Increase in brain atrophy after subdural hematoma to rates greater than associated with dementia

Abdullah Bin Zahid, MD,^{1–3} David Balser, MD,^{1–3} Rebekah Thomas,³ Margaret Y. Mahan, MS,^{2,3} Molly E. Hubbard, MD,^{1–3} and Uzma Samadani, MD, PhD^{1–3}

¹Department of Surgery, Minneapolis VA Health Care System; ²Department of Neurosurgery, University of Minnesota; and

³Department of Surgery, Hennepin County Medical Center, Minneapolis, Minnesota

OBJECTIVE Chronic subdural hematoma (cSDH) is a highly morbid condition associated with brain atrophy in the elderly. It has a reported 30% 1-year mortality rate. Approximately half of afflicted individuals report either no or relatively unremarkable trauma preceding their diagnosis, raising the possibility that cSDH is a manifestation of degenerative or inflammatory disease rather than trauma. The purpose of this study was to compare the rates of cerebral atrophy before and after cSDH to determine whether it is more likely that cSDH causes atrophy or that atrophy causes cSDH. The authors also compared atrophy rates in patients with cSDH to the rates in patients with and without dementia.

METHODS The authors developed algorithmic segmentation analysis software to measure whole-brain, CSF, and intracranial space volumes. They then identified military veterans who had undergone at least 4 brain CT scans over a period of 10 years. Within this database, the authors identified 146 patients with 962 head CT scans who had received diagnoses of either cSDH, dementia, or no known dementia condition. Volumetric analyses of brains in 45 patients with dementia (dementia group) and 73 patients without dementia (nondementia group), in whom 262 and 519 head CT scans were obtained, respectively, were compared with 11 patients in whom 81 CT scans were obtained a mean of 4.21 years before a cSDH diagnosis and 17 patients in whom 100 scans were obtained a mean of 4.24 years after SDH. Longitudinal measures were then related to disease status and the time since first scan by using hierarchical models, and atrophy rates between the groups were compared.

RESULTS Head CT scans from patients were obtained for an average time period of 4.21 years (SD 1.69) starting at a mean patient age of 74 years. Absolute brain volume loss for the 17 patients in the post-SDH group (13 were treated surgically) was significantly greater, at 16.32 ml/year, compared with 6.61 ml/year in patients with dementia, 5.33 ml/year in patients without dementia, and 3.57 ml/year in pre-SDH patients. The atrophy rate for these individuals prior to enrollment in the study was 2.32 ml/year ($p = 0.001$). In terms of brain volume normalized to cranial cavity size, the post-SDH group had an atrophy rate of 0.7801%/year, compared with 0.4467%/year in patients with dementia, 0.3474%/year in patients without dementia, and 0.2135%/year in the pre-SDH group.

CONCLUSIONS Prior to development of a cSDH, the atrophy rates in patients who ultimately develop cSDH are similar to those of patients without dementia. After development of a cSDH, the atrophy rates increase to more than twice those of patients with dementia. Chronic subdural hematoma is thus associated with a significant increase in brain atrophy rate. These findings suggest the neurotoxic consequences of cSDH and may have implications for better understanding of the pathophysiology of cerebral atrophy and dementia.

<https://thejns.org/doi/abs/10.3171/2017.8.JNS17477>

KEY WORDS chronic subdural hematoma; dementia; brain atrophy; longitudinal studies; head computed tomography scan; segmentation; trauma

DUE to an aging population, chronic subdural hematoma (cSDH) is projected to become the most common adult neurosurgical diagnosis requiring an operative procedure in the US by 2030.² Morbidity for this condition is often high, with mean lengths of hospital

stay longer than those for brain tumors,³ and a 1-year mortality of approximately 30%.²⁵ Brain atrophy, increasing age, and alcoholism all predispose a patient to the development of cSDH.^{22,26,27} Preceding trauma is often denied or noted to be unremarkable.^{10,26} Loss of consciousness is

ABBREVIATIONS AD = Alzheimer disease; BV = brain volume; cSDH = chronic subdural hematoma; ICC = intracranial cavity; ICD-10 = *International Classification of Diseases, Tenth Revision*; ICS = intracranial space; nBV = normalized BV; VA = Veterans Affairs; μ_{ICC} = average radiodensity of ICC.

