Alzheimer's disease including focal presentations

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ABSTRACT

Alzheimer's disease (AD) is the commonest neurodegenerative disease and the most frequent cause of dementia. It affects 30 million people worldwide. Current research criteria focus on biomarkers status for amyloid and tau using PET and CSF analysis, independent of clinical status,. . Current epidemiological data, which mostly rely on biomarker-undetermined AD cases, have highlighted ApoE4 and age as the main risk factors. Rare autosomal dominant mutations also account for a small fraction of early onset AD. The main clinical phenotype at presentation is the amnestic phenotype targeting episodic memory. This is followed by rarer phenotypes such as posterior cortical atrophy, logopenic variant of primary progressive aphasia, frontal variant AD, corticobasal syndrome and other even rarer presentations mimicking language variants of frontotemporal dementia. Main differential diagnoses include hippocampal sclerosis with TDP-43, primary age-related tauopathy, argyrophilic grain disease, frontotemporal lobar degeneration, Lewy body disease, chronic traumatic encephalopathy as well as non-degenerative disorders such as cerebrovascular disease, chronic alcohol consumption, limbic encephalitis, medial temporal lobe epilepsy and others. Co-occurrence of AD pathology with other neurodegenerative and vascular diseases is common and increases with age. This presents a challenge in current clinical practice due to a lack of reliable biomarkers for non-AD neurodegenerative diseases.

Key words:

Alzheimer's disease - diagnosis – CSF – epidemiology - dementia

A- AD: HISTORY, EVOLUTION OF CONCEPTS AND CURRENT DEFINITION (FIGURE 1)

Age-related dementia has been known since ancient times. AD pathology was first described in the early 20th century. Alois Alzheimer described it at the beginning of the 20th century,[1,2] and AD was integrated in medical textbooks only a few years later[3]. However it was not until the last quarter of the 20th century that AD was recognized as the major cause of dementia in the general population by the medical and scientific community . We will start with a review of this history to understand the evolution of the concepts and definitions of AD from 1907 to the 21st century to put in context the scientific literature on AD of the last 30 years.

Alzheimer's disease (AD) and dementia: a long lasting 20th century debate

Descriptions of dementia precede the discoveries of Alois Alzheimer, going back to ancient Egyptians who acknowledged age to be accompanied by memory decline[4]. Ancient Romans give us the current English word "dementia," which they used with similar meaning.

Alzheimer's first patient with dementia had the early onset form of AD. In an oral communication in 1906, published in 1907, he reported the case of Auguste Deter, a 51-year-old woman with delusions, severe memory loss, disorientation, language deficits and behavioral disturbances. She had been institutionalized in Frankfurt for these symptoms but continued to decline until she was bedridden and died 4.5 years later[1]. Autopsy revealed a diffuse atrophic brain without macroscopic focal degeneration. Microscopic examination showed "tangles of fibrils," neuronal loss and "deposition of a special substance in the cortex [that] can be observed without dye, but it is very refractory to dyeing." We have here the complete picture of AD as is currently defined: a progressive cognitive decline focusing on memory leading to dementia, associated with neurofibrillary tangles (revealed later to be the result of hyperphosphorylated Tau protein deposits) and the special substance that was found later to be an accumulation of amyloid A-beta proteins (see chapter on Neuropathology and reference 5[5]). Alzheimer thought this condition was "eine eigenartige Erkrankung der Hirnrinde" (title of the 1907 Alzheimer's article), i.e. an unusual illness of the cerebral cortex. The following years saw many more descriptions of the same brain lesions identified both in early andlate onset cases (i.e. senile dementia). Remarkably, Oskar

Fischer's clinicopathological study of 16 patients diagnosed with senile dementia came out in the very same year as Alzheimer's. It is in this study that we find the first description of neuritic plaques[6]. In spite of this, three years later Kraepelin decided to name after Alzheimer presenile dementia cases he identified as distinct from senile dementia. As discussed elsewhere, it is not entirely clear what led Kraepelin to do so[7–9]. The distinguishing characteristics he cites for early onset AD are patients' relative youth, severe dementia, focal signs and language disturbances. These characteristics we acknowledge today distinguish early and late onset AD. Alzheimer himself objected to the link Fischer claimed existed between presbyophrenic dementia (aging-related dementia) and plaques[10]. While he concurred with the fact that plaques occurred more frequently in cases of presbyophrenic dementia, he did not believe them to be pathognomonic for this condition. Plaques in his view were a marker of senile dementia, but without causing the condition. In line with this point of view, Kraepelin's textbook established a distinction which remained predominant within the scientific and medical circles for much of the 20th century, and commentators continued to rely on the old diagnostic categories of senility or senile dementia to describe a rather wide variety of commonly recognized symptoms and behaviors. They traced the etiology of these clinical symptoms to an equally wide variety of causes, all more or less loosely related to the phenomenon of old age[8].

The "Fischer/Alzheimer-Kraepelin debate" finally reemerged and was eventually settled in favor of Fischer's point of view during the last quarter of the 20th century. Furthered by demographic, political and scientific developments (see [4] for review), senile dementia became increasingly common within the aging population, beyond what could be explained by the arteriolosclerotic lesions or other known phenomena of old age. In reaction to the situation, particular attention was given to the pathological hallmarks of senile dementia and Fischer's work in the area was met with renewed interest. For example, the white paper authored by Robert Katzman, Robert Terry, and Katherine Bick at the conclusion of a 1977 workshop conference, co-organized by NIA, NINCDS and NIMH and held in Bethesda, concluded: "there is increasing recognition that most patients with clinically defined senile dementia (onset after age 65) manifest the same pathological changes in their brains as do patients in their presenium (under age 65) with Alzheimer's disease."[11] A growing consensus

following the same lines helped bring Alzheimer research into the modern era by "officially" acknowledging AD as a condition affecting patients in old age.

AD as a clinico-pathological entity and cause of dementia

Seven years later, the publication of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria of Alzheimer's disease confirmed AD as a disease, independent of age of presentation, and therefore as a cause of senile dementia[12]. Three cornerstones of these criteria were that: i) any ante-mortem clinical diagnosis of AD could be made merely on a "probable" basis, while ii) final and definite diagnosis was possible upon post-mortem examination only, and iii) the diagnosis could only be applied when the disease was advanced to the functional disability threshold of dementia. The NINCDS-ADRDA criteria established a two-step procedure for the diagnosis of probable AD. First, establishing the existence of a dementia syndrome by means of medical examination and neuropsychological testing, revealing deficits in at least two areas of cognition, one of which had to be memory. These deficits were required to be sufficiently pronounced as to significantly impact patients' daily functioning. Upon this initial identification of a dementia syndrome, the 2nd step consisted of the exclusion of other possible etiologies of dementia with blood/CSF investigations to rule out infectious, inflammatory or metabolic diseases; and with brain neuroimaging (CT scan or MRI) to exclude small vessel diseases, strategic lacunar infarcts, large vessel infarcts and/or cerebral hemorrhages, brains tumors, hydrocephalus or and other similar causes.

