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Case Report

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Biomarker-based diagnosis of cognitive disorders in a case series

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Abstract

The classical cerebrospinal fluid biomarkers of Alzheimer's Disease (namely total tau, phospho-tau and amyloid beta peptide) have received much attention, since they can detect the biochemical fingerprint of Alzheimer's disease and serve as a diagnostic aid for correct diagnosis of cognitive disorders during life. In this case series, we present 6 examples of patients with cognitive impairment of various types and severities and how biomarker data were helpful in every day diagnostic approach, combined with clinical, neuropsychological and imaging data and based on the most recent guidelines and recommendations.

Keywords: Cerebrospinal fluid, tau, phospho-tau, amyloid-beta, Alzheimer's disease, frontotemporal dementia, vascular cognitive impairment

INTRODUCTION

Until relatively recently, Alzheimer's disease (AD) was diagnosed according to clinical criteria proposed more than 30 years ago, requiring the patient to be demented[1]. With time it became evident that

AD patients may present with mild cognitive impairment[2], or may even be asymptomatic[3]. When symptomatic, amnestic dementia of the hippocampal type is the typical presentation[4,5]. However, atypical presentations are not infrequent, especially in presenile patients, including frontal-predominant, language-predominant, "posterior" or mixed presentations[4,5]. Such presentations may lead to diagnostic confusion, whilst even the typical hippocampal amnestic presentation may occur in non-AD disorders[6]. Thus, clinical presentations or phenotypes are rather viewed as syndromes, and they are by no means synonymous with a specific disease. Various types of biomarkers may be helpful in the diagnostic approach of such typical or atypical presentations, and they have been incorporated in various diagnostic criteria for AD[2,4,5].

Recently, the National Institute of Ageing and Alzheimer Association (NIA-AA) Research Framework group recommended a system for classifying subjects/patients on the basis of their biomarker profile, since it may result from different biomarker categories, especially neurochemical and imaging[7]. The objective was to update a scheme for defining and staging AD mainly across its entire spectrum, to be used for research purposes, either observational or interventional. A further shift in thinking is the separation of the syndrome from the disease, as symptoms are considered part of the disease continuum and not its definition. Looking towards a biological definition of AD, as it is identified post mortem by accumulation of amyloid-β and tau and reflected in vivo by biomarkers, the group discriminates them according to their molecular specificity [i.e., amyloid-β (Aβ) and pathological tau (phospho-tau)]. For this scope, they propose the AT(N) system[7], where A stands for amyloid-β plaques or associated pathological state, T for aggregated hyperphoshorylated tau or associated pathological state and (N) for neurodegeneration. The parentheses are to indicate that it represents cumulative brain injury/neurodegeneration from all etiologies and is not specific for any certain etiology. A (C) component is used to define mental decline and staging, from cognitively unimpaired to mild cognitive impairment and finally dementia, according to cognitive symptoms and neuropsychological testing. Thus, each biomarker category can be dichotomized as positive (+) or negative (-), resulting in eight different biomarker profiles and 3 "biomarker categories": normal [A-T-(N)-], Alzheimer's continuum [A+T-(N)-, A+T+(N)-, A+T+(N)+, A+T-(N)+] and suspected non-AD pathological change [A-T+(N)-, A-T-(N)+, A-T+(N)+][7].

Here, we present a case series of six patients with different types of cognitive disorders using this system. Cases were selected with the only criterion being that they were educationally useful and interesting for clinicians and medical students, and all co-authors helped in the selection of cases, in an unblinded manner. We describe their clinical, imaging and cerebrospinal fluid (CSF) biomarker data and how these could be suggestive of diagnosis, according to the AT(N) system. All patients were analyzed routinely in our department as part of the everyday diagnostic approach and they were not included in any particular study.

Lumbar puncture was performed at 10-11 am, after overnight fasting, at the L4-L5 interspace, according to recently proposed recommendations on standardized operating procedures (SOPs) for CSF biomarkers[8], as described elsewhere[9]. In brief, 4 polypropylene tubes were used for CSF collection. The initial tube (2 mL) was used for routine cytology and biochemistry and the 2nd tube (2 mL) was used for determination of IgG index, oligoclonal bands and for syphilis serology. The last 2 tubes (5 mL each) were immediately centrifuged, aliquoted in polypropylene tubes (750 μL each) and, finally, stored at -80 °C until analysis. Aliquots were thawed only once, just before analysis, which was performed within 6 months of storage.

