Erlangen Score predicts cognitive and neuroimaging progression in mild cognitive impairment stage of Alzheimer's disease

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Running title: *Erlangen score predicts progression in MCI*

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Abstract

Background: To alleviate the interpretation of the core Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers amyloid β_{1-42} (Aβ42), total tau (T-tau) and phosphorylated tau (P-tau), the Erlangen Score (ES) interpretation algorithm has been proposed.

Objective: In this study, we aim to assess the predictive properties of the ES algorithm on cognitive and neuroimaging outcomes in mild cognitive impairment (MCI).

Methods: All MCI subjects with an available baseline CSF sample from ADNI-1 were included (n=193), and assigned an ES between 0 and 4 based on their baseline CSF biomarker profile. Structural magnetic resonance imaging brain scans and MMSE and ADAS-Cog scores were collected at up to 7 times in follow-up examinations.

Results: We observed strong and significant correlations between the ES at baseline and neuroimaging and cognitive results with patients with neurochemically probable AD (ES = 4) progressing significantly ($p \leq 0.01$) faster than those with a neurochemically improbable AD (ES = 0 or 1), and the subjects with neurochemically possible AD (ES = 2 or 3) in-between these two groups.

Conclusion: This study further demonstrates the utility of the ES algorithm as a as a tool in predicting cognitive and imaging progression in MCI patients.

Introduction

The importance of cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) as an aid for diagnostic decisions and a measure of disease progression is growing, both in research and in the clinical setting [1-3]. Reaching early and dependable diagnosis and prognosis for patients with memory complaints and other cognitive symptoms is likely key to be able to in time administer future treatments minimizing irreparable damage to the central nervous system [4]. A well-established panel of CSF biomarkers might be able to provide needed support in this task. The four most prominent and widely used biomarkers to date reflect different aspects of AD pathology: deposition of amyloid plaques leading to decreased concentrations of CSF amyloid β_{1-42} (Aβ42) and decreased Aβ42/40 ratio; neuronal degeneration as reflected by total tau (T-tau); and neurofibrillary tangle formation correlated to phosphorylated tau (P-tau) [5, 6]. However, inter-laboratory differences in biomarkers assays, analytical procedures and pre-analytical sample collection protocols have made it hard to establish laboratory-independent cutoff values [7]. This leads to difficulties in comparing CSF results between centers, and even within a given center if a measurement method and/or preanalytical handling protocol are changed. To alleviate the interpretation of laboratory analysis results in AD, the Erlangen Score (ES) interpretation algorithm (ES) has previously been proposed [8]. The ES categorizes subjects into five ordinal categories with scores from 0 to 4 based on their CSF biomarker profile in relation to cutoff values that are given laboratory-specific. This approach reflects reality closer than the dichotomization into normal or pathologic biomarker status used in other studies [9, 10]. The ES algorithm has previously been validated in pre-dementia subjects in two multicenter studies, and its utility was supported by strong associations to the development of AD dementia (ADD) [11-13]. However, the relation of the ES to cognitive and neuroradiological measures of the disease progression in mild cognitive impairment (MCI) stage of AD has never been investigated.

Therefore, in this study we aimed to assess the validity of the ES algorithm as a tool for predicting cognitive and imaging progression in MCI. We hypothesized that a higher score would be associated with faster disease progression.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org, where inclusion/exclusion criteria are also described in detail.

Subjects

Our study population consisted of all MCI subjects with available baseline CSF samples from ADNI-1 (n=193). Briefly, all subjects included in ADNI-1 were between the ages of 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any significant neurologic disease other than AD. The MCI group had Mini Mental State Examination (MMSE) score ≥24, objective memory loss as shown on scores on delayed recall of the Wechsler Memory Scale Logical Memory II (>1 standard deviations below the normal mean), Clinical Dementia Rating scale 0.5, preserved activities of daily living, and absence of dementia.