The concept of MCI

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. The concept of mild cognitive impairment (MCI) is a response to this conundrum, allowing to label objective memory loss and/or cognitive impairment that has not yet advanced to the point of impacting activities of daily living. The term MCI was introduced in the late 1980s by Reisberg and colleagues to characterize subjects who were at

this intermediate stage. On the Global Deterioration Scale (GDS), MCI status was defined as fulfilling the criteria for Stage 3[13]. Peterson and colleagues refined the concept further by requiring a memory complaint, recognizing that awareness of decreasing mnemonic capabilities suggests that the subject is still at an early stage.[14,15] In addition, GDS stage 3 MCI admitted the occurrence of executive level functional deficits, which Petersen's MCI leaves aside as not sufficiently specific to early stage AD. The mild symptomatic phase of AD, which precedes the fully developed clinical syndrome of dementia, had, at that time, no official clinical standing and was artificially included in the spectrum of MCI. The heterogeneity of pathologies sharing clinical features but having different etiologies which were regrouped under the label MCI represented an important limitation. Subtyping MCI was proposed according to the type and number of cognitive domains impaired (e.g. amnestic vs. non-amnestic MCI and single vs. multiple-domain MCI[15,16]) as a possible solution. However, only 70% of amnestic MCI cases (the most specific cases regarding AD phenotype) who have progressed to dementia actually met neuropathological criteria for AD[17]. In parallel, NINCDS-ADRDA criteria for probable AD were found to suffer from much the same lack of specificity, with sensitivity of the criteria in a tertiary center estimated to be 70.9% to 87.3%, and its specificity 44.3% to 70.8%[18].

From a clinico-pathological definition to a clinico-radio-biological definition

NINCDS-ADRDA and MCI criteria enabled researchers to follow clinical cases and to better characterize the disease. First, the clinical phenotype of AD was elucidated: in more than 85% of cases, AD presents as a progressive amnestic disorder with a specific episodic memory impairment profile characterized by low free recall that is not improved by cueing. This distinguishes AD from normal aging and non-AD disorders. It is also useful for predicting conversion to AD in MCI patients[19] (see below). Second, postmortem studies of AD patients showed a specific hierarchical pattern of tau pathology, which begins in the memory-related areas of medial temporal lobe structures (entorhinal cortex, hippocampal formations, parahippocampal gyrus)[20,21]. In contrast, beta amyloid deposits are more diffuse in the neocortex before spreading to the deep nuclei, the pons and the cerebellum[20,22]. The AD specific episodic memory profile proved to correlate significantly with hippocampal volume and, more precisely, with the CA1 field[23,24]. Third, diagnostic accuracy of AD was also

improved because of a better characterization of non-AD neurodegenerative diseases through specific criteria. These other dementias included primary progressive aphasias, cortico-basal syndrome, fronto-temporal dementias and Lewy body dementia. The identification of these diseases, which were previously highly confused with AD, has consequently decreased its apparent heterogeneity. Finally, reliable biomarkers for AD were isolated and have now become available at least in expert centers. The incremental gains in diagnostic accuracy due to biomarkers is now well established [25–27].

Hence, a new conceptual framework for the diagnosis of AD has been proposed by the International Working Group (IWG)[28] and later by the NIA/Alzheimer's Association (NIA/AA)[29] based on two requirements: (1) earlier diagnosis; and (2) greater specificity. In 2007, the IWG provided a new conceptual framework, according to which AD moves from a clinico-pathological entity to a clinico-radio-biological entity[28]. The 2007 IWG criteria stipulated that AD can be recognized *in vivo* in the presence of two associated features. The first is the evidence of an "amnestic syndrome of the hippocampal type" seen in the typical form of the disease. The importance of a specific memory pattern was highlighted because it occurs early in the course of the disease and it is fairly specific, though not pathognomic, for AD. The second necessary feature was supportive evidence from biomarkers that were proposed for the first time for the diagnosis of AD. The biomarkers of AD were divided into two groups: i) the pathophysiologic markers - positive PET-amyloid scan or CSF AD profile (low ABeta 42 level, high total tau and high phospho-tau); these markers identified AD pathology since they were strongly correlated with post-mortem AD histopathological changes; ii) topographical markers: hippocampal atrophy on volumetric MRI or cortical regional hypometabolism on fluorodeoxyglucose FDG-PET especially the posterior associative areas including the posterior cingulate cortex (see Chapter on Neuroimaging). These reflected downstream damage and were rather markers of progression, more targeted at assessing change over time and predicting outcomes. As a consequence, CSF and MRI investigations were no longer simply for excluding other etiologies of brain dysfunction but were central to detecting AD-related changes.

An important clarification of the above criteria was brought forward in 2010, introducing the concept of "atypical forms of AD" and proposing corresponding criteria and a diagnostic framework[30]. An amnestic presentation for AD may not always be the case, and other specific clinical phenotypes could be associated with postmortem evidence of AD pathology.

These specific clinical phenotypes included non-amnestic focal cortical syndromes, such as logopenic aphasia, bi-parietal atrophy, posterior cortical atrophy, and frontal variant AD (see below). These clinical disorders were more commonly seen and treated as atypical AD, as biomarkers began to allow in-vivo confirmation of Alzheimer's pathology. Individuals without clinical symptoms but with positive biomarkers of Alzheimer pathology were considered "asymptomatic at risk of AD." "Asymptomatic at risk for AD" was used for subjects without cognitive dysfunction but evidence of amyloidosis in the brain (on PET amyloid) or AD-related changes in the CSF. The stage "presymptomatic AD" was ascribed to individuals carrying autosomal dominant monogenic AD mutations (see below) who would with time inevitably develop clinical AD, provided they lived long enough. Finally, topographical markers were no longer used because of their lack of specificity regarding AD. Thus, the only validated biomarkers for AD diagnosis were defined as CSF low Aβ42 and high T-tau or P-tau levels or evidence of amyloid retention in amyloid PET.

In line with the conceptual evolution, the NIA-AA published diagnostic criteria in 2011,[29] which refined the NINCDS-ADRDA framework to broaden the coverage of different stages of disease from the asymptomatic (preclinical), through the pre-dementia stages (MCI due to AD) and to the most severe stages of dementia. These shared many features with the IWG criteria, including the recognition of an asymptomatic but biomarker positive phase and of a pre-dementia symptomatic phase of AD. Biomarkers were given an important place in the diagnostic process, first in identifying amyloid abnormalities and second in identifying downstream neurodegeneration. These biomarkers also had the advantage of being usable in both clinical and research settings. The most interesting contribution of the NIA/AA criteria pertains to the preclinical stages of the disease. Based on the hierarchical biomarker model proposed by Jack and colleagues[31] (itself in line with the amyloid cascade hypothesis[32]), it was proposed[33] 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 gene allele carriers, who may manifest functional abnormalities before detectable Aβ fibrillar deposition[34,35]; (3) structural MRI was thought to become abnormal a bit later, as a marker of neuronal loss, and MRI retained a close relationship with cognitive performance through the clinical phases of MCI

and dementia[36]; and (4) none of the biomarkers was static - rates of change in each biomarker changed over time and followed a nonlinear time course.

