Impact of the New Conceptual Framework of Alzheimer's Disease in Imaging Studies

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R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Neurology*,
https://doi.org/10.1007/978-3-030-53168-3_13

Abstract

For both research and clinical settings, the importance of an accurate diagnosis of AD is imperative given its much-feared consequences, which cannot be understated. The diagnosis of AD should be restricted to the presence of both: (1) a clinical phenotype, either typical (characterized by an amnestic syndrome of the hippocampal type) or atypical (including the posterior variant, the logopenic variant and the frontal variant, to which it may be possible to add the corticobasal syndrome), and (2) in vivo evidence of positive pathophysiological markers, acquired with molecular neuroimaging or with cerebrospinal fluid investigation. In the preclinical state of the disease, evidence reported in the last few years suggests that the presence of tau and amyloid positivity is not sufficient to definitively predict the invariable occurrence of symptoms. Therefore, measures of pathophysiological markers are not recommended in cognitively unimpaired individuals, in the absence of therapies or prevention programs showing efficacy on delaying onset of disease (although this may happen outside the clinical setting for specific reasons, for clinical trials, research projects or cohort studies).

In this chapter we propose an overview on the evolution of Alzheimer's disease definition and of its diagnostic approach in the medical and scientific community since 1907. Finally, we expose the latest data regarding this disease in order to propose a new framework for the diagnosis of Alzheimer's disease in a clinical setting.

13.1 Alzheimer's Disease, History, and Evolution of Concepts

Alois Alzheimer first described the disease that shares his name in it at the beginning of the twentieth century (Alzheimer 1907; Stelzmann et al. 1995). However, it was not until the last quarter of the twentieth century that Alzheimer's disease (AD) was recognized as the major cause of dementia in the general population by the medical and scientific community.

Since the beginning, AD was defined as a dementia. In an oral communication in 1906, published in 1907, Alzheimer reported the case of Auguste Deter, a 51-year-old woman. We have here the complete picture of AD as is currently defined: a progressive cognitive decline, primarily involving memory and leading to dementia, associated with neurofibrillary tangles (revealed later to be the result of hyperphosphorylated tau protein deposits) and a "special substance" that was found later to be an accumulation of amyloid β-proteins. Alzheimer thought this condition was "eine

eigenartige Erkrankung der Hirnrinde," i.e., an unusual illness of the cerebral cortex (Alzheimer 1907). Three years later, Kraepelin proposed to name after Alzheimer presenile dementia cases he identified as distinct from senile dementia, and this distinction remained predominant within the scientific and medical circles for much of the twentieth century (Kraepelin 1910). As a result of demographic, political, and scientific developments, senile dementia became increasingly recognized within the aging population, beyond what could be explained by the arteriosclerotic lesions or other known phenomena of old age. In April 1976, Robert Katzman sounded the call that awakened the world to the burden of Alzheimer's disease, with an editorial in the *Archives of Neurology* (Katzman 1976), in which he included the neurodegenerative condition among the world's greatest killers and Alzheimer's disease as the leading cause of dementia. A growing consensus around this call helped bring Alzheimer research into the modern era by "officially" acknowledging AD as a condition affecting patients in old age. Seven years later, the publication of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria confirmed AD as a disease, independent of age of presentation, and therefore as a cause of senile dementia (McKhann et al. 1984).

13.2 The 1984 NINCDS-ADRDA Criteria for AD

The publication of the NINCDS-ADRDA criteria in 1984 defined Alzheimer as a **dementia** (McKhann et al. 1984). Three major tenets of these criteria were that (1) the clinical diagnosis of AD could not be definitively made until there was a requisite postmortem confirmation; (2) consequently, the clinical diagnosis of AD could only be "probable"; and (3) the diagnosis could only be applied when the disease was advanced to the functional disability threshold of dementia. Based on the NINCDS-ADRDA criteria, the diagnosis of probable AD requires that a dementia syndrome is established by clinical examination, documented by mental status questionnaire, and confirmed by neuropsychological testing with evidence of deficit in two or more areas of cognition, including memory with a progressive worsening over time responsible for a significant impact on activities of daily living. Therefore, the clinical diagnosis of AD is made using a two-step procedure: (1) an initial identification of a dementia syndrome and then (2) the exclusion of other possible etiologies of dementia with blood/CSF investigations for ruling out infectious, inflammatory, or metabolic diseases and with brain neuroimaging (CT scan or MRI) for excluding small vessel diseases, strategic lacunar infarcts, large vessel infarcts, and/or cerebral hemorrhages, brain tumors, hydrocephalus, and similar disorders. These examinations were not indicated for identifying specific features of AD but only for excluding other diseases: AD was a default diagnostic.

With time, it became obvious that the established classification of AD as purely a dementia had important drawbacks, especially in dealing with the early and prodromal stages of the disease.

13.2.1 The MCI Construct

The early changes in cognition that precede the onset of dementia were not identified at that time. They were included in a vague age-related concept described by a wide range of nosological terms including age-associated memory impairment, age-related cognitive decline, age-associated cognitive decline, mild cognitive disorder, mild neurocognitive disorder, cognitively impaired not demented, and mild cognitive impairment (MCI) (Chételat and Baron 2003; Matthews et al. 2007; Reisberg et al. 2008; Petersen et al. 1999, 2001). This latter designation of MCI has been the most widely used diagnostic label referring to individuals who have objective memory and/or cognitive impairment and whose activities of daily living are considered to be generally normal. Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from normal, but is clearly not the invariable clinical outcome at follow-up (Mitchell and Shiri-Feshki 2009; Petersen and Negash 2008; Palmer et al. 2008).

