Persistent Depressive Symptoms after Acute Coronary Syndrome Are Associated with Compromised White Matter Integrity in the Anterior Cingulate: A Pilot Study

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Abstract

Background: Persistent depressive symptoms after acute coronary syndrome (ACS) are common and increase the risk of recurrent cardiac events and mortality. However, the neurobiological correlates of post-ACS depressive symptoms have not yet been studied. **Methods:** Three months after ACS, 22 patients were scanned for the presence of cerebral deep white matter changes and microstructural abnormalities in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex. We used the Coffey Rating Scale of deep white matter changes and measures of fractional anisotropy derived from diffusion tensor imaging. Patients also completed the Beck Depression Inventory, and the number of cardiovascular comorbidities as well as modifiable cardiovascular risk factors were assessed. **Results:** Controlling for cardiovascular comorbidity, depressive symptom severity at 3 months was negatively related to fractional anisotropy in the ACC (r = –0.72, p < 0.001), but this association disappeared when controlling for cardiovascular risk factors (p = 0.21). In comparison to patients who were non-depressed at 3 months after hospitalization (n = 14), patients with persistent depressive symptoms (n = 8) exhibited more advanced deep white matter changes overall (p < 0.02), but not when controlling for cardiovascular comorbidity. Persistently depressed patients also had lower fractional anisotropy in the ACC (p < 0.05), but this effect disappeared when controlling for modifiable cardiovascular risk factors. **Conclusions:** This study provides the first evidence that persistent depressive symptoms after ACS are associated with vascular brain changes. Longitudinal studies are needed to determine whether depressive symptoms precede these changes or vice versa.

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Introduction

Structural MRI studies in elderly patients with vascular depression [1, 2] have reported increased deep white matter lesions [3, 4]; however, white matter changes have also been reported in elderly patients with depression onset at an earlier age [5], and may extend to younger age groups [6]. Specifically, white matter changes in the anterior cingulate circuit [7], and the dorsolateral prefrontal cortex (DLPFC) have been identified in vascular depression [3, 4, 6–8]. These brain areas have been implicated in emotional regulation in humans [9], suggesting a direct link between the structural changes caused by vascular lesions and subsequent negative mood states.

After acute coronary syndrome (ACS), depressive symptoms are common [10, 11]. In several studies and 2 meta-analyses, depressive symptoms emerged as reliable predictors of subsequent all-cause mortality as well as re-hospitalization for cardiac events, even at low levels of depression [12–14]. This relationship follows a dose-response fashion – the more severe the depressive symptoms, the higher the risk [15] – and there is some evidence that patients with depressive symptoms that persist across several months appear to be at highest risk for poor outcomes [12, 16, 17].

Several biological correlates of depression and vascular disease have been proposed to explain the risk conferred by persistently elevated depressive symptoms [for review, see 18], including elevated inflammatory markers [19] and dysregulation of the hypothalamic-pituitary-adrenal axis with subsequent changes in autonomic cardiac function [20]. However, the neurobiological correlates of post-ACS depressive symptoms have not yet been studied empirically. Studies showing a high comorbidity between cardiovascular disease and depression – in which about 30% of patients experience elevated depressive symptoms after an ACS and 20% have major depressive disorder [21] – suggest that at least in some patients, depressive symptoms may be of vascular origin. Using MRI, vascular lesions have traditionally been assessed using standardized rating scales [22] that quantify vascular changes at the macrostructural level. An alternative method is diffusion tensor imaging, which employs MRI techniques to measure alterations in brain tissue microstructure [23].

We explored the relationship between depressive symptoms after an ACS (assessed at hospitalization and after 3 months) and macro- and microstructural abnormalities in the brain (assessed 3 months after the ACS). Specifically, we assessed the relationship between the severity of depressive symptoms and measures of fractional anisotropy in the anterior cingulate cortex (ACC) and DLPFC, and the extent of deep white matter hyperintensities. We further compared post-ACS patients who had persistently elevated depressive symptoms to those who had no or only transient depressive symptoms on the same measures.