SUBMITTED February 22, 2017. **ACCEPTED** August 21, 2017.

INCLUDE WHEN CITING Published online March 2, 2018; DOI: 10.3171/2017.8.JNS17477.

sufficiently rare that the condition was originally named pachymeningitis hemorrhagica by Rudolf Virchow, who believed that this type of subdural bleed was distinct from SDHs of traumatic origin and resulted instead from inflammation.²²

Mechanisms underlying morbidity of cSDH include the fact that the blood in the subdural space not only compresses brain but also is physiologically active, exerting its effects using cytokines and inflammatory mediators.^{16,28,31,32} This inflammation causes scarring and leads to formation of septa within the hematoma, as well as the breakdown of red blood cells, a process that normally occurs in the spleen. The blood breakdown products, especially the iron-containing heme unit, can precipitate oxidation-reduction reactions and lead to neurotoxicity.^{1,14,15,24,33}

There is a pathophysiological basis for an intracranial hemorrhage to cause inflammation-related brain atrophy.^{16,23,28,31,32} The clinical significance of this process in cSDH when compared with other atrophy-related neurodegenerative conditions, such as dementia, has not been well defined. Our laboratory has developed software that relies on segmentation of the density on CT scans to volumetrically assess brain atrophy and cSDH volume in the brain. Previously, we demonstrated that the software accurately assesses brain atrophy in dementia patients.⁵ We now use that software to assess atrophy after resolution of cSDH.

The primary purpose of this study was to compare the rates of cerebral atrophy before and after cSDH to determine whether it is more likely that cSDH causes atrophy or atrophy causes cSDH. Understanding when the atrophy occurs relative to when the cSDH occurs could potentially enable intervention to prevent either or both. A secondary purpose was to compare atrophy rates in patients with cSDH to those in patients with and without dementia conditions. Understanding the consequences of cSDH may lead to better understanding of how its morbidity and mortality could be reduced.

Methods

Institutional review board approval was obtained for this study and the requirement of informed consent was waived.

Patient Selection

Regional Veterans Affairs (VA) databases were searched for CT head scans performed between January 2004 and April 2017. Of those who had an index scan during this period, patients were excluded if they had fewer than 3 subsequent scans or if serial scans extended over less than 1 year. From the resulting list, patients were selected if they developed SDH or were diagnosed with dementia. Diagnoses of dementia (unspecified type) and Alzheimer disease (AD) were performed by searching the medical record for *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis codes that had been entered by a clinician and verified independently by direct review of the medical record. Patients without dementia were selected from the remaining subjects with matching imaging history. The patients with SDH were

further divided into 2 groups: those in whom all scans were performed before they developed SDH and those in whom all scans were done after they developed SDH. If a patient fulfilled the imaging history criteria both before and after SDH, scans obtained before the development of SDH were excluded and the patient was included in the post-SDH group because the statistical analysis required independence of observations between subjects.

The post-SDH subset was additionally separated into 2 groups: patients in whom the SDH was surgically drained and patients whose SDH was managed medically.

Protocol for CT Scanning

All CT scans were obtained on Toshiba Aquilion 16 or Aquilion 64 helical scanners (Toshiba Medical Systems) or Philips Brilliance 16, Philips Brilliance 40, or Philips Brilliance 64 scanners (Koninklijke Philips N.V.). Acquisition parameters were as follows: peak tube voltage 120 kVp; x-ray tube current 150–300 mAs; field of view 20–25 cm yielding in-plane resolution of 0.390–0.468 mm; soft-tissue reconstruction kernel FC64, FC67, or UB; matrix size 512 × 512; 29–34 slices (10th and 90th percentiles); and axial slice thickness 4.6–5 mm (10th and 90th percentiles).

