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Predicting Progression to Mild Cognitive Impairment

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Abstract

Despite much attention to the use of biomarkers for predicting Alzheimer's disease, little information is available at the individual level. We used the population-based Mayo Clinic Study of Aging to estimate absolute risk of cognitive impairment by biomarker group. Risk increased with age and any biomarker abnormality. For example, a 75-year-old with abnormal amyloid and cortical thinning biomarkers has ≈20% chance of cognitive impairment by age 80 whereas with normal biomarkers the chance is <10%. Persons with only one abnormal biomarker had similar intermediate risks.

Keywords

Mild cognitive impairment; amyloid beta; neurodegeneration

Introduction

There is a great deal of interest in biomarker based staging of preclinical Alzheimer's disease (AD), in part due to ongoing development of therapies for early intervention[1, 2]. In the National Institute on Aging-Alzheimer's Association committees in 2011, two classes of AD biomarkers were identified: measures of amyloid (A) by CSF or amyloid PET and measures of neuronal injury (N) by CSF, FDG PET, or MRI[3–5]. When cognitively

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Author contributions

RCP, DSK, MM Mielke, and CRJ contributed to the conception and design of this study. RCP, DSK, MM Mielke, ROR, VJL, MM Machulda, YEG, and CRJ contributed to the acquisition of the data. ESL, TMT, SDW, and WKK performed statistical analyses. RCP and CRJ contributed drafting of the manuscript text. All authors approved the final version of the manuscript.

Potential conflicts of interest

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unimpaired (CU) individuals are categorized based on having normal (−) or abnormal (+) levels of A and N, the A+N+ group consistently has an elevated risk of progression to subsequent cognitive impairment[6, 7]. Whether A−N+, also termed suspected non-Alzheimer pathophysiology (SNAP)[8], is a risk factor for cognitive impairment is an important open question. Further, little is known about the implications of these biomarkers in terms of absolute risk of cognitive impairment for the elderly patient in clinical practice. Data most relevant to clinical practice should come from community-based studies, rather than highly selected referral samples, and should provide predictive information at the individual patient level. To address both of these gaps in current knowledge, we evaluated the role of imaging based biomarkers of A and N in predicting progression from CU to MCI or dementia for individual patients in a population-based study of aging and cognition[9].

Methods

Study Design and Participants

All participants in this study were enrolled in the Mayo Clinic Study of Aging (MCSA), a longitudinal, population-based study of residents of Olmsted County, Minnesota[9], and participated in brain imaging. MCSA participants were evaluated clinically approximately every 15 months. Each evaluation included separate assessments by a study coordinator, physician and a psychometrist[9]. The final clinical diagnosis is determined by consensus using previously published criteria[10]. For the purpose of this study individuals were categorized as cognitively unimpaired (CU), having mild cognitive impairment (MCI), or having dementia.

This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent at the time of enrollment.

Imaging

Amyloid PET imaging was performed using Pittsburgh Compound-B. Late uptake images were acquired from 40–60 minutes post injection. A cortical composite meta ROI was referenced to uptake in the cerebellar crus to create a standardized uptake value ratio (SUVR) as previously published[11]. Structural MRI imaging was performed at 3T. Our N measure was a composite AD-characteristic cortical thickness measure averaging entorhinal, inferior temporal, middle temporal, and fusiform gyri thickness estimated using FreeSurfer 5.3[12]. Based on a recent analysis, amyloid PET SUVR values greater than 1.42 (centiloid 19) and cortical thickness values less than 3.5mm were considered abnormal[11]. These cut-points were used to form four groups: A−N−, A+N−, A−N+, and A+N+.

Statistical Analysis

We investigated progression from CU to MCI or dementia, treating death prior to cognitive impairment as a competing event that precludes MCI or dementia. We defined *baseline* as a participant's first MCSA visit with both amyloid PET and MRI and limited our analysis to those who were CU and aged ≥70 at this baseline and had some follow-up. To estimate rates of progression to MCI or dementia by biomarker group, we used Poisson regression

including age, sex, education level, and A/N group as main effects. The absolute risk of observed cognitive impairment over time was computed using the competing risks approach described in Putter [13], i.e. accounting for the fact that some subjects will never progress to MCI/dementia because they die before doing so. We note that since MCSA visits occurred approximately 15 months apart while death could occur many years after the final clinical visit, only deaths that occurred within 15 months of a participant's last visit were counted as events.