One of the proposed advantages of MCI has been its potential utility for clinical trials directed at delaying the time to onset of AD. The intention in these trials on MCI was to include a large number of patients at a predementia stage of AD. Unfortunately, the concept of MCI has a major limitation: collecting under a single label a variety of pathological entities (Dubois and Albert 2004). When the MCI inclusion criteria of these trials were applied to an observational cohort of memory clinic patients, they had diagnostic sensitivities of 46–88% and specificities of 37–90% in identifying future AD (Beach et al. 2012). Given these numbers, these trials have clearly treated a significant number of patients who do not have AD or are not going to progress to AD for a long time. This has diluted the potential for a significant treatment effect and may have contributed to the negative outcomes where none of the tested medications were successful at delaying the time to diagnosis of AD (Jelic et al. 2006). To decrease the clinical and pathological heterogeneity, sub-typing of amnestic and non-amnestic MCI has been proposed. However, only 70% of amnestic MCI cases that have progressed to dementia actually met neuropathological criteria for AD (Jicha et al. 2006).

13.2.2 Limitations of the 1984 NINCDS-ADRDA Criteria

In the early 2000s, two major considerations emphasized the need to revise the conceptual framework of AD:

1. The NINCDS-ADRDA criteria for AD have a low specificity against other dementias

   This is mainly due to the fact that, at the time of these criteria, i.e., 1984, the clinical phenotype of AD was not specified and no reference to biomarkers of AD was proposed. This explains why AD was frequently misdiagnosed with other neurodegenerative diseases that can fulfill the NINCDS-ADRDA criteria

(Varma et al. 1999). Since 1984, great progress had been made in several domains:

(a) The clinical phenotype of AD has been elucidated: in more than 85% of the cases, AD presents as a progressive amnestic disorder (Dubois and Albert 2004; Qiu et al. 2019). Postmortem studies of AD patients have shown a rather specific pattern of cortical neuronal lesions, which appear to begin within the medial temporal lobe structures (entorhinal cortex, hippocampal formations, parahippocampal gyrus) (Braak and Braak 1991; Delacourte et al. 1999), areas known to be critical for long-term episodic memory.

(b) Diagnostic accuracy of Alzheimer's disease (AD) has also been improved in the last years because of the characterization of new dementias through specific criteria, including the primary progressive aphasias, semantic dementia, cortico-basal degeneration, posterior cortical atrophy, and Lewy body dementia. The individualization of these diseases, which were previously confused with AD, has consequently decreased its apparent heterogeneity.

(c) Reliable biomarkers for AD have been isolated. Over the past three decades since the NINCDS-ADRDA criteria were published, great progress has been made in identifying the AD-associated structural and molecular changes in the brain and their biochemical footprints. MRI enables detailed visualization of medial temporal lobe structures implicated in the core diagnostic feature of AD (Scheltens et al. 1992; Seab et al. 1988). PET using fluorodeoxyglucose (FDG) has been approved in the USA for diagnostic purposes and has been shown to be sensitive and specific in detecting AD in early stages (Ferris et al. 1980; Chase et al. 1984; Choo et al. 2007). CSF biomarkers aimed at detecting the key molecular pathological features of AD in vivo (low Aβ and high total tau/phospho-tau levels) have become available and can be assessed reliably (Engelborghs et al. 2008). Their diagnostic predictability has been extended to prodromal stage (Hansson et al. 2006). In 2004, in vivo imaging of pathology-specific proteins (Pittsburgh compound B [PiB]) (Klunk et al. 2004) was discovered that makes possible to accurately identify AD brain lesions in demented patients and also in patients at prodromal and even preclinical stages of the disease. The growing body of evidence on AD biomarkers allows these to be now incorporated into new diagnostic research criteria for AD.

2. Diagnosing AD at the dementia stage is too late

AD is already at work when the patients express the first cognitive symptoms, and there is no reason to link the diagnosis of a disease to a certain threshold of severity and to exclude from diagnosis and treatment a large number of patients who are not yet expressing a full-blown dementia. At a time where clinical trials of disease-modifying treatments of AD dementia have failed to show efficacy, at least on meaningful clinical outcomes, identification of AD at a prodromal stage and recruiting patients several years before dementia was a critical next step. Individual clinicians' experience in dementia diagnosis and the quality of the information they receive on the cognitive and functional status of the patient impact significantly on the threshold of detection of the transition to AD

(Engelborghs et al. 2008). Therefore, it was timely to elaborate new criteria, at least for research purposes, with the idea of eliminating the MCI construct, thus bypassing issues in the clinical categorization process and consequent problems with reliability.

13.3 The IWG Conceptual Framework for AD

Earlier and more specific disease recognition were the two goals of the AD diagnostic framework proposed by the International Working Group (IWG) (Dubois et al. 2007, 2010).