There are several important differences between the NIA/AA criteria and those from IWG. The NIA/AA framework held that the presence of Alzheimer pathology 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 applied a probabilistic likelihood based on the presence of AD biomarkers with designation either of biomarkers that reflect amyloidosis (CSF Abeta or amyloid PET) or those that are "downstream" indicative of neuronal degeneration (CSF phospho or total tau, FDG glucose, volumetric MRI). Based on positive, negative or intermediate results on the "amyloid" and "downstream" biomarkers – or the absence thereof – a probabilistic likelihood of "high" or "intermediate" was applied to the diagnosis. In contrast to IWG criteria, the MCI stage of AD was formally distinguished from the dementia stage, which had its own diagnostic criteria. In the dementia stage, 10 categories of dementia of the AD type were established, including probable AD dementia, possible AD dementia, probable or possible AD dementia with evidence of the AD pathophysiological process, and pathophysiologically proved AD dementia. The probable or possible AD dementia stages retained most of the features of the 1984 NINCDS-ADRDA diagnosis of probable AD[12] despite the low specificity, limited positive predictive value and poor negative predictive value of these criteria[18].

On the basis of the 2010 preliminary paper, the IWG formalized its criteria in 2014[37]. In addition, they refined the definition of the typical amnestic AD, identified with the use of list-learning and other episodic memory tests . They also introduced the notion of a co-pathology in AD with the diagnosis of mixed AD when a patient had in addition to AD a coexisting disorder identified by evidence of specific clinical and biological features of another disease, such as parkinsonism (for Lewy Body disease) or cerebrovascular disease. Additional formalizations concerned the preclinical state of AD, including the "asymptomatic at risk of AD" and "presymptomatic AD" previously described.

We can conclude that the main contribution of the IWG and NIA/AA criteria lies in the refinement they brought to the diagnosis of AD prior to the onset of dementia and their inclusion of biomarkers of Alzheimer's pathology into the diagnostic framework. Beyond this, their methodology proved useful with clinical trials and possibly with regulatory decisions. They could also set the stage for primary and secondary prevention.

From a clinico-radio-biological definition to a pure biological definition

In 2016, the joint IWG-Alzheimer's Association (IWG-AA) meeting furthered the integration of biomarkers into the definition of AD and decided to apply this definition independent of the clinical status[38]. Indeed, the new definition of AD is now purely biological and is based on the positivity of biomarkers of both amyloidosis and tauopathy independent of the clinical status. The cognitive changes are now considered as a stage of the disease which refers to a degree of disease progression (preclinical = asymptomatic, prodromal = cognitive deficit with no impact in the day living activity, and dementia = cognitive deficit with impact in the day living activity). Thus, asymptomatic individuals with positive biomarkers (evidence of both amyloid and tau biomarkers) are no longer considered "asymptomatic at risk of AD" but as the earliest form of AD (preclinical AD). As a result, the IWG-AA criteria considered that the category "asymptomatic at risk for AD" still applies in case of discrepant amyloidosis and tau biomarkers results (evidence in cognitively normal individuals of isolated Aß pathology or of isolated Tau pathology).

The NIA-AA has recently formalized this new biological definition of AD[39]. They propose an A/T(N)(C) classification relying on CSF, PET and MRI biomarkers (A = amyloid; T = tauopathy; N = neurodegeneration; C = cognitive change), where A and T positivity defines AD while N and C are not specific to AD and define the severity stage of the disease. Hence, in line with the IWG-AA 2016 paper, the focus of these criteria is no more on the symptoms but on the biological *in vivo* definition of the disease. Besides, in line with the conceptual evolution that tauopathy might not only be the downstream consequence of amyloid pathology but a parallel and independent pathological process[40–45], the hierarchy between amyloid and tau biomarkers has been softened and concomitant tauopathy and amyloidosis now represents AD. Amyloid biomarkers validated by these criteria are CSF Aβ42, or Aβ42/Aβ40 ratio and Amyloid-PET. Aggregated tau (neurofibrillary tangles) validated biomarkers include CSF phosphorylated tau and Tau-PET. Finally, biomarkers representing neurodegeneration are structural MRI, FDG-PET and CSF total tau. Nonetheless, no technical measures or thresholds are settled in these criteria, and it is clearly stated that these biomarkers will be evolving as research progresses.

Clinical definitions are restricted to the clinical phase of AD: cognitively unimpaired (normal performing subjects on cognitive testing, may report subjective cognitive decline), Mild

Cognitive Impairment (MCI: evidence of cognitive impairment and evidence of decline in cognitive performance from baseline in an individual who performs daily life activities independently), and dementia (substantial progressive cognitive impairment that affects several domains and/or neurobehavioral symptoms and results in a clearly evident functional impact on daily life).

As a whole, individuals who fulfill both the A and T biomarkers criteria qualify as having Alzheimer's disease (preclinical AD or AD with MCI or AD with dementia). Individuals who fulfill the A biomarker criteria without the T biomarker are classified as Alzheimer's pathologic change (preclinical, with MCI or with dementia)[31,41], while individuals who fulfill the T biomarker criteria without the A biomarker are classified as non-Alzheimer's pathologic change (such as the A negative, T negative, N positive individuals), in keeping with the NIA-AA pathologic definition of primary age-related tauopathy (PART) as not AD[45]. There is currently no data regarding the risk of developing subsequent AD amongst individuals diagnosed with PART. In line with the mixed AD concept introduced by the IWG criteria, the NIA-AA criteria also allow for this concept under the term "suspected Alzheimer's" and concomitant suspected non-Alzheimer's pathologic change when there is an incomplete biomarker combination (e.g. A+T-N+). In this context, the presence of other dementias may be uncertain, since biomarkers for other neurodegenerative diseases lack of specificity/sensitivity.

When no biomarker is available, the 2018 NIA-AA criteria introduced the concept of Alzheimer's clinical syndrome, which applies to both mildly impaired and demented individuals. This refers to the definitions of possible and probable AD according to the previous NINCDS-ADRDA[12] and NIA-AA[46] criteria. Nonetheless little is said regarding the precise phenotype except a vague "multi-(or single-) domain amnestic syndrome" or a "classic syndromal variant."

Research versus clinical criteria

More recent clinical criteria allow earlier and more accurate diagnosis of AD, but are very much dependent on the availability of suitable biomarkers. This is problematic, since as much as 58% of those suffering from dementia live in low and middle-income countries, according to a report of AD International[47]. Sophisticated, high-tech screenings for

biomarkers are not universally available, even in high income countries, and often limited to tertiary or research centers. This mostly limits the applicability of diagnostic approaches proposed in recent years to these contexts, i.e. facilities able to screen for a large variety of biomarkers and with access to normative data. These conditions allow for complex diagnoses such as early onset AD, frontal variant AD or primary progressive aphasias, where biomarkers are essential for sufficient accuracy in diagnosis. In less favorable circumstances, the clinical syndrome definition of AD as put forward by NIA-AA may be used for diagnosis.

