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Comparing Predictors of Conversion to Alzheimer's Disease Using the Disease State Index

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Key Words

Alzheimer's disease · Cerebrospinal fluid · Mild cognitive impairment · Magnetic resonance imaging · Positron emission tomography

Abstract

Background: The Disease State Index (DSI) is a method which interprets data originating from multiple different sources, assisting the clinician in the diagnosis and follow-up of dementia diseases. ***Objective:*** We compared the differences in accuracy in differentiating stable mild cognitive impairment (S-MCI) and progressive MCI (P-MCI) obtained from different data combinations using the DSI. ***Methods:*** We investigated 212 cases with S-MCI and 165 cases with P-MCI from the Alzheimer's Disease Neuroimaging Initiative cohort. Data from neuropsychological tests, cerebrospinal fluid, apolipoprotein E *(APOE)* genotype, magnetic resonance imaging (MRI) and positron emission tomography (PET) were included. ***Results:*** The combination of all parameters gave the highest accuracy (accuracy 0.70, sensitivity 0.71, specificity 0.68). In the different categories, neuropsychological tests (0.65, 0.65, 0.65) and hippocampal volumetry (0.66, 0.66, 0.66) achieved the highest accuracy. ***Conclusion:*** In addition to neuropsychological testing, MRI is recommended to be included for differentiating S-MCI from P-MCI. *APOE* genotype, CSF and PET may provide some additional information.

Introduction

Alzheimer's disease (AD) is the major cause of dementia among the elderly, but early diagnosis of this disease is still a challenge. Mild cognitive impairment (MCI) represents the antechamber of dementia diseases. The diagnosis of AD or prodromal AD [1] requires that the patient displays the core criterion of significant episodic memory impairment and has at least one of the supportive biomarkers: magnetic resonance imaging (MRI), positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers. However, the relative importance of each biomarker is still unclear.

The Disease State Index (DSI) is a novel tool that integrates data and presents them in a straightforward and comprehensible way, supporting the clinician in the diagnosis of AD [2]. In this study, we have used the DSI to predict MCI conversion to AD and incorporated data from neuropsychological tests, CSF, MRI, PET and apolipoprotein E *(APOE)*.

Materials and Methods

Subjects

A total of 376 MCI cases were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (http://adni.loni.ucla.edu/). Two hundred and twelve stable MCI (S-MCI) and 164

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Table 1. Demographic and clinical data of the study groups

	S-MCI	P-MCI
Patients	212	164
Gender[1], female/male	71/141	65/99
Age[2], years	75±8	75±7
Education[2], years	16±3	16±3
APOE 2/3, 3/3, 2/4, 3/4, 4/4	12/106/4/71/19	4/48/5/80/27
APOE ε4 non-carrier/carrier[1]*, %	56/44	32/68
MMSE[2]*	27±2	27±2
CSF total τ[2]*, pg/ml	95±63	115±57
CSF Aβ42[2]*, pg/ml	174±57	145±40
Left hippocampus[2]*	1,900±344	1,691±360
Right hippocampus[2]*	1,963±346	1,765±377

Results are expressed as the mean ± SD. * $p < 0.05$.
[1] Pearson's χ^2 test. [2] Independent Student's t test.

Table 2. Classification results for the DSI

	Accuracy	Sensitivity	Specificity
Neuropsychological tests (A)	0.65	0.65	0.65
MMSE	0.59	0.70	0.51
ADAS	0.64	0.62	0.66
Test battery	0.64	0.65	0.63
APOE (B)	0.61	0.68	0.56
CSF (C)	0.59	0.59	0.59
Aβ42	0.57	0.57	0.57
Total τ	0.59	0.60	0.59
Imaging	0.66	0.66	0.66
FDG-PET (D)	0.61	0.61	0.62
MRI (E)	0.65	0.67	0.63
MRI atrophy	0.61	0.62	0.61
Hippocampal volumetry	0.66	0.66	0.66
A+B	0.66	0.68	0.65
A+C	0.66	0.67	0.66
A+D	0.66	0.66	0.67
A+E	0.69	0.68	0.69
A+B+C+D (excluding MRI)	0.69	0.70	0.68
A+B+D+E (excluding CSF)	0.69	0.70	0.69
A+C+E (excluding APOE and PET)	0.69	0.70	0.68
A+B+C+E (excluding PET)	0.68	0.68	0.67
A+C+D+E (excluding APOE)	0.68	0.71	0.67
A+B+C+D+E (all parameters)	0.70	0.71	0.68

progressive MCI (P-MCI) cases were confirmed after a 3-year follow-up (table 1).

Disease State Index

The DSI is a method that calculates a value that can be used to classify the state of a disease and/or its progression. The DSI computes the relationship of patient data to positive (typically a disease) and control (typically healthy) groups using a *fitness function* that estimates the likelihood that the patient measure is from the positive group. The *relevance* shows how well the measure discriminates between the groups, based on previously diagnosed cases. The total DSI value is computed by averaging the DSI values of each measure by applying weighting with the relevance values. DSI values >0.5 correspond to the positive group while values <0.5 indicate that the patient should belong to the control group. A detailed description of the method has been provided in our previous publication [2].