CSF levels of total tau protein (τ_T), amyloid-β peptide and tau phosphorylated at threonine-181 ($\tau_{P\text{-}181}$) were measured blindly, in duplicate by double-sandwich, enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Fujirebio, Gent, Belgium) according to the manufacturer's instructions, as previously described[9]. In-house standards were used during every to ensure minimal measurement error

Table 1. Normal (cut-off) values of our laboratory[9]

CSF biomarker	Normal value
total tau protein (τ_T)	< 376 pg/mL
tau phosphorylated at threonine-181 ($\tau_{P\text{-}181}$)	< 57 pg/mL
amyloid-β peptide with 42 amino acids ($A\beta_{42}$)	> 682 pg/mL
$A\beta_{42}/A\beta_{40}$	> 0.09

CSF: cerebrospinal fluid

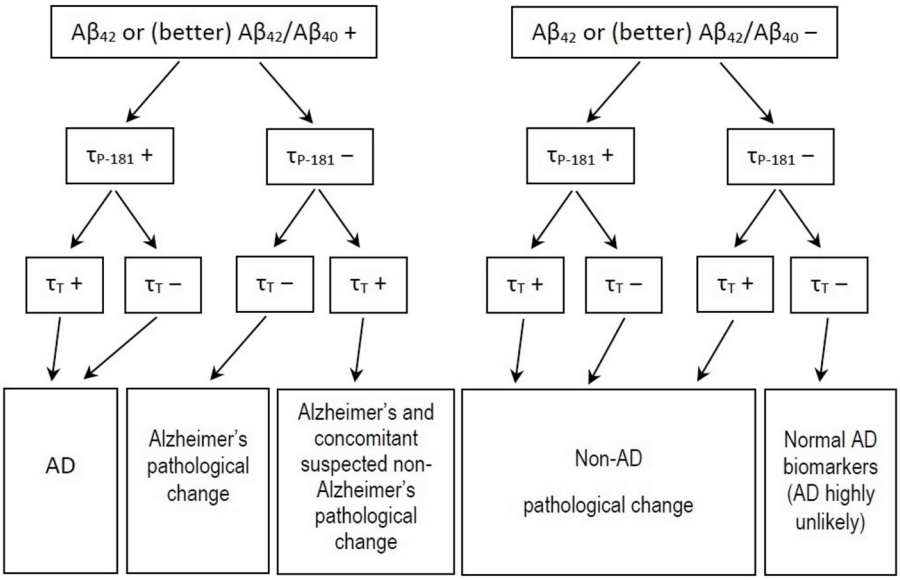

Figure 1. Flow chart of the use of cerebrospinal fluid biomarkers in clinical practice, according to the AT(N) system[7]. AD: Alzheimer's disease

(≤ 3.3%), and inter-assay and intra-assay variations were ≤ 6.6% for all biomarker assays[10]. Cut-off values have been previously calculated by receiver operating curve (ROC) analysis[9,11]. Table 1 shows the CSF biomarker categories used in our clinic/laboratory and their most recently used normal (cut-off) values[9]. Figure 1 presents a proposed simplified scheme for the diagnostic use of CSF biomarkers, according to the "philosophy" and nomenclature of the AT(N) system[7].

CASE REPORT

Case 1

A 63-year-old female patient with no significant past medical history neither family history was admitted to the neurology department for gradually developed memory complaints over the last year with no impact on activities of daily living. Neuropsychological assessment revealed mild cognitive impairment with mini mental state examination (MMSE)[12] score 27/30 and frontal assessment battery (FAB)[13] score 16/18. On magnetic resonance imaging (MRI) some degree of cortical atrophy in the parietal lobes was observed with relative preservation of the hippocampus [Figure 2]. Functional imaging study using single photon emission computerized tomography (SPECT) with ^{99m}Tc-HMPAO was normal. CSF biomarker analysis revealed increased τ_T = 545 pg/mL and $\tau_{P\text{-}181}$ = 81.8 pg/mL and decreased $A\beta_{42}$ = 480 pg/ml and $A\beta_{42}/A\beta_{40}$ = 0.059. With all 3 biomarkers abnormal, the CSF profile was compatible with AD pathology and the patient was classified as A^+ T^+ $(N)^+$, suggesting "Alzheimer's disease with mild cognitive impairment"[7]. During follow-up, she underwent two more neuropsychological assessments 4 and 8 years later, revealing progressive deterioration of cognition [Figure 3].

