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CSF Aβ$_{40}$ and P-tau$_{181}$ might differentiate atypical from typical AD phenotypes: preliminary evidence

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Short Title: Aβ$_{40}$ and P-tau$_{181}$ in atypical *vs.* typical AD
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Abstract

Objectives. This study aimed at testing whether CSF levels of amyloid β_{42} ($A\beta_{42}$), $A\beta_{40}$, total tau and phosphorylated tau (P-tau_{181}) individually contribute to the identification of atypical phenotypes among a retrospective cohort of probable AD patients diagnosed by means of the ratio between $A\beta_{42}$ and $A\beta_{40}$ ($A\beta_{42/40}$). **Methods.** The retrospective study cohort comprised 50 probable AD patients diagnosed by means of the ratio between $A\beta_{42}$ and $A\beta_{40}$ ($A\beta_{42/40}$) and for whom total tau and P-tau_{181} values were also available. Patients were clinically classified as typical, amnestic-predominant AD (*N*=39; 16 males; mean age: 73.4±7.6 years; mean disease duration: 27.4±24.7 months) or atypical phenotypes (*N*=11; 6 males; mean age: 70.2±6.5 years; mean disease duration: 35.5±24.9 months) – *i.e.*, posterior cortical atrophy (PCA; *N*=4), logopenic-variant primary progressive aphasia (lvPPA; *N*=4) and behavioural-variant AD (bvAD; *N*=3). A logistic regression allowed to predict the occurrence of atypical *vs.* typical phenotypes based on age, sex, and $A\beta_{42}$, $A\beta_{40}$, total tau and P-tau_{181} levels. **Results.** Atypical and typical AD patients were comparable for $A\beta_{42/40}$ values. Only $A\beta_{40}$ and P-tau_{181} levels positively (*p*=.015) and negatively (*p*=.019) predicted the occurrence of atypical AD phenotypes, respectively. Classification precision was of 86%, yielding excellent specificity (94.9%), but poor sensitivity (54.5%). **Conclusions.** The present study delivers promising, albeit preliminary, evidence on the utility of $A\beta_{40}$ and P-tau_{181} CSF biomarkers in differentiating atypical from typical $A\beta_{42/40}$-confirmed AD phenotypes, prompting further research and confirmation on larger cohorts.

Introduction

The Alzheimer's disease (AD) *spectrum* encompasses heterogeneous cognitive/behavioural phenotypes underpinned by a common pathology [1]. Indeed, besides the typical, amnestic-predominant variant [2], less prevalent/incident AD phenotypes exist, *i.e.* posterior cortical atrophy (PCA) [3], logopenic variant of primary progressive aphasia (lvPPA) [4] and behavioural variant of AD (bvAD) [5] – primarily characterized by visual-perceptual and spatial deficits, language impairment within the phonological and lexical-semantic components and cognitive/behavioural, dysexecutive features, respectively. Whilst the differential diagnosis among AD variants mostly relies on clinical and radiological features [1], little is known on the capability of AD-related cerebrospinal fluid (CSF) biomarkers – *i.e.* amyloid β_{42} ($A\beta_{42}$) and β_{40} ($A\beta_{40}$), total tau and phosphorylated tau ($P\text{-}tau_{181}$) [1] – in discriminating atypical from typical AD phenotypes [6]. This study aimed at testing whether each of these individual biomarkers contributes to the identification of atypical phenotypes among a retrospective cohort of probable AD patients diagnosed by means of $A\beta_{42/40}$ ratio.