Methods

Participants

Participants were a subsample of the Coronary Psychosocial Evaluation Studies (COPES) that included a consecutive sample of ACS patients who were admitted to the coronary care units of 3 university hospitals between May 1, 2003 and June 13, 2005. Diagnosis of ACS was determined by research criteria [for details, see 24]. Patients were included in the study if they met pre-specified depressive symptom levels according to the Beck Depression Inventory (BDI [13]), i.e. scores ≥ 10 or <5. A BDI score of 10 or higher indicates elevated depressive symptoms, and has been associated with increased mortality and recurrent cardiac event risk after ACS [11].

Patients were recruited after Institutional Review Board approval and informed consent. Recruitment for the MRI substudy took place at the Mount Sinai site only; of the 189 patients enrolled at the site, only 36 (19%) agreed to take part in the MRI study at 3 months. Of these, 14 participants were excluded because of metallic implants other than cardiac stents (n = 2), claustrophobia (n = 2), active alcohol or substance abuse (n = 2), cognitive impairment as indicated by a Mini-Mental State Examination (MMSE [25]) score <24 (n = 1), scanner downtime >4 weeks (n = 3), and poor data quality (n = 3). The remaining sample (n = 22) did not differ from the parent sample in terms of age, sex, ethnicity, BMI, smoking, the number of cardiovascular diagnoses, and depression history (all p > 0.21).

Clinical Variables

At baseline, within 1 week of hospitalization for ACS, patients completed a demographic form assessing age, sex, and ethnicity. Height and weight were measured, and their smoking status assessed (never smoked vs. ever smoked vs. non-smoker; in pack years). They were administered the MMSE [25] and the BDI [26]. The BDI was re-administered 3 months after enrollment. Patients who had a score of ≥ 10 on the BDI at both baseline (in hospital) and after 3 months were considered 'persistently depressed'.

All participants also underwent a semi-structured diagnostic interview (Depression Interview and Structured Hamilton [27]) to determine the presence of major and minor depressive disorder according to the DSM-IV criteria, including lifetime history of depressive illness [28]. Previous cardiovascular and metabolic diagnoses (history of peripheral vascular disease, hypercholesterolemia, diabetes, recurrent angina, history of hypertension, congestive heart failure) were collected from medical charts and summed. Severity of the index ACS was coded according to clinical criteria [29] as unstable angina, ST-segment elevation myocardial infarction, and non-ST-segment elevation myocardial infarction. Treatment of the index ACS episode was assessed in 5 catego-

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ries (no treatment; cardiac catheterization; thrombolysis; coronary artery bypass graft; other). The course of the index ACS during the first 3 months was coded dichotomously as a function of the number of clinical interventions (emergency room visits; hospitalizations; cardiac catheterization; thrombolysis; coronary artery bypass graft; other) needed during the follow-up period (0 = no intervention needed; 1 = one or more interventions needed).

MRI Procedures

Scanning was performed using a 1.5-T Siemens Vision Scanner at the Mount Sinai School of Medicine. Patients received an MPRAGE (3D-magnetization-prepared rapidly acquired gradient echo) scan [repetition time (TR) = 2,500 ms, echo time (TE) = 4.38 ms, matrix = 256 × 256, field of view (FOV) = 210 mm, number of excitations (NEX) = 1, slice thickness = 0.8 mm, 208 slices, no gap, inversion time (TI) = 1,100 ms], a fast dual-spin echo scan (TR = 6,250 ms, TE = 14/96 ms, matrix = 256 × 256, FOV = 210 mm, slice thickness = 3 mm, 45 slices, no gap), a FLAIR (fluid-attenuated inversion recovery) scan (TR = 8,340 ms, TE = 2,500 ms, matrix = 320 × 320, FOV = 230 mm, NEX = 1, slice thickness = 3 mm, 40 slices, no gap), and a diffusion tensor scan (TR = 5,100 ms, TE = 80 ms, matrix = 128 × 128, FOV = 220 mm, NEX = 7, slice thickness = 3 mm, 40 slices, no gap, b = 1,250 s/mm^2). Twelve diffusion sensitization directions were used.

Coffey Scale

The Coffey classification system [22] was used to describe the extent of deep white matter hyperintensities on anatomical scans. This grading system rates deep white matter lesions on a 4-point scale (absent, punctuate, confluent, or large). Two raters (M.A.R., D.A.L.), who were blinded to group membership, rated the scans. Inter-rater reliability was satisfactory (r = 0.83).