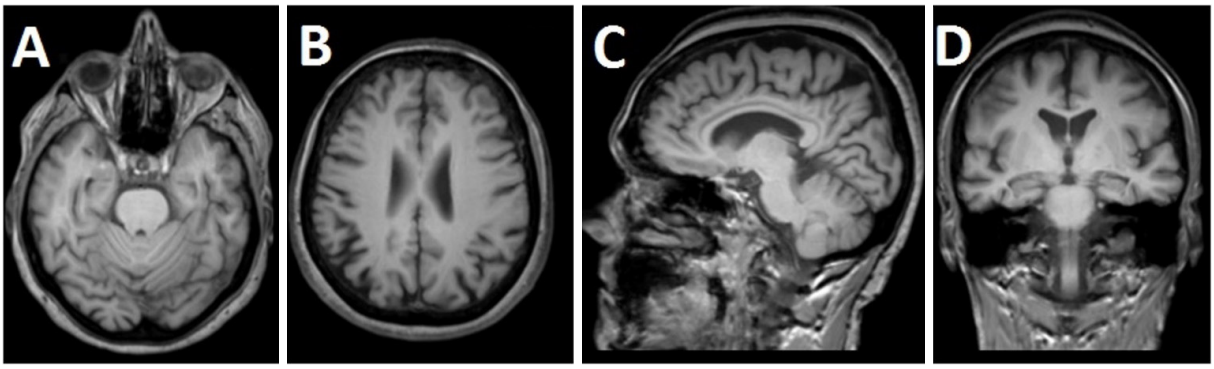

Figure 2. Brain magnetic resonance imaging of case 1 (T1 sequence), showing relative preservation of the hippocampus (A,D) and some degree of parietal atrophy (B,C)

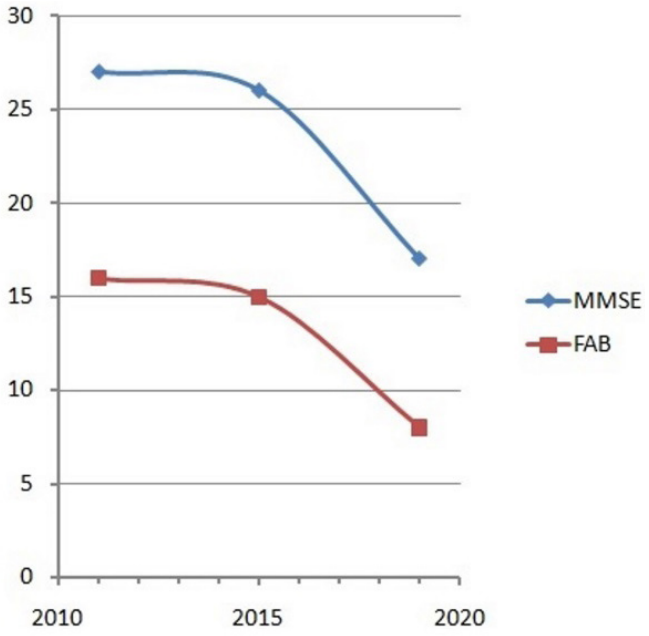

Figure 3. Progressive cognitive deterioration on mini mental state examination (MMSE) and frontal assessment battery (FAB) neuropsychological testing during the 8-year follow-up of case 1

Case 2

A 54-year-old female patient was referred for neurological evaluation due to progressive amnestic type dementia (MMSE: 21/30), with frontal and visuospatial components, evolving for approximately 5 years. MRI showed absence of atrophy. Biomarker analysis of CSF revealed normal τ_T (261 pg/mL), increased $\tau_{P\text{-}181}$ (75 pg/mL), decreased $A\beta_{42}$ (168 pg/mL) and decreased $A\beta_{42}/A\beta_{40}$ (0.04). The CSF profile was compatible with AD, and according to the most recent recommendations, the patient was classified as $A^+ T^+ (N)^-$, suggesting "Alzheimer's disease with dementia"[7]. In follow-up MRI, 3 and 4 years later, a progressive hippocampal and frontal-parietal atrophy was observed [Figure 4].