Results

Of 763 CU participants, 26% were A−N−, 15% were A+N−, 30% were A−N+, and 28% were A+N+ with demographic comparisons shown in Table 1. Men were more likely to be N + ($p=0.002$) and both A+ and N+ were associated with older age ($p<0.001$). Over a median follow-up of four years, 159 (22%) individuals progressed to MCI (n=152) or dementia (n=7). About a quarter of our sample (24%) had one 15-month follow-up visit, 13% had two, and 63% had 3 or more. In our sample, progression rates expressed as events per 100 person years (95% CI) were 2.4 (1.8–3.2) at age 75 and 6.5 (5.5–7.6) at age 85. Averaging over men and women and assuming some college education, progression rates (95% CIs) at age 75 were 3.9 (2.7–5.7) among A+N+, 1.1 (0.7–1.9) among A−N−, 2.3 (1.4–3.7) among A+N−, and 2.3 (1.5–3.4) among A−N+. By age 85, the rates increased to 8.9 (6.8–11.5) among A +N+, 2.6 (1.5–4.3) among A−N−, 5.2 (3.3–8.1) among A+N− and 5.2 (3.3–7.0) among A−N +. Treating the A−N− group as the reference, the relative rate (95% CI) for A+N+ was 3.5 (2.1– 6.2), for A+N− was 2.0 (1.1–3.9), and for A−N+ was 2.0 (1.2–3.6). Within a biomarker group, rates are an estimated 20% higher in men (RR 1.2, 95% CI 0.9–1.7) and 30% higher in those with only a high school education (RR 1.3, 95% CI 1.0–1.9).

Figure 1 shows the estimated probability of cognitive impairment accounting for the competing risk of death for a 75 year old and an 85 year old with some college education averaged among men and women to emphasize risk differences by biomarker group. The data are plotted both with age and time in study on the abscissa. Table 2 shows the 5- and 10-year risks of progressing to MCI/dementia by age and sex for two levels of education. Based on the estimated risks, a CU 75 year old A−N− woman with some college education has an estimated 6% chance of becoming cognitively impaired within 5 years. This increases to 19% assuming A+N+. Participants who were either A+N− or A−N+ had intermediate risks of progression. Table 2 also illustrates that risk clearly increases with age, is somewhat higher in men, and is somewhat lower for those with some college education.

Discussion

These results extend our work examining effects of amyloid positivity on cognition[14] to document the dual importance of amyloid positivity and neurodegeneration as substantial risk factors for cognitive impairment. Having both normal amyloid and normal neurodegeneration was protective. In contrast, individuals with both abnormal amyloid and abnormal neurodegeneration had much higher rates of progression to MCI or dementia over an average of four years of follow-up. Interestingly, in the general community setting, the

presence of either abnormal amyloid or neurodegeneration constituted a similar risk for progression.

With the availability of imaging and/or CSF biomarker information in clinical practice it is uncertain how to convey the data to patients. Our results provide easily interpretable estimates of the chance of becoming cognitively impaired in 5- and 10-year windows stratified by biomarker group. Further, estimates are reported by three important risk factors: sex, education level, and age. Of these, risk varies to the greatest degree by age but male sex and lower education are contributing factors that remain important in an era of biomarkers[15]. We have previously shown that these risk factors also influence MCSA participation[16] and therefore it is important account for them in regression analyses.

Our biomarker findings should be interpreted in the context of previous reports while recognizing that different definitions of amyloidosis and abnormal neurodegeneration using imaging based versus CSF based biomarkers make direct comparisons difficult. Using largely the same definition of A+ but an N+ based on abnormal hippocampal atrophy or abnormal FDG PET, an early report from the MCSA examining progression by 15 months found biomarker risk patterns that were quite similar to those reported here[17]. On the other hand, two somewhat comparable studies offer little evidence that A−N+ is a risk factor for progression. Vos and colleagues used CSF biomarkers[7]. Their A+N+ group had the highest cumulative incidence of progression followed by A+N−. However, the risk in their A−N+ group was comparable to that of the A−N− group. This disparate prognosis for SNAP individuals compared to our findings invites careful consideration of the processes underlying CSF-based or MRI-based definitions of N+. More recently, Burnham and colleagues reported that in the Australian Imaging, Biomarker and Lifestyle (AIBL) study, those with A+N+, compared to A−N−, had more than a five-fold increased hazard of progression to MCI; those with A+N− had a more than a two-fold increased hazard; and those with A−N+ had only a moderately elevated hazard (HR=1.3) [6]. With brain atrophy on MRI a well-established risk factor for cognitive impairment, and given our current findings, we think it likely that neurodegeneration in the absence of amyloidosis is an important risk factor for MCI. Further, recent reports suggest amyloid and neurodegeneration are important complementary risk factors for dementia[18, 19].