Image Analysis Technique

Total intracranial and total brain volumes (BVs) were assessed using previously described fully automated software, with no operator intervention.⁵ Briefly, in the first step, intracranial space (ICS) was segmented. For ICS the algorithm selects voxels with CT attenuation in the range [–500, +125] Hounsfield units. This excludes bone and air. Then, on the remaining soft tissue, 3D morphological erosion of a 6-mm radius is performed that disconnects the extracranial soft tissue from the intracranial cavity (ICC). Afterward, the largest connected component is retained that results in the exclusion of extracranial soft tissue. Finally, constrained morphological dilation is performed on the retained component, resulting in the recovery of all ICS voxels. The CSF volume was then separated from the brain tissue by labeling all ICS voxels with attenuation values within the fluid range (i.e., below 16 Hounsfield units) as CSF.⁵ The ICS voxels not classified as CSF were labeled as brain tissue. The CSF masks included the entire ventricular and sulcal space. No coregistration techniques or other normalization techniques were used. All volumes reflected absolute measurements in milliliters. All attenuation values were expressed in Hounsfield units. The output from the software was visually inspected for any gross segmentation errors. The scans with any artifact, intraparenchymal hemorrhage, SDH, or any other space-occupying lesion that could affect the segmentation algorithm were excluded. For patients with SDH, only the scans that did not have any hematoma in them were used for analysis.

Compensation for Lack of CT Calibration

Multiple factors (detector drift, x-ray tube current) affect calibration of the linear attenuation of water used as reference signal in CT, which can be corrected using equa-

tions relating the average radiodensity of ICC (μ_{ICC}) of the scans to the corrected volumes.⁵ These equations are as follows:

$$\text{BV} = \text{rBV} - 487.46 + 18.57 \times \mu_{\text{ICC}}$$

$$\text{CSF-V} = \text{rCSF-V} - 658.14 - 25.07 \times \mu_{\text{ICC}}$$

$$\text{ICC-V} = \text{BV} + \text{CSF-V}$$

$$\text{nBV} = \text{BV}/\text{ICC-V}$$

where BV is the adjusted brain volume (in milliliters), rBV is the raw brain volume, CSF-V is the adjusted CSF volume (in milliliters), rCSF-V is the raw CSF volume, ICC-V is the corrected ICC volume (in milliliters), and nBV is the ratio of the brain volume normalized to the ICC volume.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 24, IBM Corp.). Figures 1 and 2 were constructed using MATLAB r2016b (MathWorks Inc.).

Estimation of Absolute and Normalized Brain Atrophy Rates

To analyze time-series data with unequal follow-up

duration and correlated error terms, separate multilevel mixed (hierarchical) models were developed for BV and nBV by using the SPSS Mixed procedure. The models related the target measurements to the CT reconstruction method (kernel), μ_{ICC} , baseline age, and group membership (dementia, nondementia, pre-SDH, and post-SDH) and its interaction with follow-up time as fixed effects. Intercept and slope (linear term, time since first scan) were allowed to vary between individuals. To reflect the fact that very little brain atrophy happens before the age of 40 years, the age at the time of first scan minus 40 was used as the baseline age. The models were created using maximum likelihood. The covariance structure was first-order autoregressive for repeated measures and unstructured for random effects.

Effect of Surgery on Absolute and Normalized Brain Atrophy Rates

Comparison of brain atrophy rates between the surgical intervention and medical management groups of the post-SDH subset was performed by building 2 separate mixed linear models, one for absolute and the other one for nBV. Models related target measurements to the CT reconstruction method (kernel), μ_{ICC} , baseline age, and group membership (surgical management or medical management) and its interaction with follow-up time as fixed effects. Intercept and slope were entered as random effects, as above.

FIG. 1. Scatter plot showing that absolute BVs decrease fastest in patients after SDH. Patients studied after SDH (red lines, circles) are compared with the pre-SDH group (blue lines, squares), dementia patients (black lines, crosses), and patients without dementia or SDH (dotted gray lines, stars). The data points show actual BV adjusted for confounders (radiodensity of the scan and reconstruction method—see text). The lines show model fit to the data.