Erlangen Score

All study subjects were assigned an ES between 0 and 4 based on their CSF biomarker profile with a macro written in Microsoft Excel. The detailed protocol for the ES can be found elsewhere [8]. Briefly, a CSF profile with all biomarkers normal is scored 0 points; a pattern with only slight alterations in one biomarker group (either Aβ or Tau, but not both) results in the score of 1; alterations in amyloid β pathology (in this particular study, decreased Aβ1-42 concentrations) or tau metabolism (increased concentrations of T-tau and/or P-tau) but not in both pathologies is scored 2 points; a result with clear alterations in one biomarkers' group (either Aβ or Tau) accompanied by marginal alterations in the other group is scored 3 points; clear alterations in both Aβ and T-tau/P-tau result in 4 points. A simplified rendition of the interpretation algorithm used to translate the biomarker profiles of each subject is described elsewhere. Eventually, the subjects with the score of 0-1 are defined as "neurochemically improbable AD", the subjects with the score of 2-3 are defined as "neurochemically possible AD", and the subjects with the score of 4 are defined as "neurochemically probable AD".

CSF measurements

CSF collection, processing and storage procedures have been described previously [14]. CSF Aβ42, T-tau and P-tau were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium). The reference ranges used for the calculations of the scores were taken directly from the previous study [14], and applied for this study without further modifications: 192 pg/mL for Aβ1-42, 93 pg/mL for T-tau, and 23 pg/mL for P-tau. The border zones, defining "slight alterations", were set as the concentrations within the range of 173 - 192 pg/mL for Aβ1-42, within 93-102 pg/mL for T-tau, and within 23-25 pg/mL for P-tau.

Magnetic resonance imaging

Structural magnetic resonance imaging brain scans were acquired using 1.5 Tesla MRI scanners (up to 7 time points: screening, and 6, 12, 18, 24, 36 and 48 months) with a standardized protocol including T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence [15]. In brief, automated volume measures were performed with FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/fswiki) [16, 17]. We used averaged volume measurements for the right and left hippocampi for this study.

Cognitive assessments

Overall cognition was assessed by the Mini Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) tests at up to 7 time points (screening, and at 6, 12, 18, 24, 36 and 48 months after the baseline assessment).

Statistical analysis

If not stated otherwise, the results of continuous variables are presented as means and standard deviations (std. dev.) or as medians and inter-quartile ranges (IQR). ANOVA and $\chi2$ statistics were used to test differences in age and sex distribution, baseline measurements of hippocampal and whole brain volumes, and baseline MMSE and ADAS-Cog scores between the study groups. Generalized Estimating Equation (GEE) was used to discern statistical differences between ES groups in the development of MMSE scores, ADAS-Cog scores, hippocampal volumes and whole brain volumes over time. The interaction term of ES*month from baseline was used to test modifying effects of the ES on the effect of the observation time. All longitudinal changes in MMSE, ADAS-Cog scores, whole brain volumes, and hippocampal volumes were normalized to a percentage change in relation to their baseline values. Statistical significance was determined at the $p < 0.05$ level. All statistics, charts, and tables were generated with SPSS version 22 (IBM, New York, USA).

Ethics

All CSF samples analyzed in this study were collected in accordance with regional ethical guidelines as well as the ethical standards of the Helsinki Declaration of 1975.

Results

Demographics of the study cohort

Demographics and the baseline measures of the metrics analyzed in this study are presented in table 1. There were no significant differences in age between the groups. There were significant differences in the sex distribution between the groups ($p = 0.02$). The group with neurochemically improbable AD (ES = 0 or 1) had 26% female subjects, the group with

neurochemically possible AD (ES = 2 or 3) had 18% female subjects, and the group with

neurochemically probable AD (ES = 4) had 40% female subjects.

Subjects in the neurochemically improbable AD group had significantly larger hippocampal

volumes at baseline compared to the neurochemically possible (mean diff = 718 mm^3, p =

0.03) and the neurochemically probable (mean diff = 777 mm^3, p = < 0.01) AD groups. There

were no significant difference in hippocampal volumes between the neurochemically possible

and probable groups (p = 1.0).

The neurochemically improbable AD subjects also had significantly larger whole brain

volumes at baseline compared to those with neurochemically probable AD (mean diff = 6.9E5

mm^3, p < 0.01) but not compared to the subjects with neurochemically possible AD (p = 1.0).

The neurochemically possible group and the neurochemically probable group did not

significantly differen in baseline whole brain volumes (p = 0.11).

The neurochemically improbable AD group registered lower ADAS-Cog scores at baseline

compared to the neurochemically possible AD (mean diff = 5.5, p < 0.01) and the

neurochemically probable AD (mean diff = 5.5, p < 0.01) groups. No significant differences

in ADAS-Cog scores between the neurochemically possible and probable AD groups could be

found (p = 1.0).