Case 3

A 71-year-old male patient was admitted to the neurology department due to dementia of mixed amnestic and frontal type. His brain MRI revealed ischemic lesion load but also frontal, perisylvian and frontoparietal atrophy more evident in the left hemisphere on axial fluid attenuated inversion recovery images, whereas according to T1 coronal images, the hippocampus was preserved [Figure 5]. Levels of

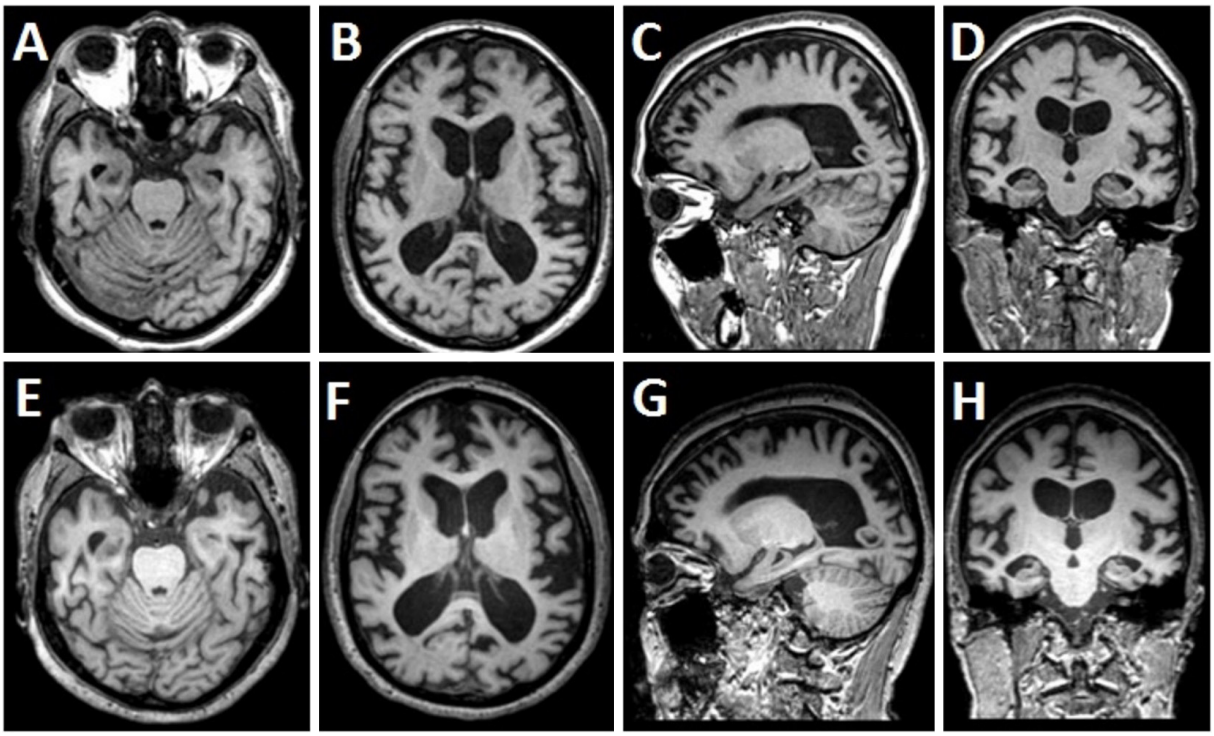

Figure 4. Brain magnetic resonance imaging of case 2 (T1 sequence) at age 57 (A-D) and 58 (E-H), showing progressive hippocampal atrophy (A, D and E, H), and frontal, perisylvian and parietal atrophy (B, C and F,G)

