Journal of Alzheimer's Disease 60 (2017) 577–583
DOI 10.3233/JAD-170574
IOS Press

Alzheimer's Disease Diagnosis Relies on a Twofold Clinical-Biological Algorithm: Three Memory Clinic Case Reports

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Accepted 12 July 2017

Abstract. The International Working Group recently provided revised criteria of Alzheimer's disease (AD) proposing that the diagnosis of typical amnesic AD should be established by a clinical-biological signature, defined by the phenotype of an "amnesic syndrome of the hippocampal type" (ASHT) combined with positive *in vivo* evidence of AD pathophysiology in the cerebrospinal fluid (CSF) or on amyloid PET imaging. The application and clinical value of this refined diagnostic algorithm, initially intended for research purposes, is explored in three memory clinic cases presenting with different cognitive profiles including an ASHT, hippocampal atrophy, and CSF AD-biomarker data. The case reports highlight that the isolated occurrence of one of the two proposed AD criteria, ASHT or positive pathophysiological markers, does not provide a reliable diagnosis of typical AD. It is proposed that the twofold diagnostic IWG algorithm can be applied and operationalized in memory clinic settings to improve the diagnostic accuracy of typical amnesic AD in clinical practice.

Keywords: Alzheimer's disease, amnesic syndrome, biomarkers, cerebrospinal fluid, diagnosis, magnetic resonance imaging

INTRODUCTION

For decades, Alzheimer's disease (AD) has been considered as a clinically heterogeneous disease because of the variety of cognitive and behavioral symptoms that frequently occur at the dementia stage [1]. The recognition of AD at an prodromal stage and the identification of the amnesic form have led to the description of typical AD as a progressive amnesic disease [2–4]. This more homogeneous concept fits with the description of neuropathological lesions starting in the medial temporal lobe structures [5] involved in episodic memory processing, and more precisely in the storage of information [6]. Based on this evidence, it has been proposed that the diagnosis of typical AD should rely on the identification of a specific pattern of episodic memory disorders related to hippocampal dysfunction: a low free recall performance, which is only marginally improved by cueing [7]. Such a memory pattern, referred to as the "amnesic syndrome of the hippocampal type" (ASHT), is reliably detected by the Free and Cued Selective Reminding Test (FCSRT)

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which uses a cueing procedure for controlling a true encoding of information and for facilitating the retrieval of the stored information [8, 9]. The ASHT was proposed as the clinical core diagnostic criterion for typical AD [8]. It has been shown to reliably predict 1) progression to AD dementia in mild cognitive impairment (MCI) subjects [10]; 2) hippocampal atrophy (HA) on MRI in typical AD [10]; and 3) abnormal cerebrospinal fluid (CSF) AD-biomarkers in MCI subjects [11].

This conceptual shift considering typical AD as a disease beginning in medial temporal lobe structures has become accepted worldwide and is used in most clinical trials where the ASHT is regularly proposed as an inclusion criterion. However, other cognitive mechanisms might interfere with the performance on the FCSRT given that episodic memory processes overlap with large-scale brain networks [12] such as working memory and semantic memory systems [13]. As a consequence, an ASHT profile detected by the FCSRT might result from an impairment of other anatomo-functional systems. In addition, HA is not specific to AD, and it has been documented in other neurodegenerative diseases such as Lewy body disease [14], frontotemporal dementia (FTD) [15, 16], and progressive supranuclear palsy (PSP) [17]. Thus, in the most recent version of the International Working Group (IWG) criteria [9], ASHT or HA in isolation cannot be considered as reliable diagnostic markers for typical AD. An important refinement of these current criteria, intended for research purposes, is the requirement of *in vivo* evidence of AD pathophysiology defined as increased brain amyloid retention on positron emission tomography (PET) imaging, or in CSF, such as the reduction of the amyloid-β peptide ($A\beta_{1-42}$) and the increase of total tau (T-tau) or hyperphosphorylated tau at threonine 181 (P-tau_{181}) [9, 18]. According to the current diagnostic IWG research criteria, the diagnosis of typical AD should therefore rely on the conjunction of both an ASHT and abnormal pathophysiological AD-biomarkers. In this work, we highlight the reliability and the relevance of the IWG research criteria in clinical practice via a series of three cases from our expert memory clinic of the Pitié Salpêtrière University Hospital.