The neurochemically improbable AD group presented higher MMSE scores than the

neurochemically possible AD (mean diff = 1.0, p = 0.04) but not the neurochemically

probable group (p = 0.20). There were, again, no significant differences between the

neurochemically possible and probable AD groups (p = 0.64).

Longitudinal changes in cognitive measures in the MCI group

Follow-times and and number of participants at each point of follow-up is presented in table

2. MMSE scores declined significantly faster in the subjects with neurochemically possible

AD (B = -0.20, p = 0.03) and with neurochemically probable AD (B = - 0.36, p < 0.01) compared to the subjects with neurochemically improbable AD (fig. 1a). There was a nonsignificant tendency towards faster decline in the MMSE score in neurochemically probable subjects compared to neurochemically possible subjects (B = - 0.16, p = .10).

Subjects with neurochemically probable AD also increased faster in ADAS-Cog scores as compared to the subjects with improbable AD (B = 0.71, p = 0.01, fig. 1b). We did not observe differences in ADAS-Cog scores increase between the neurochemically possible AD subjects compared to the neurochemically improbable AD subjects (B = 0.10, p = 0.76). There were however a significant difference in decline between the neurochemically probably and neurochemically possible AD subjects (B = 0.60, p = 0.02).

Longitudinal changes in brain structure in MCI

Whole brain volumes decreased faster in subjects with neurochemically possible AD (B = -0.032, p = 0.03) and neurochemically probable AD (B = -0.066, p < 0.01) as compared to subjects with neurochemically improbable AD (fig. 1c). Whole brain volumes also decreased faster in subjects with neurochemically probable AD (B = -0.034, p = 0.01) as compared to subjects with neurochemically possible AD.

Hippocampal volumes of patients with neurochemically possible AD (B = -0.084, p < 0.01), and neurochemically probable AD (B = -0.20, p < 0.01) decreased at a faster pace compared to the subjects with neurochemically improbable AD (fig. 1d). This was also true for subjects with neurochemically probable AD (B = -0.117, p < 0.01) as compared to subjects with neurochemically possible AD.

Discussion

In this study, we examined the utility of the Erlangen Score as a globally implementable composite AD biomarker evaluation algorithm to predict cognitive and brain imaging decline in MCI stage of AD. We found that a higher ES predicted a faster disease progression in MCI patients; the subjects with higher ES showed a faster reduction of the whole brain and the hippocampal volumes, as well as faster decrease in MMSE, and a faster increase in ADAS-Cog scores.

In all disease progress measures selected for this study there were clear and statistically significant distinctions between patients with neurochemically improbable AD (ES of 0-1) and those with neurochemically probable AD (ES of 4), and for most measures also between the subjects with neurochemically improbable AD and those with neurochemically possible AD (ES = 2 or 3). Expectedly, subjects with ES 2-3 exhibited disease developing patterns in between those with the scores score 0-1 and 4. Here, the differences between the groups were statistically weaker, probably at least partly due to the low number of subjects with ES 2 and 3 (n = 27 and n = 7, respectively). However, their statistical parameters in the GEE models as well as visual indications in the Loess regressions in figure 1 corroborate them being part of a continuum between the higher subject count groups of neurochemically improbable AD and neurochemically probable (ES = 4) AD. An interesting feature of the differences in the correlations of the cognitive and the structural measures and ES, is that the neurochemically improbable AD and the neurochemically possible AD divert from each other in structural but not in cognitive measures. One explanation for this might be that, in AD, structural decay can be radiologically visualized before cognitive decline can be detected by MMSE or ADAS-Cog [18]. This means, that the subjects with no or only moderate CSF alterations (i.e. those

with ES = 0-3) are most probably at a stage of the disease when the structural changes can already be seen, but the cognitive decline has not yet reached pathological levels. To our best knowledge, ES is the first modality/biomarker reported so far capable to predict as small as 10% drop in the MMSE score in a timespan of less than 24 months (see fig. 1a).

