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BIOMARKERS FOR THE DETECTION OF PROGRESSIVE EARLY ALZHEIMER'S DISEASE

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Introduction

- According to the National Institute on Aging and Alzheimer's Association (NIAAA) criteria, Alzheimer's disease (AD) can be defined and staged by core pathological changes, including an overabundance of amyloid β (Aβ) plaques (A+), the presence or absence of neurofibrillary tangles or tauopathy (T+), with or without neurodegeneration (N+ / N-).
- Even in the early stages of continuum, when present cognitively unimpaired (CU) or only mild cognitive impairment (MCI) in cognitive assessment, a large amount of subjects may already be A+T+ (i.e., preclinical AD, defined as A+T+ CU; and prodromal AD, defined as A+T+ MCI).The subjects with A+T+, with or without neurodegeneration, are expected to have high rate of short-term clinical progression.
- Blood-based biomarkers for Alzheimer's disease, for instance, neurofilament light (NfL), plasma tau phosphorylated at 181 (p-tau181) and total tau (t-tau) levels, have recently shown great potential for being used as accessible, cost-effective, and relatively non-invasive tools for detecting AD neuropathology and its progression.
- A novel AD resemblance structural atrophy index (AD-RAI) was developed by our team, which showed great accuracy in discriminating those who harboring A+T+ among MCI or CU subjects
- We investigated the ability of MRI, plasma, and cognitive biomarkers in detecting preclinical or prodromal Alzheimer's Disease (AD) who will progress to the next syndromal stage of the cognitive continuum.

Methods and Materials

589 subjects with longitudinal cognitive data were recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which included 227 cognitive unimpaired (CU) and 362 mild cognitive impairment (MCI) subjects.

- Preclinical or prodromal AD was defined by a low amyloid beta (Aβ)42 (A+) and high phosphorylated -tau (p-tau) (T+) on cerebrospinal fluid (CSF) assessment at baseline.
- The following baseline MRI biomarkers were derived by an automatic segmentation tool (AccuBrain®): AD-resemblance atrophy index (AD-RAI), quantitative medial temporal lobe atrophy (QMTA) and hippocampus volume (HV).
- Plasma biomarkers included p-tau 181, neurofilament (NFL) and APOE ε4. Montreal Cognitive Assessment (MoCA) score was collected for all subjects at baseline.
- Conversion (C+) was defined as subjects progressed from CU to MCI and from MCI to dementia within 4 years.

Results

- Of the 589 subjects (mean [SD] age, 72.2 [6.9] years; 314 men [53.3%]), 96 (16.3%) were A+T+C+ and 180 (30.6%) were A+T+C-.
- In the ROC analysis, AD-RAI achieved the best detection ability than other individual biomarker with a sensitivity of 83.4%, a specificity of 69.4% and an AUC of 87.8%.
- A combination of AD-RAI, plasma p-tau 181, APOE ε4 and MoCA score achieved the best detection ability with AUC of 89.8%, sensitivity of 85.1% and specificity of 80.2%.
- In the subgroup analysis, the combination of AD-RAI, plasma p-tau 181, APOE ε4 and MoCA score also showed good accuracy in identifying A+T+C+ subjects in the CU group (AUC=87.6%) and in the MCI group (AUC=89.3%).

Discussion

- The combination of plasma p-tau181, ADRAI, APOE Ɛ4 genotype plus MOCA score achieved the best metrics among CU and MCI subjects in detecting those who already presented A+T+ at baseline and progress to the next syndrome stage within 4 years.
- When using the single variable as predictor, ADRAI achieved the best performance in detecting 4-years convertors in preclinical and prodromal AD subjects than all the other neurodegeneration markers including the traditional MRI features (MTA and HV), FDG PET and CSF t-tau.
- Optimal cut-off of ADRAI is 0.6 in predicting 4-years conversion and A+T+C+
- Plasma p-tau181 showed best performance in differentiating A+T+ subjects.

Conclusions

A panel of MRI, plasma and cognitive biomarkers might help to detect progressive early AD subjects.