Materials and Methods

Data on *N*=50 $A\beta_{42/40}$-confirmed, probable AD patients (*i.e.*, with $A\beta_{42/40}$ levels below the diagnostic cut-off of 0.069) evaluated in the Department of Neurology, IRCCS Istituto Auxologico Italiano, between October 2019 and May 2022 were retrospectively collected. Exclusion criteria were: 1) (AD-unrelated) neurological diagnoses; 2) severe general-medical conditions. This study was approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano; participants provided written informed consent. Psychometric and neuroradiological records supported a diagnosis of probable, typical AD in *N*=39 patients [2] whereas of probable, atypical AD in the remaining cases (*N*=11) – which were classified as PCA (*N*=4) [3], lvPPA (*N*=4) [4] and bvAD (*N*=3) [5]. CSF-based ATN *status* was also retrieved according to the 2018 NIA-AA Research Framework [7]. CSF examinations were performed by means of automated chemiluminescence enzyme immunoassay on the Lumipulse G600II instrument (Fujirebio) [8]. For total tau and $P\text{-}tau_{181}$, cut-off values of 404 pg/mL and 56.5 pg/mL were considered, respectively, with levels above the cut-offs representing abnormal (pathological) results. These cut-offs are provided by the manufacturer, are used in the present laboratory for diagnostic purposes, and are similar to the single-center or combined cut-offs reported in the literature [8; 9]. A multiple logistic regression (MLR) model was implemented in order to predict the occurrence of atypical *vs.* typical AD phenotypes by entering, as predictors, age, sex, and $A\beta_{42}$, $A\beta_{40}$, total tau and $P\text{-}tau_{181}$ levels. Collinearity was diagnosed in the presence of a variance inflation factor (VIF) >10 and of a tolerance index <.1. MLR-based area under the curve (AUC), precision, sensitivity and specificity were computed. Model fit was evaluated *via* Akaike's information *criterion* (AIC). Analyses were run *via* jamovi 2.3.

Results

Table 1 reports patients' features and clinical variables. PCA and lvPPA patients were classified according the ATN framework as A+/T+/N+, whereas bvAD ones as either A+T-N+ (*N*=2) or A+T-N- (*N*=1). Atypical and typical AD patients were comparable for sex ($\chi^2(1)=.64$, $p=.425$), age ($t(48)=1.25$; $p=.217$), disease duration ($t(48)=.96$; $p=.342$) and $A\beta_{42/40}$ levels ($t(48)=-.83$; $p=.409$). Collinearity was detected for total tau and $P\text{-}tau_{181}$ levels only. The model provided a significant fit ($\chi^2(6)=14$, $p=.03$; AIC=52.7). $A\beta_{40}$ and $P\text{-}tau_{181}$ levels positively ($z=2.43$, $p=.015$; OR=1, CI 95% [1, 1]) and negatively predicted ($z=-2.34$; $p=.019$; OR=.94, CI 95% [.86, .99]) the occurrence of atypical AD phenotypes, respectively. No other predictors yielded significant associations ($p\geq.052$). Classification precision was of 86% (AUC=.82), yielding excellent specificity (94.9%), but poor sensitivity (54.5%).

Discussion

The present study delivers promising, albeit preliminary, evidence on the utility of $A\beta_{40}$ and $P\text{-}tau_{181}$ CSF biomarkers in differentiating typical (*i.e.*, amnestic-predominant) from atypical (*i.e.*, PCA, lvPPA and bvAD), $A\beta_{42/40}$-confirmed, AD phenotypes. Indeed, net of age, sex, $A\beta_{42}$ and total tau levels, atypical AD presentations were predicted by higher $A\beta_{40}$ and lower $P\text{-}tau_{181}$ levels when compared to typical, amnestic-predominant AD variants. Notably, in the face of a chance-level sensitivity, such a model provided excellent specificity. Higher $A\beta_{40}$ and lower $P\text{-}tau_{181}$ levels might thus support the clinical classification of a given AD patient as presenting with an atypical phenotype of the disease.

Overall, the abovementioned results suggest that the observed variability in CSF biomarker levels among AD clinical phenotypes might be underpinned by quantitative and/or qualitative differences in the biochemical processes underlying neuropathological changes [1; 7]. Namely, as regards $A\beta_{40}$, variations in terms of relative production, deposition and clearance of Aβ species could be one of the biological factors driving disease expression towards one or another phenotype, together with putative varying susceptibility of different brain networks to amyloid toxicity. Similarly, pertaining to P-tau_{181}, cortical regions most prominently involved in the different phenotypes could be characterized by varying degrees of tau phosphorylation or secretion or be variably vulnerable to tau accumulation. Interestingly, $A\beta_{40}$ has been seldom addressed as an individual biomarker within the AD *spectrum* outside of its use as denominator of the $A\beta_{42/40}$ ratio, which serves to correct $A\beta_{42}$ levels for inter-individual variations of Aβ production and for possible pre-analytical and analytical variability [10].

