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Attitudes of Neurologists Toward the Use of Biomarkers in the Diagnosis of Early Alzheimer's Disease

Juan Fortea[a,b,c], Elena García-Arcelay[d], Ángeles Terrancle[d], Blanca Gálvez[e], Verónica Díez-Carreras[d], Pablo Rebollo[f], Jorge Maurino[d,*] and Guillermo Garcia-Ribas[g]
[a]*Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[b]*Biomedical Research Institute Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c]*Center of Biomedical Investigation Network for Neurodegenerative Diseases (CIBERNED), Madrid, Spain*
[d]*Medical Department, Roche Farma, Madrid, Spain*
[e]*Medical Department, Roche Diagnostics, Barcelona, Spain*
[f]*IQVIA, Madrid, Spain*
[g]*Department of Neurology, Hospital Universitario Ramón y Cajal, Madrid, Spain*

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Abstract.
Background: Alzheimer's disease (AD) biomarkers reflect key elements of pathophysiology and improve the diagnostic process. However, their use in routine clinical practice is still limited.
Objective: We aimed to assess neurologists´ barriers and enablers to early AD diagnosis using core AD biomarkers.
Methods: We conducted an online study in collaboration with the Spanish Society of Neurology. Neurologists answered a survey exploring their attitudes towards AD diagnosis using biomarkers in mild cognitive impairment (MCI) or mild AD dementia. Multivariate logistic regression analyses were conducted to determine the association between neurologists' characteristics and diagnostic attitudes.
Results: We included 188 neurologists with a mean age (SD) of 40.6 (11.3) years, 52.7% male. Most participants had access to AD biomarkers, mainly in cerebrospinal fluid (CSF) (89.9%, $n = 169$). The majority of participants (95.2%, $n = 179$) considered CSF biomarkers useful for an etiological diagnosis in MCI. However, 85.6% of respondents ($n = 161$) used them in less than 60% of their MCI patients in routine clinical practice. Facilitating patients and their families to plan for the future was the most frequent enabler for the use of biomarkers. Short consultation time and practicalities associated with the programming of a lumbar puncture were the most common barriers. A younger neurologist age ($p = 0.010$) and a higher number of patients managed weekly ($p = 0.036$) were positively associated with the use of biomarkers.
Conclusion: Most neurologists had a favorable attitude to the use of biomarkers, especially in MCI patients. Improvements in resources and consultation time may increase their use in routine clinical practice.

Keywords: Alzheimer's disease, biomarkers, decision making, diagnosis, neurologists

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder associated with a major negative impact on quality of life for patients and their families [1–3]. The research criteria for the diagnosis of

*Correspondence to: Jorge Maurino, MD, Ribera del Loira 50, (28042), Madrid, Spain. Tel.: +34 913 24 81 00; E-mail: jorge.maurino@roche.com.

AD of the United States National Institute on Aging and the Alzheimer's Association (NIA-AA) require biomarker evidence of disease pathology [4]. The International Working Group for New Research Criteria (IWG) recommends that biomarker diagnosis should be conducted in patients with specific AD phenotypes in line with 2011 NIA-AA criteria [5, 6]. AD biomarkers in cerebrospinal fluid (CSF) and positron emission tomography (PET) are also routinely used in clinical practice in many centers and are incorporated in clinical guidelines [7, 8]. These biomarkers are especially (but not only) to advance the diagnosis of AD in the prodromal phase and mild dementia (early AD) and increase the diagnostic certainty [7–9].

An earlier and accurate diagnosis allows patients and their families to be better informed to make decisions and plan their lives, to benefit from pharmacological and non-pharmacological strategies, and to have the possibility to participate in clinical trials of potential disease-modifying therapies [7, 10]. However, the use of AD biomarkers remains limited in routine practice [7, 11–14]. The concept of therapeutic nihilism in different non-curable neurodegenerative diseases can also be observed in diagnostic procedures [7, 15]. The absence of disease-modifying treatments, the tendency to avoid giving bad news or the assumption that cognitive problems are part of the ageing process partly explain the reluctance to use AD biomarkers [11–14, 16]. In addition, other barriers such as very short consultation time, lack of facilities to perform lumbar punctures, or problems in access and funding for AD biomarkers may make their implementation in the health system more difficult [14–16].