Data Included

We included data from neuropsychological tests, CSF, *APOE* genotype, MRI and PET results from the ADNI database [3]. The following neuropsychological tests were included: Alzheimer's Disease Assessment Scale (ADAS), Mini-Mental State Examination (MMSE) and a battery of other tests [clock drawing, clock copying, logical memory, Auditory Verbal Learning Test (AVLT), digit span, category fluency, trail making, Wechsler Adult Intelligence Scale - Revised digit symbol substitution, Boston Naming Test, AVLT delayed 30 min, and American National Adult Reading Test]. The CSF parameters were the levels of amyloid-β (Aβ42) and total τ. The PET feature assessed the glucose metabolism on the brain (fluorodeoxyglucose-PET, FDG-PET) [for details on PET, see ref. 4]. The selected MRI parameters were atrophy measured as regional atrophy rate and temporal lobe atrophy, and the volume of the hippocampi. Semi-automated hippocampal volumetry was performed using Medtronic Surgical Navigation Technologies [5]. Both atrophy rates were calculated after a 6-month interval from baseline. Temporal lobe atrophy measures the cumulative temporal lobe atrophy average within an anatomically and statistically defined region of interest [6].

Evaluation of DSI

The evaluation was performed with leave-one-out cross-validation. Accuracy, sensitivity and specificity were calculated from the DSI values.

Results

Table 2 shows the accuracy, sensitivity and specificity for the classification based on the DSI value. The inclusion of all the parameters achieved an accuracy of 0.70, a sensitivity of 0.71 and a specificity of 0.68. When the individual categories were examined separately, neuropsychological tests (accuracy 0.65, sensitivity 0.65, specificity 0.65) and imaging categories (0.66, 0.66, 0.66) achieved the highest accuracy. Furthermore, within the individual parameters, hippocampal volumetry (0.66, 0.66, 0.66) was the most accurate, followed by ADAS (0.64, 0.62, 0.66) and neuropsychological test battery (0.64, 0.65, 0.63).

Discussion

Many studies have attempted to compare different biomarkers as predictors of AD [4, 7] but it is still not clear which is the best combination.

The individual addition of *APOE,* CSF, MRI or PET to the group consisting of neuropsychological tests increased the accuracy, although the effect of *APOE,* CSF and PET was modest. The highest accuracy was reached when all the techniques were included in the DSI, even though the addition of *APOE,* CSF, MRI and PET was only slightly better than the value obtained adding only MRI. With respect to the different category groups, neuropsychological tests and imaging methods were the most accurate. One previous study using ADAS and considering AVLT, CSF biomarkers, FDG-PET and hippocampal volume as candidate predictors showed that AVLT and FDG-PET predicted conversion to AD [4]. In the neuropsychological tests included in our study, ADAS and the test battery achieved the highest accuracy although MMSE displayed the highest sensitivity. This reinforces the fact that MMSE is recommended to be used as a screening test, even though for a more specific diagnosis of dementia and an evaluation of the profile and severity of cognitive impairment, more detailed tests such as ADAS are needed. In this study, CSF biomarkers were the least accurate of the methods included for predicting conversion in the ADNI cohort. However, a study of the DESCRIPA cohort [7] and a European multicenter study [8] revealed CSF biomarkers to be effective in the prediction of AD. With respect to the imaging methods, MRI was more accurate than PET, with hippocampal volumetry being the most accurate technique. For PET, we used baseline measures, while for MRI, we used a rate calculated from two points separated by 6 months, which could explain why MRI performed better in this study.

In our previous paper [9], DSI consisted of data from AVLT, visual medial temporal lobe atrophy and CSF values. We have included other neuropsychological tests, MRI methods, PET and *APOE* in this report. The individual addition of PET or *APOE* to test parameters consisting of neuropsychological tests, MRI and CSF did not increase the predictive accuracy.

This study suggests using neuropsychological tests and MRI as a first diagnostic line for the diagnosis and follow-up on MCI patients, adding CSF, PET and APOE for upholding a diagnostic certainty if needed. However, another study using ADNI data [10] indicated that although MRI and CSF help to predict conversion from MCI to AD, FDG-PET has the greatest value. Therefore, more studies including various imaging methods and particularly different MRI methods should be performed to elucidate their importance.

Conclusion

In addition to neuropsychological testing, MRI is recommended to be included for differentiating S-MCI from P-MCI. *APOE* genotype, CSF and PET may also provide some additional information.

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References

1 Dubois B, Feldman HH, Jacova C, et al: Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–746.

2 Mattila J, Koikkalainen J, Virkki A, et al: A disease state fingerprint for evaluation of Alzheimer's disease. J Alzheimers Dis 2011;27:163–176.

3 Mueller SG, Weiner MW, Thal LJ, et al: The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin N Am 2005;15:869–877, xi–xii.

4 Landau SM, Harvey D, Madison CM, et al: Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010;75:230–238.

5 Schuff N, Woerner N, Boreta L, et al: MRI of hippocampal volume loss in early Alzheimer's disease in relation to *APOE* genotype and biomarkers. Brain 2009;132:1067–1077.

6 Hua X, Hibar DP, Ching CR, et al: Unbiased tensor-based morphometry: improved robustness and sample size estimates for Alzheimer's disease clinical trials. Neuroimage 2013;66:648–661.

7 Vos S, van Rossum I, Burns L, et al: Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. Neurobiol Aging 2012;33:2272–2281.

8 Mattsson N, Zetterberg H, Hansson O, et al: CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009;302:385–393.

9 Liu Y, Mattila J, Ruiz MA, et al: Predicting AD conversion: comparison between prodromal AD guidelines and computer assisted PredictAD tool. PLoS One 2013;8:e55246.

10 Shaffer JL, Petrella JR, Sheldon FC, et al: Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. Radiology 2013;266:583–591.