Identifying healthy elderly subjects with Alzheimer Pathology more efficiently for clinical trial participation

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Introduction

Early identification of lowered CSF Aβ1-42 levels consistent with Alzheimer pathology is important for early phase drug development as the current leading hypothesis regarding pathophysiology of Alzheimer disease (AD) revolves around this toxic protein. In this study we developed an algorithm based on less-invasive biomarkers for AD to pre-select subjects who are suspected of lowered, abnormal, CSF Aβ1-42 levels consistent with the presence of AD pathology. The purpose of the algorithm is to identify potential trial subjects with an expected higher risk of having CSF Aβ1-42 levels consistent with AD, resulting in a smaller numbers of subjects requiring lumbar punctures (LPs).

Aim

To define an algorithm based on plasma biomarkers, genetic status, a computerized cognitive test battery (NeuroCart), age, hand grip strength and level of education to discriminate between CSF Aβ positive and CSF Aβ negative healthy elderly subjects.

Methods

Single-center, cross-sectional, correlation study in 200 cognitively healthy male and female elderly (MMSE>24).

- Cognitive and biomarker testing (see table 1)
- Neuropsychological questionnaires (MMSE, GDS, IADL, CDR)
- CSF sampling (Elecsys was used to measure Aβ1-42)

Results

- 189 CSF samples were obtained (average age 72 +/-4y)
- 55 (29,1%) were "Aβ42 positive", i.e. consistent with AD pathology
- Random forest algorithm: combination of 15 parameters

→7 tests (MMT, VVLT, Adaptive tracker, N-Back, SART, saccadic eye movements, EEG) + 2 blood tests (Abeta1-42/1-40 ratio, YKL-40) →

- Sensitivity: 63.6% (±0.03)
- Specificity: 66.6% (±0.09)
- Receiver operating characteristic (ROC): 66% (±0.02) (fig 2)
- 270 healthy elderly → expectation:79 Aβ+ → algorithm identifies 113 Aβ+ (64 wrongfully, 28 will be missed) → 113 LPs instead of 270

<u>= 42% reduction of lumbar punctures in healthy elderly</u>

Conclusions

- Algorithm leads to lower number of lumbar punctures in healthy subjects
- Use of the algorithm would lead to lower costs of early phase drug studies
- Ethical considerations have to be taking into account when identifying healthy subjects with an elevated risk of developing AD.

AD CSF biomarkers: Elecsys	**# AD positive** N total = 189
Aβ1-42 <1000 pg/ml	N = 55
Total Tau >235 pg/ml	N = 72
Overlap Aβ1-42 + TTau	N = 30
Phosphorylated Tau >18 pg/ml	N = 103
Overlap Aβ1-42 + TTau + PTau	N = 26

Table 1: Biomarker profile of study population

Biomarkers	**Cognitive Tasks**	**Other**
Simoa: Plasma NfL	Adaptive Tracking: attention (x 2)	Education
Simoa: Plasma Total Tau	VVLT: Visual Verbal Learning Task: memory (x 18)	Age
Simoa: Plasma Aβ40, Aβ42	MMT: Milner Maze Test: visuospatial memory (x 15)	Gender
Plasma_Aβ42/40 ratio	Face Encoding and Recognition (x 3)	
APOE Status	N-Back: working memory (x 6)	
YKL-40	SART: Sustained Attention to Response: attention (x 6)	
	Finger Tapping: motor speed (x 2)	
	EEG (x 30)	
	Saccadic and Smooth Eye Movement (x 3)	
	JAMAR Handgrip	

Table 2: Input in algorithm

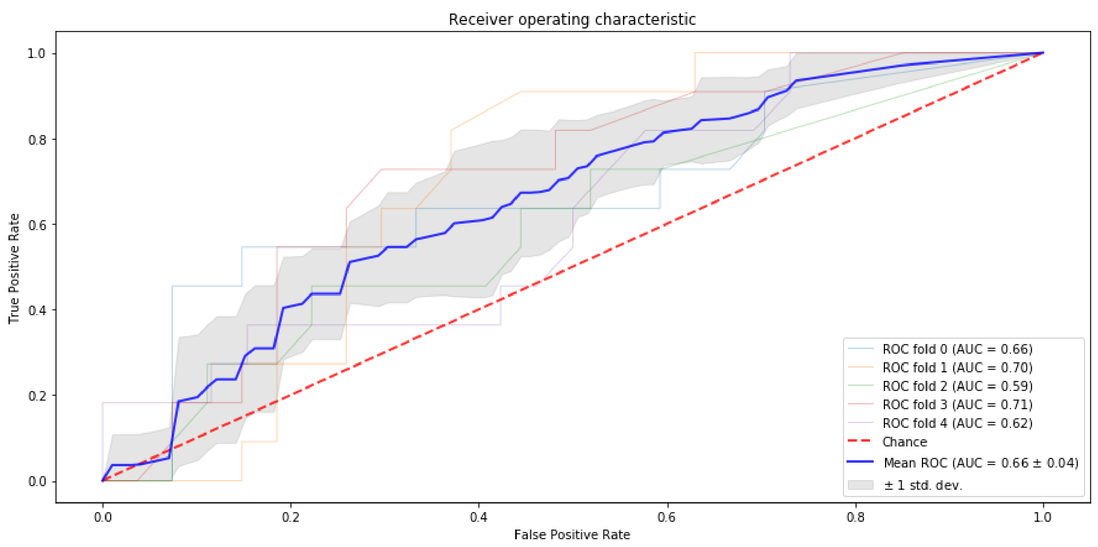

Figure 1: ROC algorithm

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