13.3.1 The 2007 IWG Criteria

In 2007, the IWG provided a new conceptual framework according to which AD moves from a clinicopathological entity to a *clinico-biological entity* (Dubois et al. 2007). The new IWG criteria stipulate that AD can be recognized in vivo based on the presence of two associated features. The first is the evidence of an *amnestic syndrome of the hippocampal type* at least in the typical form of the disease (Dubois and Albert 2004). The importance of a specific memory pattern was highlighted because none of the other cognitive changes, which can be encountered in AD even at a prodromal stage, are specific of the disease. The second necessary feature is supportive evidence from biomarkers that were proposed for the first time for the diagnosis of AD. These include abnormalities on structural (medial temporal lobe atrophy on MRI) and molecular neuroimaging (abnormalities in glucose metabolism or amyloid burden on PET scanning) and in CSF protein concentrations. As a consequence, neuroimaging and CSF investigations are no longer proposed for excluding other etiologies of brain dysfunction but are primarily used for detecting AD-related changes. The added value of biomarkers and therefore the specificity of the IWG criteria for the diagnosis of AD were further confirmed (de Jager et al. 2010; Bouwman et al. 2010; Schoonenboom et al. 2008; Galluzzi et al. 2010). This is a requirement for research projects where a highly specific diagnosis is needed: (1) for the study of specific outcomes of AD that requires the follow-up of well-phenotyped cohorts of patients; (2) for the discovery or validation of new biomarkers which cannot be conducted on heterogeneous populations with a low/intermediate likelihood of diagnostic accuracy; or (3) for inclusion in clinical trials. The 2007 IWG criteria were successfully implemented in current Phase 2 clinical trials for prodromal AD with gamma secretase inhibitors and immunotherapies, and they have been qualified by the European Medicine Agency (EMA) for use in AD clinical trials (Isaac et al. 2011).

The use of biomarkers made it possible to extend the concept of AD to the *prodromal* (predementia) stage because biomarker changes are not completely linked to disease stages: their positivity reinforces the diagnosis of the disease at any stage.

Accordingly, the presence of a specific memory profile with a positive biomarker moves the patient from an undetermined MCI status to that of prodromal AD.

13.3.2 Further Refinements of the 2007 IWG Criteria for AD

1. *The first important refinements of these criteria came in 2010* where several clarifications were proposed (Dubois et al. 2010).
   (a) Typical versus atypical AD. The diagnostic framework introduced the concept of "atypical forms of AD." An amnestic presentation for AD may not always be the case, and other specific clinical phenotypes can be associated with postmortem evidence of AD pathology, in 15% of the cases. These specific clinical phenotypes include non-amnestic focal cortical syndromes, such as logopenic aphasia, bi-parietal atrophy, posterior cortical atrophy, and frontal variant AD. With the advent of biomarkers providing in vivo confirmation of Alzheimer's pathology, it is now possible to include these clinical disorders as atypical AD if there is convincing biomarker support.
   (b) Preclinical states. There was also an elaboration beyond symptomatic stages of AD. In approximately 20–30% of normal individuals over age 70, the presence of positive biomarkers (reduced CSF levels of Aβ 1-42 or increased deposits of Aβ in the brain as evaluated by amyloid PET) suggests an underlying AD pathology (Morris et al. 2009; Resnick et al. 2010; Stomrud et al. 2007). As the percentage of persons who will progress from this state to symptomatic clinical conditions within their life span was at that time unknown (some elderly with positive biomarkers will never develop AD symptoms), these individuals without clinical symptoms but with positive biomarkers of Alzheimer pathology were considered as *asymptomatic at risk of AD* (ARAD). Asymptomatic at risk for AD refers to subjects with a normal cognitive condition and evidence of amyloidosis in the brain (on PET amyloid) or Alzheimer pathologic changes in the CSF. Additionally, a designation of the stage of *presymptomatic AD* was reserved for individuals carrying autosomal dominant monogenic AD mutations as they will inevitably develop clinical AD if they live long enough. Since then the understanding of AD as a continuous clinical-biological entity encompassing both asymptomatic and symptomatic stages has grown in consensus.
2. *Data on the respective values of biomarkers were obtained*. No hierarchy between the biomarkers was proposed in the 2007 paper. Each biomarker was considered as having the same weight, in the absence of evidence for distinguishing between biomarker performance and accuracy at that time. However, new evidence had shown that biomarkers have different specificity properties. For instance, it appears that the specificity of hippocampal volume for AD may be influenced by several conditions, such as aging (Van De Pol et al. 2006), diabetes, sleep apnea, bipolar disorders (Fotuhi et al. 2012), and by other brain disorders including limbic age-related TDP-43 encephalopathy (LATE), Lewy-related pathology, argyrophilic grain disease, and frontotemporal dementia

(Barkhof et al. 2007; Galton et al. 2001). All these confounding factors make volumetric measure of medial temporal lobe structures less pertinent, at least on an individual level.

The 2010 revision of the IWG criteria divides biomarkers of AD into two groups: (1) *pathophysiological markers* which identify AD pathology since they are strongly correlated with postmortem AD histo-pathological changes. They are considered as markers of diagnosis and mainly consist of positive PET-amyloid scan results or CSF abnormalities; (2) *topographical markers* reflect downstream damage and are markers of progression, more targeted at assessing change over time and predicting outcomes. They mainly consist of hippocampal atrophy on volumetric MRI or hypometabolism on FDG-PET.

CSF changes were promising pathophysiological markers given their good correlations with postmortem AD changes (Buerger et al. 2006; Seppälä et al. 2012; Strozyk et al. 2003; Tapiola et al. 2009) reaching a sensitivity for AD detection of 96.4% (Shaw et al. 2009). However, Aβ alone may not be a sufficient marker given evidence of an overlap with other forms of dementias (such as diffuse Lewy body dementia and cerebral amyloid angiopathy) and because of its presence long before clinical AD. Numerous studies have shown that the combination of the three CSF biomarkers improves their discriminating accuracy (Blennow et al. 2010). Finally, Amyloid-PET imaging showed very high postmortem validation (Clark et al. 2011; Ikonomovic et al. 2008), good predictability for progression to AD dementia (Jack et al. 2010a; Koivunen et al. 2011), but low sensitivity to change in the clinical stages (Ossenkoppele et al. 2012).

