{93}

Numerous publications compiled by the AlzGene database report associations between AD and hundreds of supposed risk alleles in other genes.\textsuperscript{84} The neuronal sortilin-related receptor (SORL1) has been genetically associated to late-onset AD in a population of heterogeneous ethnicity in the United States.\textsuperscript{95,96} A recent meta-analysis showed evidence of association of genetic susceptibility polymorphisms located at chromosome 1 (CR1), chromosome 7 (PICALM) and 8 (CLU), although without the same impact odds ratio of the APOE.\textsuperscript{97} Cholesterol is believed to modulate central processes in the pathogenesis of AD. The association of the APOE, CH25H, CLU, LDLR, and SORL1 genes with AD could be mediated by cholesterol-related mechanisms or by direct effects of these proteins on amyloid-\beta metabolism.\textsuperscript{98}

In general, all people with Down’s syndrome (trisomy of chromosome 21) develop neuropathologic markers for AD after 40 years while more than half of this patient group have cognitive decline. This believed to be caused by overexpression of the gene of APP at chromosome 21, leading to increased production of the amyloid-\beta peptide.\textsuperscript{99}

Most individuals with early-onset MCI and mutations in the genes APP, PSEN1 or PSEN2, develop AD, as do individuals with late-onset AD and one or two e4 alleles of the APOE.\textsuperscript{61,99}

**Indication of genetic testing for AD**

In general, clinical use of the genetic test for APOE with predictive intent in asymptomatic individuals is not recommended because the presence of the e4 allele is not necessary nor sufficient to reach a diagnosis of AD.\textsuperscript{100,101} Family history on the other hand, represents a better predictor of risk for AD.\textsuperscript{101} Empirically, first-degree relatives of a single individual with AD have a 20–25% chance of developing the disease during their lifetime compared to 10% for individuals with no family history of the disease.\textsuperscript{95}

With regard to the diagnosis of pre-clinical AD, the role of biomarkers for detecting and tracking this stage of the disease is of central importance for the development of effective treatments. In this context, monitoring of carriers...
of the ε4 allele of the APOE suggests evidence of very early onset synaptic dysfunction (young and middle-aged individuals) on functional neuroimaging studies. It should be underscored that recommendations for diagnosing preclinical AD apply exclusively for research purposes, having no clinical implications at present.62

The presence of the ε4 allele of the APOE is not sufficiently specific for inclusion in the new criteria for probable AD with a high degree of certainty.62 Clinico-pathologic series in which the genotyping of the APOE was estimated were not favorable for introduction of the test for the gene in clinical practice. The sensitivity and specificity of clinical diagnosis alone were 93% and 55%, respectively, whereas for the genotyping of the APOE this was 68% and 65%, respectively.102

Although the ε4 allele of the APOE is an important predictive factor for conversion of MCI into AD, its use in clinical practice is not yet established.91,102 However, in future studies of potential pre-morbid biomarkers for AD, the inclusion of genetic genotyping is indicated to increase accuracy.102

Genetic susceptibility tests for asymptomatic adults at risk for early-onset AD due to APP, PSEN1 and PSEN2 mutations are clinically available. There is a general consensus that these tests should not be performed in childhood.101 Moreover, there is consensus that the performing of tests must be preceded by thorough and extensive genetic counseling and assessment of the favorable and unfavorable aspects of disclosure. Monitoring of these individuals who receive genetic information should also be carried out.102,103-105

**Recommendations** – (1) Genotyping of APOE is not recommended for diagnostic purposes in patients with AD, nor as a predictive factor of developing the disease in individuals that are asymptomatic or who have MCI in clinical practice (Standard). The same holds for other susceptibility polymorphisms described to date (Standard). (2) Investigation of the mutations of APP, PSEN1 and PSEN 2, when available, is recommended in cases of AD with a family history consistent with autosomal-dominant inheritance (Standard). (3) Investigation of mutations of APP, PSEN1 and PSEN 2, when available, in asymptomatic individuals with family member(s) who have genetically-confirmed diagnosis of AD should only be indicated after extensive genetic counseling and with the full consent of the individual (Practice Option).

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