Finally, the predictive value of these biomarkers in asymptomatic populations needs to be confirmed to validate criteria for the preclinical stages. Indeed, while they have largely proved their ability to predict cognitive decline in patients with MCI (e.g. [26]), their ability to correctly predict the natural clinical course of AD in asymptomatic patients remains to be established. More data is needed, since current results are scarce or incomplete (e.g. [48–50]). Moreover, none of these biomarkers have 100% specificity and sensitivity for AD pathology (i.e. amyloidosis and tauopathy), so that every physician should remain extremely cautious when assigning a diagnosis based on biomarkers only, especially if there are no therapeutic disease-modifying consequences.

Future evolution: mixed pathology and mixed diseases* in vivo *diagnoses?

There is increasing evidence that, when the diagnosis of AD is confirmed by neuropathological examination according to the NIA-AA criteria[5], pure AD pathology is not the rule (~30% of cases according to age) (Figure 2). Instead there is often the co-occurrence of other pathologies such as Lewy body disease, vascular pathology, argyrophilic grain disease or TDP43 pathology (e.g. [51–58]) that influence both the clinical trajectory and the phenotypes[54–57] (Figure 2). Unfortunately biomarkers for these other pathologies are not currently reliable enough for use in clinical practice (e.g. [59]). Therefore, one should be cautious: using the NIA-AA 2018 criteria for AD is more specific and sensitive for neuropathologically diagnosed AD, but cannot fully take into account co-pathologies. This is important for prognostication of cognitive decline, understanding of AD pathophysiology *in vivo*, and for clinical trials. Targeting a single pathophysiological mechanism may explain the lack of success of the last 10 years of anti-amyloid immunotherapies (e.g. reference 60 [60]).

Therefore, future biomarkers for these neurodegenerative pathologies, to allow for an *in vivo* mixed pathology diagnosis, will help us diagnose *in vivo* these "multiple pathology neurodegenerative diseases" and offer personalized combination therapies[61].

B- ALZHEIMER'S DISEASE EPIDEMIOLOGY

Having in mind these definitions of AD and their evolution across time allows us to make a critical review of relevant epidemiological data. Much of the data relies on the NINCDS-ADRDA 1984 clinical criteria (or DSM dementia definitions) and does not include biomarkers or neuropathology data. Therefore, most of what follows relates more closely to "Alzheimer's clinical syndrome" than to AD, i.e. lacking biological mechanism specificity (see above and Figure 1). Nonetheless, according to neuropathological series, AD remains the most frequent cause of neurodegenerative disease and represents about two thirds of dementias (see [62] for review). The incidence of AD increases exponentially with age, plateauing around 85 years of age. After 85 years of age, different studies find diverging results – either a decline in incidence, stable incidence rates, or a deceleration in the increase in incidence rate[63–67]. Interestingly, as the incidence of AD rates decreases with advanced old age, the incidence of "pure" vascular dementia also decreases, while mixed pathologies show greater incidence with extremely old age[68]. As a whole, this allows us to have only a rough estimation of AD prevalence. The World Alzheimer Report 2015[69] estimated 46.8 million people have dementia around the world, with an estimated yearly cost of 880 billion US dollars. Using these numbers, one can estimate the number of people with AD to be 30 million (including pure and mixed AD cases) around the world. The mean duration of survival with AD is estimated to be 5-6 years at the time of the dementia stage of the disease, and longer with earlier age at onset. It therefore reduces life expectancy[70,71].

The frontier between early onset AD (EOAD) and late onset AD (LOAD) has been somewhat arbitrarily defined by age at first manifestation of symptoms (< or > 65 years). LOAD represents the vast majority of AD cases (>95%)[72,73]. Nonetheless, EOAD remains the most common cause of early-onset neurodegenerative dementia. In contrast to LOAD, which is a complex disorder with a heterogeneous etiology and a heritability (according to some models) of 70 to 80%, EOAD is almost entirely genetically determined, with a heritability

ranging between 92% to 100%[74,75]. Between 35-60% of EOAD patients have at least one affected first-degree relative, and in 10% to 15% of those with familial EOAD patients, the mode of inheritance is autosomal dominant [76–78]. Rare high-penetrant mutations in APP, PSEN1, and PSEN2 genes explain only a small fraction of EOAD families (5%–10%), leaving a large group of autosomal dominant pedigrees genetically unexplained [74,79]. Patients with Down syndrome (DS), caused by chromosome 21 (partial) trisomy, present with a similar brain pathology of amyloidosis and tauopathy as AD patients[80]. In fact AD neuropathology appears in virtually all DS patients above 40 years of age[81], and DS is thus considered a genetic cause of AD. Finally, the APOE ε4 allele also increases the risk for EOAD in carriers of at least one ε4 allele, and is highest in those with a positive family history[77]. In carriers, homozygosity for the APOE ε4 allele is sufficient to significantly increase the risk for EOAD, independent of other genetic factors. In contrast, in carriers heterozygous for the APOE ε4 allele, risk is only significantly increased in the presence of a positive family history of disease, indicating that the presence of one ε4 allele is insufficient to increase the risk for AD before the age of 65 years.

Amongst LOAD, an interesting systematic review has been recently performed by Hersi and colleagues[82] regarding LOAD risk factors. There is an increased risk of AD associated with head injury in males, depression, mild cognitive impairment, age, diabetes mellitus, conjugated equine estrogen use with medroxyprogesterone acetate, and exposure to pesticides. With respect to genetic factors, APOE e4 remains the strongest predictor of LOAD. The presence of one or two copies of the APOE ε4 allele increases the risk to develop LOAD by a factor of 3- or 15-fold, respectively [83,84]. Polymorphisms of IL-1b, IL-1a, IL-10, ACE, APOE promoter, TNF-a, OLR1, BIN1, ABCA7, MS4A4E and CD2AP genes are all associated with an increased risk of AD. Several identified genetic factors appear to confer susceptibility to AD in specific populations. Polymorphisms of MTHFR and VLDLR genes are associated with an increased risk of AD in Asians. Other associations include ALDH2 gene in East Asian men, PS-1 2/2 gene in Europeans, CR1 gene in Caucasians, SORL1 gene in whites and Asians, and he BACE1 gene in APOE e4 non-carriers. Statin use and several genetic factors, including APOE e2, polymorphisms of MS4A6A and CD33 genes, are associated with a reduced risk of AD. Genetic factors that are associated with a protective effect in specific populations include polymorphisms of PS-1 2/2, CLU and PICALM genes in Caucasians, VLDLR gene in

non-Asians, SORL1 gene in whites and Asians (other SNP than those responsible for a risk factor), and BACE1 gene in APOE e4 carriers. Regarding lifestyle factors, current smoking and lower social engagement are identified as factors associated with an increased risk of AD. The available evidence is suggestive of a reduced risk of AD associated with light-to-moderate alcohol consumption, compliance with a Mediterranean diet, higher educational attainment, and regular engagement in physically and cognitively stimulating activities. Physical and cognitive activities are associated with a beneficial effect on cognitive function and other indicators of dementia progression, while higher educational attainment is associated with faster cognitive decline. While a number of risk factors appear to be associated with risk of AD onset, the associations are weak, at best, for a majority of factors.