3. *The 2014 IWG-2 criteria*: On the basis of these refinements, the IWG proposed in 2014 that the diagnosis of AD can be simplified, requiring the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer's pathology (CSF Aβ and tau changes or Amyloid PET positivity) (Dubois et al. 2014). Downstream topographical biomarkers of the disease, such as volumetric MRI and fluorodeoxyglucose PET, might better serve in the measurement and monitoring of the course of disease (Dubois et al. 2014). In addition, the IWG introduced the notion of co-occurrence of pathologies in AD and proposed the diagnosis of mixed AD with Lewy body disease or cerebrovascular disease.

13.3.3 The 2011 NIA-AA Criteria

In line with the conceptual evolution in the field, the NIA/AA published diagnostic criteria in 2011 (Jack et al. 2011; Sperling et al. 2011; McKhann et al. 2011; Albert et al. 2011) that had the advantage of being applicable in both clinical and research settings. They similarly advanced from the NINCDS-ADRDA framework to broaden the coverage of stages of disease from the asymptomatic (preclinical), through the predementia stages (MCI due to AD) and through the most severe stages of dementia. They shared many features with the IWG criteria including recognition of an asymptomatic biomarker positive phase and of a predementia symptomatic

phase of AD. They also integrated biomarkers into the diagnostic process that were categorized into two types, one identifying amyloid abnormalities and one the downstream neurodegeneration. The most interesting contribution of the NIA/AA criteria was the one concerning the preclinical stages of the disease. Based on the biomarker model introduced by Jack and colleagues (2010b), it was proposed (Sperling et al. 2011) that (1) Aβ accumulation biomarkers become abnormal first and a substantial Aβ load accumulates before the appearance of clinical symptoms; (2) biomarkers of synaptic dysfunction, including FDG and functional MRI (fMRI), may demonstrate abnormalities very early, particularly in APOE ε4allele carriers, who may manifest functional abnormalities before detectable Aβ deposition (Reiman et al. 2004); (3) structural MRI is thought to become abnormal a bit later, as a marker of neuronal loss, and MRI retains a close relationship with cognitive performance through the clinical phases of MCI and dementia (Risacher et al. 2009); and (4) none of the biomarkers is static; rates of change in each biomarker change over time and follow a nonlinear time course.

The NIA/AA criteria differed conceptually from the IWG criteria in a number of important ways. At the preclinical stages, the position taken in this framework has been that the presence of Alzheimer pathologic changes indicates the diagnosis of AD and that this diagnosis is applicable at this "in situ" stage for research purposes. At the pre-dementia (MCI) stage, the framework is probabilistic and applies a likelihood of progression based on the presence of AD biomarkers, with designation either of biomarkers that reflect amyloidopathy (CSF Aβ or amyloid PET) or those that are "downstream" indicative of neuronal degeneration (CSF tau, FDG glucose, volumetric MRI). The likelihood of progression is determined by the specific combination of positive, negative, or indeterminate results on the "amyloid" and "downstream" biomarkers. Differently from the IWG criteria, the MCI stage of AD is formally distinguished from the dementia stage, which has its own diagnostic criteria. In the dementia stage, ten categories of dementia of the AD type are established including probable AD dementia, possible AD dementia, probable or possible AD dementia with evidence of the AD pathophysiological process, and pathophysiologically proven AD dementia. The later stage retains most of the features of the past diagnosis of probable AD (McKhann et al. 1984) despite the low specificity, the limited positive predictive value, and poor negative predictive value of these criteria (Varma et al. 1999).

13.3.4 The 2015 Consensus on the Preclinical Stage of AD

In 2015, a consensus meeting brought together experts from the International Working Group (IWG), the National Institute of Aging (NIA), and the Alzheimer Association (AA) for the definition, natural history, and diagnostic criteria of preclinical AD (Dubois et al. 2016). The fact that the disease process starts many years before the development of symptoms and that effective interventions could be initiated at this time in the future makes the definition of the preclinical stage necessary. Theoretically, the definition of preclinical AD would span from the first

neuropathological brain lesions to the onset of the first clinical symptoms of AD. In practice, however, these boundaries are challenging, and the definition also relies on a *low/high risk dichotomy* to further develop clinical AD. The risk—defined as the probability for a patient to develop the clinical symptoms during the remainder of his/her lifetime—is due to how fast the individual is progressing (determined by established risk enhancing modifiable or non-modifiable factors, such as age, modifying genes, cognitive reserve, and comorbidities) *and* how advanced the individual is on his/her curve of progression (stage of biomarker expression). Based on this classification, it was proposed to distinguish between: (1) an already developed AD pathology evidenced by the co-occurrence of amyloid AND tau pathology (that can be inferred in vivo with the use of pathophysiological biomarkers), whatever the stage (preclinical stage or symptomatic/prodromal and dementia stage), and (2) a situation at risk of AD (ARAD) mainly in asymptomatic individuals exhibiting an isolated brain amyloidopathy (asymptomatic A+) or tauopathy (asymptomatic T+). This reflects the separation between the disease itself and the presence of risk factors. Therefore, "preclinical AD" was defined by the presence of both Aβ and Tau markers beyond pathological thresholds.

