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Global Cerebral Atrophy Detected by Routine Imaging: Relationship with Age, Hippocampal atrophy, and White Matter Hyperintensities

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Abstract

Background and Purpose—Interpreting the clinical significance of moderate-to-severe global cerebral atrophy (GCA) is a conundrum for many clinicians, who visually interpret brain imaging studies in routine clinical practice. GCA may be attributed to normal aging, Alzheimer's disease (AD), or cerebrovascular disease (CVD). Understanding the relationships of GCA with aging, AD, and CVD is important for accurate diagnosis and treatment decisions for cognitive complaints.

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Methods—To elucidate the relative associations of age, moderate-to-severe white matter hyperintensities (WMH), and moderate-to-severe medial temporal lobe atrophy (MTA), with moderate-to-severe GCA, we visually rated clinical brain imaging studies of 325 participants from a community based sample. Logistic regression analysis was conducted to assess the relations of GCA with age, WMH, and MTA.

Results—The mean age was 76.2 ($\pm$ 9.6) years, 40.6% were male, and the mean educational attainment was 15.1 ($\pm$ 3.7) years. Logistic regression results demonstrated that while a 1-year increase in age was associated with GCA (OR=1.04; p =0.04), MTA (OR=3.7; p <0.001) and WMH (OR=8.80; p <0.001) were strongly associated with GCA in our study population. Partial correlation analysis showed that the variance of GCA explained by age is less than the variance attributed to MTA and WMH (r =0.13, 0.21 and 0.43, respectively).

Conclusions—Moderate-to-severe GCA is most likely to occur in the presence of AD or CVD and should not be solely attributed to age when evaluating clinical imaging findings in the workup of cognitive complaints. Developing optimal diagnostic and treatment strategies for cognitive decline in the setting of GCA requires an understanding of its risk factors in the aging population.

Keywords

global cerebral atrophy; cerebrovascular disease; Alzheimer disease

Introduction

Interpreting the diagnostic significance of moderate-to-severe global cerebral atrophy (GCA) is a conundrum for many clinicians, who visually interpret structural brain magnetic resonance imaging (MRI) in routine clinical practice. Many clinicians attribute GCA to the normal aging process.¹ Others may invoke degenerative processes such as Alzheimer's disease (AD), and yet others may relate these changes to cerebrovascular insults and disease (CVD).^{2,3} Understanding the relationship of GCA with aging, AD, and CVD would help inform accurate diagnosis and selection of appropriate interventions to maintain brain volume, cognition, and function.

Irrespective of the cause of GCA, strong associations across multiple studies argue that it is a reliable if non-specific marker of cognitive and functional impairment in the aging population.^{4,5} GCA can be readily identified using conventional imaging techniques, such as MRI and computed tomography (CT) scans, and so is evaluated by examining clinicians in virtually every case presenting with cognitive impairment.⁶ GCA can be reliably classified on a semi-quantitative basis using standardized protocols⁷ and further quantified using volumetric analysis techniques. In routine clinical practice, however, it is uncommon to use sophisticated volumetric techniques and instead qualitative assessment prevails. Similarly, vascular changes—such as white matter hyperintensities (WMH)—and medial temporal lobe atrophy (MTA) can be graded semi-quantitatively using visual rating scales.^{8,9} These features may also be analyzed using more sophisticated quantitative volumetric measures, which again are not commonly relied on by clinicians for making diagnostic or therapeutic decisions in routine clinical practice.

Potential contributors to GCA include age,¹⁰ WMH associated with CVD,² and AD.³ Many studies have shown that the severity of GCA is associated with increased age.^{1,10–14} Resnick et al. showed no detectable GCA over one year, but reported 15 cubic centimeter increase in ventricular volume over the same period in cross-sectional data analyses.¹⁵ A subsequent analysis of two- and four-year follow-up data from the cohort later revealed a significant association between GCA and age.⁶ In summary, although the literature is ambiguous, the hypothesis that GCA is associated with age per se has become strongly fortified for many practicing clinicians and radiologists.