CASE REPORTS

Case 1

A 71-year-old Caucasian male with 7 years of education demonstrated a 4-year history of progressive memory loss. His wife noted an increasing loss of memory skills at the age of 67 and concomitant depressive symptoms. There was no significant change in personality or behavioral symptoms. He underwent long-term antidepressant therapy (paroxetine 30 mg daily), but despite a partial improvement of depressive symptoms, there was progressive memory worsening over time. His family history was characterized by a maternal uncle diagnosed with Parkinson's disease and an 85-year-old maternal grand-mother having cognitive problems. General neurological examination was normal. Cognitive testing with the FCSRT showed an ASHT characterized by a low free recall of 11/48 (cutoff = 17/48) and a decreased total cued recall of 34/48 (cutoff = 40/48) [10], indicating poor memory storage capacities. The Mini-Mental State Examination (MMSE) [19] score was 24/30 and the Frontal Assessment Battery (FAB) [20] score was 11/18. Brain MRI showed HA predominating on the right side, without evidence of hippocampal sclerosis, infarction, microbleeds or significant white matter T2 hyperintensities (Fig. 1a, first column/Case1). MRI also showed mild atrophy in dorsolateral prefrontal areas (Fig. 1b first column/Case1). Single-photon emission computed tomography (SPECT) showed a right mesial temporal and right mesial prefrontal hypoperfusion. CSF biomarkers were analyzed using the Enzyme-Linked Immuno Sorbent Assay (ELISA) kit (Innogenetics, Ghent, Belgium). The levels of $A\beta_{1-42}$, T-tau and P-tau_{181} were 980 pg/ml (normal > 500), 251 pg/ml (normal < 500) and 46 pg/ml (normal < 60), respectively [21–24]. P-tau/$A\beta_{1-42}$ ratio was 0.05 (normal < 0.21) [25]. Beyond current investigations in clinical practice we intended to further assess potential AD-related brain deposits by applying amyloid PET imaging using ^{18}F-florbetapir. In line with CSF AD-biomarker results, there was no increased cortical tracer uptake. Thus, pathophysiological AD-biomarkers were inconsistent with the diagnosis of AD.

Progressively, the patient's family reported alterations in behavior and personality characterized by apathy, inappropriate familiarity, loss of empathy, and abnormal eating behavior (cravings for more sweets and stuffing himself with food). His insight was preserved for memory problems but only partially for behavioral changes. No hallucinations were reported. Fifteen months after the first cognitive screening, the patient underwent a second neuropsychological assessment which revealed a moderate impairment of executive functions, of facial emotion

