Emotional neglect in childhood and cerebral infarction in older age

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ABSTRACT

Objective: The purpose of the study was to test the hypothesis that a higher level of childhood adversity is associated with increased risk of cerebral infarction in old age.

Methods: Older participants in a longitudinal clinical–pathologic study rated adverse childhood experiences (e.g., emotional neglect, parental intimidation and violence) on a previously established 16-item scale. During a mean of 3.5 years of follow-up, there were 257 deaths, with 206 brain autopsies (80.2%). Number of chronic cerebral infarcts (gross plus microscopic; expressed as 0, 1, or >1) was determined in a uniform neuropathologic examination, which had been completed in 192 individuals at the time of these analyses.

Results: Childhood adversity scores ranged from 0 to 31 (mean = 8.3, SD = 6.4). In an ordinal logistic regression model adjusted for age, sex, and education, higher adversity was associated with higher likelihood of chronic cerebral infarction. In analyses of childhood adversity subscales, only emotional neglect was associated with infarction (odds ratio [OR] = 1.097; 95% confidence interval [CI] 1.048–1.148). The likelihood of infarction was 2.8 times higher (95% CI 2.0–4.1) in those reporting a moderately high level of childhood emotional neglect (score = 6, 75th percentile) vs a moderately low level of neglect (score = 1, 25th percentile). Results were comparable in subsequent analyses that controlled for lifetime socioeconomic status, cardiovascular risk factors, and an anxiety-related trait.

Conclusion: Emotional neglect in childhood may be a risk factor for cerebral infarction in old age. *Neurology*® 2012;79:1534–1539

GLOSSARY

CI = confidence interval; **OR** = odds ratio.

Epidemiologic studies have established that children are often subjected to emotional neglect and physical abuse.[1,2] Childhood is a unique time of psychological and cognitive development, and adults with a history of maltreatment during childhood are at increased risk for a range of psychiatric problems.[3,4] Adverse childhood experience also is associated with health outcomes such as cerebrovascular disease risk factors[5–12] and microstructural white matter abnormalities[13,14] seen in cerebrovascular disease. However, few studies have examined the association between childhood maltreatment and cerebrovascular disease, and results have been inconclusive.[15,16] We are not aware of clinical–pathologic research directly examining the relation of adverse childhood experience with cerebrovascular disease.

In the present study, we test the hypothesis that adverse childhood experience is associated with cerebral infarction found at autopsy. Older participants in a longitudinal clinical–pathologic study completed a self-reported scale-based assessment of childhood adversity. During a mean of 3.5 years of follow-up, 192 individuals died and a brain autopsy was performed.

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Supplemental data at www.neurology.org

Supplemental Data

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Chronic cerebral infarcts were identified on neuropathologic examination. We assessed the relation of childhood adversity to cerebral infarction in a series of regression models.

METHODS **Participants.** Persons in this study are from the Rush Memory and Aging Project, an ongoing longitudinal clinical–pathologic cohort study that began in 1997.[17] Eligibility for the project required age at enrollment ≥55 years, absence of a diagnosis of dementia, and agreement to annual clinical evaluations and brain autopsy at death. Older people in and around Chicago were recruited from continuous-care retirement communities, subsidized housing facilities, churches, and senior centers.

At the time of these analyses, 1,040 people had completed the questionnaire about adverse childhood experiences. During a mean of 3.5 years of follow-up, 257 persons died. A brain autopsy was performed on 206 (80.2%) but could not be performed on the remaining 51 individuals. At the time of these analyses, a uniform detailed neuropathologic examination had been completed for the first (consecutive) 192 persons. We based analyses on these 192 individuals (67.7% women), who died at a mean age of 88.5 years (SD = 6.0) and had a mean of 14.3 years of schooling (SD = 2.5).

Standard protocol approvals, registrations, and patient consents. After a presentation about the project, interested individuals were contacted by study personnel, who obtained informed written consent following a detailed discussion about the study. The institutional review board of Rush University Medical Center approved the project.

