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Variability in Depressive Symptoms Predicts Cognitive Decline in Age-related Macular Degeneration

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Abstract

Objective—The measurement of affective phenomena in older persons who decline cognitively is uncertain. We investigated whether mood variability predicts dementia in patients with age-related macular degeneration (AMD).

Design—Three year observational study following a clinical trial.

Setting—Community follow-up of outpatients ascertained from retina clinics.

Participants—160 patients with AMD.

Measurements—Geriatric Depression Scale (GDS) administered every 2 weeks for 6 months to subjects; Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) administered to subjects' knowledgeable informants.

Results—Twenty three subjects (14.4%) declined cognitively. Age, education, baseline GDS score ≥ 5 , and variability in GDS scores (i.e., fluctuations between adjacent time points) were associated with cognitive decline. For GDS variability, each 1 unit increase in the residual standard deviation of the GDS increased the risk for cognitive decline by 93% (IDR=1.92; 95% CI [1.27, 2.91]). Thus, subjects with a residual standard deviation of 1 were nearly twice as likely to become demented as subjects with no variability in GDS scores. The risk for subjects with standard deviations of 2 increased more than threefold (IDR=3.68; 95% CI [1.61, 8.47]). A multiple regression analysis showed that GDS variability was a significant risk factor for dementia after controlling for significant covariates.

Conclusion—These data suggest a useful approach to conceptualizing and measuring depressive symptoms in older persons. Variability in self-reported mood may be an early sign of dementia and may offer new insights into the neurobiological mechanisms linking depression and cognition.

Keywords

Depression; Mood Variability; Cognitive Decline

Objective

Studies of depressive symptoms preceding dementia suggest that depression may represent a risk factor, prodrome, or reaction to cognitive decline.¹⁻⁶ A lifetime history of depression, particularly early-onset depression, is associated with Alzheimer disease (AD) pathology that may be caused by hyperactivity of the hypothalamic-pituitary-adrenal axis.⁷⁻¹¹ Depression may also be a symptom of AD that is associated with a distinctive neuropathology or biomarker profile.^{12, 13} Sun et al (2008), for example, recently found that a high plasma A β ₄₀:A β ₄₂ ratio in late-life depression may be a prodromal manifestation of AD (so-called “amyloid-associated depression”).¹³

Wilson et al (2008), however, observed no increase in depressive symptoms during the AD prodrome but, as have other researchers, found that depressive symptoms at baseline predicted subsequent dementia.^{2,5,14} Their data suggest that depressive symptoms are a risk factor for rather than a sign of disease. Not all studies confirm an association, however, citing differences in samples, study designs, and measurement of depression.^{15,16} For example, Dotson et al (2008) described differential associations of concurrent, baseline, and average depressive symptoms with cognitive decline, and indicated that different approaches to depression measurement can lead to different outcomes.¹⁷

One measurement approach that has not been well studied is variable ratings of mood over time. Just as cognitive symptoms may appear intermittently early in the course of AD as neuronal reserve is depleted, variability in depressive symptoms may also indicate diminishing neuronal integrity and represent a sign of incipient dementia. The objective of this study was to investigate whether variability in depressive symptoms was associated with cognitive decline.

We investigated that possibility in this study of cognitive decline in patients with age-related macular degeneration (AMD). AMD is a degenerative disease of the macular region of the retina that leads to geographic atrophy (one type of dry AMD) or choroidal neovascularization (wet AMD).¹⁸ It is the leading cause of legal blindness in older persons in the United States, affects more than 10 million people, and prevents many from reading, driving, socializing, and pursuing valued activities.¹⁹⁻²²

From 2001 to 2005 we conducted a randomized, controlled clinical trial, “Preventing Depression in AMD”, to test the efficacy of Problem-Solving Therapy (PST) to prevent depression in patients with AMD.²³ The main outcome measure was a clinical diagnosis of a depressive disorder at 2 and 6 months. Additionally, we administered the Geriatric Depression Scale (GDS) to all subjects by telephone every 2 weeks over 6 months as an exploratory outcome measure.

In this paper, we report the results of an investigation that we conducted approximately 3 years after the clinical trial was completed. We interviewed the knowledgeable informants of subjects who were enrolled in the trial to identify risk factors for cognitive decline. One of the hypotheses that we tested was whether depression and/or variability in subjects' GDS scores (i.e., fluctuations between adjacent time points) during the clinical trial would predict cognitive decline.