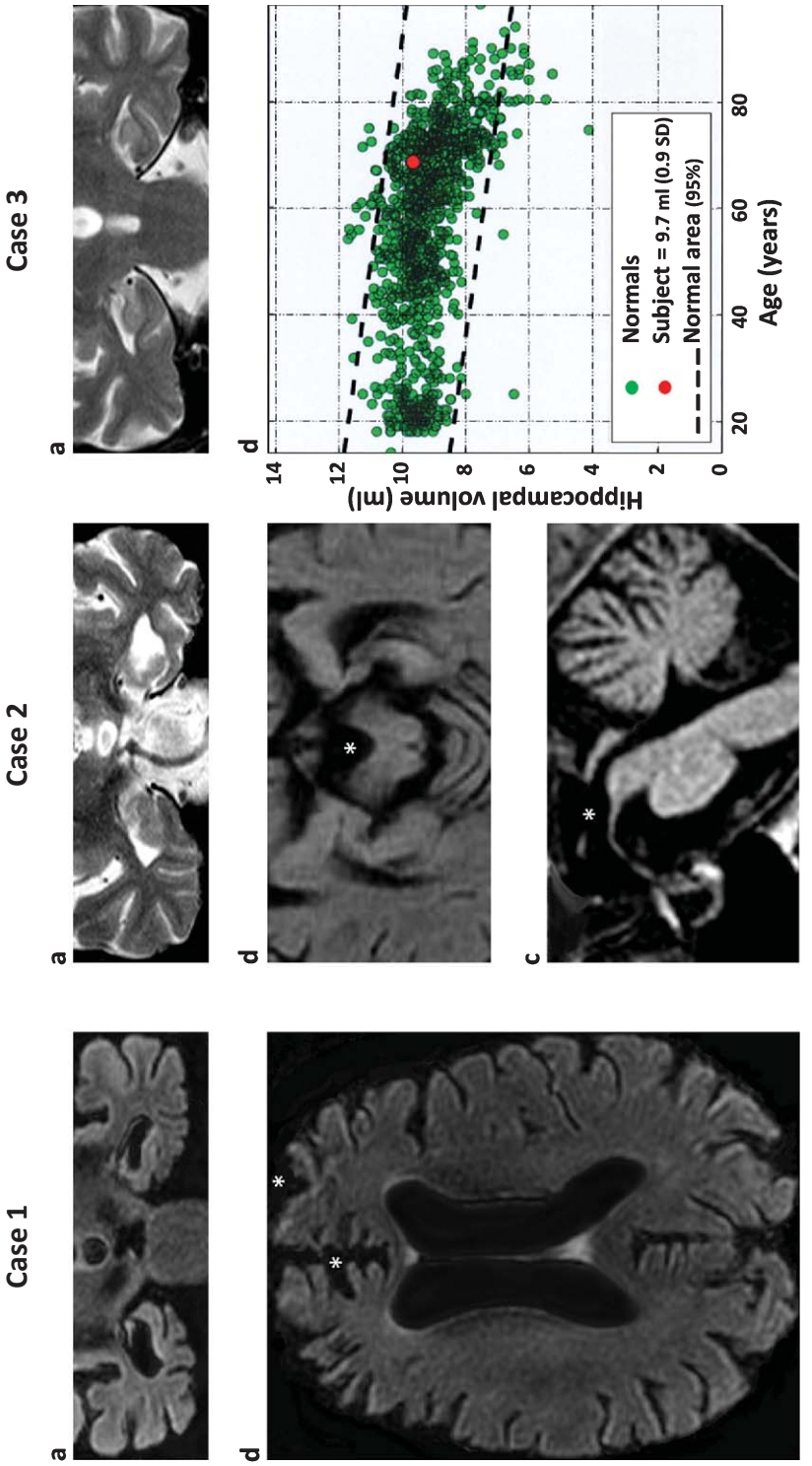

Fig. 1. Assessment of brain atrophy by structural MRI in the three reported cases. In Case 1 and Case 2, MRI shows HA (a, first column and second column), whereas there is no HA in Case 3 (a, third column). In Case 1, MRI also reveals prefrontal atrophy (b, first column; indicated by asterisks), and in Case 2, there is midbrain atrophy (b, second column; indicated by an asterisk) as well as the midbrain "hummingbird sign" (c, second column; indicated by an asterisk). In Case 3, quantified region-of-interest based volumetry shows a total hippocampal volume of 9.7 ml (red spot) which was similar to hippocampal volumes in healthy controls (green spots) (b, third column).

recognition and of Theory of Mind. The FCSRT revealed a worsening of the impairment in episodic memory storage (free recall 1/48, total cued recall 25/48). The MMSE was 19/30 and the FAB was 8/18. No significant visuospatial or language deficits were detected. In summary, the clinical data satisfied the diagnostic consensus criteria of 'behavioral variant of frontotemporal dementia' (bvFTD) [26].