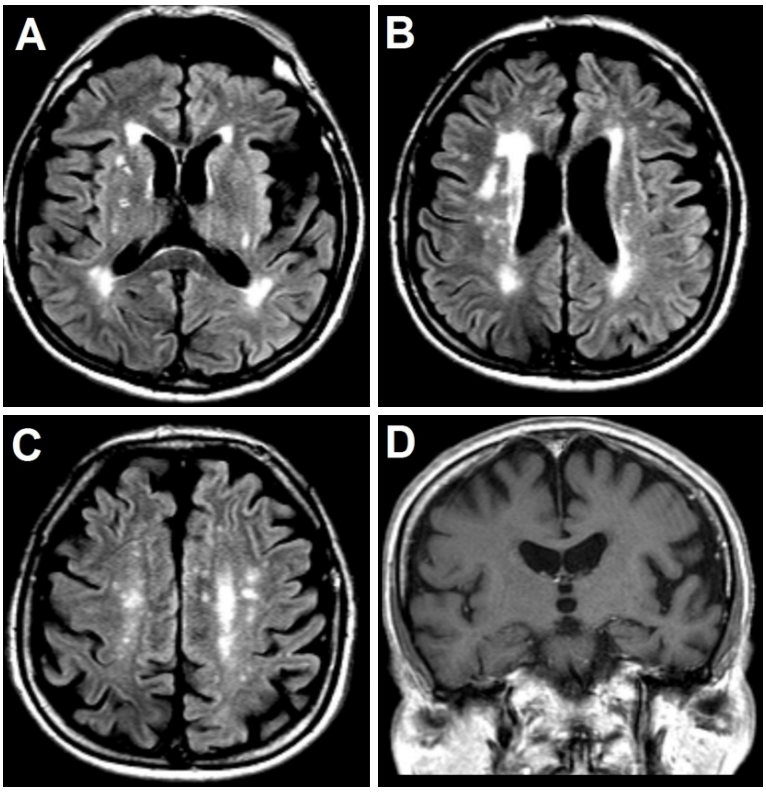

Figure 5. Brain magnetic resonance imaging of case 3. Fluid-attenuated inversion recovery images (A, B, C) show ischemic lesion load and frontal, perisylvian and frontoparietal atrophy more evident in the left hemisphere. In coronal T1 section (D), the hippocampus is preserved

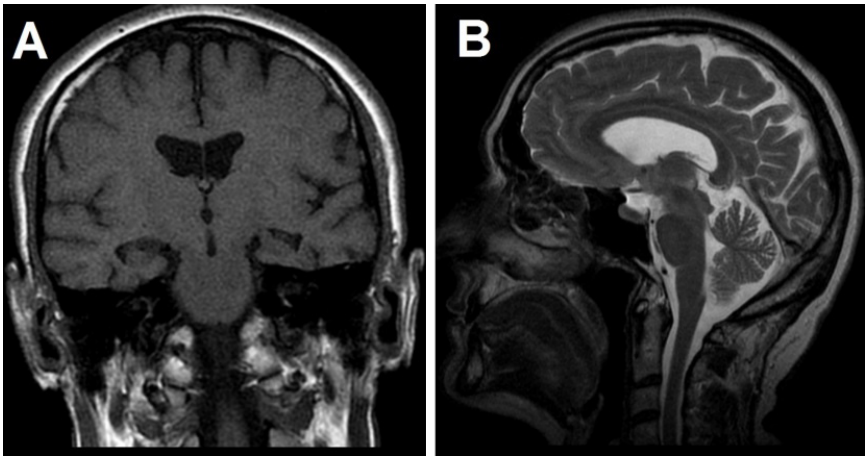

Figure 6. Brain magnetic resonance imaging of case 4. Coronal T1 section (A) reveals hippocampal atrophy. In sagittal T2 section (B), some degree of posterior frontal and parietal atrophy is observed

CSF biomarkers were: τ_T = 963 pg/mL, $A\beta_{42}$ = 495 pg/mL, $\tau_{P\text{-}181}$ = 87 pg/mL and $A\beta_{42}/A\beta_{40}$ = 0.061. With all 3 biomarkers abnormal, the CSF profile was compatible with AD pathology[7] (in addition to subcortical small vessel disease).

Case 4

A 59-year-old female patient with typical amnestic dementia, fulfilling the clinical diagnostic criteria for probable AD[1], was referred to the neurology department for evaluation. Hippocampal atrophy was observed on coronal T1 sequences and, additionally, some degree of posterior frontal and parietal atrophy on sagittal T2 sequences [Figure 6]. The CSF biomarker levels were: τ_T = 308 pg/mL, $A\beta_{42}$ = 921 pg/mL, $\tau_{P\text{-}181}$ = 36 pg/mL and $A\beta_{42}/A\beta_{40}$ = 0.11. Clinically, this "suspected non-Alzheimer disease pathophysiology" (SNAP)[14] was otherwise compatible with an AD phenotype. However, with all 3 biomarker levels well within normal limits, the CSF profile was not compatible with AD[15] and, according to the most recent recommendations, the patient was classified as $A^- T^- (N)^+$ suggesting "non-Alzheimer's pathological change"[7].