13.3.5 A/T/N/ Classification

Rather than considering AD as a combination of symptomatic and neuropathological changes, Jack and a group of co-authors (Jack et al. 2016a, 2018a) recently proposed a descriptive, biomarker-based research framework of the disease, completely agnostic to clinical symptomatology. This "ATN" framework, developed by the NIA-AA working group, is centered around a biomarker definition of disease according to amyloid (A), tau (T), and neurodegeneration (N) status with an AD diagnosis characterized by the presence of both amyloid and tau positivity (A+T+). Therefore, even in the absence of any cognitive signs or symptoms, those subjects who have both abnormal amyloid and tau biomarkers (A+T+) are diagnosed as AD and those with abnormal amyloid biomarker only (A+T− or A+N−) are considered within an AD continuum. The A/T/N classification moved from a definition of AD as an illness with a phenotype to a definition of AD as a conjunction of pathological findings, which would cover all preclinical and clinical stages of the disease. In consequence, under this AD classification, there is an extended continuum from individuals who are cognitively normal to severely demented patients in the end stages of disease.

The NIA framework constitutes the summation of the previous works. It definitively disentangles the diagnosis of AD from the label dementia and opens up the possibility for research into the biological cause before symptoms occur, which is imperative to develop drugs for the earliest stage. For research purposes, the model

of dynamic biomarkers of Alzheimer's pathological cascade has the advantage of providing an unbiased framework useful for operationalizing the therapeutic roadmap by the identification of the sequence of biological events.

The "ATN" classification is easily applicable on an individual level, where "A+" corresponds to the presence of amyloid determined by amyloid PET or analysis of CSF Aβ42; "T+" is consistent with neurofibrillary tangles ascertained by tau PET or CSF phospho-tau; and "N+" is associated with a downstream neurodegeneration biomarker, such as hippocampal atrophy on structural MRI, hypometabolism in the brain as evidenced by FDG-PET, or CSF total tau. However, though relevant for research purposes, this "framework is not intended for general clinical practice," as underlined by the authors themselves (Alzheimer 1907).

These 2018 NIA AA criteria have engendered significant debate about the biomarker-based disease diagnosis, with clinical symptoms and phenotype being removed from the diagnostic framework and used only for staging. This debate has highlighted the need for clinical validation of this research (Garrett 2018; Glymour et al. 2018; Rabinovici and Carrillo 2019; Jack et al. 2019a; Jack 2020; Morris et al. 2018; Jagust et al. 2019; Louie 2019; McCleery et al. 2019a, b; Sweeney et al. 2019; Frisoni et al. 2019; Langa and Burke 2019). Recently Jack and co-authors have put ATN classification to the test (Jack et al. 2019b) and showed that 50% of cognitive changes with older age was associated with underlying AD pathology. However, it remained unclear what accounted for the other 50% of cognitive changes. While "ATN" classification may be relevant for use in secondary prevention clinical trials, allowing patients to be stratified based on their prognostic profile, it still remains purely a research construct and has several limitations. Evidence reported in the last few years suggests that the presence of tau and amyloid positivity is not sufficient to definitively predict the occurrence of symptoms (see below). Besides this limitation, several additional points should be raised. First, more work needs to be done to understand the role of age in the prediction of individual patients and prognosis. Second, while "ATN" classification incorporates neuroimaging advances in the AD field, such as amyloid and tau PET, its application may be cost-prohibitive in many research projects and clinical trials. Amyloid PET reimbursement remains limited to specific situations, while tau PET tracer approval by the regulatory authorities is still pending. Third, equating AD to solely the presence of neuropathological lesions could lead to the risk of marketing medicinal products, which decrease brain pathology without proof of their efficacy on clinical symptoms. Last but not least, "ATN" research criteria may not apply for the clinical practice, as underlined by the authors ("this framework is not intended for general clinical practice" (Reisberg et al. 2008)). This being said, "ATN" classification represents an important advancement in the conceptualization of AD, making a step further to the in vivo early biomarker-based diagnosis of AD and understanding of its biological continuum.

13.4 Perspectives

13.4.1 General Considerations About a Biological Diagnosis of AD

For both research and clinical settings, the importance of an accurate diagnosis of AD is imperative given its much-feared consequences, which cannot be understated.

1. *In clinical setting*—When there are no symptoms, reliance on a biomarker only diagnosis must require a very secure and tightly elaborated natural history connecting the biomarker with invariable subsequent expression of clinical symptoms. It is only with a high level of confidence in these parameters that a diagnosis is ready for disclosure to patients or to their families. Recent experience with the Sokrates study underscores some of the uncertainties that are inherent in revealing amyloid PET results alone (Mozersky et al. 2018).
2. *For research purposes*—The model of dynamic biomarkers of the Alzheimer's pathological cascade has the advantage of providing an unbiased framework useful for operationalizing the therapeutic roadmap by the identification of the sequence of biological events. In clinical trials, there is a trend today to target the earliest stages of the disease, and even the preclinical stage, because it is considered that patients with dementia are too advanced in the disease for hoping for a recovery or even a stabilization of their symptoms with therapy. The utility of applying biomarkers to clinical phenotype in prodromal AD has transformed clinical trials in the early symptomatic stages of disease and has been associated with the first preliminary evidence of benefits with monoclonal Aβ passive immunotherapy (Budd-Haeberlein et al. 2018; Swanson et al. 2018). However, for those who are asymptomatic at risk through biomarkers characterization, the evidence of invariable progression is still needed.