Table 1. Summary of demographics

Characteristics	Total (n=589)	Training set (n=294)			Validation set (n=295)		
		A+T+C+ (n=49)	Not A+T+C+ (n=245)	P value	A+T+C+ (n=47)	Not A+T+C+ (n=248)	P value
Age (years), mean (SD)	72.2±6.9	73.4±7.2	72.1±6.6	0.233	73.6±6.4	71.7±7.1	0.086
Male (n [%])	314(53.3)	26(53.1)	129(52.7)	0.873	26(55.3)	133(53.6)	0.874
Education (years), mean (SD)	16.4±2.6	16.6±2.5	16.2±2.6	0.456	16.0±2.5	16.6±2.5	0.096
Baseline diagnosis (n [%])							
CU	226(38.4)	4(8.2)	109(44.5)	< 0.001	7(14.9)	106(42.7)	< 0.001
MCI	363(61.6)	45(91.8)	136(55.5)	< 0.001	40(85.1)	142(57.3)	< 0.001
MMSE, mean (SD)	28.4±1.7	27.6±1.7	28.6±1.5	< 0.001	27.6±1.9	28.6±1.5	< 0.001
Δ MMSE(per year), mean (SD)	0.3±0.8	1.4±1.3	0.2±0.5	< 0.001	1.4±1.4	0.1±0.5	< 0.001
MOCA, mean (SD)	24.2±3.1	21.8±3.1	24.7±3.0	< 0.001	21.8±2.5	24.7±2.7	< 0.001
APOE ε4 genotype (n [%])	239(40.6)	30(61.2)	84(34.3)	< 0.001	39(83.0)	86(34.7)	< 0.001
FDG PET SUVR, mean (SD)	1.3±0.1	1.17±0.1	1.3±0.1	< 0.001	1.18±0.1	1.3±0.1	< 0.001
ADRAI, mean (SD)	0.5±0.4	0.9±0.2	0.4±0.4	< 0.001	0.8±0.2	0.4±0.4	< 0.001
CSF t-tau(pg/ml), mean (SD)	81.4±55.8	124.0±68.3	74.1±54.3	< 0.001	120.3±61.6	72.7±46.0	< 0.001
CSF $A\beta_{42}$ (pg/ml), mean (SD)	198.6±142.5	135.9±24.1	203.6±130.1	< 0.001	130.9±20.9	218.6±171.2	0.001
CSF p-tau(pg/ml), mean (SD)	39.3±22.8	65.0±29.8	35.0±19.5	< 0.001	58.4±20.1	34.8±19.5	< 0.001
Plasma p-tau181(pg/ml), mean (SD)	17.1±11.2	26.3±18.3	16.3±10.7	< 0.001	24.8±10.2	14.7±8.1	< 0.001
Plasma NfL, (pg/ml), mean (SD)	37.4±21.2	45.1±17.5	36.0±23.0	0.010	46.3±19.1	35.5±19.7	0.001

Table 2 Performance of individual biomarkers in detecting A+T+C+ subjects

Variables	Training set (n=294)			
	AUC	95%CI	Sensitivity	Specificity
ADRAI	0.834	0.787-0.875	87.76	69.39
HV(ml)	0.704	0.648-0.755	67.35	67.76
HF	0.758	0.705-0.806	59.18	82.45
QMTA	0.716	0.661-0.767	53.06	83.67
MOCA	0.740	0.685-0.789	63.27	78.78
FDG PET SUVR	0.778	0.725-0.824	77.55	68.44
CSF t-tau(pg/ml)	0.739	0.685-0.789	73.47	71.02
Plasma p-tau181(pg/ml)	0.736	0.682-0.785	53.06	88.57
Plasma NfL, (pg/ml)	0.696	0.640-0.748	83.67	50.61
APOE ε4 genotype	0.635	0.577-0.690	61.22	65.71

Table 3. Cutoff of ADRAI for detecting A+T+C+

ADRAI	Odds ratio (95% CI)	p	AUC (95% CI)	Sensitivity	Specificity
0.1	17.698 (2.395-130.812)	0.005	0.624 (0.566-0.680)	0.980	0.269
0.2	15.667 (3.719-65.991)	< 0.001	0.680(0.623-0.733)	0.959	0.400
0.3	18.835 (4.474-79.284)	< 0.001	0.702(0.646-0.754)	0.959	0.445
0.4	15.972 (4.837-52.737)	< 0.001	0.724(0.670-0.775)	0.939	0.510
0.5	21.497 (6.506-71.030)	< 0.001	0.761(0.708-0.809)	0.939	0.583
0.6	19.375 (6.746-55.649)	< 0.001	0.776 (0.723-0.822)	0.918	0.633
0.7	12.560 (5.608-28.128)	< 0.001	0.773(0.721-0.820)	0.837	0.710
0.8	11.030 (5.205-23.372)	< 0.001	0.767(0.715-0.814)	0.796	0.739
0.9	10.956 (5.482-21.896)	< 0.001	0.761 (0.708-0.809)	0.694	0.829

Figure 1. Nomogram for predicting A+T+C+

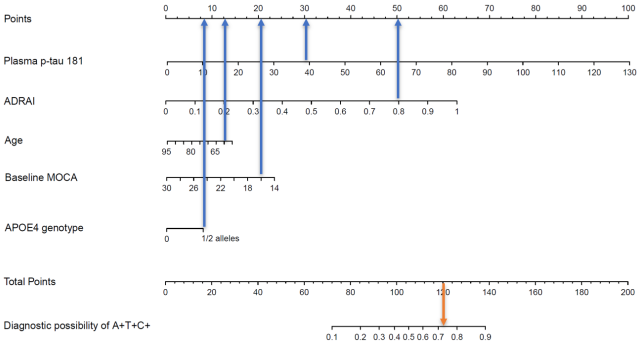

Table 4. Performance of the model in detecting A+T+C+ subjects

Variables*	Training set(n=294)					Validation set(n=295)				
	AUC	95%CI	Sensitivity	Specificity	P value	AUC	95%CI	Sensitivity	Specificity	P value
Plasma p-tau181+ADRAI	0.869	0.825-0.905	0.817	0.820	Reference	0.863	0.819-0.900	0.872	0.677	Reference
Plasma p-tau181+ADRAI +APOE genotype	0.872	0.825-0.906	0.878	0.739	0.639	0.882	0.839-0.916	0.702	0.879	0.002
Plasma p-tau181+ADRAI +MOCA	0.872	0.828-0.908	0.706	0.808	0.736	0.878	0.835-0.913	0.915	0.673	0.008
Plasma p-tau181+ADRAI +MOCA+APOE genotype	0.875	0.832-0.910	0.939	0.698	0.541	0.898	0.852-0.926	0.851	0.802	< 0.0001

*All model adjusted by age

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