Case 5

A 54-year-old female patient presented to our department with frontal-behavioral dementia, language disorder (mixed non-fluent and semantic components) and clinical and electrophysiological evidence of upper and lower motor neuron involvement. Her family history was positive for autosomal dominant dementia and/or ALS. On MRI T1 sequences, frontal and frontoparietal atrophy more evident to the left were present with relative preservation of the hippocampus [Figure 7]. Levels of CSF biomarkers were: τ_T = 268 pg/mL, $A\beta_{42}$ = 513 pg/mL, $\tau_{P\text{-}181}$ = 20.4 pg/mL and $A\beta_{42}/A\beta_{40}$ = 0.125. Although the clinical presentation was suggestive of frontotemporal dementia (FTD)-amyotrophic lateral sclerosis (ALS), reduction of $A\beta_{42}$ was unexpected. However, correction for the total amyloid status revealed a normal $A\beta_{42}/A\beta_{40}$ ratio, excluding amyloid reduction[16,17] and suggesting non-AD pathology. Given the clinical presentation, a TDP-43 proteinopathy was considered the most probable disorder. Indeed, genetic testing was positive for *C9orf72* repeat expansion.

Case 6

A 40-year-old female with no past medical history was referred to the neurology department for presenile dementia. Neuropsychiatric symptoms began at the age of 34 and cognitive symptoms began three years later at the age of 37 and gradually deteriorated, fulfilling the clinical criteria for probable behavioral variant frontotemporal dementia[18]. MRI showed atrophy in the frontal and parietal lobes [Figure 8]. Levels

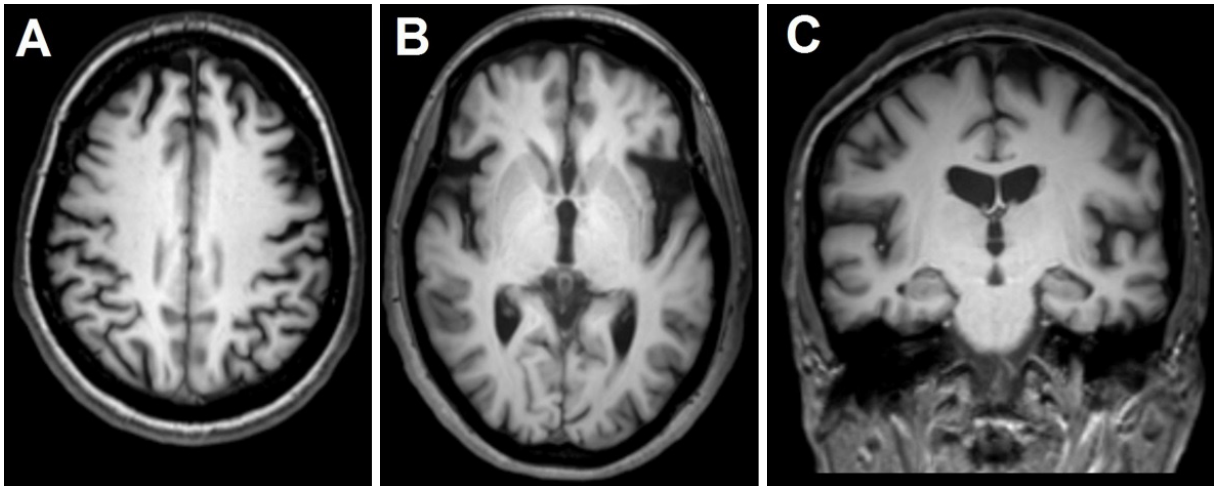

Figure 7. Brain magnetic resonance imaging (T1 sequence) of case 5, showing frontal frontoparietal and sylvian atrophy more evident to the left (A,B) with preservation of the hippocampus (C)