13.4.2 Diagnosing AD: Biomarkers Alone May Not Be Sufficient

Evidence reported in the last few years suggests that the presence of tau and amyloid positivity is not sufficient to definitively predict the invariable occurrence of symptoms:

- *Postmortem examinations* have long described significant AD brain lesions in cognitively normal subjects without signs of decline, adding weight to the early twentieth-century debate on the relevance of these lesions to the pathophysiology underlying cognitive decline (Alzheimer 1911; Katzman et al. 1988; Villain and Dubois 2019). This was reinforced by recent large postmortem cohorts using quantification and digital neuropathological methods, from the Baltimore Longitudinal Study of Aging and the Nun Study (Iacono et al. 2014; Mortimer 2012; Perez-Nievas et al. 2013; Boluda et al. 2014; Mufson et al. 2016), and by a study of Braak et al. (Braak et al. 2011) which, in a systematic postmortem

brain examination, showed that AD brain lesions (including both amyloid and tau lesions) are found in more than half of subjects aged 70 years and older, regardless of clinical status, i.e., well beyond the prevalence of having cognitive impairment, expected in up to 30% (Knopman et al. 2016). This pathological-clinical discrepancy is also found in cross-sectional molecular neuroimaging studies: for instance, 19% of 576 cognitively unimpaired elderly subjects (mean age 71 years) were found to have both amyloid and diffuse tau (i.e., outside the medial temporal lobe) pathologies (Knopman et al. 2016), i.e., with a probable signature of intermediate or high AD pathology according to neuropathological criteria (Lowe et al. 2018).

- Moreover, postmortem examinations have found neurofibrillary tangles (NFT) in the medial temporal regions in almost every cognitively normal individual over 70 years old (Braak et al. 2011; Hyman et al. 2012; Braak and Braak 1997; Duyckaerts and Hauw 1997). This primary age-related tauopathy (PART) is an age-related normal occurrence of tauopathy in the absence or with a low extent of Amyloid pathology (Thal Aβ Phase ≤2 (Katzman and Kawas 1994)). It is noteworthy that the cognitive decline of these patients (T+ A±) is significantly slower than that of patients with AD (Crary et al. 2014). This last finding indicates that low A(+) (i.e., Thal Aβ Phase ≤2) associated with T(+) does not necessarily lead to an accelerated cognitive decline and dementia.
- *Longitudinal molecular neuroimaging studies* are also inconsistent in predicting a reliable outcome at an individual level for those who are amyloid positive and unimpaired cognitively, even after long-term follow-up. A large majority of A+ subjects remain cognitively stable over time without progression even after several years (Jack et al. 2019b, 2016b; Bell et al. 2019; Clark et al. 2018; Sperling et al. 2019; Petersen et al. 2016; Mormino et al. 2014, 2017; Villemagne et al. 2013; Bilgel et al. 2018; Donohue et al. 2017; Monsell et al. 2014; Machulda et al. 2017; Lilamand et al. 2019; Burnham et al. 2016; Lim et al. 2018; Albert et al. 2018), although these studies do consistently report a significant group effect on cognitive decline. These later findings may have resulted from the admixture of a small proportion of progressors with those who were A+ nonprogressor subjects. In the INSIGHT-preAD study, 76 out of the 88 amyloid-positive subjects, with a mean age of 77 years at the entrance, had no changes in any cognitive, behavioral, and neuroimaging parameters when compared to baseline or to amyloid negative individuals after a 5-year follow-up (Bilgel et al. 2018). The same observations were reported in the Australian AIBL cohort, where only 19% (26/137) of amyloid-positive cognitive unimpaired elderly, with a mean age of 75 years old at the entrance, converted to MCI or AD dementia after a 6-year follow-up (Mormino et al. 2017). When data from 13 cohorts in the USA and Europe were pooled together, the lifetime risk of AD dementia for asymptomatic amyloid-positive individuals ranged between 5% and 23% according to age and sex (Dubois et al. 2018; Brookmeyer and Abdalla 2018). More recent studies show that a significant proportion of cognitively unimpaired A+T+ individuals also remain cognitively stable over time, even after several years: results from the ADNI cohort show that the A+T+ status increases moderately the 5-year risk

of clinical conversion (HR = 2.8) (Parnetti et al. 2019), and similar findings were observed in data from pooled cohorts (Yu et al. 2019). By the same token, a long-term longitudinal amyloid and tau PET study showed that, after 7 years of follow-up, only 35% (6/17) of amyloid-positive cognitive unimpaired elderly converted to MCI or AD dementia. It is noteworthy that there was no significant difference at baseline in term of tau lesions (mean SUVR) between the amyloid-positive converters and non-converters (Younes et al. 2019), indicating that baseline tau levels do not predict the evolution.

Furthermore, longitudinal Tau PET studies showed no or only minimal acceleration of Tau binding in the following 1 or 2 years in amyloid-positive compared to amyloid-negative cognitive unimpaired elderly participants (Hanseeuw et al. 2019; Jack et al. 2018b; Harrison et al. 2019), in contradiction with the prevalent model where the presence of brain amyloid lesions triggers a systematic spreading out of the tau lesions outside the medial temporal lobes (Cho et al. 2019; He et al. 2018). The relationships between co-occurrence of tau and amyloid pathology on the one hand and the development of cognitive decline and neurodegeneration on the other hand remain uncertain. This is confirmed, beyond all the studies devoted to this topic, by everyday practice during the follow-up of Amyloid-positive cognitively unimpaired subjects (Raj et al. 2015).

13.4.3 Preclinical AD and Normal Aging

The limitation of a biological definition of AD in clinical practice concerns the asymptomatic stage of the disease where, by definition, the pattern of cognitive changes does not support the presence of the disease. This is not the case for patients with cognitive/behavioral changes because the identification of specific clinical phenotypes is the expression of an illness that the biomarkers will ascertain. The assumption of equivalence between symptomatic and asymptomatic biomarker positive, in line with the linear amyloid cascade hypothesis, leads to the risk of considering all cognitively normal individuals with biomarker positivity as persons that are certain to experience subsequent cognitive decline, whereas a maximum of 5–42% will develop dementia in their lifetime (Dubois et al. 2018).

