Neuropsychiatric Symptoms (NPS) as Predictors of Progression to Severe Alzheimer's Dementia and Death: The Cache County Study

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ABSTRACT

Background. **Little is known about factors influencing the rate of progression of Alzheimer's dementia (AD). Using data from the Cache County Dementia Progression Study (DPS) we examined the link between clinically significant neuropsychiatric symptoms (NPS) in mild AD and progression to severe AD or death.** ***Aims.*** **(1) Examine the association between individual, clinically significant NPS and progression to severe dementia; (2) Examine the association between individual, clinically significant NPS and progression to death; (3) Repeat the above analyses for psychotic and affective clusters of NPS.** ***Methods.*** **DPS is a longitudinal study of dementia progression in incident cases of the condition. Survival analyses included unadjusted Kaplan-Meier (KM) plots and multivariate Cox proportional hazard models. Hazard ratio (HR) estimates controlled for age of dementia onset, gender, education level, General Medical Health Rating (GMHR), and apolipoprotein E epsilon 4 (APOE-ε4) genotype.** ***Results.*** **Three hundred thirty-five patients with incident AD were studied. Sixty-eight (20%) developed severe AD over the follow-up. Psychosis, agitation/aggression, or any one clinically significant NPS were associated with more rapid progression to severe AD. Psychosis, affective symptoms, agitation/aggression, mildly symptomatic NPS, and clinically significant NPS were associated with earlier death.** ***Conclusions.*** **Specific NPS are associated with more rapid progression from mild to severe AD and/or death. The treatment of specific NPS in mild AD should be examined for its potential to delay time to severe AD or death.**

INTRODUCTION

- U.S. annual costs for dementia will increase from $200 billion in 2012 to $1.1 trillion in 2050 (1).
- Delaying progression of dementia may increase meaningful time spent with those afflicted.
- The Cache County Dementia Progression Study (DPS) previously reported the following to be predictive of shorter time to severe AD:
  - Female gender
  - Less than high school education
  - At least one clinically significant NPS at baseline
  - Age of dementia onset (youngest and oldest tertiles)
  - Worse health
- The relationship between individual NPS or clusters of NPS and progression to severe dementia or death is not fully understood.

AIMS

1. Examine the association between individual, clinically significant NPS and progression to severe dementia.
2. Examine the association between individual, clinically significant NPS and progression to death.
3. Repeat the above analyses for psychotic and affective clusters of NPS.

METHODS

- The Cache County Study (3) and DPS (4) have been described in detail elsewhere.
  - 90% of all permanent residents of Cache County, Utah ≥65 years were enrolled (n=5677).
  - All were screened for dementia in a multi-staged assessment protocol.
  - DPS focused on individuals who converted from no dementia to AD over 5 years.
- The neuropsychiatric inventory (NPI) (5) was used to assess NPS as follows:
  - ≥ one psychosis NPS domain (delusions and hallucinations)
  - ≥ one affective NPS domains (depression, anxiety, and irritability)
  - Individual NPS of apathy/indifference or agitation/aggression
  - Total NPI scores divided as no, mild, or clinically significant symptoms
- Analyses were performed as follows:
  - Unadjusted Kaplan-Meier (KM) plots for each NPI group.
  - Bivariate and multivariate Cox proportional hazard models for each group. Multivariate models controlled for:
    - Age of dementia onset
    - Gender
    - Education level
    - General Medical Health Rating (GMHR)
    - APOE-ε4 genotype status.

Additional models controlling for psychotropic medication use did not significantly change the results (data not shown)

RESULTS

- 335 incident cases of possible or probable AD were studied.
- Mean age of onset was 84.3 (SD=6.4) years
- Mean time between dementia onset and diagnosis was 1.7 (SD=1.3) years.
- 68 individuals developed severe AD over the course of the study and 273 were deceased.
- Median time to severe AD for the sample was 8.4 years (95% CI: 7.6-9.2)

Table 1. Multivariate Cox Regression Models for Time to Severe Dementia
*****controlled for age of dementia onset, gender, education level, GMHR, and APOE-ε4 status*****