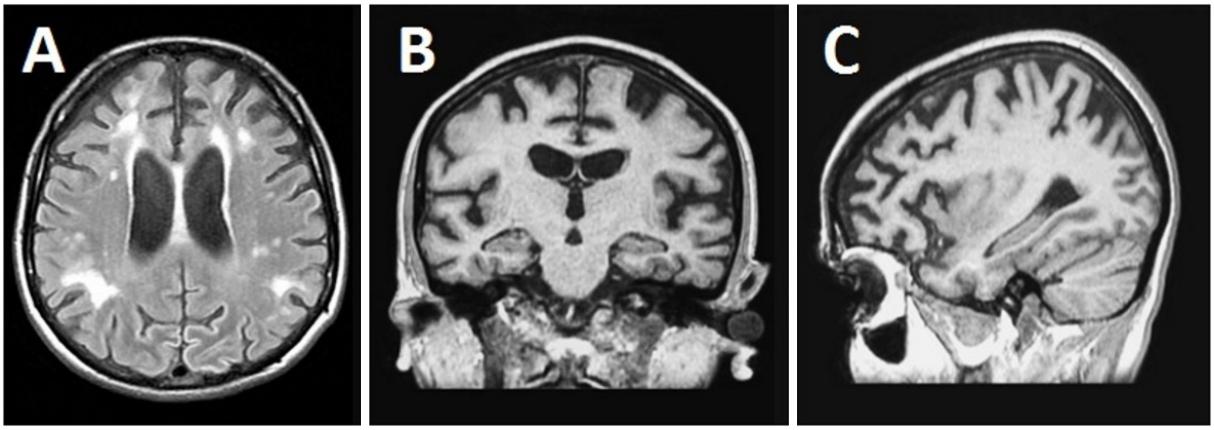

Figure 8. Brain magnetic resonance imaging of case 6. Axial fluid-attenuated inversion recovery image (A) showing white matter hyperintensities; coronal (B) and sagittal (C) T1 images reveal atrophy in frontal and parietal lobes (with some degree of left predominance) and preservation of the hippocampus

of CSF biomarkers were: τ_T = 1813 pg/mL, $A\beta_{42}$ = 706 pg/mL, $\tau_{P\text{-}181}$ = 67 pg/mL and $A\beta_{42}/A\beta_{40}$ = 0.12. With 2 biomarkers abnormal, the patient was classified as $A^- T^+ (N)^+$, suggesting "non-Alzheimer's pathological change with dementia". Given the increased levels of $\tau_{P\text{-}181}$, it was tempting to assume that frontotemporal dementia with tau pathology would be the most probable diagnosis[19]. Cerebral biopsy revealed severe tauopathy without accumulation of amyloid-β or the presence of astrocytic plaques or tufted astrocytes. Genetic testing was negative for mutations in the *MAPT* and *GRN* genes.

DISCUSSION

We presented 6 patients as examples of a combined diagnostic approach based on clinical, imaging and CSF biomarkers, according to the AT(N) system[7]. In case 1, the diagnosis of AD was made in a symptomatic yet predementia stage (MCI). Case 2 was an amnestic dementia patient, and atypical features included presenile onset and absence of atrophy at presentation; however, CSF biomarkers revealed AD biochemistry and clinical-imaging progression was typical.

In case 3, a moderate ischemic lesion load could have contributed to the patient's symptoms, but AD was additionally present. This is a frequent scenario[20], and CSF biomarkers are helpful in the discrimination between cases with pure vascular cognitive impairment and mixed cases (with additional AD)[21,22].

In case 4, a 59-year-old-female, clinically fulfilled the clinical criteria of an amnestic dementia of the AD type[1]. However, clinical presentation does not always predict brain pathology. For example, AD can present with common amnestic dementia but also with a frontal behavioral-dysexecutive syndrome, the so-called "frontal variant of AD"[4,5]. Likewise, patients with FTLD pathologies may also present with an amnestic, AD-like syndrome. The term limbic-predominant age-related TDP-43 encephalopathy (LATE) has been recently introduced for at least some of these cases, and consensus-based recommendations and guidelines for diagnosis and staging have been formulated[6]. Thus, clinical, biochemical, neuropsychological and imaging data, all should be considered. Of course, there is always the possibility of false-negative or false-positive results. Since all biomarkers become abnormal during prodromal stages of AD, all would be expected to be abnormal in a well-established AD dementia[23]. However, in this patient, all biomarkers were normal, dramatically reducing the possibility of false-negative results and pointing to a non-AD pathology. Indeed, with all CSF biomarkers normal, AD is considered highly unlikely according to recent recommendations[15]. Clinically the patient is not compatible with dementia with Lewy bodies (DLB), and to our knowledge, there are no robust, evidence-based data to support the use of standard AD treatments in non-AD, non-DLB patients. Thus, correct diagnosis would also avoid possibly unnecessary treatment(s) suitable for other diseases.

In case 5, TDP-43 proteinopathy was strongly considered from clinical presentation of combined phenotype FTD-ALS in the family, which is known to be related to a TDP-43 histopathology[24,25]. The CSF biomarker profile was compatible with non-AD pathology. In case 6, an AT(N) profile suggestive of non-AD pathology was also observed. However, in this patient, $\tau_{P\text{-}181}$ was increased. Recently, it has been suggested that in an FTD-like patient, with no AD biomarker profile, increased $\tau_{P\text{-}181}$ is more compatible with tau-pathology, while low $\tau_{P\text{-}181}$ may be compatible with TDP-43 pathology[19]. Thus, the tauopathy observed in brain biopsy was in accordance with this notion.

