Are Cerebrospinal Fluid Biomarkers Useful for the Diagnosis of Cognitive Disorders in Older Patients? A 10-Year Retrospective Study in a Geriatric Memory Clinic at Lille University Medical Center (Lille, France)

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Brief report

Are Cerebrospinal Fluid Biomarkers Useful for the Diagnosis of Cognitive Disorders in Older Patients? A 10-Year Retrospective Study in a Geriatric Memory Clinic at Lille University Medical Center (Lille, France)

Dominique Huvent-Grelle[1]*, Yaohua Chen[1], Claire Vaudreuil[1], Susanna Schraen[2], Jean Baptiste Beuscart[1], Eric Boulanger[1] and François Puisieux[1]

[1]*Pôle de Gérontologie, CHU LILLE, France*

[2]*Pôle de Biologie Pathologie Génétique, CHU LILLE, France*

Abstract

We focused on the diagnostic value of Cerebrospinal Fluid (CSF) biomarker assays in older patients. Literature data on this topic are very scarce. CSF biomarkers now constitute an additional body of evidence in the diagnosis of Alzheimer Disease, along with clinical observations, neuropsychological data and imaging findings. We present data obtained in a geriatric memory clinic (Lille, France) over 10 years. We included solely patients having undergone Lumbar Puncture (LP) with diagnostic intent, i.e., when the clinical, neuropsychological and imaging data had not enabled the clinic's physicians to establish a certain diagnosis. A total of 3,236 patients attended our memory clinics; 37 of them underwent LP. The application of CSF biomarker assays enabled rectification of the clinical diagnosis in 35.1% of cases. The diagnosis of cognitive disorders must always be based on a personalized approach.

Keywords: Cerebrospinal fluid biomarkers; Cognitive disorders; Lumbar puncture; Older patient

***Corresponding author:** Dominique Huvent-Grelle, Pôle de Gérontologie, CHU LILLE, France, E-mail: dominique.huvent@chru-lille.fr

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Introduction

Twenty years ago, research on biomarkers in Alzheimer's Disease (AD) was initiated by the publication of guidelines from the International Working Group and the National Institute on Aging - Alzheimer's Association [1,2]. Cerebrospinal Fluid (CSF) biomarkers now constitute an additional body of evidence in the diagnosis of AD, along with clinical observations, neuropsychological data and imaging findings. CSF biomarkers enable AD to be diagnosed 20 to 30 years before clinical signs appear and also facilitate differential diagnoses with regard to other neurodegenerative or cerebrovascular diseases [3]. This technique is approved in France for the diagnosis of young adults, atypical forms of AD or rapidly progressing cognitive disorders. At present, three markers are assayed: total tau, phosphorylated tau and beta-amyloid peptide. Although the incidence of dementia rises markedly with age, few real-life data on the value of CSF biomarkers in very older people are available [4]. Here, we present data obtained in a geriatric memory clinic at Lille University Medical Center (Lille, France) over 10 years.

Methodology

We analyzed the data on patients having undergone Lumbar Puncture (LP) in our memory clinic over a 10-year period (2010 to 2019). In fact, we included solely patients having undergone LP with diagnostic intent, i.e., when the clinical, neuropsychological and imaging data had not enabled the clinic's physicians to establish a certain diagnosis. Patients with certain diagnoses in the absence of CSF assays, patients having refused LP, and patients on anticoagulants or with a severe rheumatic disease (making LP impossible, even when guided by a radiologist) were not evaluated. Each patient's hemostatic profile was checked before LP. All patients gave their written, informed consent to the procedure.

Results

Over the study period, a total of 3,236 patients (mean age: 83) attended our memory clinics; 37 of them underwent LP. In 13 (1/3) of these 37 cases, there was a mismatch between the initial clinical diagnosis and the results of the CSF biomarker assays. The diagnosis has been rectified for these patients (Table 1).