Nonetheless, as stated earlier, the vast majority of these studies have been conducted without biomarkers. For instance, in clinical-autopsy studies, diabetes was associated with cognitive impairment (and the clinical diagnosis of probable AD); however, the pathologic basis for this association was vascular brain injury and not Aβ plaques and neurofibrillary tangles[85–87]. Thus, there is a need to disentangle AD from dementia, using the new biological definition of the disease, to update well-known established data regarding epidemiology and genetic risk factors of the disease.

C- ALZHEIMER'S DISEASE CLINICAL PHENOTYPES (FIGURE 3)

The recent focus on the biological definition of the disease should not give us cause to neglect clinical phenotypes of AD in the prodromal or dementia stages of the disease. Given the lack of an efficient disease-modifying treatment, the need in clinical practice for a biological preclinical diagnosis remains low. The appearance of such treatments in the future may change this. Meanwhile, we still need to identify in clinical practice the specific phenotypes and indications for a reasonable and relevant use of MRI, CSF, PET and blood tests.

1- IWG typical and atypical AD phenotypes

Regarding this specific question, the IWG 2014 criteria are the most recent criteria specifying the specific clinical phenotypes of the disease. Typical AD is the progressive amnestic

presentation of the disease, described long before the discovery of AD itself[88] (Figure 3). The memory disorder of AD is complex and varies with the stage of the disease[88,89]. In 1881, Ribot first described progression of memory deficits amongst patients who went on to develop senile dementia: "The progressive destruction of memory follows a logical progression, a law. It goes from unstable to stable. It starts with recent memories, weakly settled in the nervous elements, seldom repeated and consequently weakly associated to the others, which represent the weakest level of organization. It ends up with this instinctive, sensorial memory, settled in the organism that has become a part of it, or even the organism itself, which represents the strongest level of organization."[88] We now know that the earlier symptoms described by Ribot corresponded to episodic memory impairment. The famous case studies of HM and KC, with lesions of the hippocampus, later localized episodic memory to the hippocampus [90,91]. To quantify episodic memory deficits, Grober & Buschke[92] developed, at the end of the 1980s, a free and cued selective reminding test (FCSRT), a list learning test that controls for successful encoding (achieved by cued recall) and facilitates retrieval processing (with the same semantic cues) of new words in episodic memory. With this they highlighted a amnestic pattern specific to AD as opposed to normal aging and other dementias. The test in AD patients often showed a low immediate recall score and a low performance despite cueing across successive rehearsals/recall trials [19,92,93]. Moreover, AD patients also produce numerous intrusions, i.e. the patient offers a word which was not in the list of words to be remembered [94]. This pattern has been confirmed years later using biomarkers-based criteria[95]. Impaired FCSRT performance can be correlated with hippocampal atrophy, grey matter loss of the medial temporal lobe, and the presence of Alzheimer's CSF biomarkers, even during the prodromal stage [23,24,96–99]. It has shown discriminative utility for predicting conversion to AD in MCI patients[100]. Hence, the free and cued selective reminding test (FCSRT) is specifically recommended in the IWG criteria. Other tests which can be useful in identifying the amnestic syndrome of AD focus on list learning and delayed recall of information, for example paired-associate learning and the Rey auditory verbal learning tasks (e.g. [101]). The DMS48 tests visual recognition and has shown to correlate with AD patterns in patients with MCI[102]. It is one of several neuropsychological tests designed to identify amnestic impairment with a pattern which is specific for early pathological involvement of the entorhinal-perirhinal cortex. The short-term memory binding test might also be a good marker for AD given its high specificity in patients with

familial AD and in asymptomatic carriers with PSEN1 autosomal dominant gene mutations[103,104].

The natural history of AD is progression of cognitive decline and spread to other cognitive domains; for example, other memory systems than episodic memory, aphasia, apraxia, visuo-spatial functions, executive functions, etc.[89] In addition, various neuropsychiatric disturbances can be observed in patients with AD: apathy, dysphoria and agitation are common during the course of the disease[105]. In the early stages of AD, apathy, expressed by profound disinterest in non-routine and interpersonal activities, can often be observed, whereas psychosis (delusions or hallucinations) is more typical for advanced AD. Deterioration of cognition and behavior to a level which interfere with activities of daily living is the basis of a diagnosis of dementia. Ultimately, loss of self-care, eating, dressing, ambulation, incontinence and motor dysfunction lead to bedridden status and death[106]. Epilepsy (generalized convulsive seizures or complex partial seizures) can also occur in AD, but is not among the commonest manifestations of the disease[107]. Younger age and increasing dementia severity are the most reliable risk factors for seizures in AD[107].

Main differential diagnoses for this clinical form encompass all neurodegenerative diseases that target the hippocampus early and preferentially. The long list of differential diagnoses includes cerebral age-related hippocampal sclerosis with TDP-43 (CARTS)[62,108], primary age-related tauopathy (PART)[45,109], argyrophilic grain disease (AGD)[55,110], atypical forms of frontotemporal lobar degeneration (FTLD)[18,111] including 17q21.31 duplications[112], MAPT R406W mutations[113], GRN mutations[114,115], C9ORF72 hexanucleotide expansions[116] globular glial tauopathy[117], atypical Lewy body disease[18,118,119], atypical chronic traumatic encephalopathy[120,121] and PRNP mutation[122,123] (Figure 3). Biomarkers in these cases should help the clinician to address the correct AD diagnosis. This is complicated by the presence of multiple pathologies and the absence of reliable biomarkers for most other causes (Figure 2). Non-degenerative etiologies for a progressive amnestic syndrome include chronic alcohol consumption with or without Korsakoff's syndrome[124], limbic encephalitis[125], cerebrovascular disease[18,111,126], and medial temporal lobe epilepsy[127]. Finally progressive memory impairment is a common feature in a range of neurological disorders (e.g. Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, normal pressure hydrocephalus…), mental disorders (e.g. depression, post-traumatic stress

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disorder, schizophrenia, bipolar disorder) or general medical diseases (e.g. obstructive sleep apnea, hypothyroidism, vitamin deficiency, amongst other). These alternative diagnoses and mimics may be ruled out by meticulous clinical investigation, neuropsychological memory impairment profile, blood testing and brain imaging [128,129].

Beyond this typical amnestic AD profile, several atypical presentations of AD have been described and account for about 6–14% of AD cases[130–132]. These atypical forms of AD stand out by a relative intactness of memory function but a recognizable (or characteristic) phenotype that might be accompanied by topographical evidence of brain damage (regional atrophy or hypometabolism) in related regions. Atypical forms of AD generally occur at an earlier age at onset than does typical amnestic AD. IWG criteria thus propose precise definitions for atypical AD presentations, including a posterior cortical atrophy variant of AD, a logopenic variant of AD, and an executive variant of AD.