MTA can be associated with both AD and to a lesser extent with normal aging.^{12,16} A recent report from the Alzheimer's Disease Neuroimaging Initiative (ADNI) showed that absolute MTA two years after the baseline MRI scan ranges from a 1–7% loss of medial temporal lobe volume in addition to a 10% increase in ventricular size.¹⁷ While ventricular changes may be readily discernable to the naked eye, MTA at a rate of only 1–7% per / year is difficult to detect in routine qualitative clinical evaluation of patient scans, especially if the atrophy rate is closer to 1% than 7%.

GCA has also been shown to be associated with CVD, and both share many common risk factors.² Prior studies examining healthy participants found that subcortical T2 signal changes in the white matter (i.e. WMH) were strongly associated with GCA.^{18–22} These studies suggested that the magnitude of the association between WMH and GCA in cognitively intact subjects may be double that associated with aging in the absence of WMH.⁴ However, these findings have been disputed in several other studies that reported no association between GCA and WMH.^{23,24}

In order to further elucidate the relative associations of age, WMH (as a surrogate for CVD), and MTA (as a surrogate for AD), with GCA, we examined MRI and CT with semi-quantitative metrics of each from 325 participants in a community-based longitudinal study of aging and cognition. Participants in the current study span the cognitive continuum.

Methods

Subjects

Both MRI and CT scans were acquired during routine clinical evaluation of study participants in the University of Kentucky Alzheimer Disease Center Cohort (n=325). Details of the recruitment and longitudinal evaluation of these participants have been published previously.²⁵ This study was approved by the University of Kentucky Institutional Review Board.

Visual rating of brain images

Visual rating of clinical brain images was performed independently by three physicians including a general neurologist (PP), neuroimaging specialist (CDS), and a behavioral neurologist (GAJ) using the standardized visual rating scales described below. Discrepant rating scores were adjudicated in a consensus conference including all three raters.

Representative images from a young normal, and elderly normal subjects with and without imaging findings of WMH, MTA and GCA are presented in Figure 1.

Global cerebral atrophy

GCA was visually rated on scale of 0–3 using T1 MRI or CT structural images based on the semi-quantitative rating scale due to Pasquier and colleagues.⁷ The raw data were then dichotomized with scores of 0 and 1 considered as negative for significant atrophy (see Figure 2 panel C and D), and scores of 2 and 3 considered as positive for moderate-to-severe atrophy (see Figure 2 panel G, H, K and L).

Medial temporal lobe atrophy (MTA)

MTA was rated based on the 5-point semi-quantitative scale developed by Scheltens and colleagues.⁹ using T1 MRI or CT scans. The raw data were dichotomized as follows: scores of 0, 1 and 2 were considered negative for significant atrophy, demonstrating only no or mild atrophy (see Figure 2 panel B), while scores of 3 and 4 were considered positive for moderate-to-severe atrophy (see Figure 2 panel F and J).

White Matter Lesions

We visually rated WMH using the 4-point modified Fazekas scale²⁶ using CT scan or fluid attenuated inversion recovery (FLAIR) sequence of the MRI. We added a score of 0 for subjects with WMH burden less than mild grade in the modified Fazekas scale. We did not differentiate between the periventricular and deep WMH; instead we rated both periventricular and deep WMH and assigned one score for the total WMH. The raw data were then dichotomized with scores of 0 and 1 considered as negative for significant WMH volume (see Figure 2 panel A), and scores of 2 and 3 considered as positive for moderate-to-severe WMH volume (see Figure 2 panel E and I).

Statistical Analysis

Descriptive statistics were used to summarize the study sample. A Spearman analysis was conducted prior to multivariable analysis to assess the degree correlation among the study measures. Simple and multivariable logistic regression models using dichotomous measures for GCA (as described above) were performed to examine the association with age, WMH, MTA and MMSE, such that the predictors were first examined separately and then simultaneously. Potential two-way interactions between age, WMH and MTA were assessed in the fully adjusted model. Finally, a partial and semi-partial correlation analysis was conducted to assess the variance of GCA that can be attributed to age, MTA and WMH. Statistical analyses were performed using Stata 14.

Results

Demographic and clinical features of the participants are presented in Table 1. The mean participant age was 76.2 ($\pm$ 9.6), (range 41–96) years, 40.6% were male, and the mean number of years of formal education was 15.1 ($\pm$ 3.7) years.