There is little information on neurologists' preferences leading to specific diagnostic choices in early AD patients, especially exploring professional profile, clinical settings, and attitudes. The aim of this study was to assess these attitudes and barriers to the use of AD biomarkers in patients with early AD in a sample of Spanish neurologists.

METHODS

ATTITUDES-AD was an online, non-interventional, cross-sectional study conducted in collaboration with the Spanish Society of Neurology (SEN). Neurologists involved in the management of patients with cognitive disorders were invited to participate in the study by e-mail. The study was approved by the Research Ethics Board of Hospital Universitario Clínico San Carlos, Madrid, Spain (reference: 22/226-E). All participants provided a written informed consent and were recruited from April 22 to June 28, 2022.

Study objectives and outcome measures

The primary objective was to assess attitudes and barriers of neurologists towards using core AD biomarkers (CSF amyloid and tau levels and/or amyloid PET) in patients with mild cognitive impairment (MCI) or mild AD dementia [17]. We also assessed participants´ demographic characteristics, professional profile and clinical setting, and different behavioral characteristics, including healthcare-related regret, attitudes toward adoption of evidence-based innovations, and burnout [18–20]. Participants were exposed to 14 closed questions exploring the availability of AD biomarkers at participants' centers, perceived usefulness and frequency of use in clinical practice, enablers and barriers, and two case scenarios or vignettes depicting a patient with MCI and another older patient with suspected mild AD dementia. This study survey was developed by a research team led by JF and GGR based on common situations experienced by neurologists in clinical practice and literature review [11–14, 16].

Regret is a negative emotion experienced when one believes that the current situation would have had a better outcome by choosing a different course of action [18]. The experience of regret in the context of patient care is a common phenomenon that may lead to suboptimal medical decisions and negative health consequences for physicians and nurses [18]. The Regret Intensity Scale (RIS-10) is a 10-item validated questionnaire to assess care-related regret among healthcare professionals [21]. Each item is scored on a Likert scale with an overall scale range from 1 to 5. Higher scores indicate higher regret intensity. The Evidence-Based Practice Attitude Scale (EBPAS) is a 15-item validated instrument to assess healthcare professionals' willingness to adopt new evidence-based treatments, interventions, and practices [19]. Total score ranges from 0 to 4, with higher scores indicating a more positive attitude toward innovations. Physician burnout is common work-related state of physical or emotional exhaustion negatively influencing physicians´ health and the overall quality of patient care [20]. Burnout was assessed using a single-item measure from the Physician Work Life Study scored on a five-category ordinal scale

Table 1
Main characteristics of the sample

	N = 188
Age, y, mean (SD)	40.6 (11.3)
Sex, male, *n* (%)	99 (52.7%)
Expertise	
General neurologist, *n* (%)	114 (60.6)
Specialist in cognitive disorders, *n* (%)	39 (20.7)
Type of hospital, academic, *n* (%)	152 (80.9)
Patients with cognitive disorders managed per week, median (IQR)	20 (10, 30)
Co-investigator in clinical trials, *n* (%)	101 (53.7)
Authorship of manuscripts/abstracts in peer-reviewed journals, *n* (%)	151 (80.3)
RIS-10 score, mean (SD)	2.0 (0.8)
RIS-10 score ≥3, *n* (%)	22 (11.7)
EBPAS score, mean (SD)	3.1 (0.5)
Burnout score ≥3, *n* (%)	39 (20.7)

EBPAS, Evidence-Based Practice Attitude Scale; IQR, interquartile range; RIS-10, Regret Intensity Scale; SD, standard deviation.

[22]. A cut-off score ≥3 indicates the presence of burnout.