The present study is of course not free of limitations. First, the sample size was relatively small, thus limiting the generalizability of the present findings. Relatedly, the small number of PCA, lvPPA and bvAD patients did not allow to separately compare each of these subgroups to typical AD patients, thus preventing from determining whether the results herewith delivered were driven by a specific phenotype. To conclude, the present report suggests a role for $A\beta_{40}$ and P-tau_{181} in supporting the discrimination between typical *vs.* atypical AD phenotypes, although further investigations addressing larger patient cohorts are necessary for confirmation. Such future larger studies might provide the opportunity to include those analyses in classification trees in order to detect the best predictors of AD phenotype in terms of classification performance. This could potentially result in the integration of those biomarkers into diagnostic algorithms supporting clinical diagnosis.

Statements

Statement of Ethics

This study was approved by the Ethics Committee of IRCCS Istituto Auxologico italiano (approval number 2021_05_18_04). Participants provided written informed informed consent and data were treated according to current regulations.

Conflict of Interest Statement

Vincenzo Silani received compensation for consulting services and/or speaking activities from AveXis, Cytokinetics, Italfarmaco, Liquidweb S.r.l., and Novartis Pharma AG, receives or has received research supports from the Italian Ministry of Health, AriSLA, and E-Rare Joint Transnational Call. He is in the Editorial Board of *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *European Neurology*, *American Journal of Neurodegenerative Diseases*, *Frontiers in Neurology*. Barbara Poletti received compensation for consulting services and/or speaking activities from Liquidweb S.r.l. Nicola Ticozzi received compensation for consulting services from Amylyx Pharmaceuticals and Zambon Biotech SA. He is Associate Editor for *Frontiers in Aging Neuroscience*.

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Author Contributions

Federico Verde, Vincenzo Silani: conceptualization, resources, data collection, drafting, revision; Edoardo Nicolò Aiello: conceptualization, statistical analyses, drafting, revision; Eleonora Giacopuzzi Grigoli, Ilaria Milone, Antonella Dubini, Antonia Ratti, Barbara Poletti, Nicola Ticozzi: resources, data collection, revision.

Data Availability Statement

The dataset associated with the present study is open accessible at: https://zenodo.org/record/6974922#.Yw4r5HZBxPZ . Further enquiries can be directed to the corresponding author.

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Tab 1. AD patients' background and clinical variables.

	Variant	
	Atypical	**Typical**
N	11	39
Age at lumbar puncture	70.2±6.5 (57-78)	73.4±7.6 (53-88)
Disease duration at lumbar puncture (months)	27.4±24.7 (3-96)	35.5±24.9 (9-96)
Sex (M/F)	6/5	16/23
Phenotype (*N*)		
PCA/lvPPA/bvAD	4/4/3	-
$A\beta_{42}$ (pg/mL)	473.55±100.27 (379-677)	442.38±111.93 (142-706)
$A\beta_{40}$ (pg/mL)	10959.81±4332.84 (6441-22013)	9639.21±2745.27 (3676-14731)
$A\beta_{42/40}$ (pg/mL)	0.046±0.01 (0.03-0.059)	0.047±0.01 (0.028-0.065)
Total tau (pg/mL)	791.73±496.37 (260-1801)	796.35±415.24 (267-1931)
P-tau_{181} (pg/mL)	120.26±85.39 (40.9-285)	132.17±68.69 (49-307.3)
ATN *status* (*N*)		
A+T+N+	8	36
A+T+N-	-	1
A+T-N+	2	-
A+T-N-	1	2

Notes. AD=Alzheimer's disease; M=male; F=female; PCA=posterior cortical atrophy; lvPPA=logopenic variant of primary progressive aphasia; bvAD=behavioural variant of Alzheimer's disease; $A\beta_{42}$=amyloid β_{42}; $A\beta_{40}$=amyloid β_{40}; $A\beta_{42/40}$=ratio between amyloid β_{42} and amyloid β_{40}; P-tau_{181}= tau phosphorylated at residue 181; ATN=amyloidosis/tauopathy/neurodegeneration.
Continuous data are shown as *M±SD* (*range*).