Assessment of childhood adversity. The scale is adapted from the Childhood Trauma Questionnaire[18] and other inventories[5,19] and focuses on self-report of emotional and physical trauma during the first 18 years of life, as previously described.[20] Item scores are summed to yield a total score, which has been previously shown in this cohort to be internally consistent (Cronbach coefficient $\alpha = 0.84$), temporally stable (6-month test–retest correlation = 0.92), and negatively related to measures of psychosocial adjustment.[20] In addition, supported by a factor analysis, the scale includes subscores for emotional neglect (6 items; e.g., "felt loved"), parental intimidation (4 items; e.g., "made you afraid"), parental violence (2 items; e.g., "punished you with a belt or other object"), family turmoil (2 items; e.g., "divorce"), and financial need (2 items; e.g., "not enough to eat").

Assessment of covariates. The structured uniform annual clinical evaluations included a medical history, physical and neurologic examinations, and neuropsychological testing.[17] Some covariates were derived from the baseline evaluation. Thus, mother's education, father's education, and father's occupational prestige were converted to *z* scores and averaged to form an index of childhood socioeconomic status[21]; current income and income at age 40, estimated with a 10-level show-card approach, were used as indicators of adults' socioeconomic status. Smoking status was based on self-report. Neuroticism was assessed with a standard 48-item scale,[22] with item agreement rated from 1 to 5 and ratings summed to yield the total score.

The remaining covariates were assessed at baseline and annual follow-up evaluations. The Hypertension Detection and Follow-up program protocol[23] was used to assess blood pressure. Two readings were taken with the subject seated and the right arm resting at heart level. The resulting values were averaged to yield measures of systolic and diastolic blood pressure. Diabetes status was based on use of insulin or oral hypoglycemic agents, reported diagnosis, or both. Body mass was expressed as weight in kilograms divided by height in meters squared. Physical activity was measured with questions adapted[24] from the 1985 Health Interview Survey[25] about frequency and duration of participation in 5 activities (i.e., walking, bicycling, calisthenics, gardening or yard work, swimming or water exercise) in the last 2 weeks. The score was total activity minutes per week.[26]

Neuropathologic examination. A standard protocol was followed for brain removal, tissue sectioning and preservation, and quantification of pathologic findings,[27,28] with examiners blinded to all clinical data, including childhood adversity. The cerebral hemispheres were coronally cut into 1-cm slabs, the cerebellar hemispheres were sagittally cut into 1-cm slabs, and the brainstem was bisected at the level of the mid pons. Each slab was visually examined for cerebral infarcts. Slabs from 1 cerebral hemisphere and 1 cerebellar hemisphere plus all lesions that included infarcts were fixed in 4% paraformaldahyde. The age (acute, subacute, chronic), size (height, width, length), and location of gross infarcts were recorded. Gross subcortical (including basis pontine and cerebellar subcortical) infarcts with dimensions that did not exceed 10 mm were classified as lacunar. Each suspected gross infarct was further dissected for histologic confirmation.[27,29]

We examined one hemisphere for microinfarcts (visible on microscopy but not gross visual inspection), using 6-μm paraffin-embedded sections stained with hematoxylin & eosin. Nine regions were assessed, including 6 cortical sites (mid frontal, middle temporal, entorhinal, hippocampal, inferior parietal, anterior cingulate cortices), 2 subcortical sites (anterior basal ganglia, anterior thalamus), and midbrain. The hemisphere examined was pseudorandomly selected, and a subset of cases included 1 or sometimes 2 blocks from the other hemisphere. The age and location of each lesion were recorded. Chronic microinfarcts included cavitated lesions with few remaining macrophages and fibrillary gliosis or incomplete infarcts.[29]

Cerebral atherosclerosis refers to the accumulation of fatty deposits on the walls of large vessels. It was rated from 0 (none) to 5 (severe) on the basis of gross inspection of the anterior, middle, and posterior cerebral arteries and their proximal branches at the circle of Willis. Cerebral arteriolosclerosis indicates concentric eosinophilic hyaline thickening and luminal narrowing of small vessels and was rated from 0 (none) to 6 (severe) on the basis of microscopic inspection of 6-μm hematoxylin & eosin–stained sections of anterior basal ganglia (caudate, putamen, globus pallidus, and internal capsule). In analyses, each rating was collapsed to a 4-point ordinal scale.