Methods

For the clinical trial, “Preventing Depression in AMD”, we recruited 206 subjects over age 65 with bilateral AMD from retina clinics associated with Wills Eye Institute in Philadelphia, PA. The exclusion criteria were DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) diagnoses of depressive disorder, current treatment for depression, and cognitive impairment,

or a history of cognitive decline. All subjects signed an informed consent form approved by Thomas Jefferson University's Institutional Review Board.

We screened for cognitive impairment at baseline for the clinical trial using an abbreviated version of the Mini-Mental Status Examination (MMblind) that omits vision-dependent items.²⁴ This version includes orientation to time (i.e., day, month, and year), spelling “world” backwards, and delayed recall of 3 words. Possible scores range from 0 to 11 with higher scores indicating better cognition. To be eligible for the clinical trial, subjects needed to answer the 3 orientation questions correctly, score at least 3 of 5 on “world” backwards, and recall 2 of 3 words on delayed recall. We repeated the MMblind one year later at the end of the clinical trial.

Following the baseline assessment, 206 subjects were randomized to PST or usual care. PST-trained therapists administered six weekly 30-45 minute PST sessions over 8 weeks to PST-assigned subjects. PST is a manual-driven psychological treatment that teaches problem-solving skills to define problems, establish realistic goals, generate and implement solutions, and evaluate outcomes.²⁵ Subjects in the control condition received usual care from their ophthalmologists and other health care providers.

Assessments during the Clinical Trial

Research nurses conducted clinical examinations in subjects' homes masked to treatment assignment. Demographic characteristics included age, race, sex, years of education, and marital status. Incident DSM-IV defined-depressive disorders were identified at months 2 and 6 using the Modified Schedule for Affective Disorders and Schizophrenia and the Structured Interview Guide for the Hamilton Rating Scale.^{26,27} Every two weeks from baseline to 6 months, a research assistant administered the 15-item GDS to all subjects by telephone (maximum of 14 assessments). The GDS is a self-report depression screening scale comprised of 15 items, scored yes or no (range 0 to 15), that discriminates depressed from nondepressed older persons and includes symptoms such as low mood, poor motivation, loss of interest, and memory difficulty occurring over the preceding week.^{28,29} A number of investigators have demonstrated the GDS's reliability and validity in persons with mild dementia in clinical, community, and nursing home settings.³⁰⁻³² McGivney *et al* (1994) found that persons with Mini-Mental Scores ≥ 15 were able to provide valid GDS responses.³³ Burke *et al* (1995) demonstrated the GDS's reliability and validity when administered by telephone to patients with mild dementia.³⁴

At baseline and one year later at the end of the clinical trial we assessed best-corrected distance visual acuity using the ETDRS chart and converted scores to the logarithm of the minimum angle of resolution (logMAR).³⁵ We assessed medical comorbidity using the Chronic Disease Score, which is derived from a weighted sum of medications taken for chronic illness.³⁶ Higher scores indicate greater impairment on both measures. We also created a vascular conditions variable at baseline (i.e., hypertension, diabetes, and stroke) to examine as a possible risk factor for cognitive decline.

Informant Interviews after Completion of the Clinical Trial

From May to September 2006, we administered the short form of the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) on one occasion by telephone to each of the 160 knowledgeable informants who were available for follow-up.³⁷ The 160 subjects (76.6% of the 206 subjects enrolled in the clinical trial) on whom informants provided IQCODE data did not differ in their baseline demographic or clinical characteristics or incidence rate of depression from the 46 subjects for whom IQCODE scores were unavailable (data not shown). The average length of time (and standard deviation) from subjects' baseline evaluation for the

clinical trial to the IQCODE administration was 3.00 (.93) years. The standard deviation reflects the relatively longer time to enroll the clinical trial sample (i.e., 3.5 years) in relation to the 4 month time period during which informants were interviewed.

The IQCODE measures cognitive decline from a premorbid level (past 5 to 10 years) using informant reports (e.g. decline in recalling recent conversations, knowing the day and month). Each of the 16 items is scored on a 5-point scale from 1-“better than before” to 5-“much worse” (3=no change). Ratings are averaged to give an overall score from 1 to 5. We specifically asked informants to distinguish difficulties due to cognitive rather than visual impairment. Factor analyses show that the IQCODE measures a single general factor of cognitive decline. A number of studies have demonstrated its test-retest reliability over a few days (0.96) and one year (0.75), and its validity against measures of cognitive change over time, clinical diagnoses, neuropathology, and neuroimaging results.³⁷ Jorm *et al* (2004) cited a variety of cut scores in different populations that maximize sensitivity and specificity: in community populations, cut-scores range from 3.3-3.6 and in patient samples from 3.4-4.0.³⁸ None of the samples studied, however, closely resemble the visually impaired older adults that we studied. For this reason, we took a conservative, empirical approach to define an appropriate cut-score that maximized specificity (to avoid false positives). We defined subjects as having cognitive decline if their IQCODE scores exceeded one standard deviation above the mean for this population. A cut-score of 3.81 met this criterion.