Characteristic	N= 37	N	%
Sex	Females Males	23 14	62.2 37.8
Age (years, mean (SD))	Females Males	76 (8.13) 74 (8.51)	
Place of residence	Own home Nursing/care home	34 3	91.9 8.1
Cardiovascular risk factor	YES	29	78.4
Antiplatelet agents	YES	15	40.5
Imaging	MRI PET CT	36 6 1	97.3 16.2

MMSE score out of 30	Mean (SD)	26 (2.38)	
Mattis Dementia Rating Scale score out of 144	Mean (SD)	130 (10.41)	
Diagnosis before the LP	SCI MCI[1] AD[2] FTD[3]	1 25 10 1	67.5 27
Diagnosis after the LP	SCI MCI AD FTD LATE[4] PSP	1 22 11 1 1 1	59.4 29.8
Complication post LP		0	
Diagnosis rectified for 13 patients (35.1%)	6 diagnoses of MCI were changed to AD. 5 diagnoses of AD were changed to MCI. 1 diagnosis of AD was changed to LATE. 1 diagnosis of PSP, based on the neurological, imaging and biomarker findings.		

Table 1: Characteristics of the study population.

SCI: Subjective Cognitive Impairment - MCI: Mild Cognitive Impairment- AD: Alzheimer's Disease- FTD: Frontotemporal Dementia - LATE: Limbic-Predominant age-related TDP-43 Encephalopathy - PSP: Progressive Supranuclear Palsy

[1]Petersen, 2006

[2]NIA/AA 2011

[3]McKhann 2011

[4]Nelson, 2019

Discussion

According to the participants in the National Institutes of Health workshop in 1998, "the ideal biomarker should be reliable, predictive, unique, reproducible, repeatable and strictly related to the pathological process" [5]. The diagnostic use of CSF biomarkers is subject to various difficulties and limitations. Some sources of assay variability are linked to technical factors (the type of tubes used and the sample collection, transport and storage procedures), the absence of assay standardization, and the lack of internationally agreed cut-off values [3]. In the present analysis, our patients were not extremely old, were living at home and had a high mean Mini Mental State Examination score (Table 1); this is in line with the literature data [3,6,7]. It should also be borne that amyloid disease biomarkers are present in 30% of "cognitively normal" older adults [7]. Other factors must not be forgotten, such as visual disorders, presbycusis and polypharmacy [6].

There are many arguments in favor of the use of biomarker assays in older patients. In our study (as in the literature), we did not encounter any complicating factors [3,6]. The more widespread diagnostic use of this technique might enable the formation of homogeneous populations (e.g. the A/T/N classification) [2]. It must be also emphasized that dementia is not always linked to amyloid or tau pathology, and the latter diseases can also coexist with cerebrovascular pathologies and hippocampal sclerosis [6]. Matsson et al., have shown that biomarker levels do not vary with age [8], and Herruka et al., have graded recommendations for the conversion of mild cognitive impairment to AD as a function of the levels of three biomarkers [9]. Mouton-Liger et al., reported a mismatch between the initial clinical diagnosis and the LP results in a third of cases; in 77% of these mismatches, the clinician changed his/her initial diagnosis to coincide with the biochemical findings [10]. In the present study, the application of CSF biomarker assays enabled rectification of the clinical diagnosis in 35.1% of cases (Table 1).

Conclusion

The diagnosis of cognitive disorders must always be based on a personalized approach. The use of data on CSF biomarkers can complement and improve a "composite diagnosis" formed after a clinical examination, a neuropsychological assessment and imaging. These assays enable the accurate differential diagnosis of various types of dementia. The development of less invasive blood biomarker assays would be of assistance to the clinician and would also increase the currently low level of enrollment of older patients in AD clinical trials.

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Sponsor's Role

The sponsor was not involved in the study design, methods, subject recruitment, data collection, analysis and preparation of the paper.

Conflict of Interest

None of the authors have any financial conflicts of interest to disclose. This study was designed and conducted in accordance with the tenets of the Declaration of Helsinki.

Author Contributions

Dominique Huvent-Grelle conceived and designed the study. Susanna Schraen supervised the analysis of the samples. Dominique Huvent-grelle, Yaohua Chen and Claire Vaudreuil drafted the manuscript. Eric Boulanger and Jean-Baptiste Beuscart searched the literature. François Puisieux revised the manuscript. All authors contributed to the interpretation of the results and approved the final version to be published.

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