FIG. 2. Scatter plot of BVs from Fig. 1, but as a fraction of the ICC in patients studied after SDH (red lines, circles) compared with the pre-SDH group (blue lines, squares), dementia patients (black lines, crosses), and patients without dementia or SDH (dotted gray lines, stars). Notice the precipitous decline after the development of SDH. Data for 1 post-SDH patient are not shown because the brain atrophy values were less than 0.75.

Effect of Hematoma Volume on Absolute and Normalized Brain Atrophy Rates

To analyze the effect of the volume of SDH on brain atrophy rate, the SDH was manually segmented by an expert on a CT scan. If a patient had multiple scans, the one with the highest hematoma volume was selected. The volume of segmented SDH was calculated in milliliters and normalized to cranial cavity size. Two mixed linear models (one for absolute brain and SDH volumes and the other for normalized brain and SDH volumes) with the following specifications were built. Target measurements were related to the CT reconstruction method (kernel), μ_{ICC} , baseline age, and volume of hematoma and its interaction with follow-up time as fixed effects. Intercept and slope were entered as random effects.

Results

A total of 962 CT scans for 146 patients (262 scans for 45 patients with dementia, 519 scans for 73 patients without dementia, 81 scans for 11 patients pre-SDH, and 100 scans for 17 patients post-SDH) were analyzed. Figure 3 shows the progression of atrophy across head CT scans over time. The most common indications for CT scans were altered mental status, fall, dizziness, head trauma, syncope, cerebrovascular accident evaluation or suspected transient ischemic attack, headache, trauma, ataxia, motor deficits, weakness, focal deficit, and memory loss. Of the 17 patients in the post-SDH group, 1 underwent twist drill

drainage, 6 had bilateral burr hole drainage, and 6 had unilateral burr hole drainage. The other 4 patients were managed medically. The association of their head injury with trauma is as follows: 5 were associated with a fall from standing, 3 were associated with a severe head injury event (such as a motor vehicle collision), 6 were associated with a minor head injury more than 1 week prior to evaluation, and 3 had an incomplete or unreliable head trauma history. The descriptive statistics are given in Table 1. All patients in this study were males. For each individual, scans were available over a mean duration of 4.21 years (SD 1.69, range 0.96–9.05 years).

Longitudinal Changes in Absolute BVs

Figure 1 and Table 2 show changes in absolute BVs for all 4 groups. The analysis demonstrated a statistically significant rate of BV loss in all groups (intragroup comparison, mixed model: type III test of fixed effects; $p < 0.001$ for the interaction of group membership with time). In the nondementia group, the rate of loss was -5.33 ml/year (95% CI -3.93 to -6.74). It was approximately 3 times greater, or -16.32 ml/year (95% CI -12.97 to -19.66) in the post-SDH group ($p < 0.001$ vs the nondementia group). The loss in the post-SDH group was also 2-fold greater than in the dementia group (-6.61 ; 95% CI -4.74 to -8.47). Although the atrophy rate in the dementia group was greater than that in the nondementia group, the difference did not reach significance ($p = 0.27$). The BV in all groups declined at a steady

FIG. 3. Progression of atrophy is shown in a typical patient in the post-SDH group, with the CSF identified in red and the brain in blue. Each image sample of the 3D segmentation was taken 1 slice above the rostral thalamus. The scans were done 16 (scan 1), 26 (scan 2), 28 (scan 3), and 38 (scan 4) months after the SDH. The BVs were 1252, 1223, 1212, and 1189 ml, respectively.

rate of 2.32 ml/year between the ages of 40 and 74 years (mean age at enrollment in the study). The groups did not differ in terms of atrophy prior to enrollment in the study ($p > 0.05$ for interaction of age with group; type III test of fixed effects, mixed model). It should be noted that this rate is very close to that in pre-SDH patients, but substantially lower than that in the dementia or nondementia group.