Statistical analysis

We used descriptive statistics to report frequency distributions of qualitative variables, measures of central tendency and dispersion of quantitative variables using non-parametric tests, and 95% confidence intervals. Multivariate logistic regression analysis was conducted to identify factors associated with the use of biomarker (defined as the decision to make an etiological diagnosis with biomarkers in both simulated cases scenarios, one of a patient with MCI and the other with suspected mild AD dementia). Statistical significance was set at $p < 0.05$. The analysis was performed using IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The Spanish Society of Neurology invited 1,580 neurologists to participate in the study: 267 agreed and 188 completed the survey (response rate of 11.9%). The mean age (SD) was 40.6 (11.3) years and 52.7% were male. Participants were predominantly general neurologists (60.6%) managing a median of 20 patients (interquartile range 10.0–30.0) with cognitive disorders weekly. Burnout was found in 39 (20.7%) participants, and 22 (11.7%) reported care-related regret. Table 1 shows the main characteristics of the study population.

CSF biomarkers were the most widely available (89.9%; $n = 169$), followed by amyloid PET (56.9%, $n = 107$) (Table 2). The majority of participants (95.2%, $n = 179$) considered CSF biomarkers useful or extremely useful for an etiological diagnosis in MCI patients. However, 85.6% of respondents ($n = 161$) use them in less than 60% of their MCI patients in their routine clinical practice (Table 3). Facilitating patients and their families to plan for the future was the most frequent enabler to the use of biomarkers (Table 4). Short consultation time and practicalities associated with the programming of a lumbar puncture were the most common barriers.

Table 2
Availability of diagnostic tools

	N = 188
Brain MRI, *n* (%)	184 (97.9)
Amyloid PET, *n* (%)	107 (56.9)
FDG PET, *n* (%)	162 (86.2)
$A\beta_{42}$, total-tau, and phosphorylated-tau in CSF, *n* (%)	169 (89.9)

CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

The context of use was evaluated with two clinical vignettes, one of a (younger) patient with MCI and the other with mild AD dementia. The majority of participants (79.3%; $n = 149$) considered AD biomarkers necessary to make an etiological diagnosis in the patient with MCI versus 38.3% ($n = 72$) in the (older) mild AD dementia patient (Table 5). A younger neurologist age (OR = 0.85, CI 95% 0.76–0.96; $p = 0.010$) and a higher number of patients managed weekly (OR = 60.4, CI 95% 1.28–>999.9; $p = 0.036$) were positively associated with the use of biomarkers. Sex, practice setting, specialization in cognitive disorders, attitude towards innovations,

Table 3
Usefulness and frequency of use of diagnostic tools

How useful do you consider the following tools to establish an etiological diagnosis of Alzheimer's disease in patients with MCI?	Not at all	Slightly	Useful	Very	Extremely	N = 188
MRI	1 (0.5%)	45 (23.9%)	71 (37.8%)	49 (26.1%)	22 (11.7%)	
CT scan	25 (13.3%)	84 (44.7%)	52 (27.7%)	18 (9.6%)	9 (4.8%)	
Amyloid-PET	7 (3.7%)	13 (6.9%)	35 (18.6%)	82 (43.6%)	51 (27.1%)	
FDG-PET	5 (2.7%)	26 (13.8%)	70 (37.2%)	81 (43.1%)	6 (3.2%)	
$A\beta_{42}$, t-tau, and p-tau in CSF	1 (0.5%)	8 (4.3%)	35 (18.6%)	78 (41.5%)	66 (35.1%)	
How often do you use the following tools to establish an etiological diagnosis of Alzheimer's disease in patients with MCI?						
	0–20% of patients	20–40% of patients	40–60% of patients	60–80% of patients	>80% of patients	
MRI	25 (13.3%)	28 (14.9%)	38 (20.2%)	43 (22.9%)	54 (28.7%)	
CT scan	31 (16.5%)	34 (18.1%)	16 (8.5%)	22 (11.7%)	85 (45.2%)	
Amyloid-PET	156 (83.0%)	18 (9.6%)	8 (4.3%)	5 (2.7%)	1 (0.5%)	
FDG-PET	108 (57.4%)	40 (21.3%)	25 (13.3%)	15 (8.0%)	0 (0%)	
$A\beta_{42}$, t-tau, and p-tau in CSF	78 (41.5%)	49 (26.1%)	34 (18.1%)	23 (12.2%)	4 (2.1%)	