Two hundred thirteen clinical scans were MRI and 112 were CT. The MRI subgroup were younger (74.5 ± 9.4 vs. 79.5 ± 9.1 years), had higher education (15.6 ± 3.4 vs. 14.0 ± 4.0 years) and a higher percentage of moderate-to-severe MTA compared to the CT scan subgroup (39% vs 28%, respectively). However, the CT subgroup showed a higher percentage of moderate-to-severe WMH compared to the MRI subgroup (69% vs 36 %, respectively). Likewise, the CT subgroup had a higher percentage of participants with moderate-to-severe GCA compared to the MRI subgroup (74% vs 54%, respectively) (Table 1).

Spearman correlation analysis showed that age, WMH and MTA were all positively and significantly correlated with GCA, with the strongest correlation between WMH and GCA ($\rho=0.54$). MMSE scores were negatively correlated with GCA (Table 2). WMH, MTA, and GCA severity were found to be positively and significantly correlated with age in the Spearman correlation analysis, while MMSE scores were found to be negatively significantly correlated (Table 2).

Simple logistic regression models using the dichotomized GCA variable (GCA of moderate-to-severe atrophy vs. no or mild atrophy) showed that the unadjusted odds of having moderate-to-severe GCA increased 7.5% with each one-year increase in age (Model 1, Table 3). Participants with moderate-to-severe MTA had 5.3 times the odds of moderate-to-severe GCA than those with no or mild MTA (Model 2, Table 3). Similarly, the odds of having moderate-to-severe GCA were 13.6 times higher in participants with moderate-to-severe WMH than those with no or mild WMH (Model 3, Table 3). Finally, the unadjusted odds of having moderate-to-severe GCA decreased 4.9% with each one-point increase in the MMSE score (Model 4, table 3).

In the multivariable logistic regression model, age remained significantly associated with the risk of having moderate-to-severe GCA and showed that the odds of having moderate-to-severe GCA increased 3.6% with each one-year increase in age, after adjustment for WMH, MTA, MMSE score and scan type (Model 5, Table 3). Furthermore, participants with moderate-to-severe WMH had 8.8 times the odds of having moderate-to-severe GCA compared to those with no or mild WMH. Additionally, subjects with moderate-to-severe MTA had 3.7 the odds of moderate-to-severe GCA than those with no or mild MTA (Model 5, Table 3). Finally, the odds of having moderate-to-severe GCA decreased 6.7% with each one-point increase in the MMSE score (Model 5, Table 3). None of the two-way interaction terms were significant, and they were not retained in the final model.

Finally, in order to estimate the variance of GCA that can be attributed to age versus that attributed to WMH and MTA, we conducted partial and semi-partial correlation analyses. Results showed that the variance of GCA that can be attributed to variance in age is less than contribution from variance in MTA and WMH ($r=0.13$, 0.21 and 0.43 , respectively) (Table 4).

Discussion

These data support the hypothesis that moderate-to-severe GCA seen on brain imaging studies should not be solely attributed to normal aging (see Figure 1, panels D, E, F). CVD, and to a lesser extent AD, should also be considered as proximate causes of moderate-to-severe GCA (see Figure 1, panels G, H, I & J, K, L). Such understanding may help direct appropriate diagnosis and treatment strategies for those undergoing evaluation of memory complaints or more significant cognitive decline.

Consistent with the current literature, the present study demonstrates a decline in MMSE score in relation to age^{27,28} as well as the pathological imaging features of GCA, WMH and MTA.^{5,29} The association of GCA with MMSE, however, was independent of age, supporting the notion that GCA alone is correlated with cognitive decline, a finding that is consistent with many prior studies that have reported a significant correlation between rate of brain atrophy and the rate of MMSE score decline.^{30,31}

In the context of potential neuropathologic injury to the brain, age appears to be relatively a minor contributor to moderate-to-severe GCA, in line with the results from prior studies in the field. Fjell et al. reported that the rate of GCA progression due to normal aging is 0.5% annually.³² Similarly, Hua et al. and Scahill et al. also found a small but significant decrease in regional and whole brain volumes and a concomitant small increase in ventricular volume with increasing age.^{1,33}