Primary analyses were based on the number of chronic (gross plus microscopic) infarcts, expressed on a 3-point ordinal scale: 0 infarcts, 1 infarct, and >1 infarct. In secondary analyses, infarcts were separated into gross vs microscopic and cortical vs subcortical categories, and gross subcortical infarcts were categorized as lacunar (no dimension >10 mm) vs nonlacunar.

Statistical analysis. The hypothesized association of childhood adversity score, treated as a continuous measure, with likelihood of chronic cerebral infarction, treated as a 3-point ordinal scale, was tested in ordinal logistic regression models. All analyses included terms for age at death, sex, and education. Initial models included terms for childhood adversity or one of the adversity subscores. Subsequent models focused on childhood emotional

neglect and controlled for stroke, socioeconomic status, vascular risk factors, neuroticism, or all covariates simultaneously.

We examined the relation of childhood emotional neglect to pairs of ordinal vascular outcomes in a series of Bivariate Dale Models.[30,31] The paired ordinal outcomes were atherosclerosis and arteriolosclerosis, gross and miscroscopic infarction, cortical and subcortical infarction, and lacunar and nonlacunar gross subcortical infarction. This approach allowed us to estimate the relation of emotional neglect to each outcome and to determine whether emotional neglect modified the association between outcomes.

The proportional odds assumption was assessed with the score test,[32] with separate tests for each outcome in the Bivariate Dale Models. The assumption was found to be adequately met.

RESULTS Scores on the composite measure of adverse childhood experience ranged from a low of 0 to a high of 31, with a slight positive skew to the distribution (mean = 8.3; SD = 6.4; skewness = 1.3). Lower level of education ($r = -0.17$; $p = 0.016$) and male gender ($Z = 2.24$; $p = 0.013$) were associated with higher level of adversity. Age at death was not related to adversity ($r = -0.09$; $p = 0.216$).

Neuropathologic examination showed that 103 persons had no chronic cerebral infarcts (53.7%), 42 had 1 (21.9%), and 47 had 2 or more (24.5%). Chronic cerebral infarction was not related to age at death ($r = -0.004$; $p = 0.959$), education ($r = -0.05$; $p = 0.451$), or sex ($\chi^2 = 1.98$; $p = 0.384$).

The association of childhood adversity with cerebral infarction was assessed in a series of ordinal logistic regression models adjusted for age at death, sex, and education. In the initial analysis, higher adversity was associated with higher likelihood of cerebral infarction (odds ratio [OR] = 1.10; 95% confidence interval [CI] 1.05–1.15). On average, the likelihood of infarction was 2.20-fold higher (95% CI 1.50–3.20) in those reporting a moderately high level of adversity (score = 12, 75th percentile) than in those reporting a moderately low level of adversity (score = 3.5, 25th percentile).

To determine whether the association was based on particular forms of childhood adversity, we separately analyzed the adversity subscores. As summarized in table 1, emotional neglect (mean = 4.1; SD = 4.2; skew = 1.1) was robustly related to likelihood of infarction, but the other subscores were not. A moderately high level of emotional neglect (score = 6, 75th percentile) was associated with a 2.83-fold increase (95% CI 1.95–4.09) in the likelihood of infarction, in comparison with a moderately low level of emotional neglect (score = 1, 25th percentile). We conducted all subsequent analyses on emotional neglect because it was the only component of adversity associated with cerebral infarction.

There were 40 individuals with evidence of stroke by history or examination. Stroke was marginally related to gross infarction ($\chi^2_3 = 5.2$; $p = 0.073$) but unrelated to microscopic infarction ($\chi^2_3 = 1.2$, $p = 0.540$) or total infarction ($\chi^3_3 = 1.0$; $p = 0.608$). When a term for stroke was added to the model, the association of childhood emotional neglect with chronic cerebral infarction was unchanged (estimate = 1.23; 95% CI 1.15–1.33).

To assess whether results were biased by the side of the brain examined for microinfarcts (102 right, 90 left), we repeated the analysis of emotional neglect with terms for hemisphere examined and the interaction of the indicator with emotional neglect. There was no hemisphere effect (estimate = −0.016; SE = 0.297; $p = 0.957$) or interaction (estimate = −0.022; SE = 0.072; $p = 0.761$).