There is likely risk associated with AD biomarker levels that are just below those deemed abnormal. Further, the biomarker groups examined here do not address important neuropathological features such as cerebrovascular pathology, tau-based neurofibrillary tangles, TDP-43, and alpha synuclein. For a given individual, there are likely many factors contributing to cognitive function in aging [20]. Still, our absolute risk estimates may be useful to clinicians in counseling patients with respect to the role of AD biomarkers in aging or those planning clinical trials. And because these data were from a population-based sample they are less subject to biases that may be encountered in referral settings.

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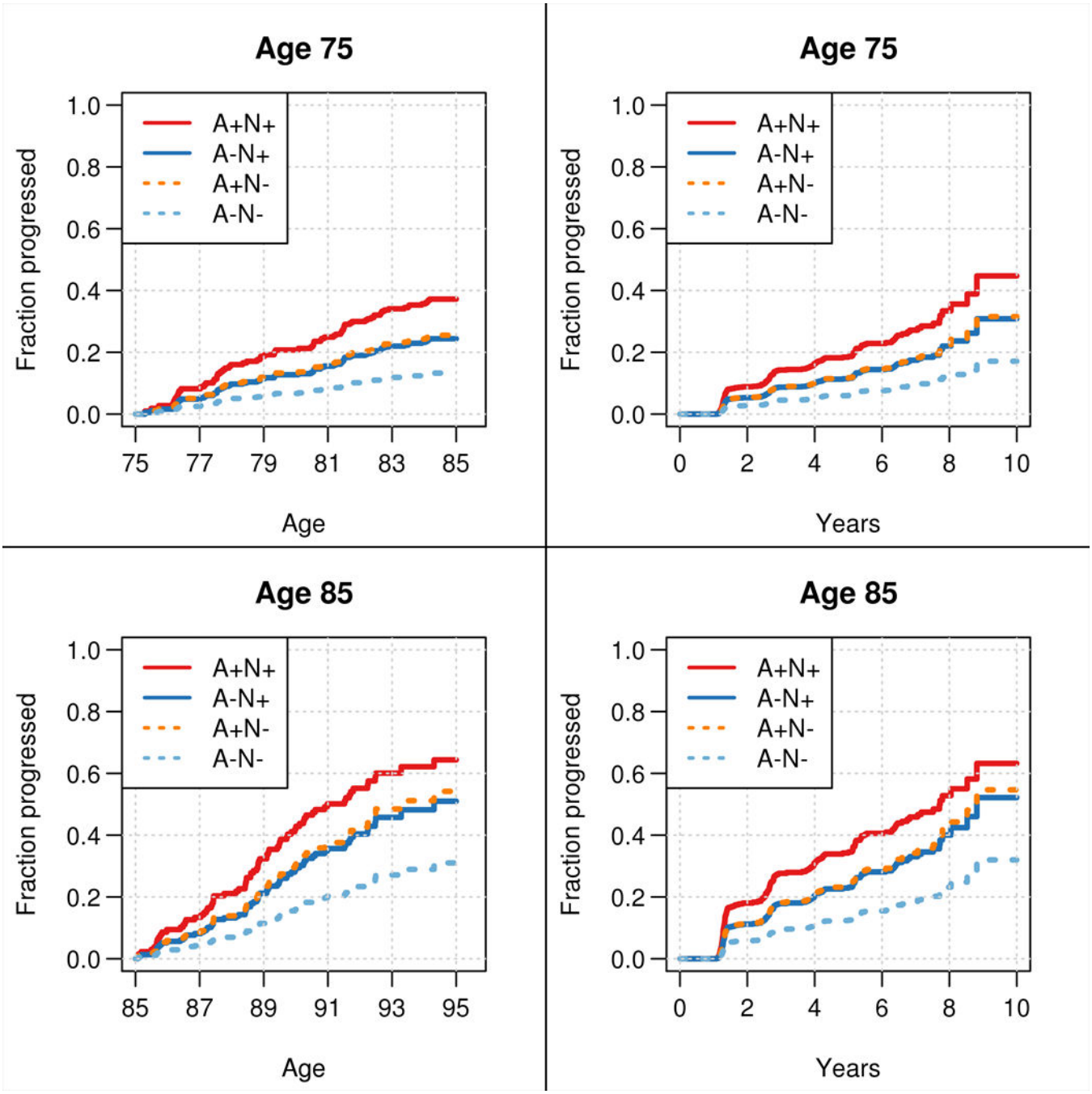

Figure 1.

Probability of MCI or dementia over time accounting for the competing risk of death. Cause specific survival models were fit using age as the time scale (left column) and using years from imaging as the time scale (right column). Probabilities depend on age and ages 75 and 85 were chosen to illustrate this dependence. For simplification of presentation, estimates are shown averaged over sex and for an individual with some college education (i.e., ≥13 years).

Table 1.

