Hippocampal Volume Changes in Patients with Asthma

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ABSTRACT

Background: Prior research suggests a possible association between asthma and decreased hippocampal volumes.

Objective: This study examines the association between asthma and hippocampal volume.

Methods: We conducted an analysis of participants in the Dallas Heart Study (DHS). The DHS collected an epidemiological sample of Dallas County residents to explore risk factors for heart disease. Included were 1,287 adults with complete data on study variables and without history of stroke, emphysema, or more than 5 drinks per day. Study variables included gender, age, race, and education as demographic characteristics, cognitive ability measured by the Montreal Cognitive Assessment (MoCA), and brain segment volumes measured by FreeSurfer. Study outcome variables were total, right, and left hippocampal volumes measured using FreeSurfer. General Linear Models (GLM) were conducted to examine the association of asthma diagnosis with hippocampal volumes after controlling for demographic characteristics, total MoCA score, and brain segment volume. Analysis of Variance (ANOVA) was used to examine the effect of gender on hippocampal volumes.

Results: The prevalence of lifetime asthma diagnosis among our study samples was 10.8% with 9.6% in males and 11.7% in females. Our study participants with a self-reported asthma diagnosis had significantly smaller estimated total, right, and left hippocampal volumes (95% CI 0.13%-2.9%; p = 0.03) than those without an asthma diagnosis. Asthma was significantly associated with total, right, and left hippocampal volumes in males, while not significantly associated in females after controlling for demographic characteristics, total MoCA score, and brain segment volume. Total, right, and left hippocampal volumes of males with asthma diagnoses, respectively, were 3.0% smaller (95% CI 0.77%-5.2%; p = 0.008), 2.9% smaller (95% CI 0.58%-5.2%; p = 0.014), and 3.1% smaller (95% CI 0.70%-5.6%; p = 0.012) than males without asthma.

Conclusion: Hippocampal volume in a large and diverse sample of adults was significantly smaller in people with asthma as compared to those without asthma. This difference in volume was limited to males. These findings suggest that asthma may be associated with structural brain differences as well as respiratory effects. Because the hippocampus is a brain region involved in memory formation these findings may have implications for treatment adherence.

INTRODUCTION

- Asthma is an increasingly prevalent, multifactorial chronic disease that currently affects 1 in 12 people in the U.S. [1] Its prevalence in the U.S. increased 15% between 2001 and 2010 (from 7.3% to 8.4% of the population) and currently accounts for nine deaths per day. [2,3] Asthma costs the U.S. over $56 billion dollars per year in healthcare expenses, missed work and school, and early deaths. [1] In 2001, one fourth of all U.S. emergency department (E.D.) visits were asthma-related, and in 2007 asthma accounted for 1.75 million E.D. visits. [2]
- Asthma may be associated with pathology that extends beyond the airways and may include changes in the brain. Anxiety and depression are more common in patients who have asthma than in the general population. [4,5] Emerging literature also suggests that cognitive impairment may be common even in patients with mild asthma. [6]
- These behavioral and cognitive findings may be associated with neuroanatomical changes in asthma patients. Depression has been linked to brain volume changes in the hippocampus, anterior cingulate gyrus, amygdala, and dorsal frontomedian cortex. [7-9]
- Oral corticosteroid use, common among moderate to severe asthma patients, has also been linked to decreased hippocampal and amygdalar volumes. [10-12] A small subset of asthma patients with severe exacerbations or end-stage lung disease may exhibit hypoxia requiring ventilator support. Hypoxia is associated with hippocampal neuronal death and may affect other brain volumes as well. [13]
- To our knowledge only two clinical studies exist exploring the relationship in humans between asthma and brain volume. These studies are limited in sample size and control methods, but nevertheless indicate that further research involving asthma and its potential effect on brain volumes is warranted and necessary. [14-15]
- Our data comes from two large Dallas Heart Study surveys sampling a multi-ethnic, probability-based population. The surveys (DHS-1) were collected in three stages between 2000-2002 and a subsequent evaluation (DHS-2) was performed from September 2007 to December 2009. These surveys collected a large amount of data from participants including self-reported health diagnoses, brain MRIs, and the Montreal Cognitive Assessment (MoCA) .
- Our aim in this study is to determine whether participants with asthma demonstrate regional brain volume differences as compared to participants without asthma. Additionally, we will also investigate whether regional brain volume differences in asthma patients are related to co-occurring depression or associated with performance on a cognitive task.