Changes in BVs Adjusted for Head Size

Figure 2 and Table 2 show changes in BVs after dividing by the volume of the ICC. Again, there was a significant loss of BV for all groups (intragroup comparison, mixed

model: type III test of fixed effects; $p < 0.001$ for the interaction of group with time). The loss was $-0.3474\%/year$ for the nondementia group (95% CI -0.4145 to $-0.2803\%/year$). In the post-SDH group, it was $-0.7801\%/year$ (95% CI -0.9376 to -0.6226% of ICC/year), or 2 times greater than that in the nondementia group ($p < 0.001$ for loss of percent BV compared with the nondementia group). Again, although the normalized atrophy rate in the dementia group was greater than that in the nondementia group, the difference did not reach significance ($p = 0.078$). The atrophy rate in terms of brain normalized to cranial cavity was -0.1052% between the ages of 40 and 74 years (the

TABLE 1. Descriptive statistics of cohort by groups

Parameter & Group	No. of Patients	Mean	Median	SD	Range*
Baseline age, yrs					
Dementia	45	80.25	80.8	8.86	40.11
Post-SDH	17	72.47	76.22	11.25	32.79
Pre-SDH	11	72.82	74.39	13.49	35.99
Nondementia	73	70.84	72.81	11.62	50.13
Follow-up, yrs					
Dementia	45	4.01	4.01	1.55	6.52
Post-SDH	17	4.24	4.16	2.22	8.09
Pre-SDH	11	4.21	3.86	1.87	6.24
Nondementia	73	4.33	4.61	1.63	7.66
Baseline BV, ml					
Dementia	45	1105.17	1102.77	84.2	377.31
Post-SDH	17	1271.91	1252.58	147.14	704.15
Pre-SDH	11	1170.9	1156.59	94.84	305.95
Nondementia	73	1139.56	1153.14	104.24	404.55
Baseline nBV, % of ICC					
Dementia	45	82.163	82.054	1.76	8.494
Post-SDH	17	80.681	80.868	3.028	13.746
Pre-SDH	11	83.441	83.239	2.87	8.02
Nondementia	73	83.385	83.805	2.526	11.246

* The range is the result of the maximum minus minimum value (not shown); e.g., baseline age spanned 40 years (from 55 to 95 years) for dementia.

TABLE 2. Estimated yearly atrophy rates for dementia, post-SDH, pre-SDH, and nondementia groups

Parameter	Atrophy Rates					
	BV Loss (ml/yr)			Normalized Rate (% of ICC/yr)		
	Value	95% CI		Value	95% CI	
		Lower	Upper		Lower	Upper
Intercept	1517.63	1441.29	1593.97	102.4075	100.0732	104.7418
Baseline age*	-2.32	-3.66	-0.99	-0.1052	-0.1417	-0.0687
Dementia	-6.61	-8.47	-4.74	-0.4467	-0.5369	-0.3564
Post-SDH	-16.32	-19.66	-12.97	-0.7801	-0.9376	-0.6226
Pre-SDH	-3.57	-7.09	-0.05	-0.2135	-0.3845	-0.0426
Nondementia	-5.33	-6.74	-3.93	-0.3474	-0.4145	-0.2803

* To take into account the fact that very little atrophy occurs before the age of 40 years, the baseline age reflects real age minus 40 at the time of enrollment in study.

mean age at enrollment in the study). The groups did not differ in terms of BV loss prior to enrollment in the study ($p = 0.672$ for interaction of age 40 years minus age at enrollment with group; type III test of fixed effects, mixed model), indicating a healthy, normal status prior to the development of diseases.

Effect of Surgery on Absolute and Normalized Brain Atrophy Rates

The brain atrophy rates between treatment types for the post-SDH group were compared to determine whether there is a difference between medically treated patients ($n = 4$) and individuals who underwent surgery ($n = 13$). Mixed linear modeling with random effects was performed as described in *Methods*. The analysis demonstrated similar rates in both groups ($p = 0.664$ for difference in absolute decline in BV). The surgical arm had an atrophy rate of 11.17 ml/year versus 13.13 ml/year for medically treated individuals. When adjusted for cranial cavity size, the surgical arm demonstrated an atrophy rate of 0.414%/year versus 0.351%/year for medically treated individuals ($p = 0.777$).

Effect of Hematoma Volume on Absolute and Normalized Brain Atrophy Rates

The hematoma volume as a linear variable was used to predict the atrophy rate after suffering an SDH in 11 patients from the post-SDH group for which the volume measurements were available. Absolute volume of SDH was not a significant predictor of the brain atrophy rate (absolute) that ensued ($p = 0.329$). Similarly, the SDH volume normalized to cranial cavity size did not predict the normalized brain atrophy rate ($p = 0.306$).