Image Processing

In-house software (CYT) was used to compute the anisotropy and vector maps. MEDx v3.4.3 software (Medical Numerics Inc., Sterling, Va., USA) was used to inspect and define regions of interest (ROIs) in the ACC and DLPFC on the fractional anisotropy images. Two adjacent axial planes were selected to contain the same voxel locations. ROI dimensions for the fractional anisotropy images were set to 3 × 3. Each 3 ROIs were placed in ACC and DLPFC. Fractional anisotropy values of the white matter underlying each ROI were averaged for each area and extracted. Fractional anisotropy data were missing for 3 patients (2 did not complete scanning, 1 due to accidental data loss).

Statistical Analyses

The χ^2 test for categorical variables and t test for continuous variables were used to assess depression group differences in descriptive variables and covariates. The associations between depression severity, depression groups, and Coffey scores were examined using non-parametric statistics (Kendall's tau$_b$ and χ^2 test). For non-parametric analyses of covariance, we used a logistic regression approach to control for covariates at each dichotomous category step (e.g. for the Coffey scale, absent vs. punctuate, punctuate vs. confluent, and confluent vs. large) and then compared the residuals as a function of depression group using χ^2 tests [for a similar approach, see 30]. Fractional anisotropy measures were treated as continuous variables; bivariate Pearson correlations were used to assess the relation between fractional anisotropy measures and depressive symptom severity, and hierarchical linear regression was used to control for potential covariates. Univariate ANOVA was used to assess depression group differences in fractional anisotropy measures; analysis of covariance was used to control for covariates. Two-tailed tests of significance were employed with α set at <0.05. All analyses were performed using statistical software (SPSS Inc., Chicago, Ill., USA).

Results

Demographic and Clinical Characteristics

The overall study group (n = 22) comprised 9 women (40.9%) and 13 men, with a mean age of 56.09 years (SD = 9.53). At baseline, 16 patients had significant depressive symptoms, and 6 were non-depressed. Eight patients remained persistently depressed after 3 months (BDI score ≥10), the other 14 remained non-depressed or remitted to a BDI score <10 by 3 months. No patient developed new significant depressive symptoms during that time.

Table 1 displays the demographic characteristics of persistently depressed patients in comparison to patients without depression or those with transient depressive symptoms only.

White Matter Lesions (Coffey Scale)

Depressive symptoms at 3 months were significantly correlated with white matter lesions (τ = 0.41, p < 0.02). A similar albeit weaker and non-significant correlation was observed for depressive symptoms at baseline (τ = 0.20, p = 0.24).

Patients with persistent depressive symptoms exhibited more advanced deep white matter changes, as assessed by the Coffey Scale, compared to post-ACS patients with no or transient depressive symptoms (χ^2 = 5.25, d.f. = 1, p < 0.02; fig. 1). This difference remained significant when adjusting for age, sex, ethnicity, BMI, and smoking status (χ^2 = 4.47, d.f. = 1, p < 0.03). When controlling for the number of cardiovascular diagnoses, including diabetes, however, this effect diminished (p = 0.31). Neither the type of treatment (p = 0.34) nor the severity (p = 0.18) nor the course (p = 0.48) of the ACS index episode had an effect on deep white matter changes. In addition, the presence versus absence of a lifetime history of depression did not have an effect on deep white matter changes (p = 0.21).