Statistical Methods

Descriptive statistics for baseline demographic and clinical variables are presented as means and standard deviations for continuous data and frequencies and percents for categorical data.

In addition to examining the distribution of GDS scores at each time point, we also characterized subjects based on the percent of assessments in which they endorsed the GDS item “do you feel you have more problems with memory than most”. These percent scores were calculated by dividing the number of assessments that the item was endorsed by the total number of assessments completed. For example, if someone completed 12 GDS assessments and endorsed the “memory” item in 3 of them, their percent score would be .25 (3/12). Because the resulting percent score is continuous, we used a oneway ANOVA to determine whether there were group differences (cognitive decline vs. no cognitive decline) in the percent of assessments in which memory problems were reported.

Due to the variability in follow-up time, we used Incidence Density Ratios (the number of new cases divided by the total person years of follow-up) to evaluate the relationships between independent variables and cognitive decline. An independent variable was considered statistically significant if the p value was <.05. Poisson regression with robust standard errors was used to model the incidence of cognitive decline while adjusting for different amounts of follow-up time from the 12 month assessment. Clinically relevant variables were evaluated in the multivariate model if they had a p value < 0.05 at the bivariate level.

The relationship between variability in GDS scores and cognitive decline was assessed using a two-stage procedure. To estimate variability in GDS scores, a quadratic curve in time was fit to the GDS scores of each subject who had eight or more GDS measurements and the residual variance was calculated separately for each subject (97.5% of the sample). At the second stage of analysis, the square-root of this residual variance (the “residual standard deviation”) was considered as a predictor of cognitive decline in the poisson regression model.

Results

Sample Characteristics

The mean age and education (+/- standard deviation) of the sample was 81.0 (5.7) and 12.5 (3.2) years, respectively; 70% were women; 98.1% were white; and 41.5% lived alone.

IQCODE scores at 3 years

The distribution of IQCODE scores was skewed to the right and had the following characteristics: range 2.63-5.00; median 3.13; and mean 3.30 (0.51). Twenty three subjects (14.4% of the sample) met the criterion for cognitive decline, representing an incidence density of 48.6 cases per 1000 person years at risk.

Table 1 presents descriptive statistics for the sample and the bivariate relationships between the study measures and cognitive decline at follow-up. The relationships are reported as incidence density ratios, which are based on Poisson regressions with number of years from baseline to follow-up as an offset variable. The Table shows that age, education, and a baseline GDS score ≥ 5 were associated with cognitive decline at follow-up: each 5 year increment in age increased the risk of cognitive decline by 57%, and each 4 year increment of education increased the risk by 35%. The other baseline variables of gender, MMblind score, visual acuity in the better eye, medical comorbidity, and vascular risk factors were unrelated to cognitive decline.

Table 1 also shows that the following longitudinal variables were unrelated to cognitive decline: incident depressive disorder at months 2 or 6, treatment with PST or Usual Care, change in visual acuity, or decline on the MMblind by more than one point during the 12 month clinical trial. There was no significant correlation between change in visual acuity and cognitive decline ($r = -.12$, $df = 149$; $p < .154$).

GDS Variability

The average number of GDS assessments over the 6 month study period was 12.85 (SD 1.41); 156 subjects (97.5% of the sample) had 8 or more assessments. The distribution of GDS scores at each post-baseline assessment resembled the baseline distribution [the average GDS score at baseline was 1.69 (SD 1.92); the median score was 1.00 (range 0-9)]. Figure 1 shows the average GDS scores at each assessment for subjects who did and did not decline cognitively. Although GDS scores tended to be low in both groups, subjects who declined cognitively had GDS scores ≥ 5 more often than those who did not decline: an average of 24% of their 14 assessments (SD 32%) had elevated GDS scores compared to 9% (SD 19%) in subjects who did not decline [$F(1,159) = 9.92$; $p = .002$].