In the clinical setting, defining the disease by its lesions only—and no more to a clinical phenotype—exposes to the risk of confusion with aging in old subjects (where the risk of clinical progression despite AD lesions is low (Dubois et al. 2018)). This undermines the distinctions that have been worked out around well-identified specific clinical presentations supported by biomarkers. Publications in the field of dementia, which propose that the disease is a myth (Stanley et al. 2019) or a decoy (Whitehouse et al. 2008), illustrating the confusion between Alzheimer and old age, are worrying. Moreover, equating Alzheimer's disease with only the presence of neuropathological lesions might lead to the risk of marketing AD medicinal products that decrease brain pathology, with no more the need to prove their efficacy on clinical symptoms. Finally, diagnostic disclosure becomes more

challenging ethically when the physician should announce to an asymptomatic individual the diagnosis of an irreversible disease based on biomarkers even where the clinical trajectory is very uncertain (Saint Jean and Favereau 2018).

13.4.4 Asymptomatic Subjects and Risk Profiling

In line with this notion of a "risk of an illness" among patients with preclinical AD, it may be postulated that at early, asymptomatic stages, other contributing factors are needed for the occurrence of symptoms, in addition to AD neuropathological change. Occurrence of symptoms is a complex phenomenon, which has to be integrated in a network where modulating factors may aggravate or slow down the impact of the lesions (Schermer and Richard 2019). There is interplay between different factors (i.e., neuroinflammation, synergy between neuronal lesions, genetic/environmental risk/protective factors, cognitive/brain reserve, and comorbidities) whose final outcome is the occurrence of the illness or the resilience against it. The intervention of modulating factors in order to explain the inconsistency between pathological lesions and clinical symptoms has long been hypothesized and has given rise to the concept of "brain resilience" that encompasses the notion of "cognitive reserve," "brain reserve," and "brain maintenance" (Medina et al. 2017; Rothschild and Trainor 1937; Stern 2012; Arenaza-Urquijo and Vemuri 2018; Stern et al. 2018). This assumption has also received several evidences from basic neuroscience (Perneczky et al. 2019).

Therefore, it is possible that some asymptomatic biomarker-positive subjects may neither develop cognitive decline (Jack et al. 2019b, 2016b; Bell et al. 2019; Clark et al. 2018; Sperling et al. 2019; Petersen et al. 2016; Mormino et al. 2014, 2017; Villemagne et al. 2013; Bilgel et al. 2018; Donohue et al. 2017; Monsell et al. 2014; Machulda et al. 2017; Lilamand et al. 2019; Burnham et al. 2016; Lim et al. 2018; Albert et al. 2018; Brookmeyer and Abdalla 2018; Parnetti et al. 2019; Yu et al. 2019) nor demonstrate a frank acceleration of Tau lesions accumulation (Hanseeuw et al. 2019; Jack et al. 2018b; Harrison et al. 2019), an assumption theorized under the concept of "brain resistance" to AD pathology (Stern 2012), which is in line with observations of longitudinal cohorts.

13.4.5 Refining the IWG Framework

Given the nonlinear relationship between lesions and symptoms and the very high uncertainty of individual clinical trajectories, we propose (1) that the presence of both Amyloid and Tau lesions alone is insufficient for establishing the diagnosis of AD in cognitively normal subjects and (2) that we should distinguish in these cognitively normal subjects two subgroups for scientific, clinical, and ethical purposes:

- *Asymptomatic stable*: probably the most prevalent in numbers, refers to subjects stable over time, who may never (or very late in life) develop symptoms. Because

of not yet identified factors (including cognitive reserve, ApoE2 status, protective genetic predisposition, absence of synergy between neuronal lesions, and so forth), these individuals may (1) compensate and maintain a normal functioning despite the presence of an ongoing neurodegeneration process or (2) never develop the hallmarks of an accelerated degeneration of neurons, synapses, and cognitive functions.

- *Asymptomatic progressors*: another subgroup of subjects, less prevalent but more interesting for clinical trials, consists of progressors who demonstrate signs of accelerated neurodegeneration and whose compensatory mechanisms are overwhelmed. They are on the way to prodromal AD.

It is essential to separate the two groups in order to define the factors of prevention/compensation on the one hand and the algorithm of progression on the other hand.

13.4.6 The Proposal P+A+ T+ (at Least for Clinical Practice) (See Table 13.1)

Based on the current and aforementioned evidence:

1. *The diagnosis of AD* should be restricted to the presence of pathological evidence of disease in the presence of a clinical phenotype. The specific clinical phenotypes (typical and atypical AD) identified during the last 30 years have proved good sensitivity and specificity as markers of an ongoing accelerated cognitive decline (Matthews et al. 2007) and also proved to be a good surrogate marker of Tau pathology acceleration.

Table 13.1 The two categories of patients

1. Alzheimer's disease (P+A+T+)
2. Asymptomatic at risk for AD (ARAD) (P-):
(a) Asymptomatic with high risk: cognitively normal individuals subjects with
• CSF or PET A (+) and T (+)
• Tau PET (+) outside the limbic cortex (Braak ≥5)
• ApoE4 homozygous
(b) Asymptomatic with undefined risk*: cognitively normal individuals subjects with an incomplete biomarker pattern:
• A(+) and T(−)
• A(−) and T(+)
**to be worked out depending on the presence of modulating factors*
3. Genetic forms of AD

We define AD as a clinico-biological entity, characterized by:

(a) A clinical phenotype (P+): in the majority of cases (85%), this phenotype is described as *typical* when it combines memory disorders (an amnestic syndrome of the hippocampal type (Dubois and Albert 2004)) with other cognitive changes in language, visual recognition, spatiotemporal orientation, gestures, etc. (Qiu et al. 2019; Villain and Dubois 2019). Other cases may present with an *atypical phenotype*, and three different types have been well identified: the posterior variant, the logopenic variant, and the frontal variant (to which it may be possible to add the cortico-basal syndrome). It is noteworthy that (P+) refers to a specific cognitive phenotype of AD and not to subjective cognitive decline (SCD) as the more at risk are not always those who complain the more (Dourlen et al. 2019; Cacciamani et al. 2017).

