The clinical use of cerebrospinal fluid biomarkers for Alzheimer's disease diagnosis: the Italian Selfie

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Introduction

Most of the studies on CSF biomarkers focus on the diagnostic utility (Molinuevo et al., 2014, Blennow et al., 2015), or on analytical and pre-analytical factors hampering their use (Mattsson et al., 2013, Menendez-Gonzalez, 2014, Niemantsverdriet et al., 2016), but we lack studies evaluating how frequently and where AD biomarkers are really used.

By a survey, we aimed at doing a "selfie" of the use of CSF biomarkers in the clinical practice in Italy, to understand the diffusion of CSF analysis, the distribution of centralized laboratories, the standardization of preanalytical procedures and the harmonization of ranges of normality.

Methods

We conducted a nationwide survey in March-May 2016, using an online questionnaire, sent as an e-mail link to the members of SINdem-ITALPLANED, SIBioC and to main Neurological Clinics all over Italy (n=1815). Anonymous data were collected and analyzed.

Results

In Italy, CSF biomarkers analysis is performed in 25 laboratories, which can be distinguished as "internal laboratories" performing analysis just for their own hospital (10/25), and "centralized laboratories" (15/25), which provide biomarkers analysis for their own and for a network of neighboring hospitals. Indeed, 15 hospitals lack the service of an internal laboratory and send CSF samples to external or centralized laboratories, situated in the same or near city. In sum, 40 neurological centers use CSF biomarkers. Interestingly, a Dem-RC is present only in 32.5% of the Hospitals using CSF biomarkers (n=13), showing that CSF biomarkers are not used exclusively by the centers dedicated to the study of cognitive impairment (Table 1). Notably, almost all Dem-RC participating to the survey use CSF biomarkers, and have an internal laboratory; one hospital with Dem-RC sends CSF sample to a centralized laboratory, whereas only one Dem-RC does not use the CSF biomarkers (no sending and no internal CSF Laboratory).

The number of samples analyzed per month in each laboratory is generally low, i.e. less than 10 (41.66 % of the responses) and less than 20 (45.83% of the responses). Only in a few laboratories the amount of CSF assays is more than 20 per month (12.50%)(Table 1).

Standardization of pre-analytical procedures is present in 62.02% of the laboratories participating to the survey. Moreover, only about half (56%) participate in International Quality Control Programs (e.g. Alzheimer's Association Quality control, JPND, or others).

Finally, there is no harmonization of cut-offs among laboratories (Table 2).

Conclusions

To the best of our knowledge, this report is the first one systematically assessing the use of CSF biomarkers in a large multicenter context, focusing on critical issues in the clinical use of CSF biomarkers.

The data of our "selfie" show that 25 laboratories perform CSF biomarker analyses in Italy, on samples coming from 40 different centers located in 13 out of the 20 Italian regions (65%). Then we could consider "the glass half full", because in most of the regions there is at least one laboratory for CSF biomarkers. Oppositely, the glass could be considered "half empty", because despite the apparent high number of centralized laboratories (15/25), the number of samples received from external hospitals is relatively small, and in the majority of the laboratories the number of assays is less than 10 or 20 per month. However, the low number of CSF tests per center could be proportional to the number of new patients with mild to moderate cognitive impairment requiring an etiological diagnosis, according to a recent survey on the use of CSF biomarkers in Europe (Bocchetta et al., 2015).

In conclusion, our data demonstrate that the use of CSF biomarkers is still limited in clinical practice and only a restricted number of patients receive an integrated clinico-biological diagnosis in Italy.

Obstacles to the diffusion of CSF biomarkers in clinical practice can be represented by: 1) difficulties and prejudices to perform LP in patients with dementia; 2) lack of standardization of pre-analytical and analytical procedures; 3) variability of cut-offs among different centers.