The rate of GCA in the presence of AD is accelerated compared to that seen in normal aging (1.3% compared to 0.5% annually), with the fastest rate of atrophy affecting the medial temporal lobe (2.5% annually).³² Moreover, the rate of GCA and ventricular enlargement is accelerated even in young subjects (60–70 years) with MCI, reflecting the aggressiveness of neurodegenerative disease processes in young compared to old adults in even the earliest stages of cognitive decline.³³ The pattern of brain atrophy in AD also differs from that seen in normal aging. In AD, the medial temporal lobe is involved early in the disease course. Subsequently, the lateral temporal and frontal lobes are affected, with eventual involvement of the sensorimotor and visual cortices. Such progression eventually leads to the development of moderate-to-severe GCA that is not a part of the normal aging process.³⁴

Another important factor to consider as a contributor to the development of moderate-to-severe GCA is CVD. CVD may be present without evidence for GCA, but if progressive, can eventually result in moderate-to-severe GCA secondary to subcortical vascular damage that can lead to severe white matter atrophy.³⁵ In addition, progressive ischemic injury can lead to widespread neuronal atrophy and attrition in the grey matter that can be visualized on structural imaging as cortical thinning which can further contribute to the picture of moderate-to-severe GCA.³⁶ The STandard for ReportIng Vascular changes on nEuroimaging working group (STRIVE) has proposed terms and definitions to describe neuroimaging features of small vessel disease that include using GCA as an imaging correlate of CVD.³⁶ Few studies have failed to report an association between WMH and GCA, and those that did not report this association were unable to control for factors such as sample sizes or inclusion of participants with minimal to no CVD risks.^{23,24}

There are several limitations to the present study, including its cross-sectional design. While we have identified associations among age, MTA, WMH and the presence or absence of GCA, our data does not assess the temporal sequence of findings, limiting our ability to draw inferences on potential causality. Additionally, our analysis sample combined MRI and CT scans. Our data showed the percentage of participants with moderate-to-severe MTA was higher in the MRI subgroup than in the CT subgroup. This may be due to availability of a coronal view in the MRI subgroup, which enables clinicians to better evaluate the severity of MTA, compared to the availability of axial sections only for the CT subgroup. We have also relied on a convenience sample drawn from a community-based cohort, enriched in highly educated Caucasian subjects that may limit the generalizability of the present findings.

However, a major strength of our study also lies in our study sample, which is derived from a well characterized community-based cohort, spanning the cognitive continuum from intact cognition to dementia. Furthermore, the wide age range (41–96 years) increases the generalizability of the findings. The use of visual rating scales derived from standard clinical images is also a major strength, allowing us to examine structural imaging findings that are part of the normal clinical workup for memory complaints. These assessments are directly applicable to imaging review procedures used in routine clinical practice rather than relying on advanced volumetric analysis techniques that are seldom available to the practicing clinician.

In conclusion, our study demonstrates that qualitative appraisals of structural imaging findings that are used routinely in clinical settings are an appropriate means of evaluating the differences between imaging correlates of normal aging and those related to specific disease processes. Such information may help direct accurate diagnoses and treatment strategies designed to maximally address cognitive and functional impairments that may be seen in mild forms as part of the normal aging process, or in more moderate to severe forms as the sequelae of AD or CVD. Further studies exploring other imaging features with an eye to practical clinical utility in diagnosis and care are much needed in the field.

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Figure 1.

Descriptive figure showing representative magnetic resonance imaging images from A–C) a young normal, D–F) an elderly subject without significant white matter hyperintensity (WMH), medial temporal lobe atrophy (MTA), or global cerebral atrophy (GCA), G–I) an elderly subject with significant MTA and GCA without WMH, and J–L) an elderly subject with significant WMH and GCA without significant MTA.

Figures A, D, G, J are axial fluid attenuated inversion recovery images. Figures B, E, H, K are coronal T1 images. Figures C, F, I, L are sagittal T1 images.

Figure 2.

Descriptive figure showing the contribution of vascular damage (represented as white matter hyperintensity) and Alzheimer's Disease (represented as medial temporal lobe atrophy) to global cerebral atrophy.