METHODS

Study Design

- We conducted a retrospective study of adults who took part in the Dallas Heart Study surveys 1 and 2 conducted in 2000-2002 and in 2007. Of these participants, 1,287 adults with complete study variable data, without conditions of stroke or emphysema, and who did not have more than 5 drinks per day were included for our study.
- The DHS-1 survey asked about asthma diagnosis but did not include MRI scans. Therefore, asthma diagnosis was obtained from DHS-1 data, while Montreal Cognitive Assessment (MoCA) [16] and brain volume data were collected during DHS-2. The 1,287-participant sample used was limited to subjects who participated in both DHS-1 and DHS-2.
- Asthma diagnosis was obtained via self-report at DHS-1, by asking if the participant had ever received a diagnosis of asthma from a doctor or health care professional. Possible responses were “yes,” “no,” and “don’t know,” and or refusal to answer the question. We limited our sample to those patients who responded “yes” or “no” to the question.
- Study variables included gender, age, race, and education as demographic characteristics, cognitive ability measured by the Montreal Cognitive Assessment (MoCA), and brain segment volumes measured by the FreeSurfer image analysis suite, Version 4.4, which is documented and freely available for download online. Study outcome variables were total, right, and left hippocampal volumes measured using FreeSurfer.
- The MoCA was administered at DHS-2. It is an 8-part test assessing visual spatial/executive function, naming ability, memory, attention, language, abstraction, delayed recall, and orientation, with a maximum possible score of 30 points.
- DHS participants were excluded for self-reported stroke, emphysema, or consumption of more than 5 drinks per day. Individuals with previous surgery for brain aneurysms; metal fragments in the eyes, brain, or spinal canal; cardiac pacemaker; implantable cardiodefibrillators; cochlear implant; spinal cord stimulators or other internal electrical devices; pregnancy; and occupations associated with exposure to metal fragments were excluded from MR imaging.
- Brain MR images were obtained on a 3T MR imaging scanner (Achieva; Philips Healthcare, Best, the Netherlands) by using 3D magnetization-prepared rapid acquisition of gradient echo. Images were obtained from the vertex of the skull to the foramen magnum in true axial orientation.

Statistical Analysis

- General Linear Models (GLM) were conducted to examine the association of asthma diagnosis with hippocampal volumes after controlling for demographic characteristics, total MoCA score, and brain segment volume.
- Analysis of Variance (ANOVA) was used to examine the effect of gender on hippocampal volumes. IBM SPSS Statistics (version 22) was used for statistical analyses, and a p-value < 0.05 was set as a criterion for statistical significance.

RESULTS

- Demographic data can be found in Table 1. The participants excluded due to missing data or exclusionary diagnoses were demographically similar to the participants included in the analysis except their mean age was about two years older. The prevalence of lifetime asthma diagnosis among our study sample was 10.8%, with 9.6% in males and 11.7% in females. The average age of our study participants was 50 years, and average education was 13.6 years (some college education).
- Participants with an asthma diagnosis had a significantly smaller total hippocampal volume (95% CI 0.13%-2.9%; p = 0.03) than those without an asthma diagnosis. Estimated right and left hippocampal volumes for asthma participants were 1.5% (95% CI 0.09%-2.9%; p = 0.037) and 1.5% (95% CI 0.01%-2.9%; p = 0.049) smaller than non-asthma participants, respectively.
- ANOVA analysis revealed that there was a significant between- and within-gender effect on total, right and left hippocampal volumes (total: F (1,1285)=170.91, P=<0.0001; right: F (1,1285)=145.31, P=<0.0001; left: F (1,1285)=175.87 P=<0.0001), which led us to examine the association between asthma and hippocampal volumes separately by gender.
- Asthma was significantly associated with decreased total, right, and left hippocampal volumes in males, while not significantly associated with decreased hippocampal volumes in females after controlling for demographic characteristics, total MoCA score, and brain segment volume.
- Total, right, and left hippocampal volumes of males with asthma diagnosis, respectively, were 3.0% smaller (95% CI 0.77%-5.2%; p = 0.008), 2.9% smaller (95% CI 0.58%-5.2%; p = 0.014), and 3.1% smaller (95% CI 0.70%-5.6%; p = 0.012) than males without asthma, respectively.
- We also conducted GLM analysis with two additional covariates of inhaled corticosteroid use and depressive symptoms measured by self-report Quick Inventory of Depressive Symptomology (QIDS) per gender group. The relationship between asthma and hippocampal volume remained significant when these were added to the regression.

Table 1. Demographic Information of Participants, Dallas Heart Study

Variable		Included Participants		Excluded Participants	*P* value[1]
		Asthma group n=139	Non-asthma group n=1148	n=329	
Gender	Male	n=52 (37.4%)	n=489	n=155	.0970
	Female	n=87 (62.6%)	n=659	n=174	
Race	Non-Hispanic African-American	n=56 (40.3%)	n=547	n=147	0.2482[2]
	Non-Hispanic White	n=67 (48.2%)	n=393	n=135	
	Hispanic	n=13 (9.4%)	n=185	n=40	
	Other	n=3 (2.1%)	n=23	n=7	
Mean age		49.66 (s.d. 10.66)	49.71 (s.d. 10.18)	51.36 (s.d. 9.59)	0.0080
Mean education years		14.14 (s.d. 2.98)	13.56 (s.d. 3.02)	13.43 (s.d. 2.94)	0.3439

1. Two-sided t-test was conducted between study participants and those excluded from the study.
2. Chi-square test was conducted to examine an association of race with study participation.