		Psychosis Cluster		Affective Cluster		Agitation/Aggression		Apathy/Indifference		NPI Total	
	Variable	HR	P-value	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Unadjusted, bivariate value*		2.024	0.018	1.387	0.191	2.321	0.009	1.176	0.604	--	--
ADJUSTED MODEL	AD onset age	0.290	<0.001	0.313	<0.001	0.351	0.001	0.279	<0.001	0.295	<0.001
	AD onset age²	1.008	<0.001	1.007	<0.001	1.007	0.001	1.008	<0.001	1.008	<0.001
	Female	1.949	0.031	1.888	0.038	1.885	0.039	1.998	0.025	1.852	0.047
	Education^	1.791	0.79	1.910	0.048	1.934	0.041	1.888	0.56	0.756	0.095
	APOE-ε4 Carrier	0.940	0.823	1.076	0.767	1.109	0.706	1.070	0.808	1.106	0.711
	GMHR	1.554	0.140	1.585	0.128	1.511	0.174	1.527	0.146	1.737	0.074
	Dementia duration at baseline	0.811	0.026	0.827	0.042	0.753	0.006	0.821	0.038	0.763	0.005
	Psychosis Cluster	2.007	0.028								
	Affective Cluster			1.512	0.119						
	Agitation/Aggression					2.946	0.004				
	Apathy/Indifference							1.552	0.172		
	All										
	NPI Total									--	0.002
	Mild symptoms									1.077	0.832
	One or more clinically significant									2.682	0.001

1. Cox regression models were controlled for age of dementia onset, gender, education level, GMHR, and APOE-ε4 status; *Bivariate unadjusted model for each NPI symptom or cluster; ^Reference category is greater than or equal to high school.

Table 2. Multivariate Cox Regression Models for Time to Death
*****controlled for age of dementia onset, gender, education level, GMHR, and APOE-ε4 status*****

		Psychosis Cluster		Affective Cluster		Agitation/Aggression		Apathy/Indifference		NPI Total	
	Variable	HR	P-value	HR	P-value	HR	*P-value*	HR	P-value	HR	P-value
Unadjusted, bivariate value*		1.567	0.006	1.192	0.195	1.276	0.251	1.074	0.683	--	--
ADJUSTED MODEL	AD onset age	1.092	<0.001	1.100	<0.001	1.096	<0.001	1.095	<0.001	1.102	<0.001
	Female	0.706	0.018	0.725	0.028	0.701	0.017	0.733	0.034	0.694	0.013
	Education^	1.226	0.229	1.268	0.160	1.278	0.148	1.269	0.173	1.221	0.242
	APOE-ε4 Carrier	1.067	0.656	1.114	0.451	1.168	0.282	1.116	0.443	1.134	0.385
	GMHR	1.593	0.002	1.560	0.004	1.558	0.004	1.622	0.002	1.577	0.003
	Dementia duration at baseline	0.781	<0.001	0.780	<0.001	0.761	0.004	0.781	<0.001	0.752	<0.001
	Psychosis Cluster	1.537	0.011								
	Affective Cluster			1.510	0.003						
	Agitation/Aggression					1.942	0.004				
	Apathy/Indifference							1.261	0.211		
	All										
	NPI Total										<0.001
	Mild symptoms									1.448	0.024
	One or more clinically significant									1.951	<0.001

1. Cox regression models were controlled for age of dementia onset, gender, education level, GMHR, and APOE-ε4 status; *Bivariate unadjusted model for each NPI symptom or cluster; ^Reference category is greater than or equal to high school.

Figure 1. Unadjusted Kaplan-Meier Plot for Agitation and Severe Dementia

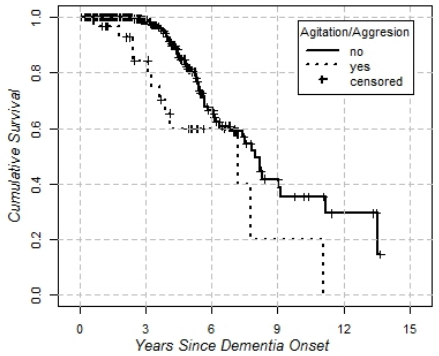
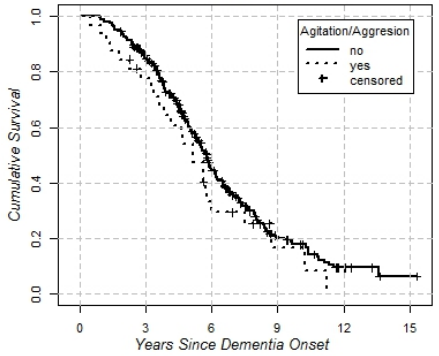


Figure 2. Unadjusted Kaplan-Meier Plot for Agitation and Death



CONCLUSIONS

- In this population-based study, psychosis, agitation/aggression, and clinically significant NPS predicted earlier severe dementia or death.
- Affective NPS and mild NPS were associated with earlier death, but not progression to severe dementia.
- The treatment of specific NPS in early dementia should be examined for potential to delay time to severe dementia or death.
- Limitations: no incident cases <65 years, small number with severe AD, and homogeneity of the population.
- Strengths: its epidemiologic sampling; high participation rate; prospective, longitudinal data; and state-of-the-art assessments.
- We recommend replication of these findings in further study populations.

CITATIONS

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This research was supported by the Cache County Memory Study, Dementia Progression Study, and the Joseph and Kathleen Bryan ADRC