Baseline characteristics of the study participants by biomarker group

	All (N=763)	A–N– (N=202)	A+N– (N=118)	A–N+ (N=229)	A+N+ (N=214)
Age, y					
Median (IQR)	77 (74, 82)	75 (72, 78)	76 (72, 81)	78 (75, 84)	80 (77, 84)
Range	70 to 95	70 to 92	70 to 93	70 to 93	70 to 95
Sex, n (%)					
Male	414 (54%)	91 (45%)	61 (52%)	136 (59%)	126 (59%)
Female	349 (46%)	111 (55%)	57 (48%)	93 (41%)	88 (41%)
Education, median (IQR), y	14 (12, 16)	14 (12, 17)	14 (12, 17)	14 (12, 17)	14 (12, 16)
Education level, n (%)					
High school or less	244 (32%)	68 (34%)	36 (31%)	77 (34%)	63 (29%)
Some college	519 (68%)	134 (66%)	82 (69%)	152 (66%)	151 (71%)
APOE status, n (%)					
Carrier	202 (26%)	37 (18%)	57 (48%)	30 (13%)	78 (36%)
Non-carrier	561 (74%)	165 (82%)	61 (52%)	199 (87%)	136 (64%)
Cognitive z scores, median (IQR) *					
Global	0.0 (−0.7, 0.7)	0.3 (−0.4, 1.0)	0.1 (−0.6, 0.8)	0.0 (−0.6, 0.7)	−0.3 (−1.0, 0.4)
Memory	0.0 (−0.8, 0.7)	0.1 (−0.5, 0.9)	0.1 (−0.5, 0.8)	0.0 (−0.7, 0.7)	−0.3 (−1.1, 0.4)
Attention	0.1 (−0.6, 0.7)	0.4 (−0.2, 1.0)	0.2 (−0.5, 0.7)	0.1 (−0.7, 0.6)	−0.3 (−0.9, 0.5)
Language	0.1 (−0.6, 0.7)	0.3 (−0.4, 0.9)	0.1 (−0.5, 0.8)	0.1 (−0.5, 0.7)	−0.2 (−0.8, 0.4)
Visuospatial	0.1 (−0.6, 0.7)	0.2 (−0.6, 0.9)	0.0 (−0.7, 0.7)	0.2 (−0.5, 0.7)	−0.1 (−0.8, 0.5)
Follow-up, y †					
Median (IQR)	4.4 (2.4, 6.5)	5.1 (2.7, 6.6)	5.1 (2.6, 6.7)	5.1 (2.5, 6.5)	3.8 (1.5, 6.2)
Range	0.3 to 11.4	0.6 to 9.0	1.0 to 10.3	1.1 to 11.4	0.3 to 11.0
No. progressed to MCI or dementia	159	17	22	49	71
No. died before MCI or dementia	39	5	2	10	22

*Cognitive domain z scores are averages 3 tests for memory, 2 tests for attention, 2 tests for language, and two tests for visuospatial normed to subjects in the study. The global domain score is an average of four domains normed to subjects in the study.

†Follow-up calculated as time from baseline to MCI or death within 15 months of last visit. Some individuals died before a return visit.

Table 2.

Probability or risk of progression to MCI or dementia stratified by biomarker group over 5- and 10-year time horizons after adjusting for the competing risk of death. Estimates are shown separately for men and women and by education level.

Age	Time horizon (y)	Education*	A−N−		A+N−		A−N+		A+N+	
			Female	Male	Female	Male	Female	Male	Female	Male
70	5	High school	5%	6%	10%	12%	10%	12%	16%	19%
		Some college	4%	5%	8%	9%	7%	9%	12%	15%
	10	High school	12%	15%	24%	28%	23%	27%	36%	41%
		Some college	10%	12%	19%	22%	18%	21%	29%	33%
75	5	High school	8%	9%	16%	19%	15%	18%	24%	28%
		Some college	6%	7%	12%	15%	12%	14%	19%	23%
	10	High school	16%	18%	29%	34%	28%	33%	43%	48%
		Some college	12%	14%	23%	28%	22%	26%	35%	40%
80	5	High school	8%	10%	17%	20%	16%	19%	25%	29%
		Some college	7%	8%	13%	16%	12%	15%	20%	23%
	10	High school	25%	29%	45%	51%	43%	48%	57%	61%
		Some college	20%	23%	37%	42%	35%	40%	48%	52%
85	5	High school	19%	22%	35%	40%	33%	38%	48%	53%
		Some college	15%	17%	28%	33%	27%	31%	40%	44%
	10	High school	36%	41%	61%	67%	57%	63%	71%	74%
		Some college	29%	33%	51%	57%	48%	54%	63%	66%

*High school education is defined as 12 or fewer years of education while some college is defined as 13 or more