Neuropsychiatric symptoms at baseline shorten time to severe dementia in a Population-Based Sample of Incident Alzheimer's Disease:

The Cache County Dementia Progression Study

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Abstract

Background. Little is known about factors influencing the rate of progression of Alzheimer's disease (AD), although their identification might identify targets for intervention. Previously, we reported that those with at least one clinically significant neuropsychiatric symptom (NPS) exhibited shorter time to severe AD. Here, we examine whether specific NPS's explain this association. ***Methods.*** 335 cases of *incident* dementia (i.e., first characterized *before* the onset of dementia) were identified through the Cache County Memory Study. Participants were examined every 6-18 months with the Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR), and Neuropsychiatric Inventory (NPI). Severe dementia was defined as MMSE <= 10 or CDR= 3. Endorsement of NPS clusters (psychosis, affective, agitation, and apathy) were examined as predictors of time to severe dementia in Cox Regression models.
Results. Stratified by interval between onset age and diagnosis (within 2 years or more), more rapid decline to severe dementia [Hazard Ratios (HR) and 95% confidence intervals] was associated with the presence of psychotic symptoms [HR = 2.21 (1.17, 4.17)] and agitation [HR= 2.88 (1.39, 5.96)]. There was a slight increased risk for severe dementia with affective symptoms [HR = 1.56 (0.93, 2.63)]. In models that considered the 3 NPS types together, agitation [HR = 2.62 (1.24, 5.51)] and psychotic symptoms [HR= 1.96 (1.01,3.77)] predicted more rapid decline to severe dementia, whereas affective symptoms did not [HR = 1.21 (0.69, 2.14)]. ***Conclusions.*** Results are consistent with previous findings of worse prognosis with the early presence of psychosis and agitation.

Introduction

- Little is known about factors influencing the rate of progression of Alzheimer's disease (AD), although their identification might identify targets for intervention.
- Previously we reported that females, those with less than high school education, the youngest or oldest onset ages, and those with at least one clinically significant neuropsychiatric symptom (NPS) exhibited shorter time to severe AD[1]
- In the present study, we examine whether specific NPS explain the above associations.

Methods

- The Cache Dementia Progression Study[2] is a population-based study of the course of dementia and modifying factors among individuals with *incident* (i.e., first characterized *before* the onset of dementia) dementia, identified in the Cache County Study on Memory in Aging[3]
- 335 cases of dementia were diagnosed with AD by consensus panel. Mean (sd) onset period between dementia onset and diagnosis was 1.69 (1.25) years
- Participants were examined every 6-18 months with the Mini-Mental State Exam (MMSE)[4] to examine cognitive ability, Clinical Dementia Rating[5] (CDR) to examine functional ability, and the Neuropsychiatric Inventory (NPI)[6] to examine NPS
- Severe dementia was defined as MMSE <= 10 or CDR=> 3
- NPS clusters (psychosis, affective, agitation, and apathy) were examined as predictors of time to severe dementia in Cox Regression models
- Covariates tested included dementia onset age, gender, presence/absence of APOE E4 allele, and education (less than HS grad/GED)

Results

Sample Characteristics:

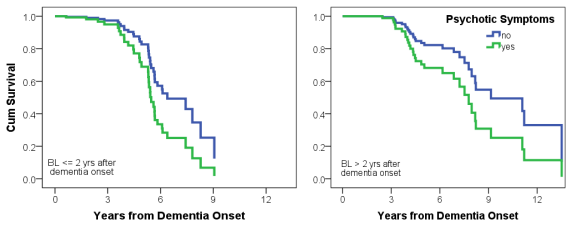
- Most participants were female (66.0%) with mean (sd) age of onset of AD = 84.27 (6.39)
- Severe dementia occurred in 68 subjects at a mean (sd) of 5.4 (2.3) years from dementia onset.

Cox Regression Modeling:

- Stratified by interval between onset age and diagnosis (within 2 years or more), more rapid decline to severe dementia [Hazard Ratios (HR) and 95% Confidence Intervals] was associated with psychotic symptoms [HR- 2.21 (1.17, 4.17)] and agitation [HR= 2.88 (1.39, 5.96)]. There was a slight increase in risk for severe dementia with affective symptoms [HR= 1.56 (0.93, 2.63)].
- In models that considered the 3 NPS clusters together, agitation [HR= 2.62 (1.24, 5.51)] and psychotic symptoms [HR= 1.96 (1.01,3.77)] predicted more rapid decline to severe dementia, whereas affective symptoms did not [HR= 1.21 (0.69, 2.14)]
- The figures display the survival plots for psychotic, agitation and affective clusters stratified by dementia duration at diagnosis

Figure 1

Psychotic symptoms at baseline predict shorter time to severe dementia



The figures above display the association between baseline psychosis and time to severe dementia from Cox regression models, controlling for gender, APOE, education, and onset age. The plot on the left shows those diagnosed within two years of onset, and the one on the right displays those diagnosed more than two years after onset.

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Figure 2

Agitation at baseline predicts shorter time to severe dementia

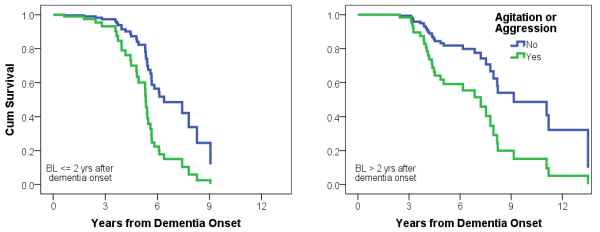

Figure 3

Affective symptoms at baseline are not predictive of decline to severe dementia

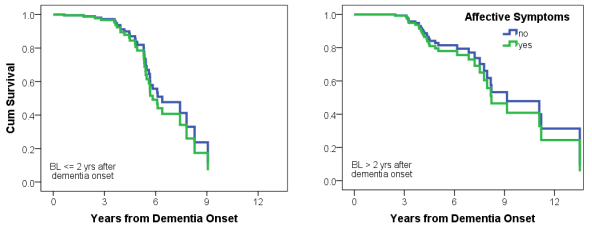

Figure 2 displays the association between baseline agitation and time to severe dementia from Cox regression models, controlling for gender, APOE, education, and onset age. The plot on the left shows those diagnosed within two years of onset, and the one on the right displays those diagnosed more than two years after onset. Affective symptoms were no longer significantly associated with severe dementia in Cox models (Figure 3).

Conclusions

- Results are consistent with previous findings of worse prognosis with the early presence of psychosis and agitation
- Identification of variables influencing rate of decline of AD should be incorporated into intervention studies and begin to point in the direction of variables that might be targeted in developing disease modifying intervention strategies

Citations

1. Rabins, P.V., Schwartz, S., Black, B., et al. Predilctors of progression to severe Alzheimer's disease in an incidence sample. *Alz & Dement*, in press.
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