The visual variant of AD presents as a posterior cortical atrophy (PCA)[133] and generally results in several signs and symptoms that distinguish two subtypes: an occipito-temporal variant[130] with a predominant impairment in the visual identification of objects, symbols, words, or faces; and a more common biparietal variant[134] with predominant visuospatial dysfunction, as well as features of Gerstmann or Balint syndromes, limb apraxia, or neglect (Figure 3). AD is the main cause of PCA (~62-100% according to neuropathological series), while other neurodegenerative etiologies include Lewy body disease, corticobasal degeneration (CBD) and prion-associated diseases[135–138] (Figure 3).

Commenté [GDM1]: What is this?

Commenté [Y2]: I put the acronym next to its first appearance in the text.

The language variant of AD, which presents as logopenic variant primary progressive aphasia, is defined by a progressive impairment in single-word retrieval and in repetition of sentences in the context of spared semantic, syntactic, and motor speech abilities[139] (Figure 3). AD represents, according to neuropathological series, about 55-100% of logopenic primary progressive aphasias, while other etiologies include FTLD-tau or TDP, CBD and prion-associated diseases [140–142] (Figure 3).

The frontal variant of AD presents similarly to the behavioral variant of frontotemporal dementia, with progressive apathy or behavioral disinhibition, stereotyped behaviors, and predominant executive dysfunction on testing[143–145]. The behavioral predominant variant of AD is usually an EOAD with more severe dysexecutive than behavioral features, while

episodic memory is usually impaired[145] (Figure 3). On the other hand, the dysexecutive-predominant variant AD is also usually an EOAD with a relatively pure dysexecutive syndrome, while behavior and episodic memory are usually relatively spared[145] (Figure 3). AD is a relatively rare cause of degenerative behavioral frontal dementia (i.e. behavioral variant of fronto-temporal dementia[146]): between 2 and 20% according to neuropathological series, and etiology is largely dominated by FTLD[137,147–150] (Figure 3). Regarding the dysexecutive-predominant variant AD, the differential diagnosis is much wider. Indeed, prominent impairments in attention and executive functioning probably have the widest differential diagnoses and constitute many of the potentially reversible conditions. The neurodegenerative differentials include FTLD, Lewy body disease, and "subcortical neurodegenerative diseases" (Huntington's disease, Parkinson's disease, PSP, CBD) (Figure 3). Non-neurodegenerative causes include normal pressure hydrocephalus, cerebrovascular disease, alcohol-related cognitive impairment, white matter disease (multiple sclerosis, leukodystrophies, radiation-induced leukoencephalopathy), chronic encephalitides (HIV dementi), toxic-metabolic diseases (e.g. hypothyroidism, medications, obstructive sleep apnea), fatigue, psychiatric disorders (e.g. depression, post-traumatic stress disorder, schizophrenia, bipolar disorder) (e.g. [151]).

2- Rare AD phenotypes

Cortico-basal-syndrome is the most frequent atypical form of AD that was not included in the IWG criteria. It is defined as a progressive asymmetric clinical presentation including limb rigidity or akinesia, limb dystonia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit, and alien limb phenomena[152] (Figure 3). AD represents, according to neuropathological series, about 24-50% of patients with cortico-basal syndromes, confirmed by biomarkers in clinical series (~18%), while other etiologies include CBD, progressive supranuclear palsy, ~~and~~ FTLD-TDP and diffuse Lewy body disease[137,153–155] (Figure 3).

Other rare focal presentations have also been described (Figure 3). Mesulam and colleagues[141] have reported two cases (12%) of non-fluent variants of primary progressive aphasia due to AD pathology at autopsy. There was also one case (33%) of semantic variant of primary progressive aphasia due to AD. This is confirmed by Alladi and colleagues'

work,[137] where they identified 12 cases (46%) of non-fluent variants of primary progressive aphasia due to AD pathology and 2 cases (10%) of semantic variant of primary progressive aphasia (Figure 3). Note that the relatively high prevalence of AD amongst non-fluent variants of primary progressive aphasia in this last study was not reproduced by other studies, and may have included logopenic variants of primary progressive aphasia (0 AD in 33 cases of non-fluent variant of primary progressive aphasia pooled from Harris et al.[140] and Spinelli et al.[142] studies).

3- Early Onset Alzheimer's disease (EOAD) vs. Late Onset Alzheimer's disease (LOAD)

Data regarding EOAD have recently been reviewed by Mendez[156]. The EOAD is much more heterogeneous than LOAD and includes a higher percentage of nonamnestic cognitive syndromes: 22% to 64% of patients with EOAD can have predominant cognitive syndromes involving language, visuospatial abilities, behavioral/executive functions, and limb praxis. These cognitive syndromes can also differ from typical AD in that they have a higher mortality[157], potentially different predisposing factors (see above), and neuropathological involvement (relative hippocampal sparing, relatively greater tau burden and greater white matter involvement and selective vulnerability of long, projection neurons).

The three pathogenic gene mutations, PSEN1, APP and PSEN2, which lead to aberrant cleavage or aggregation of the APP, result in the more typical amnestic AD, but can also have distinctive features such as spastic paraparesis, early myoclonus, seizures, dysarthria, pseudobulbar affect, more extensive amyloid angiopathy, and atypical amyloid plaque morphology and distribution[158].

Auguste Deter had severe language impairment and limb apraxia, which may have been worse than her memory impairment. Hence, Alois Alzheimer's original patient was a non-amnestic presentation with EOAD, though there is still a debate on whether she had a PSEN1 mutation or not[159,160]. As we have seen, current data confirm that LOAD and EOAD have differences in terms of epidemiology, neuropathology and clinical presentation. Thus, current data to some extent supports both sides of the "Fischer/Alzheimer-Kraepelin debate" we outlined earlier[161] even if nowadays there is more evidence to consider them as two variants of a same disease than different diseases.

D- CONCLUSION

The definition of AD has changed fundamentally in the last 30 years (Figure 1). Alzheimer's disease and its variants continue to challenge the physician, with the ever-diversifying neurodegenerative disease which can mimic AD. We now know that neuropathologies co-occur, especially with increasing age, but we do not yet know the provenance of this newfound complexity (Figure 2). Research on neuroimaging or biological biomarkers should help us disentangle these diseases and help us design better clinical trials. With the shift from a clinic definition to biological definitions for AD, we may look more suspiciously at older epidemiological data, and by renewing the data in light of biomarkers be better in discovering risk factors, mechanisms and therapies.