Discussion

Significance of Findings

Although cerebral atrophy is associated with the development of cSDH,^{20,21} our data suggest that this atrophy develops after rather than before cSDH development. The post-SDH atrophy rate is greater than that seen in AD. The mechanisms of the physical effects of intracerebral hemorrhage and SDH leading to atrophy are similar. In intracerebral hematoma, neutrophil extravasation is

thought to result in increased apoptosis in a transitional zone of neurons surrounding the collection of blood, causing atrophy.⁸ Chronic SDH is characterized by an oxidative burst of neutrophils surrounding the hematoma membrane.²⁹ Local inflammatory and oxidative products in cases of intracerebral and subdural hemorrhage probably contribute to surrounding tissue damage and the resulting atrophy.

Iron by-products from heme degradation in intracerebral hemorrhage have been shown to result in cerebral atrophy.^{14,15} Free iron is directly toxic to neurons by way of oxidative stress,²⁴ and overloading local cerebral tissue with high-iron substances is known to cause degenerative pathology.¹ Chronic SDHs were long thought to have a protective dural border preventing diffusion of hematoma contents to adjacent cerebral tissue, but the subdural membrane exists in a flux of inflammation from damage to dural border cells, resulting in a cycle of membrane disruption and new membrane creation.⁷ In addition to helping explain the recurrence and loculation formation common in cSDHs, the cycle of damage to the subdural membrane surface raises the possibility that subdural fluid contents—such as iron and other cytokines—may exude into the surrounding space, causing local cell damage and atrophy along the subdural border in a manner similar to that in intracerebral hemorrhage. Unfortunately, no studies to date have assessed the presence of elevated SDH products in the adjacent cerebral tissue.

The atrophy rate in SDH has not been well studied, and therefore establishing parameters of clinical significance is challenging. Brain atrophy rate has been used as a biomarker for the progression of AD in several studies.^{4,6,11,17,19} Generalized linear models have been used to measure brain atrophy rates in aggregate longitudinal studies.¹¹ In our work, the confidence intervals of the atrophy rate in the pre-SDH group overlapped with those in the nondementia and dementia groups. The atrophy rate increased 2- to 3-fold after SDH diagnosis. In comparison, atrophy rates increase less than 2 times after the onset of AD in at-risk groups in a study by Jack et al.¹⁹ No equivalent biomarker exists for SDH, despite the finding of the greater change in atrophy rate. We speculate that this may be due to the perception of SDH as a surgically treated acute or subacute disease rather than as a chronic condition, and therefore clinical monitoring for BV through

various imaging modalities has been performed less frequently in patients with cSDH. Understanding whether patients in the post-cSDH group develop cognitive decline or are neurologically well would be informative regarding how much atrophy correlates with cognitive decline. The association between atrophy and cognitive decline is well established in dementia but has not been as well studied after cSDH.

Limitations of the Study

Our results must be interpreted with some caution because this study's population is subject to at least 2 types of selection bias. The participants are military veterans, which introduces an age and gender bias toward older males. Veterans are at increased risk of traumatic and nontraumatic SDH compared with the general population,² and the mechanism of their precipitating injury or cause may differ from that of a person in the civilian population. The second source of bias is that everyone in the study was required to have more than 3 head CT scans free of hematoma over the 7-year study period and to be alive for 1 year after the SDH diagnosis. Any individual with serial head CT scans or MR images is more likely to have one or more neurological problems that may affect atrophy rate, cognitive function, and mortality. Thus, our study has an ascertainment bias created by the inclusion of more symptomatic individuals.

An additional limitation of this study is that veterans may have had treatment outside of the VA system. Head CT scans and ICD diagnosis dates were used to classify study participants into groups. Any CT scans performed outside the VA system and not integrated into the VA database are missing data points that affect the atrophy rate calculation.