It should be noted that figure 1 is intended as an illustration, while the GEE model provide statistical proof of differences. Some seeming anomalies between the GEE results and the graphical representations of data in the local regression illustrations occur. For instance the local regression lines representing the MMSE progression of the improbable and the possible AD groups cross paths, but still differ significantly in the GEE model. This likely stem from the linear nature of the GEE model contrasting with the adaptive nature of the local regression, and also the low number of participants, particularly at follow up, in the neurochemically probable AD group.

Interestingly, in our recent study we found that MCI patients with neurochemically possible AD had, compared to the patients with neurochemically improbable AD, 6 - 8 times higher hazards to progress to the dementia stage of AD in the first three follow up years, and then their hazards decreased and became comparable to those with improbable AD; on the other hand, MCI patients with neurochemically probable AD had hazards to develop AD dementia 8 - 12 times higher compared to the patients with neurochemically improbable AD [13].

The most serious limitation of this study is the unavailability of results of CSF Aβ1-40 in this cohort, which precluded integration of the Aβ42/40, a biomarker known to better reflect the amyloid β pathology than Aβ1-42 concentration [19, 20], into the calculation of the ES. This can perhaps explain, why some subjects categorized as neurochemically improbable AD

based on the three available CSF biomarkers (ES = 0 or 1), show progression in neuroimaging modalities (see fig. 1c and d). Certainly, some of these subjects would move to the neurochemically possible AD category (ES = 2 or 3), if their Aβ42/40 ratio had been available and turned out pathologic. Nevertheless it must be stressed that even in the absence of Aβ42/40 ratio, the interpretation based on the ES performed very well in this validation study.

The findings of this study outline a new property of the ES that has not been demonstrated before, namely its predictive features of disease progression rates in MCI. This adds to the value of the algorithm that has previously been shown, including: (a) precise estimation of risk to develop dementia in pre-dementia AD. (b) Allowing inter-laboratory comparisons of lab test results, despite use of different assays and biomarker cut-offs between centers. (c) Interpretation and presentation of all possible biomarker patterns, including those that are inconsistent with hallmark AD-like biomarker patterns.

Competing interests:

company at the University of Gothenburg. PL received consultation and lectures honoraria from Innogenetics/Fujirebio Europe, IBL International, AJ Roboscreen, and Roche.

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Table 1 Demographics and the cognitive and neuroimaging results. M/F, number of the male/female subjects; Mdn., median; IQR, inter-quartile range; Std. dev., standard deviation; MMSE, mini-mental state examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; E3, $*10^3$; E6, $*10^6$. All measures were collected at the baseline.

Erlangen score	Sex	Age (years)		MMSE (points)		ADAS-Cog (points)		Whole brain volume (mm3)		Hippocampal volumes (mm3)	
	M/F	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)	Mean (Std.dev.)	Mdn (IQR)
0-1	12/35	73.8 (7.9)	74 (67.5-80.4)	27.4 (1.7)	28 (26-29)	14.8 (5.4)	15.8 (11.3-17.3)	1.05E6 (.12E6)	1.05E6 (0.98E6-1.08E6)	6.98E3 (1.28E3)	7.20E3 (6.05E3-7.68E3)
2-3	6/28	76.8 (7.5)	77.2 (73.9-80.9)	26.4 (1.9)	26 (25-28)	20.3 (6.2)	19.9 (15.7-24.7)	1.04E6 (0.12E6)	1.07E6 (0.96E6-1.13E6)	6.26E3 (1.28E3)	6.50E3 (5.34E3-7.11E3)
4	45/67	78.1 (7.1)	79.1 (70.3-85.9)	26.9 (1.8)	27 (25-28)	20.3 (6.0)	21 (16.3-24.3)	0.99E6 (0.10E6)	0.98E6 (0.92E6-1.05E6)	6.20E3 (0.87E3)	6.11E3 (5.57E3-6.75E3)

Table 2 Participants at follow-up times

Follow-up		Baseline	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months
Erlangen score	0 or 1	47	45	43	40	36	33	30	21	6	3
	2 or 3	34	33	31	29	27	27	22	10	5	3
	4	112	108	106	98	91	81	75	36	16	10

Figure legends

Fig. 1. Correlations between follow up time and the neuropsychologic and neuroimaging population-averaged (marginal) metrics in the three ES categories:

1a. MMSE score change from the baseline;

1b. ADAS-Cog score change from the baseline;

1c. whole brain volume change from the baseline;

1d. hippocampal volume change from the baseline.

Figure 1.