Case 2

A 71-year-old Caucasian male, retired chief executive officer, was assessed in 2009 for memory decline that evolved progressively since 2008. He had no personal medical antecedents and had no medication. His deceased mother presented memory impairment of unknown origin since the age of 75 years. Neurological examination was normal. Cognitive testing with the FCSRT could not be applied because of the profound memory encoding deficits, but the 5-word memory test [27] showed a poor free recall (0/5) and no effects of cuing during the total recall (0/5), indicating an ASHT. The MMSE was 27/30, and the FAB was 14/18. Brain MRI showed moderate HA predominating on the left side, without evidence of hippocampal sclerosis, brain infarction or significant white matter T2 hyperintensities. CSF AD-biomarker showed low levels of $A\beta_{1-42,}$ (324 pg/ml; normal > 500) but normal levels of T-tau (288 pg/ml; normal < 500) and P-tau_{181} (38 pg/ml; normal < 60). The P-tau/Aβ ratio was 0.12 (normal < 0,21). This biomarker pattern was inconsistent with the diagnosis of AD.

Progressively, the memory problems increased during the following years. The family also reported a tendency to falling due to postural instability, impairment in speech articulation and swallowing, and changes in personality of insidious onset with progressive apathy. The patient underwent a second neurological and neuropsychological examination. Motor examination showed reduced left arm swing and bilateral akinesia. Smooth-pursuit eye movement exam revealed saccadic pursuits, numerous square-waves jerks, and hypometric vertical saccades. Neuropsychological testing with the FCSRT showed massive memory encoding deficits. The MMSE score was 16/30. There was also a dysexecutive syndrome, evidenced by a FAB score of 9/18. Speech assessment showed tachylalia and, hypokinetic dysarthria. Brain MRI showed a progression of the HA with a visual Scheltens' rating score of 4 and 2 for left and right hippocampus, respectively (Fig. 1a, second column/Case2). Midbrain atrophy with enlargement of the inter-peduncular cistern was also evident in axial sequences (Fig. 1b, second column/Case2), associated with the presence of the hummingbird sign on midsagittal sequences (Fig. 1b, second column/Case2) and a mild cerebellar vermian atrophy. There was no evidence of brain infarction or significant white matter T2 hyperintensities. Brain ^{18}F-2-fluoro-2-deoxy-D-glucose PET (FDG-PET) showed asymmetrical prefrontal hypometabolism predominating on the left side, as well as left parietal, operculo-insular and hippocampal hypometabolism. Dopamine transporter imaging with Ioflupane ^{123}I-FP-CIT SPECT showed bilateral dopaminergic denervation predominating on the left putamen. In summary, the clinical and imaging data satisfied the diagnostic consensus criteria of PSP [28].

Case 3

A 67-year-old Caucasian female, retired accountant, was assessed in 2013 because of memory complaints over three previous years. Prior clinical history included chronic insomnia, arthrosis, and depression. Her deceased mother had a diagnosis of AD after the age of 70. She was taking no medications. Neurological examination was normal. Cognitive assessment with the FCRST showed a low free recall of 13/48 (cut off = 17) normalized by cueing (42/48, cut off = 40) [7, 10], indicating the absence of an ASHT. The MMSE score was 26/30 and the FAB 17/18. The follow-up assessment in 2015 revealed the emergence of an ASHT as reflected by a free recall of 6/48, and total cued recall of 26/48. There was also a mild executive impairment (FAB 12/18) and some naming difficulties. The MMSE score was 23/30. Brain MRI showed no significant evidence for HA (Fig. 1a, third column/Case3), hippocampal sclerosis, infarction, microbleeds, or white matter T2 hyperintensituies. Beyond current investigations in clinical practice, we wished to further evaluate hippocampal volumes using an atlas-based volumetry approach [29] comparing the patient to a normative database of HA (Biometrica AD, Jung diagnostics Hamburg, Germany; Fig. 1b, third column/Case3). No deviation from normative data [30] was revealed, with right and left hippocampal volumes quantified 4.7 ml (0.6 SD) and 4.9 ml (1.1 SD), respectively. Individual patterns of grey matter atrophy, analyzed by voxel-based morphometry and implemented by SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/) after stereotactical

normalization, were inconsistent with HA. FDG-PET showed significant cortical hypometabolism predominantly in posterior temporal-parietal association areas predominating on the right side. CSF AD-biomarker analyses showed decreased $A\beta_{1-42}$ (485 pg/ml; normal > 500), and increased T-tau (1200 pg/ml; normal < 500) and P-tau_{181} (190 pg/ml; normal < 60), indicating a biological AD diagnosis.