Fractional Anisotropy in the ACC and the Dorsolateral Prefrontal Circuit

Fractional anisotropy in the ACC was significantly related to depression severity at 3 months (r = −0.72, p < 0.001; fig. 2). This association remained significant when
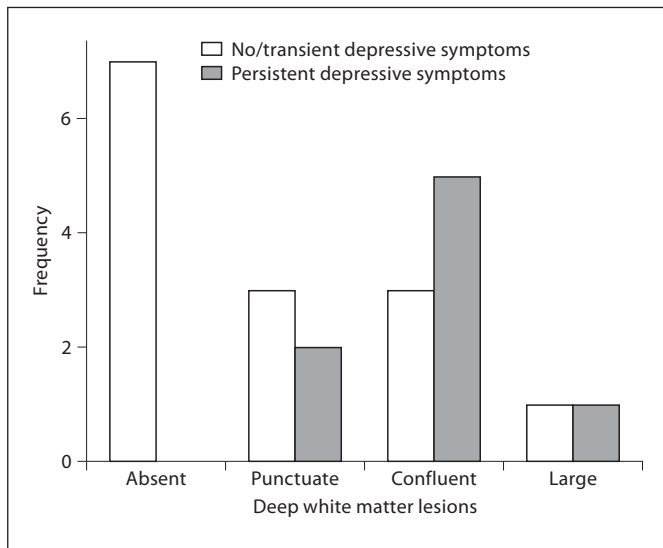
Fig. 1. Deep white matter lesions as a function of depressive symptom stability 3 months after ACS.
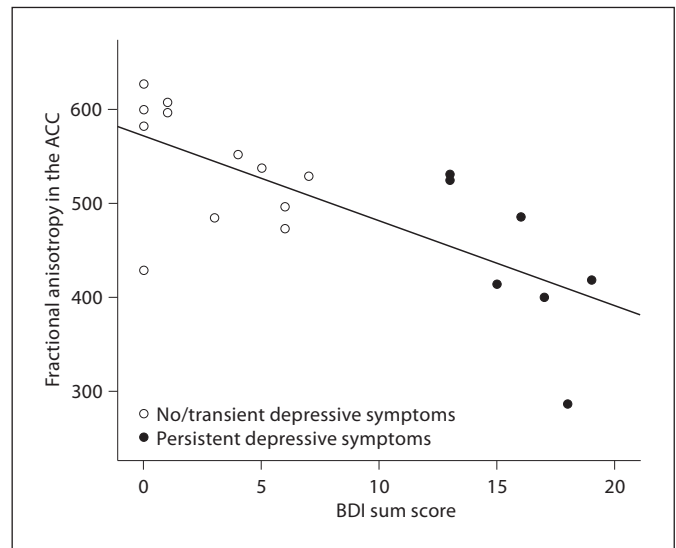
Fig. 2. Relationship between depression severity and fractional anisotropy in the ACC at 3 months after ACS. Three patients are missing fractional anisotropy data (n = 19, see 'Methods').

Table 1. Demographic and clinical characteristics of patients with no/transient depressive symptoms and patients with persistent depressive symptoms

	No/transient depressive symptoms (n = 14)	Persistent depressive symptoms (n = 8)	p
Age, years	56.14 ± 10.60	56.0 ± 8.0	0.97
Females	4 (28.6)	5 (62.5)	0.19
Hispanic	3 (21.4)	5 (62.5)	0.08
Smoking, pack years	21.94 ± 18.49	24.60 ± 36.89	0.85
MMSE score	29.79 ± 0.43	29.13 ± 1.25	0.08
Previous cardiovascular diagnoses (including diabetes)	3.15 ± 4.86	2.63 ± 1.23	0.77
Index ACS			
Unstable angina	6 (42.9)	5 (62.5)	
Non-ST-segment elevation myocardial infarction	2 (14.3)	2 (25.0)	
ST-segment elevation myocardial infarction	6 (42.9)	1 (12.5)	0.34
Treatment of index ACS			
Catheterization	9 (64.3)	4 (50.0)	
Thrombolysis	4 (28.6)	3 (37.5)	
Coronary artery bypass surgery	1 (7.1)	0 (0.0)	
Other	0 (0.0)	1 (12.5)	0.62
Interventions needed in first 3 months after ACS	11 (78.6)	7 (87.5)	0.60
Body mass index	26.34 ± 2.4	32.86 ± 5.34	0.001
BDI score at 3 months	2.86 ± 2.89	16.88 ± 3.60	<0.001
Depressive disorder status at 3 months			
Minor depression	0	5 (62.5)	<0.001
Major depressive episode	0	2 (25.0)	
History of depression	7 (50.0)	7 (50.0)	0.67

Data represent means ± SD or n (%).

controlling for sex, ethnicity, smoking status, body mass index, and number of cardiovascular diagnoses (β = –0.66, p < 0.05). Fractional anisotropy in the ACC was not, however, significantly related to depressive symptom severity at baseline (r = –0.23, p = 0.34). Neither the type of treatment, nor the severity, nor the course of the ACS index episode had an effect on fractional anisotropy in the ACC (all p > 0.32) or DLPFC (all p > 0.53). In addition, the presence versus absence of a lifetime history of depression did not have an effect on fractional anisotropy (p = 0.27).