Computed tomography scans that revealed hematoma were excluded from the analysis. The amount of atrophy cannot be calculated in a CT scan with a substantial fluid collection in the extraaxial space, because the resulting compression of the brain misrepresents BV and brain border measurements. Because inclusion criteria required the patients to be alive for at least 1 year after the SDH, the impact of hematoma in patients who die of the disease remains to be explored. A clinically significant difference in atrophy rate was reported despite exclusion of these early deaths from presumably more severe cases of SDH, and so it is likely that cSDH has an impact on patients.

The type of head trauma associated with SDH onset varied among the participants in the study, as did the cSDH density. Almost half of the patients with a detailed clinical history of an admission associated with an SDH diagnosis did not recall any recent trauma. Furthermore, because association of cSDH and subsequent atrophy does not prove causation, we cannot exclude the possibility that the nature of head trauma, density of hemorrhage, or other iatrogenic factors may affect long-term atrophy rates. It is unknown whether the presence of the SDH or the nature of its precipitating brain injury is the actual cause of the subsequent atrophy.

An additional limitation of this study is that we do not know whether the atrophy seen after cSDH has clinical significance. This question will be addressed in future studies.

Cerebral Atrophy as a Biomarker for Cognitive Decline

This study uses brain atrophy as an outcome measure. The rate of change in global cerebral volume loss is strongly correlated with the rate of change in cognitive assessments.⁹ Global cortical atrophy has been linked to increased risk of dementia diagnosis and the rate of clinical progression of dementia.^{4,6,12} Compared with cognitive tests, brain atrophy can reveal the actual progress of the disease, which may be masked by symptomatic treatments or other temporary cognitive issues (e.g., delirium).¹² Cognitive testing in our cohort of patients, if it had been available, would have provided insight into whether atrophy is necessarily associated with dementia or can occur independently.

Dementia and Cerebral Atrophy

In this study, we analyzed longitudinal CT scans of patients with both AD and multiinfarct dementia. Neurodegeneration visible as cerebral atrophy on imaging has been well established as a predictive and parallel biomarker to clinical cognitive impairment in AD.⁴ The rate of ventricular expansion in a healthy aging population without dementia is known to be 1.3 ml/year,¹⁸ which is comparable to the global atrophy rate (ventricular expansion plus loss of gray matter) of 2.09 ml/year in our study. In our study, we did not find a significant difference between the dementia and nondementia groups in atrophy rates. We hypothesize that this is secondary to the various neurological disorders in the nondementia group, which necessitated repeated CT scans. In our previous work, we established that in such a scenario a difference may not be apparent in linear atrophy rates; however, it is seen in acceleration (quadratic term).⁵ Chan et al. found the rate of general cerebral atrophy on MRI in patients with familial AD to be 2.8% at the onset of dementia.⁶ Because this study was of patients with familial AD, the vastly higher brain atrophy rate is consistent with atrophy rate as an indicator of cognitive disease severity. Jack et al.¹⁹ reported that the rate of brain atrophy in patients right before the development of AD was 7 ml/year, which is concordant with our rate of 6.61 ml/year reported in this study. The slight difference in the rates can be attributed to the differences in the study populations.

Our study findings may also have implications for better understanding of the pathophysiology of dementia. In light of recent failed trials targeting amyloid deposition,³⁰ consideration of atrophy-inducing aspects of cSDH may provide insight into the pathophysiology of atrophy development and potentially suggest therapeutic targets that are not related to protein deposition.

Subdural Hematoma and Cerebral Atrophy

Previous cross-sectional volumetric studies of patients with SDHs demonstrate an association between SDH and atrophy.^{20,21} However, what has remained unclear is whether atrophy facilitates the development of hematoma or vice versa. Our data suggest that SDH leads to atrophy instead of atrophy leading to SDH.

Subdural fluid contains increased concentrations of cytokines, inflammatory mediators, and fibrinolytic fac-

tors.^{16,28,31,32} The neurotoxicity of iron and thrombin by-products of blood breakdown is well established.^{1,14,15,24,33} A constant, local presence of neurotoxic compounds in the vicinity of the brain suggests a causative relationship with subdural atrophy. This is in accordance with Martin et al.,²³ who demonstrated a correlation between traumatic brain injury–associated intraparenchymal hemorrhage volume, BV, and cognitive testing over a 6-month period.