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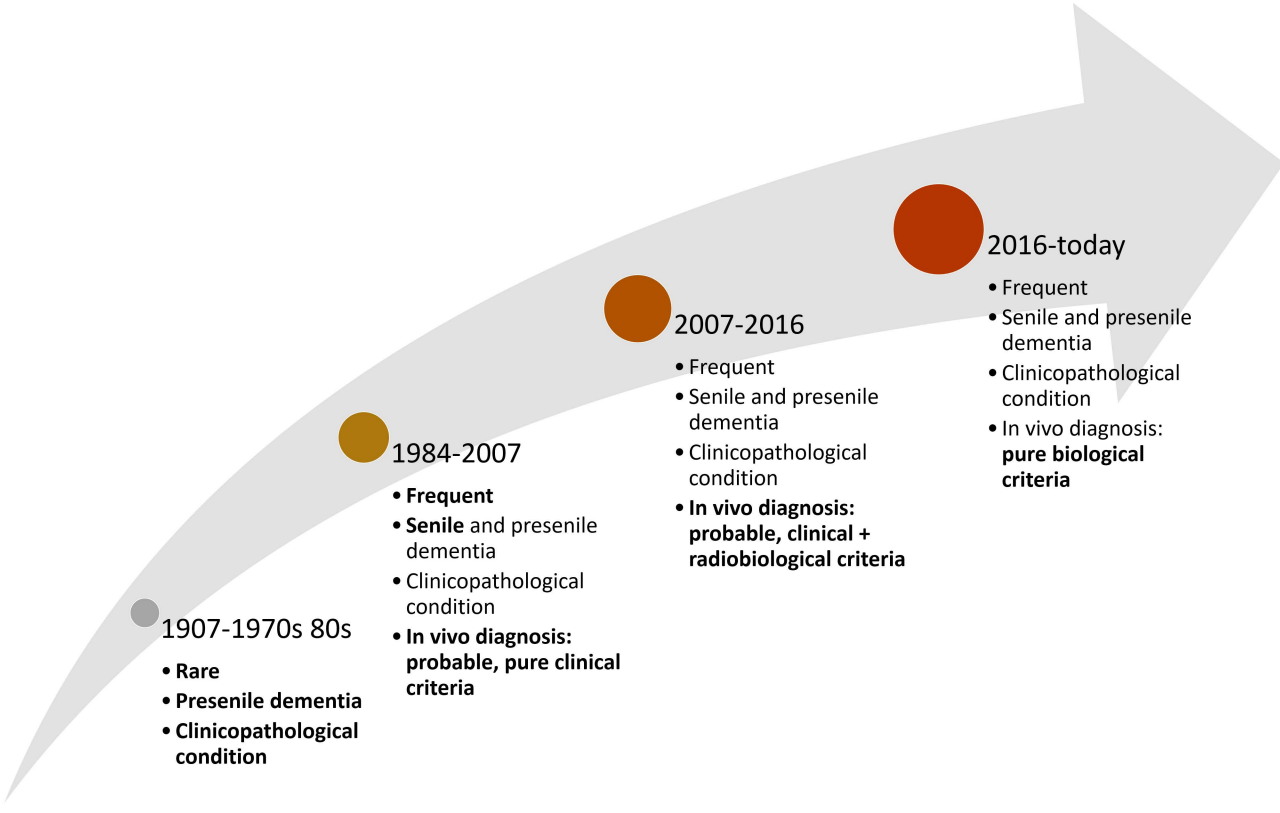
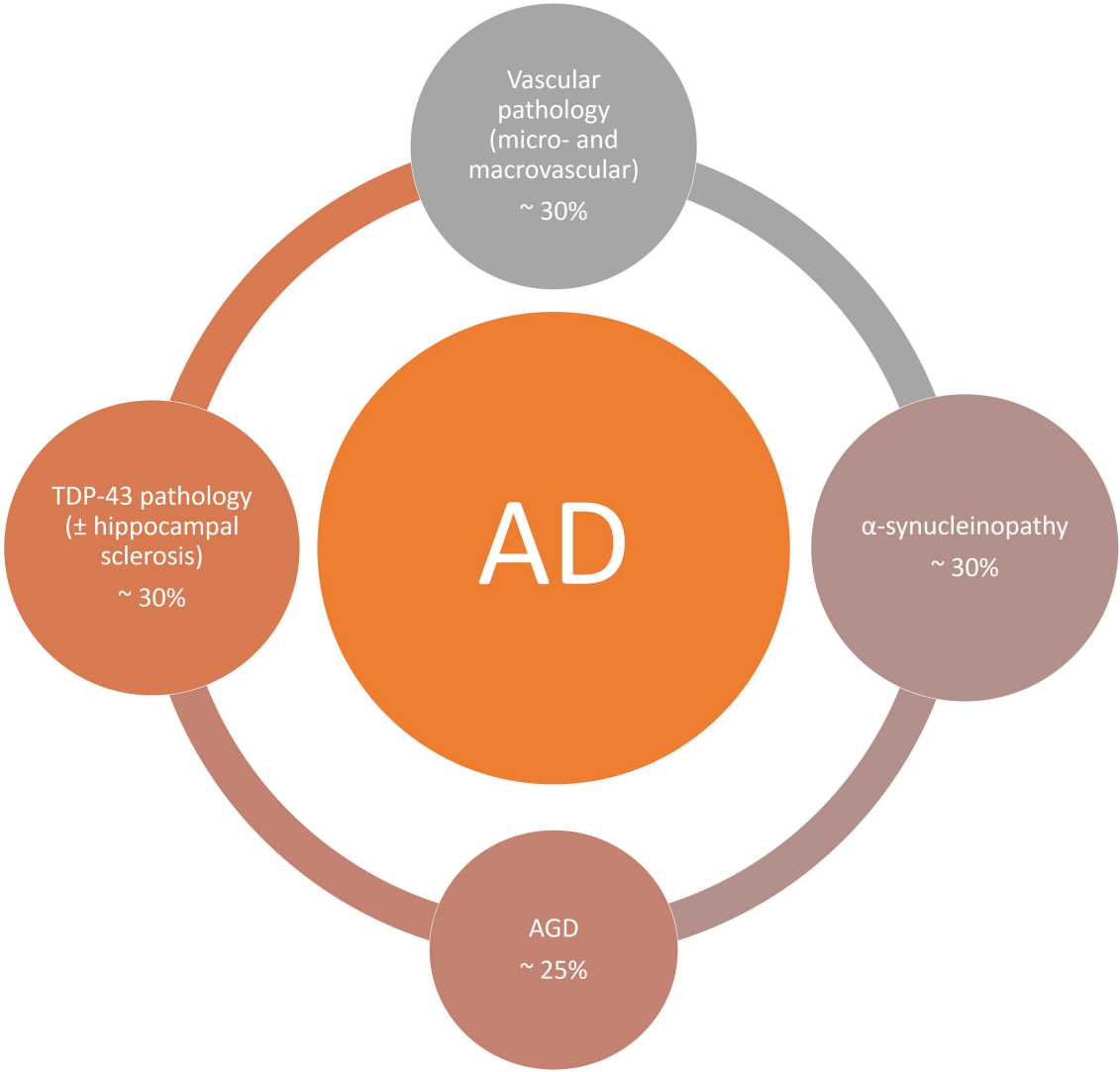
Figure captions