(b) The presence of pathophysiological biomarkers: they reflect, in vivo, the underlying pathology (amyloid and tau lesions), present at any stage of the disease, even at the asymptomatic one. The positivity of both amyloid and tau biomarkers is required because, on the one hand, an isolated amnesic syndrome of the hippocampal type with only Amyloid positivity is not specific of AD and can be observed, for instance, in the case of a limbic-predominant age-related TDP-43 encephalopathy (LATE) with Amyloid co-pathology (Jack et al. 2018a) or in cases of cerebral amyloid angiopathy and amnestic vascular cognitive impairment (Hanseeuw et al. 2020). On the other hand, an isolated amnestic syndrome of the hippocampal type with only tau lesions can be observed in the case of primary age-related tauopathy (PART) or frontotemporal lobar degeneration (Villain and Dubois 2019; Katzman and Kawas 1994). CSF investigation is interesting by providing simultaneous information on the two types of biomarkers. However, CSF investigation only quantifies the level of tau changes but does not provide information on the topographical distribution of tau pathology (limbic only or neocortical), which can be relevant for certain stages of the disease (Jang et al. 1999). We recommend to take into account CSF P-tau or PET tau and not CSF T-tau due to its lack of specificity regarding the ongoing neurodegeneration process (Mattsson et al. 2018). Alternatively, a less invasive but expensive option can be the acquisition of two PET scans (amyloid and tau PET).

2. *Asymptomatic A+T+ subjects should not be diagnosed as AD*, but only at-risk for AD (ARAD), with different levels of risk (high or undefined), depending on the amount and aggressivity of the brain lesions and on the existence of modulating factors whose influence for each of them remains to be determined (see Table 13.2).
3. *Genetic forms of AD*: Separate from AD and ARAD, are carriers of autosomal dominant monogenic mutations for AD (APP, PSE1, PSE2, or T21) who can be A, T, P (+), or (-), depending on the natural history of their disease. They have an absolute risk to develop the disease.

Table 13.2 currently established modulating factors for a personalized risk profile

1. Factors that may increase the risk:
(a) Increased age
(b) Sex female
(c) Low education level
(d) ApoE status with an increased risk in case of heterozygous ApoE 4 status
(e) Familial history
(f) Memory complaints/SCD
(g) Presence of markers of neurodegeneration:
• Isolated hippocampal MRI atrophy
• FDG-PET hypometabolism; or elevated CSF NF-L
(h) Polygenic risk factors beyond ApoE
(i) Co-pathology α-synucleinopathy
(j) LATE
• Argyrophilic grain disease (AGD)
• Cortical aging-related tau astrogliopathy (ARTAG)
(k) Vascular pathology
2. Factors that may decrease the risk
(a) Protective genes, such as the presence of ApoE2 allele
(b) Higher education and cognitive reserve
3. Factors that need to be further confirmed:
(a) Pattern of neuroinflammation (e.g., using ^{18}F-DPA-714 PET)
(b) Occupation complexity
(c) Functional brain marker of cognitive reserve (e.g., using fMRI connectivity)

13.5 Conclusion

The major advance of the IWG Criteria and of the subsequent National Institute on Aging/Alzheimer's Association (NIA/AA) criteria (Jack et al. 2011; Sperling et al. 2011; McKhann et al. 2011; Albert et al. 2011) was to support the diagnosis of AD prior to the onset of dementia and integrate biomarkers of Alzheimer's pathology into the diagnostic framework.

The new framework establishes AD as a single disease on a continuum that includes different stages (preclinical, prodromal, and dementia stages) that are identified by a specific phenotype and supported by pathophysiological biomarkers. These criteria are particularly useful for research projects. However, for clinical practice we recommend to disclose an AD diagnosis only in the case of the presence of a specific phenotype and to mention a risk for AD to asymptomatic patients.

Glossary

AD dementia When cognitive symptoms interfere with activity of daily living.
Alzheimer's disease (AD) The whole clinical phase, no longer restricted to the dementia syndrome.
Alzheimer's pathology Underlying neurobiological changes responsible for AD
Asymptomatic at risk Cognitively normal individuals with positive pathophysiological biomarkers.
Atypical AD Less common but well-characterized clinical phenotypes that occur with Alzheimer's pathology. The diagnosis of AD needs in vivo evidence of pathophysiological markers.
Mild cognitive impairment (MCI) Patients for whom there is no disease clearly identified.
Mixed AD Patients who fulfill the criteria for AD and additionally present with clinical and biomarkers evidence of other comorbid disorders.
Pathophysiological markers Biological changes that reflect the underlying AD pathology (CSF changes; PET-amyloid). They are markers of diagnosis.
Prodromal AD The early symptomatic, predementia phase of AD.
Topographical biomarkers Downstream markers of neurodegeneration that can be structural (MRI) or metabolic (FDG-PET). They are markers of progression.
Typical AD The most common clinical phenotype of AD, characterized by an amnestic syndrome of the hippocampal type.

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