In view of the association of socioeconomic status with childhood adversity[33] and cardiovascular health in adulthood,[34] we repeated the analysis of emotional neglect with terms added for childhood and adulthood socioeconomic status. Because of missing data on income, only 160 individuals were included in this analysis. The association of emotional neglect with cerebral infarction in this model (OR = 1.23; 95% CI 1.14–1.34) was nearly identical to the association in the original model, whether conducted on all 192 participants (table 1) or restricted to the 160 without missing income data (OR = 1.23; 95% CI 1.14–1.34).

In prior research, childhood adversity has been associated with vascular risk factors,[5–12] and in this cohort emotional neglect in childhood had marginal Spearman correlations with 3 risk factors at baseline: diabetes ($r = 0.13$; $p = 0.067$), physical activity ($r = -0.13$; $p = 0.085$), and smoking ($r = 0.14$; $p = 0.056$). Therefore, we repeated the analysis with terms added for diabetes, physical activity, and smoking. Emotional neglect was still associated with likelihood of chronic cerebral infarction in this analysis (OR = 1.25; 95% CI 1.15–1.35) and in another analysis that also controlled for body mass index, systolic blood pressure, and diastolic blood pressure (OR = 1.23; 95% CI 1.14–1.33). Results were unchanged when we controlled for the mean level of each risk factor across the full observation period (except smoking, which was not assessed beyond baseline) rather than at baseline alone (OR = 1.23; 95% CI 1.12–1.35). In a subsequent Bivariate Dale Model, emotional neglect was not associated with postmortem ratings of atherosclerosis (OR = 1.03; 95% CI 0.96–1.11) or arteriolosclerosis (OR = 1.04; 95% CI 0.98–1.11).

Because anxiety is related to childhood adversity[3] and risk of cardiovascular disease,[35,36] we repeated the initial emotional neglect model with a term added for neuroticism, an anxiety-related trait. In this anal-

Table 1 Association of specific forms of childhood adversity with chronic cerebral infarction[a]

Form of childhood adversity	Estimate	SE	p	OR	95% CI
Emotional neglect	0.208	0.038	<0.001	1.231	1.143-1.326
Parental intimidation	0.022	0.069	0.749	1.022	0.894-1.169
Parental violence	−0.088	0.162	0.585	0.915	0.667-1.257
Family turmoil	0.017	0.124	0.389	1.113	0.873-1.419
Financial need	0.141	0.103	0.173	1.151	0.941-1.409

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Estimated from 5 separate ordinal logistic regression models adjusted for age at death, sex, and education.

ysis, higher level of neuroticism was marginally related to increased likelihood of infarcts (OR = 1.02; 95% CI 1.0004–1.03), but the association of emotional neglect with likelihood of infarcts was unchanged (OR = 1.22; 95% CI 1.13–1.35).

We constructed one more model that included all covariates from the preceding analyses except stroke and microinfarct hemisphere. In this fully adjusted model, emotional neglect continued to be associated with likelihood of chronic cerebral infarction (OR = 1.23; 95% CI 1.13–1.35).

To determine whether emotional neglect in childhood was related to some types of infarction but not others, we constructed a series of Bivariate Dale Models that allowed us to simultaneously model 2 vascular outcomes. As shown in table 2 (model A) and figure e-1 on the *Neurology*® Web site at www.neurology.org, higher level of neglect was associated with higher likelihood of both gross and microscopic infarction. Emotional neglect was related to microscopic cortical but not microscopic subcortical infarction (table 2, model B; figure e-1). In contrast, emotional neglect was related to both subcortical and cortical gross infarction (table 2, model C; figure e-1) and, within the gross subcortical category, both lacunar and nonlacunar infarction (table 2, model D; figure e-1).

Table 2 Association of emotional neglect in childhood with subtypes of chronic cerebral infarction[a]

Model	Paired infarction subtype	OR	95% CI
A	Gross	1.21	1.13-1.31
	Microscopic	1.11	1.03-1.20
B	Microscopic subcortical	1.07	0.97-1.17
	Microscopic cortical	1.16	1.06-1.27
C	Gross subcortical	1.25	1.14-1.36
	Gross cortical	1.17	1.07-1.28
D	Gross subcortical lacunar	1.23	1.13-1.34
	Gross subcortical nonlacunar	1.25	1.13-1.38

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Estimated from 4 separate Bivariate Dale Models, adjusted for age at death, sex, and education.