Figure 1 also suggests that GDS scores were more variable over time in subjects who declined cognitively. To evaluate whether this variability or "noisiness" of GDS scores over time was related to cognitive decline, we first examined the distribution of the residual standard deviations found after removing each subject's trend over time. It was skewed to the right and ranged from 0 to 2.72. The quartiles of the standard deviations were: 1st quartile = 0.44; median = 0.84; 3rd quartile = 1.30. The regression model showed that the relationship between variability in GDS scores and cognitive decline was significant: for each 1 unit increase in the residual standard deviation of the GDS, cognitive decline increased by 92% (IDR=1.92; 95% CI [1.27, 2.91]; Wald $X^2 = 9.42$, $df = 1$; $p = .002$). Thus, subjects with a residual standard deviation of 1 were nearly twice as likely to become demented as subjects with no variability in their GDS scores. The risk for subjects with standard deviations of 2 increased more than threefold (IDR=3.68; 95% CI [1.61, 8.47]). There was no significant correlation between GDS

variability and baseline MMblind ($r = -.029$, $df = 154$; $p = .715$) or change in MMblind scores from baseline to 12 months ($r = -.051$, $df = 154$; $p = .553$).

Interestingly, the GDS memory item (“do you feel you have more problems with memory than most”) was significantly more often endorsed in subjects who declined than in those who did not [21.5% of assessments vs. 2.6%, respectively; $F(1, 155) = 46.69$; $p \leq .001$]. To evaluate the extent to which the memory item accounted for the association of GDS variability with cognitive decline, we excluded this item from the GDS and found that the relationship remained statistically significant (IDR = 1.75, 95% CI [1.11 - 2.73]; Wald X^2 5.91, $df = 1$, $p < .015$).

Table 2 presents the results of a multiple regression analysis showing that GDS variability remains a significant independent risk factor for cognitive decline after controlling for the significant covariates of age, education, and baseline GDS ≥ 5 .

Conclusions

Many studies have established the high prevalence and disabling effects of depression in dementia.^{1,2} Less clear is whether depression preceding dementia is a prodromal symptom, an understandable reaction, a causal factor, or an independent, unrelated phenomenon.³⁻¹⁰ Although we do not address this question directly, our data suggest a useful approach to conceptualizing and measuring depressive symptoms in this regard. Previous studies have examined depression as a categorical diagnosis or a dimensional measure of severity, both cross-sectionally and longitudinally, and have had conflicting results. Investigators have cited differences in study samples and methods but, in fact, the nature and measurement of affective phenomena in older persons are uncertain, particularly in those who are destined to decline cognitively. Although previous longitudinal studies and the current study have established that depressive symptoms at baseline are associated with later cognitive decline, measuring depressive symptoms frequently enabled us to discern the novel role of symptom variability in this relationship.^{2,14}

We found that variability in responses to the GDS was an independent risk factor for dementia after controlling for other significant covariates. There are several plausible explanations for this finding. The first is that patients with preclinical cognitive deficits or incipient dementia were unable to accurately recall or appraise their emotional status. Their memory impairment, mild though it may have been, may have prevented them from remembering their mood and thoughts in the preceding two weeks. Alternatively, early executive dysfunction may have diminished their ability to appreciate the meaning of the GDS questions. In both instances, GDS scores would be unstable or unreliable. Many studies have demonstrated, however, the GDS's reliability and validity in patients with mild dementia.³⁰⁻³⁴ Furthermore, although our cognitive screen may have missed patients with mild impairments of cognition, none were clinically demented.

The second possible explanation is that, to the extent that the GDS is a valid measure of depression, GDS score variability may reflect mood dysregulation due to brain damage. Alzheimer's disease (AD), for example, is known to affect the amygdala and associated brain regions that are involved in emotional processing and expression.³⁹ Thus, mood lability, as evidenced by variable GDS scoring, may be a sign of preclinical dementia in patients with AMD. In fact, some researchers have noted intriguing relationships between AMD and AD.⁴⁰ In both conditions, misfolded amyloid beta peptides accumulate (in the retina and in the brain, respectively) and may play a central role in their onset.⁴¹ If this is the case, cognitive and vision impairment in AMD may reflect a shared pathogenesis. The specific role of mood dysregulation in this context, however, remains speculative.