Soon after its publication, the AT(N) system triggered a lot of discussion and criticism. The concept of a disease viewed as a pathological/pathophysiological/biochemical entity unrelated to symptoms may not be easily accepted by some clinicians or the community[26]. However, given that the same disease may present with different clinical syndromes and that the same clinical presentation may be caused by different diseases, this new view is really a step forward, and this holds true not only for AD but also for many other neurodegenerative disorders. Furthermore, since the AD pathological process starts even decades prior to symptomatic onset, whilst CSF or imaging biomarkers become abnormal in the preclinical stage[23], the need for adopting such a view/concept is further strengthened. However, many questions seek answers. For example, what about an $A^+T^+N^+$ patient with a clinical presentation suggestive of DLB. Is this due to mixed pathology (synucleinopathy and AD)[5,27] or due to AD with atypical presentation[28]? Another related question is a DLB-like patient with only amyloid biomarkers being positive. This is very common in DLB[29]. But, is this due to the synucleinopathy alone somehow triggering amyloid deposition unrelated to AD mechanisms, or are such patients "destined" to develop full-blown AD pathology if they live long enough? Furthermore, reduced $A\beta_{42}$ levels have been observed in some patients with pure vascular dementia[20], including patients with inherited subcortical small vessel disease[30], who do not have additional AD pathology, raising questions as to whether reduced $A\beta_{42}$ always suggests Alzheimer's pathological change.

Other CSF biomarkers may be of further help and improve the AT(N) system. Other forms of phospho-tau such as $\tau_{P\text{-}217}$ may perform better, compared to $\tau_{P\text{-}181}$[31]. TDP-43 combined with τ_T and $\tau_{P\text{-}181}$ could enhance the diagnostic accuracy in the FTD spectrum[32,33]. CSF α-synuclein levels could be useful in discriminating patients with AD from cognitively unimpaired subjects, patients with DLB and patients with Parkinson's disease dementia[34,35]. Blood-based biomarkers are quite promising as well, since classical AD biomarkers may also be measured in plasma. Plasma $\tau_{P\text{-}181}$ could differentiate AD dementia from non-AD neurodegenerative diseases with accuracy similar to that of CSF $\tau_{P\text{-}181}$ and tau-PET[36], while plasma $A\beta_{42}$/

$A\beta_{40}$ ratio has been associated with amyloid PET status in cognitively normal subjects[37].

Inflammation biomarkers in CSF and blood have received much attention; however, whether they offer any added diagnostic value remains a matter of investigation. CSF α1-antichymotrypsin levels are increased both in vascular cognitive impairment (VCI) and clinically evident AD, while elevated peripheral CRP levels may be associated with increased risk for VCI, but not AD[38]. Serum interleukin-15 levels have been found to be significantly lower in patients with AD in comparison to healthy subjects and patients with VCI[39]. On the other hand, CSF interleukin-15 levels are increased in AD and FTD, compared to patients with non-inflammatory neurological disorders[40], while CSF interleukin-12 is reduced in AD, indicating altered inflammatory reactions[41].

In neurodegenerative disorders, diagnosis should be established as soon as possible and preferably in a prodromal phase, before the onset of clinically significant dementia. Additionally, new emerging treatments or medications under investigation may be more effective when given in early stages. Therefore, timely and accurate diagnosis is mandatory to obtain potential benefits of novel treatments, but also for accurate inclusion of patients in clinical trials and for determining prognosis. As noted above in case 4, clinical phenotypes are not always tightly linked to the underlying pathology[5,6,9] in contrast to biomarkers, some of which may have high molecular specificity. Nonetheless, CSF biomarkers are not a panacea, and their value should not be over-rated. They have disadvantages mainly due to the heterogeneity of research to date, but they still offer a very useful tool in early etiological diagnosis of neurodegenerative diseases, especially when combined with clinical and neuroimaging data[17].

DECLARATIONS

Authors' contributions

Concept and definition of intellectual content: Kapaki E, Paraskevas GP
Clinical data acquisition and interpretation: Kapaki E, Constantinides VC, Pyrgelis ES, Paraskevas PG, Papatriantafyllou JD, Paraskevas GP
Biomarker determinations and interpretation of results: Kapaki E, Paraskevas GP
Manuscript preparation, editing and review: Kapaki E, Pyrgelis ES, Paraskevas PG, Papatriantafyllou JD, Paraskevas GP

Availability of data and materials

Not applicable.

Financial support and sponsorship

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Conflicts of interest

The authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All patients and/or relatives gave informed consent for publication of their clinical, biochemical and imaging data.

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