DISCUSSION

We presented a series of three case reports with patients initially demonstrating a clinical phenotype of ASHT suggestive of typical amnesic AD, which was related to different pathologies: FTD, PSP, and typical AD. In the FTD case, the low free recall probably resulted from a frontal-related retrieval deficit, whereas the poor efficacy of the cueing was presumably related to hippocampal involvement known to occur in FTD [15, 31], and evidenced by HA on MRI. The normality of pathophysiological CSF biomarkers excluded the diagnosis of AD, and symptom evolution confirmed bvFTD. In the PSP case, as in the FTD case, the ASHT was probably related to HA as evidenced by MRI. However, the normality of CSF AD-biomarkers excluded an AD diagnosis and the clinical and imaging evolution indicated PSP. These two cases demonstrate that ASHT and HA have a relatively low specificity for typical amnesic AD diagnosis. The third case with typical AD illustrates that topographical markers such as HA have a low sensitivity for the diagnosis as opposed to pathophysiological markers [16, 32]. This finding was already included in the IWG research criteria prosing that topographical imaging markers reflect disease progression and not underlying AD pathology [33, 34]. A summary of the three case diagnoses based on the IWG algorithm are illustrated in Table 1.

Taken together, the diagnosis of typical AD cannot be achieved with the isolated occurrence of one of the two core features proposed by the IWG: ASHT or positive pathophysiological markers. The identification of an ASHT should be used cautiously as a standalone diagnostic criterion given that abnormal FCSRT scores reflecting ASHT do not have an absolute specificity for typical AD. A recent large-scale cohort study including several neurodegenerative diseases has shown that a ASHT on the FCSRT has an excellent sensitivity (100%) for the detection of typical AD whereas its specificity is only of 75% [35]. A similar reasoning holds for HA which is correlated with the severity of ASHT [10]. As proposed by the IWG it should not be used for the diagnosis of typical AD but for the quantification of disease progression [36]. In the same vein, HA has been shown to lack pathological specificity for AD [16, 37, 38].

Table 1
Summary of the case reports based on the IWG algorithm for typical amnesic AD

	Case 1	Case 2	Case 3
Specific clinical phenotype			
ASHT	+	+	+
In vivo evidence of Alzheimer's pathology			
CSF AD-biomarkers or amyloid PET	–	–	+
Final diagnosis	non AD	non AD	Typical AD

In contrast to ASHT and HA, pathophysiological markers have a reliable sensitivity and specificity for detecting AD pathology at any stage of the disease. However, positivity of pathophysiological biomarkers without an ASHT excludes the diagnosis of typical amnesic AD and indicates the diagnosis of other neurodegenerative diseases which can be underpinned by AD pathology [35]. Such degenerative conditions linked to AD pathology have opened the AD spectrum to atypical AD variants, including cases of primary progressive aphasia, FTD, or posterior cortical atrophy. Hence, positive AD-biomarkers without an ASHT should encourage clinicians to screen for non-amnesic disorders such as dysfunction of language, visuo-spatial capacities or behavioral impairments.

In summary, the three case reports support the application of the revised IWG criteria for typical AD in clinical practice. Only the proposed twofold ASHT-biomarker characterization allows for the reliable detection of typical AD in both research settings and at the individual level. We therefore propose that the IWG diagnostic algorithm should be applied and operationalized in memory clinic settings. These criteria represent a stringent diagnostic approach which increases the likelihood of detecting AD in real-life clinical routine, and facilitates the early detection of amnesic MCI individuals with a prospective risk of cognitive decline [39].

ACKNOWLEDGMENTS

This work was supported by the program "Investissements d'avenir" ANR-10-IAIHU-06 (Agence

Nationale de la Recherche-10-Investissements-Avenir-Institut Hospitalo-Universitaire-06).

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/17-0574).

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