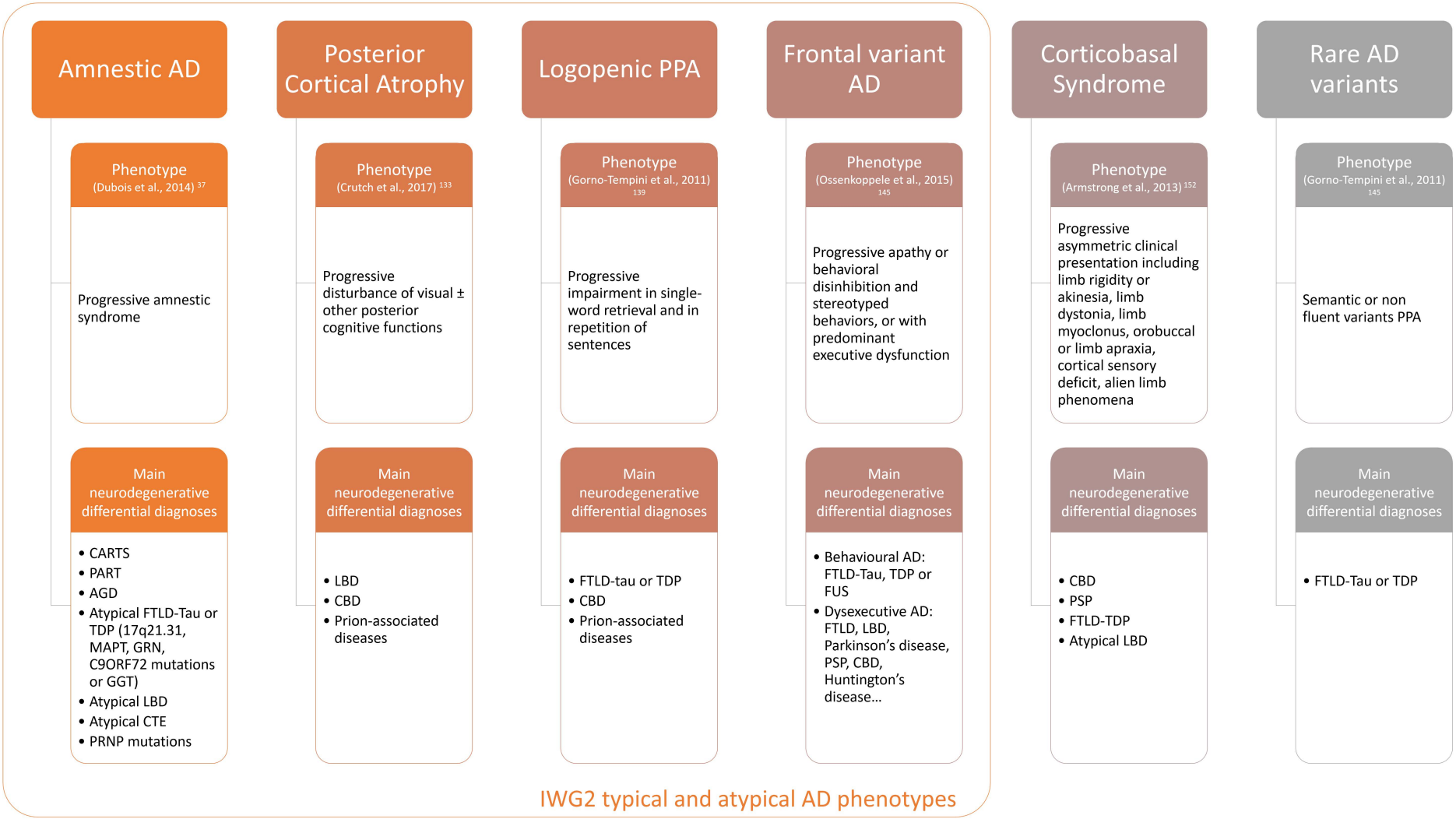
Figure 1. Conceptual evolution of Alzheimer's disease (AD) and its diagnosis criteria since its first description by Alois Alzheimer in 1907.

Figure 2. Alzheimer's disease as a mixed disease. Neuropathological assessments of AD encounter frequent copathologies including vascular pathology, TDP-43 pathology, argyrophilic grain disease and α-synucleinopathy (rough estimation of their prevalence in AD brains with neuropathogical confirmation is indicated in percentage: note that figures are highly variable from one study to another). Pure AD is supposed to represent about one third of all AD cases with neuropathogical confirmation.[51,53,54,57,58]

Figure 3. Main clinical phenotypes and differential diagnoses (including only neurodegenerative diseases) of Alzheimer's disease (AD), included or not in the IWG2 criteria[37]. See text for details. CARTS = cerebral age-related hippocampal sclerosis with TDP-43; PART = primary age-related tauopathy ; AGD = argyrophilic grain disease; FTLD = frontotemporal lobar degeneration; LBD = Lewy body disease; CTE = chronic traumatic encephalopathy; PRNP = PRioN protein; CBD = cortico-basal degeneration; TDP = TAR DNA-binding protein; FUS = fused in sarcoma; PSP = progressive supranuclear palsy; PPA = primary progressive aphasia; GGT = globular glial tauopathy


1907-1970s 80s
• Rare
• Presenile dementia
• Clinicopathological condition
1984-2007
• Frequent
• Senile and presenile dementia
• Clinicopathological condition
• In vivo diagnosis: probable, pure clinical criteria
2007-2016
• Frequent
• Senile and presenile dementia
• Clinicopathological condition
• In vivo diagnosis: probable, clinical + radiobiological criteria
2016-today
• Frequent
• Senile and presenile dementia
• Clinicopathological condition
• In vivo diagnosis: pure biological criteria


Vascular pathology (micro- and macrovascular)
~ 30%
TDP-43 pathology (± hippocampal sclerosis)
~ 30%
AD
α-synucleinopathy
~ 30%
AGD
~ 25%


Amnestic AD
Phenotype (Dubois et al., 2014) 37
Progressive amnestic syndrome
Main neurodegenerative differential diagnoses
• CARTS
• PART
• AGD
• Atypical FTLD-Tau or TDP (17q21.31, MAPT, GRN, C9ORF72 mutations or GGT)
• Atypical LBD
• Atypical CTE
• PRNP mutations
Posterior Cortical Atrophy
Phenotype (Crutch et al., 2017) 133
Progressive disturbance of visual ± other posterior cognitive functions
Main neurodegenerative differential diagnoses
• LBD
• CBD
• Prion-associated diseases
Logopenic PPA
Phenotype (Gorno-Tempini et al., 2011) 139
Progressive impairment in single-word retrieval and in repetition of sentences
Main neurodegenerative differential diagnoses
• FTLD-tau or TDP
• CBD
• Prion-associated diseases
Frontal variant AD
Phenotype (Ossenkoppele et al., 2015) 145
Progressive apathy or behavioral disinhibition and stereotyped behaviors, or with predominant executive dysfunction
Main neurodegenerative differential diagnoses
• Behavioural AD: FTLD-Tau, TDP or FUS
• Dysexecutive AD: FTLD, LBD, Parkinson's disease, PSP, CBD, Huntington's disease…
Corticobasal Syndrome
Phenotype (Armstrong et al., 2013) 152
Progressive asymmetric clinical presentation including limb rigidity or akinesia, limb dystonia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit, alien limb phenomena
Main neurodegenerative differential diagnoses
• CBD
• PSP
• FTLD-TDP
• Atypical LBD
Rare AD variants
Phenotype (Gorno-Tempini et al., 2011) 145
Semantic or non fluent variants PPA
Main neurodegenerative differential diagnoses
• FTLD-Tau or TDP
IWG2 typical and atypical AD phenotypes