DISCUSSION As part of a longitudinal clinical-pathologic study, older persons completed a structured self-report scale about adverse childhood experiences. During a mean of 3.5 years of follow-up, 192 individuals died and underwent a neuropathologic examination. The likelihood of chronic cerebral infarction was nearly threefold higher in those with moderately high levels of emotional neglect in childhood than in those with moderately low levels. The results suggest that emotional neglect in childhood may be a risk factor for cerebral infarction in old age.

There has been little prior research on the association of childhood adversity with cerebrovascular disease.[15,16] Because the few relevant studies have been of self-reported stroke in young to middle-aged adults, few cases have been identified (<1%,[15] <4%[16]), statistical power has as a result been limited, and findings have been inconclusive. By contrast, there have been many studies of the association between adverse experiences in childhood and cardiovascular health in adulthood. These studies have consistently found that higher levels of childhood abuse and neglect are associated with a higher likelihood of cardiovascular disease in adulthood.[5] Childhood adversity has also been associated with risk factors for cerebrovascular and cardiovascular disease, including hypertension,[6,7] diabetes,[8,9] obesity,[5,9–11] smoking,[5,12] physical inactivity,[5] and lower socioeconomic status.[33] Thus, the present results are consistent with prior knowledge and extend it by identifying a previously unrecognized association of childhood adversity with pathologically proven cerebral infarction.

The association of adversity with cerebral infarction was exclusively due to emotional neglect. This was unexpected, given the interrelatedness of different forms of childhood maltreatment.[35] That the subscales of parental intimidation, parental violence, family turmoil, and financial need were based on few items and assessed experiences that were relatively less common in this cohort may have contributed to the null findings. However, emotional neglect, which often begins early and is difficult to identify, may differ from more overt forms of maltreatment in its impact on psychological and health outcomes. For example, in a study of relatively highly functioning women, childhood emotional neglect and emotional abuse were associated with psychological and physical distress, even after accounting for childhood

physical and sexual abuse.[36] Thus the absence of a nurturing emotional environment early in life may thwart psychological and cognitive development and over time may lead to maladaptive behaviors and poor psychological health outcomes.[37]

The mechanisms underlying the association of early-life emotional neglect with late-life cerebral infarction are not clear. Emotional neglect may contribute to poor self-care, and it is possible that aspects of physical health underlie the association. However, emotional neglect was not related to postmortem measures of cerebral atherosclerosis and arteriolosclerosis, and its association with infarcts was not affected by controlling for traditional vascular risk factors. Chronic anxiety has been associated with childhood adversity[3,4] and cardiovascular disease,[38,39] but adjusting for an anxiety-related trait did not substantially affect results. Child neglect is the most common form of childhood adversity,[40] and its robust association with cerebral infarction in old age underscores the need for future studies that clarify the basis of this association.

Strengths and limitations of these data should be noted. Childhood adversity was assessed with a previously established scale. A high proportion of deceased participants underwent a brain autopsy, minimizing the likelihood that selective attrition affected results. Cerebral infarcts were assessed in a uniform neuropathologic examination that allowed for identification of microscopic as well as macroscopic lesions and was done blinded to all clinical data. An important limitation is that results are based on deaths to date in a selected group, and therefore their generalizability remains to be determined. In addition, childhood adversity was retrospectively assessed, indicating that recall bias could have affected results. Microscopic infarcts were assessed in only one hemisphere and therefore were certainly underestimated. Finally, because data on cause of death from the National Death Index are not yet available for all subjects, we cannot rule out the possibility that the association of childhood neglect with infarction reflects a more general association with vascular death.

AUTHOR CONTRIBUTIONS

Drafting/revising the manuscript for content and study concept or design: Drs. Wilson, Boyle, Levine, Anagnos, Buchman, Schneider, and Bennett. Analysis or interpretation of the data: Drs. Wilson, Boyle, Levine, Yu, Anagnos, Buchman, Schneider, and Bennett. Acquisition of data: Drs. Bennett and Schneider. Statistical analysis: Dr. Yu. Study supervision or coordinator: Dr. Bennett. Obtaining funding: Drs. Wilson, Boyle, Levine, Buchman, and Bennett.

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