Our finding needs to be understood in the context of the study's limitations. For one, the subjects were not representative of most patients with AMD or the general population of older persons and a relatively small number of them declined cognitively; thus, the results may have limited generalizability. Moreover, we excluded patients with depressive disorders at baseline, which truncated the range of depressive symptoms and further limits generalizability. Second, we have no knowledge of whether mood variability persisted over time or whether other mood disturbances evolved in relation to the appearance of cognitive symptoms. Interestingly, although a clinical diagnosis of a depressive disorder at months 2 and 6 was not related to cognitive decline, more frequent GDS assessments with scores above 5 were related to cognitive decline. Our uncertainty why this is highlights the need for further study of the measurement of depression and the mechanisms linking it with cognitive decline. Third, we relied on only one informant to assess cognitive status, conducted no formal clinical or neuropsychological assessments to accurately characterize the cognitive function of the sample, nor had clinical validation of dementia diagnoses at follow-up. We attempted to minimize enrolling cognitively impaired subjects, however, by excluding patients with a history of cognitive decline or objective evidence of cognitive impairment on the MMblind. Nevertheless, the MMblind may well have misclassified subjects at baseline and was insensitive to change over time. Thus, we cannot exclude the possibility that GDS variability may well have represented an early sign of dementia in some subjects, or that the outcome (as measured by the IQCODE) did not overlap with period of exposure. Other researchers, however, have used similar MMSE versions and have found equivalent power to distinguish demented from nondemented individuals.⁴² Moreover, the incidence rate of cognitive decline that we observed is comparable to that reported in similar age cohorts (ranging from 32.6 to 59.9 cases per 1,000 patient years), which supports the validity of our findings.⁴³

In summary, we found that variability in responses to the GDS, which we administered bimonthly for 6 months, was strongly related to cognitive decline on average 3 years later in patients with AMD. This finding suggests that mood variability may well complement existing diagnostic and symptom level measures of depression and offer new insights into the neurobiological mechanisms linking depression and cognition. Along with depression, multiple demographic, behavioral, medical, and genetic risk factors for dementia have been identified.⁴⁴ Because identifying risk factors and presymptomatic signs of dementia is necessary for preventative and disease-modifying treatment strategies, detecting an early sign of disease, such as mood variability, may be extremely important.

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Figure 1.
GDS Means Over Time by Cognitive decline

Table 1
Bivariate Incidence Density Ratios of Study Measures with Cognitive Decline (n = 156)*

	Descriptive Statistics	Incidence Density Ratio	95% CI	Wald χ^2	P value
<u>Baseline Variables:</u>					
Age (mean, SD) ¹	81.0 (5.72)	1.57	1.12-2.20	6.92	.009
Education (mean, SD) ²	12.5 (3.15)	1.35	1.03-1.77	4.64	.031
GDS $\geq$ 5(n, %)	13 (8)	2.94	1.36-6.34	7.51	.006
MM Blind (mean, SD)	10.0 (.96)	.96	.75-1.24	.09	.760
Visual acuity (mean, SD)	.58 (.37)	.81	.21-3.10	0.91	.763
CDS ³ (mean, SD);	5.2 (3.08)	.89	.59-1.33	.35	.554
Female (n, %)	109 (70)	1.95	.93-4.11	3.12	.077
Assigned to PST ⁴ (n, %)	80 (51)	1.43	.66-3.10	.81	.369
Vascular Conditions (i.e., stroke, hypertension, diabetes) (n, %)	113 (71)	.78	.35-1.75	.36	.559
<u>Longitudinal Variables:</u>					
Depression diagnosis at months 2 or 6 (n, %)	47 (30)	1.78	.82-3.89	2.10	.148
Decline on MMBLind $\geq$ 1 point, BL to 1 Yr* (n, %)	20 (13%)	1.88	.77-4.57	1.92	.165
Visual Acuity Change, BL to 1 Yr*	-.13 (.32)	.48	.20-1.14	2.78	.096
GDS Variability	.96 (.66)	1.92	1.27-2.91	9.42	.002

5. GDS grand mean over 6 months

¹ Based on 5 year increments

² Based on 4 year increments

³ Chronic Disease Score

⁴ Problem-Solving Treatment

* Assessments at baseline and one year only. Poisson regression with robust standard errors was used to compute the IDRs and p-values. The df for all analyses is 1.

Table 2
Multiple Regression of Predictors of Cognitive Decline*

	df	Incidence Density Ratio	95% CI	Wald χ^2	P value
Education	1	1.35	1.07-1.71	6.41	.011
Age	1	1.61	1.07-2.44	5.11	.024
Baseline GDS ≥ 5	1	2.57	1.12-5.91	4.91	.027
GDS Variability	1	1.57	1.02-2.42	4.11	.043

* df = 1