CSF, cerebrospinal fluid; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 4
Enablers and barriers

According to your clinical experience, when you have made an early diagnosis of mild cognitive impairment due to AD, in which of the following aspects do you think it has benefited patients and relatives?	It was possible to take actions (occupational therapy, neurocognitive stimulation, etc.) that slowed down progression of the disease	146 (77.7%)
	It was possible to delay institutionalization of the patient	47 (25.0%)
	Dangerous or difficult situations for the patient were avoided or reduced	115 (61.2%)
	The patient and family members were able to organize the necessary help for the care required later	157 (83.5%)
	The stress and insecurity of patients and their families were avoided or reduced	130 (69.1%)
	The patient and his/her family were able to organize legal matters well, including advance directives	132 (70.2%)
Which of the following factors contribute to limiting the use of AD biomarkers in patients with MCI?	Making the etiological diagnosis of AD in early stages consumes health resources that are better dedicated to patients with dementia in more advanced stages	7 (3.7%)
	Making the etiological diagnosis of AD in early stages requires excessive consultation time and the performance of a lumbar puncture that consumes care time	56 (29.8%)
	Confirming the etiological diagnosis of AD in early stages means having to explain to the patient and family members that they have a disease that has no treatment	28 (14.9%)
	Making the etiological diagnosis of AD in early stages requires excessive consultation time given the workload in neurology and the large number of patients with dementia	38 (20.2%)
	Confirming the etiological diagnosis of AD can cause unnecessary stigmatization of the patient	19 (10.1%)
	The center does not have the necessary techniques for etiological diagnosis of AD	29 (15.4%)
	None of the above	84 (44.7%)

AD, Alzheimer's disease; MCI, mild cognitive impairment.

Table 5
Case vignettes

A 74-year-old patient with MCI, predominantly amnesic, as revealed by a neuropsychological assessment, a neuroimaging test with no relevant findings and who requires some assistance in activities of daily living. Which of the following options best reflects your initial attitude?	I consider it necessary to make an etiological diagnosis with AD biomarkers	149 (79.3%)
	I consider the etiological diagnosis with AD biomarkers only if requested by the patient or family	22 (11.7%)
	I do not consider making an etiological diagnosis of the patient as it is sufficient with what has been done so far	17 (9.0%)
An 84-year-old patient with suspected mild AD dementia, as revealed by a neuropsychological assessment, a neuroimaging test with no relevant findings and who requires some assistance in activities of daily living. Which of the following options best reflects your initial attitude?	I consider it necessary to make an etiological diagnosis with AD biomarkers	72 (38.3%)
	I consider the etiological diagnosis with AD biomarkers only if requested by the patient or family	33 (17.6%)
	I do not consider making an etiological diagnosis of the patient as it is sufficient with what has been done so far	83 (44.1%)

AD, Alzheimer's disease; MCI, mild cognitive impairment.

care-related regret, and burnout were not associated with willingness to use AD biomarkers.

DISCUSSION

Biomarkers have changed the landscape of AD diagnosis in the decade [4, 5]. Eleven European scientific societies and Alzheimer Europe are working on the design of a workflow for biomarker-based etiological diagnosis in patients with MCI and mild AD dementia through literature review and Delphi methodology [23]. In a first round, the participants agreed that patients with mild cognitive or behavioral complaints should receive an accurate etiological diagnosis. However, their use in clinical practice remains exceptional due to multiple factors, including lack of access and skepticism in the absence of disease-modifying treatments [24].

The ATTITUDES-AD study assessed neurologists' views on the use of core AD biomarkers in patients with early AD in collaboration with the Spanish Society of Neurology. We found that most participants recognized the need and had a favorable attitude towards the use of biomarkers, especially in patients with MCI. However, this positive attitude did not translate into routine clinical practice even in a sample of neurologists working mostly in academic hospitals with research activity and access to CSF biomarkers.