The upper row is an example of a subject with no-to-mild white matter hyperintensity (WMH) on the fluid attenuated inversion recovery (FLAIR) image (A) and medial temporal lobe atrophy (MTA) on the coronal T1 image (B). Note that the subject with no-to-mild WMH and MTA has no-to-mild global cerebral atrophy (GCA) as shown in the transverse and sagittal T-1 image in the upper row (C and D respectively). The middle row is an example of a subject with moderate-to-severe WMH on the FLAIR image (E) and MTA on the coronal T1 image (F), which is associated with moderate-to-severe GCA seen on the transverse and sagittal T-1 image (G and H respectively). The lower row represents a second example of moderate-to-severe WMH on the FLAIR image (I) and MTA on the coronal T-1

image (J). Note that this subject also has moderate-to-severe GCA as shown in the transverse and sagittal T-1 image in the lower row (K, and L respectively).

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Table 1

Participant demographic, clinical, and imaging characteristics.

Participant Characteristics	Total (N=325)	MRI (n=213)	CT (n=112)
Age (mean $\pm$ SD)	76.2 $\pm$ 9.6	74.5 $\pm$ 9.4	79.4 $\pm$ 9.1
Sex (male, n [%])	132 (40.6)	89 (42.0)	43 (38.1)
Education (mean $\pm$ SD)	15.1 $\pm$ 3.7	15.6 $\pm$ 3.4	14.0 $\pm$ 4.0
Cognitive Diagnosis (n [%])			
Normal	87 (26.7%)	68 (32.1)	19 (16.8)
Mild Cognitive Impairment	129 (39.7%)	83 (39.1)	46 (40.7)
Dementia	109 (33.6%)	61 (28.8)	48 (42.5)
MMSE (mean $\pm$ SD)	23.2 $\pm$ 7.8	24.2 $\pm$ 7.4	21.1 $\pm$ 8.3
Imaging Results [*] (n [%])			
GCA	198 (60.9)	114 (53.8)	84 (74.3)
MTA	115 (35.4)	83 (39.1)	32 (28.3)
WMH	155 (47.7)	77 (36.3)	78 (69.0)

^{*} Results presented are for moderate-to-severe ratings.

Notes: SD = standard deviation; n = number of subjects; GCA = global cerebral atrophy; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden.

Table 2

Correlations among age (in years), white matter hyperintensity burden (rated 0–3), medial temporal lobe (rated 0–4) and global cerebral atrophy (rated 0–3).

	Age	MTA		WMH		GCA		MMSE	
		rs	P	rs	P	rs	P	rs	P
Age	--	0.26	0.0000 [‡]	0.43	0.0000 [‡]	0.35	0.0000 [‡]	- 0.12	0.033 [*]
MTA	--	--	--	0.29	0.0000 [‡]	0.35	0.0000 [‡]	- 0.14	0.013 [*]
WMH	--	--	--	--	--	0.54	0.0000 [‡]	- 0.11	0.044 [*]
GCA	--	--	--	--	--	--	--	- 0.18	0.001 [‡]

GCA = global cerebral atrophy; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden; rs = Spearman correlation coefficient.

^{*} P < 0.05

[‡] P 0.001

Table 3

Odds ratios (95% CI) for moderate-to-severe global cerebral atrophy based on participant age, white matter hyperintensity, medial temporal lobe atrophy and mini-mental state examination score.

Comparison	Model 1	Model 2	Model 3	Model 4	Model 5
Age (1 year)	1.07 (1.04–1.10)	--	--	--	1.03 (1.00–1.07)
MTA (moderate-to-severe vs. no or mild)	--	5.35 (3.05–9.38)	--	--	3.68 (1.82–7.48)
WMH (moderate-to-severe vs. no or mild)	--	--	13.60 (7.59–24.36)	--	8.79 (4.49–17.23)
MMSE	--	--	--	0.95 (0.92 – 0.98)	0.94 (0.90 – 0.99)

Models 1–4 are simple binary logistic regression, and Model 5 is multivariable binary logistic regression adjusted for scan type, sex and education.

MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden; MMSE = mini-mental state examination score.

Table 4

Partial and semi-partial correlation analysis to examine the variance of the global cerebral atrophy that can be attributed to variance in age, white matter hyperintensities and medial temporal lobe atrophy.

Variable	Partial Correlation	Semi-partial Correlation	P-value
Age	0.13	0.10	0.0246
WMH	0.43	0.38	0.0000
MTA	0.21	0.17	0.0002
MMSE	– 0.11	– 0.09	0.0543

WMH = white matter hyperintensities; MTA = medial temporal lobe atrophy; MMSE = Mini-Mental State Examination score.