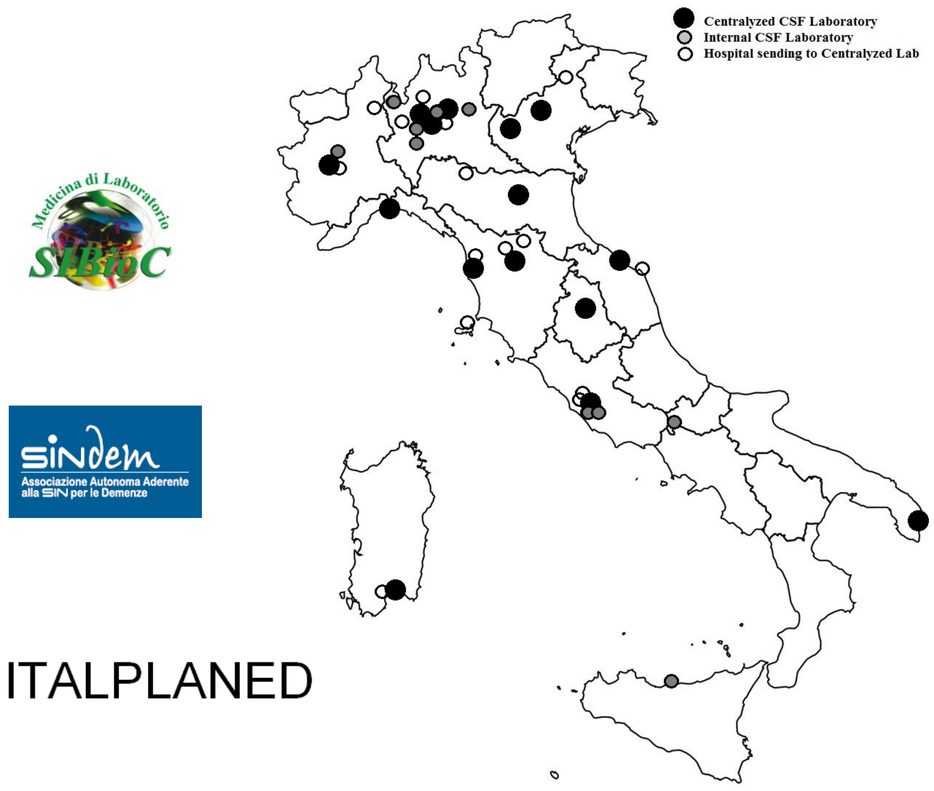
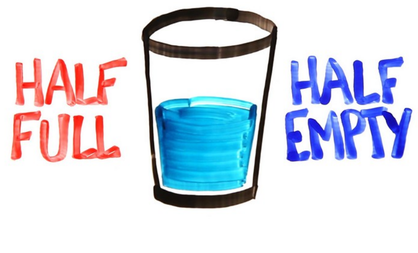


Figure 1. Diffusion of Laboratories of CSF biomarkers.

Labs of CSF biomarkers	Centralized Labs 15	Internal Labs 10	Hospitals sending 15
Labs supporting Memory and Dementia Regional Centers (Dem-RC) §	Yes 32.50%	No 67.5%	
Number of analysis per month §	Less than 10 41.66 %	Less than 20 45.83%	More than 20 12.50%
Standardization of pre analytical procedures *	Yes 62.02%	No 37.98%	
External Quality control §	Yes 56%	No 44%	

Table. 1. Centralized Laboratories provide biomarkers analysis for a network of neighboring hospitals; Internal Laboratories perform CSF biomarkers analysis for own inpatients independently. **Results are reported as percentage of collected questionnaires (*) or percentage of laboratories using CSF biomarkers (n=40)(§).**



Biomarker	Normal value	Number of laboratories
Amyloid β_{42}	>450 >500 > 550 567-1022 >600 790±228	(n=2) (n=10) (n=4) (n=1) (n=1) (n=1)
T tau	<300 <350 <375 <400 <450 <500 170-512 243 ± 127	(n=4) (n=3) (n=2) (n=1) (n=4) (n=1) (n=2) (n=1)
p-tau181	<35 33-66 <52 <61 <65 <67	(n=1) (n=1) (n=2) (n=11) (n=1) (n=1)

Table 2. Normal values of CSF biomarkers. N= Number of laboratories; values are expressed in ng/L.

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