Our results are in line with previous works. A negative psychological impact for the patient, absence of disease-modifying therapies, and the absence of appropriate institutions for the management of these disorders were the most common perceived risks of making a diagnosis of a cognitive disorder in a survey involving 719 primary care physicians, neurologists, geriatricians, and other healthcare professionals in France [25]. The patients' right to know their diagnosis was not one of the most prioritized benefits. Similarly, a survey involving 108 hospitals and memory clinics in Germany showed important heterogeneity in the use of biomarkers for the diagnosis of patients with early AD in clinical practice [12]. Improving research and facilitating planning for patients and their families were the most common positive aspects of biomarker diagnosis, while stigmatization and psychological problems associated with receiving an AD diagnosis were the most important perceived negative consequences. A biomarker-based diagnosis in people with no or mild cognitive impairment was not considered worthwhile in a qualitative study with 15 primary care physicians, neurologists, and geriatricians in the Netherlands [14]. An older age of patients, variability in biomarker knowledge, and the lack of disease-modifying therapies were the main considerations behind this perception. In a survey conducted in 37 European AD centers, 60% and 43% of participants considered that CSF biomarkers and amyloid-PET had a crucial role in the diagnosis of MCI due to AD, respectively [11]. However, 78% and 97% of responders only used them in less than 60% of their patients in clinical practice, in close alignment with our results.

In 2018, the Spanish Society of Neurology revised its guidelines for the management of dementia [8]. CSF biomarkers were recommended in patients with early-onset dementia (under 65 years of age), in the prodromal stage, and in atypical presentations.

This could explain the low percentage of participants (38.3%) in our study who considered it necessary to make a diagnosis using biomarkers in the vignette of the elderly patient with a clinical diagnosis of mild AD dementia. A younger participant age and a higher outpatient volume were the factors associated with the use of AD biomarkers in both patient profiles.

The diagnostic landscape of AD could even become more complex in the coming years with the approval of blood-based biomarkers and disease-modifying therapies [26–28]. In a systematic review, Low et al. found that healthcare professionals' decision to perform an etiological diagnosis of dementia is influenced by their own beliefs about dementia and their therapies, the patient's clinical situation, including level of awareness and severity of symptoms, idiosyncratic cultural aspects such as stigma, and the characteristics of the health and social care system [29]. Uncertainty is one of the most important factors affecting healthcare decision-making, especially in neurodegenerative diseases without curative treatments [30, 31]. Healthcare professionals may often underestimate the patient's and family's desire to know the diagnosis and overestimate the negative consequences of receiving it [32, 33]. Therefore, it is crucial to reframe the neurologists´ attitudes towards an early etiological diagnosis of AD going beyond the negative effects, challenging skepticism, and focusing on resilience and support measures that can be offered to patients and their families [34, 35]. In addition, health authorities and policy makers should allocate more resources to improve consultation times and facilitate access to diagnostic procedures such as lumbar punctures and amyloid PET scans.

Our study has some limitations that deserve mention. A possible selection bias may have occurred impacting on the representativeness of the sample. Although all SEN members were invited to participate in the study, it is possible that the survey was completed mainly by those with the greatest interest in cognitive disorders and Alzheimer's disease and/or those with the closest regular collaboration with this scientific society. Further research is needed to confirm the study findings and explore their generalizability to other countries with different cultural backgrounds and healthcare systems.

Conclusions

Most neurologists had a favorable attitude to the use of AD biomarkers, especially in patients with MCI. The results of this study may enable the development of neurologist-targeted educational interventions and health policy strategies that ultimately improve resources, consultation time, as well as the well-being and outcomes of patients with early AD and their families.

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CONFLICT OF INTEREST

Elena García-Arcelay, Verónica Díez-Carreras, Ángeles Terrancle, and Jorge Maurino are employees of Roche Farma Spain. Blanca Gálvez is an employee of Roche Diagnostics Spain. Pablo Rebollo is an employee of IQVIA Spain. Guillermo Garcia-Ribas declares no potential conflict of interest.

DATA AVAILABILITY

The datasets generated during the analysis of the study are available from the corresponding author on reasonable request.

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