In comparison to patients with no or only transient depressive symptoms, patients with persistent depressive symptoms had significantly lower fractional anisotropy in the ACC ($F_{1,\ 17}$ = 9.74, p < 0.01, η^2 = 0.36). This difference remained significant when controlling for age, sex, ethnicity, and the number of vascular diagnoses, including diabetes, and the severity, course, and treatment of the index ACS ($F_{6,\ 13}$ = 5.29, p < 0.05, η^2 = 0.31), but disappeared when controlling for modifiable risk factors of BMI and smoking in pack years (p = 0.28). There was no association between depressive symptom severity or depression group and lower fractional anisotropy in the DLPFC (p = 0.46 and 0.97, respectively).

Discussion

We found distinct differences in macrostructural deep white matter changes in post-ACS patients as assessed by semi-quantitative ratings (Coffey Scale [22]) as a function of depressive symptom severity and persistence after 3 months. This difference remained significant when controlling for modifiable risk factors, but disappeared when controlling for the number of cardiovascular diseases. Furthermore, we found a significant relationship between fractional anisotropy, reflecting microstructural changes in the ACC, and depressive symptom severity and persistence. This association remained significant when controlling for cardiovascular diseases; however, when controlling for modifiable risk factors, this association was not significant anymore.

Our findings show that depression after ACS is associated with vascular brain lesions in an area critical to the pathophysiology of depression [7–9], suggesting that in some patients, post-ACS depression is related to vascular lesions consistent with models of vascular depression [1, 2] and earlier findings of depression persistence in the presence of vascular brain changes, both on the microstructural [7, 8] and the macrostructural [2–4]

levels. We propose that white matter changes on the micro- and macrostructural levels may both contribute to depression vulnerability [11] in post-ACS patients, may perpetuate depression beyond adjustment processes after ACS [12, 13], and may be a critical biomarker for the depression-mortality association reported after ACS [11–16]. Our findings suggest that the severity of cardiovascular disease mediates the association between depression and macrostructural changes, whereas modifiable risk factors mediate the association between depression and microstructural changes. However, it has to be noted that directional causality cannot be inferred from our data, and there is indeed evidence that depression may precede cerebrovascular lesions and risk factors [31, 32].

Several limitations have to be considered. First, we cannot rule out the possibility that other biological mechanisms, such as inflammatory response [19] and dysregulation of the hypothalamic-pituitary-adrenal axis with subsequent changes in autonomic cardiac function [20], may be related to vascular changes in post-ACS depression, since we lack these data in our study. Second, the extent of cerebrovascular lesions could be related to the severity of cardiovascular comorbidities, but we lack specific data on the severity of these diagnoses in our sample. Treatment of the index ACS, however, including the use of stenting, did not explain the observed differences in cerebrovascular lesions in our study. Third, this study is limited by its small sample size and limited number of patients with major depressive disorder. This did not allow us to examine the contribution of specific depressive disorder subtypes that have recently been shown to predict post-ACS mortality and event recurrence, such as the distinction between incident and recurrent major depressive episode [33, 34]. In that realm, the study provides only preliminary data and is of pilot nature.

Given the finding that cardiovascular diagnoses account for a significant amount of variance in macrostructural (deep white matter) changes, while cardiovascular risk factors account for a significant amount of variance in microstructural changes (fractional anisotropy), one may speculate that modifiable risk factors may have a specific impact on microstructural changes associated with persistent depression. Recently, it has been proposed that depressive symptomatology lies along a continuum of subsyndromal and prodromal stages of depressive disorders [35]. In light of our finding of an association between cerebrovascular lesions and depressive symptomatology, even below the threshold for major depressive disorder [26], such a continuum may well be related to

continuous alterations on a neurobiological level. Furthermore, it has been suggested that residual symptoms of depression may be especially amenable to non-pharmacological interventions beyond pharmacological treatment effects [36], and this insight may be especially valuable in the study of post-ACS depression, since additional factors – such as medication adherence [37], lifestyle adaptations to mitigate behavioral risk factors, and adherence to other preventive measures – may strongly depend upon individually tailored non-pharmacological interventions in this population [38].

Despite its preliminary nature, this study establishes post-ACS depressive symptoms as 'vascular' depression [1, 2] consistent with deep white matter hyperintensities and microstructural white matter abnormalities in the ACC. The identification of the neurobiological correlates of post-ACS depression can guide further investigation aimed at enhancing therapeutic interventions and disentangling causal mechanisms in the relationship between depression and cardiovascular disease.

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