Table 2. GLM (male participants only)

Dependent Variable	Parameter		B	Std. Error	95% C.I.	*P* value
Total Hippocampal Volume	Asthma Diagnosis	+	-254.34	96.17	(-443.25, -65.43)	0.008
		-	--	--	--	
	Race	Non-Hispanic African American	-258.88	161.88	(-576.88, 59.12)	0.110
		Non-Hispanic White	-199.06	161.63	(-516.58, 118.45)	0.219
		Hispanic	6.77	174.02	(-335.09, 348.63)	0.969
		Other	--	--	--	
	Age		-5.62	3.12	(-11.75, 0.51)	0.072
	MOCA Score		22.69	9.43	(4.17, 41.20)	0.016
	Brain Segment Volume		0.005	0.000	(0.005, 0.006)	<0.0001
Right Hippocampal Volume	Asthma Diagnosis	+	-121.88	49.54	(-219.20, 24.55)	0.014
		-	--	--	--	
	Race	Non-Hispanic African American	-184.02	83.40	(-347.86, -20.19)	0.028
		Non-Hispanic White	-158.60	83.27	(-322.18, 4.99)	0.057
		Hispanic	-24.36	89.66	(-200.49, 151.76)	0.786
		Other	--	--	--	
	Age		-3.14	1.61	(-6.30, 0.02)	0.051
	MOCA Score		11.70	4.86	(2.16, 21.23)	0.016
	Brain Segment Volume		0.003	0.000	(0.002, 0.003)	<0.0001
Left Hippocampal Volume	Asthma Diagnosis	+	-132.47	52.41	(-235.41, 29.52)	0.012
		-	--	--	--	
	Race	Non-Hispanic African-American	-74.85	88.22	(-248.15, 98.44)	0.397
		Non-Hispanic White	-40.47	88.08	(-213.50, 132.56)	0.646
		Hispanic	31.14	94.83	(-155.16, 217.43)	0.743
		Other	--	--	--	
	Age		-2.48	1.70	(-5.82, 0.86)	0.145
	MOCA Score		10.99	5.14	(0.904, 21.08)	0.033
	Brain Segment Volume		0.003	0.000	(0.002, 0.003)	<0.0001

Table 3: GLM (female participants only)

Dependent Variable	Parameter		B	Std. Error	95% C.I.	*P* value
Total Hippocampal Volume	Asthma Diagnosis	+	-45.93	68.44	(-180.30, 88.44)	0.502
		-	--	--	--	
	Race	Non-Hispanic African-American	-39.71	213.24	(-458.34, 378.93)	0.110
		Non-Hispanic White	-184.11	214.48	(-605.18, 236.96)	0.219
		Hispanic	68.48	220.92	(-365.23, 502.19)	0.969
		Other	--	--	--	
	Age		3.23	2.26	(-1.21, 7.66)	0.154
	MOCA Score		11.94	6.74	(-1.291, 25.18)	0.077
	Brain Segment Volume		0.006	0.000	(0.005, 0.006)	<0.0001
Right Hippocampal Volume	Asthma Diagnosis	+	-28.04	35.90	(-98.52, 42.44)	0.435
		-	--	--	--	
	Race	Non-Hispanic African American	3.28	111.85	(-216.30, 222.86)	0.028
		Non-Hispanic White	-67.34	112.50	(-288.20, 153.52)	0.057
		Hispanic	78.74	115.88	(-148.75, 306.22)	0.786
		Other	--	--	--	
	Age		1.51	1.19	(-0.815, 3.84)	0.202
	MOCA Score		6.72	3.54	(-0.223, 13.66)	0.058
	Brain Segment Volume		0.003	0.000	(0.003, 0.003)	<0.0001
Left Hippocampal Volume	Asthma Diagnosis	+	-17.89	36.69	(-89.92, 54.14)	0.626
		-	--	--	--	
	Race	Non-Hispanic African American	-42.99	114.31	(-267.41, 181.43)	0.397
		Non-Hispanic White	-116.77	114.98	(-342.50, 108.96)	0.646
		Hispanic	-10.26	118.43	(-242.76, 222.25)	0.743
		Other	--	--	--	
	Age		1.71	1.21	(-0.665, 4.09)	0.158
	MOCA Score		5.22	3.61	(-1.87, 12.32)	0.149
	Brain Segment Volume		0.003	0.000	(0.003, 0.003)	<0.0001

CONCLUSIONS

- In a sample of 139 people with asthma and a control group of 1148 participants, asthma was associated with a significantly smaller total, right, and left hippocampal volume compared to controls after controlling for demographic characteristics, years of education, brain segment volume, and global cognitive performance score.
- This finding is consistent with previous research demonstrating below-average declarative memory performance in patients with generally moderate to severe persistent asthma. [17] A smaller hippocampal volume and poorer memory performance may negatively impact the clinical care of asthma patients.
- Male participants demonstrated a 3.0% smaller total hippocampal volume than controls, while female participants demonstrated only a 0.6% smaller total hippocampal volume. This gender difference may be explained by several studies which demonstrate a trend of decreased neuroprotection and plasticity and increased susceptibility to hypoxia in male animal models. [18-20]
- Our study suggests further investigation into the etiologies of this gender difference as well as the mechanisms by which asthma can lead to hippocampal volume reduction and perhaps other neurotoxic/neurodegenerative effects yet to be elucidated.

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