Atrophy-Associated Death

Brain atrophy is an indirect marker of cognitive decline, and has an association with increased mortality rates, despite the lack of a causal link. Global cortical atrophy increases the risk of death from cerebrovascular disease 6-fold in the presence of microbleeds.¹³ A cohort study of the brain atrophy rate as a risk factor for death across several atrophy-associated diseases would be the next step in determining this relationship.

Conclusions

Prior to development of a cSDH, the atrophy rates in patients who will ultimately develop cSDH are similar to those in other patients. After development of a cSDH, the atrophy rates increase to more than twice those in patients with dementia. Chronic subdural hematoma is thus associated with a significant increase in brain atrophy rate. These findings further confirm the neurotoxic consequences of cSDH and may have implications for better understanding of the pathophysiology of cerebral atrophy and dementia.

Acknowledgments

This work was supported by Merit Review Award #I01 CX000887 from the US Department of Veterans Affairs Clinical Sciences Research and Development Program, awarded to Dr. Samadani.

References

- Altamura S, Muckenthaler MU: Iron toxicity in diseases of aging: Alzheimer's disease, Parkinson's disease and atherosclerosis. *J Alzheimers Dis* 16:879–895, 2009
- Balser D, Farooq S, Mehmood T, Reyes M, Samadani U: Actual and projected incidence rates for chronic subdural hematomas in United States Veterans Administration and civilian populations. *J Neurosurg* 123:1209–1215, 2015
- Balser D, Rodgers SD, Johnson B, Shi C, Tabak E, Samadani U: Evolving management of symptomatic chronic subdural hematoma: experience of a single institution and review of the literature. *Neurol Res* 35:233–242, 2013
- Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al: Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 367:795–804, 2012
- Bin Zahid A, Mikheev A, Srivatsa N, Babb J, Samadani U, Rusinek H: Accelerated brain atrophy on serial computed tomography: potential marker of the progression of Alzheimer disease. *J Comput Assist Tomogr* 40:827–832, 2016
- Chan D, Janssen JC, Whitwell JL, Watt HC, Jenkins R, Frost C, et al: Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. *Lancet* 362:1121–1122, 2003
- Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ: Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J Neuroinflammation* 14:108, 2017
- Felberg RA, Grotta JC, Shirzadi AL, Strong R, Narayana P, Hill-Felberg SJ, et al: Cell death in experimental intracerebral hemorrhage: the “black hole” model of hemorrhagic damage. *Ann Neurol* 51:517–524, 2002
- Fox NC, Scahill RI, Crum WR, Rossor MN: Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology* 52:1687–1689, 1999
- Gelabert-González M, Iglesias-Pais M, García-Allut A, Martínez-Rumbo R: Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. *Clin Neurol Neurosurg* 107:223–229, 2005
- Gorbach T, Pudas S, Lundquist A, Orädd G, Josefsson M, Salami A, et al: Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiol Aging* 51:167–176, 2017
- Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, et al: Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nat Rev Drug Discov* 9:560–574, 2010
- Henneman WJ, Sluimer JD, Cordonnier C, Baak MM, Scheltens P, Barkhof F, et al: MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. *Stroke* 40:492–498, 2009
- Hua Y, Keep RF, Hoff JT, Xi G: Brain injury after intracerebral hemorrhage: the role of thrombin and iron. *Stroke* 38 (2 Suppl):759–762, 2007
- Hua Y, Nakamura T, Keep RF, Wu J, Schallert T, Hoff JT, et al: Long-term effects of experimental intracerebral hemorrhage: the role of iron. *J Neurosurg* 104:305–312, 2006
- Ito H, Komai T, Yamamoto S: Fibrin and fibrinogen degradation products in chronic subdural hematoma. *Neurol Med Chir (Tokyo)* 15:51–55, 1975
- Jack CR Jr: Brain atrophy on magnetic resonance imaging as a biomarker of neurodegeneration. *JAMA Neurol* 73:1179–1182, 2016
- Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al: Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* 132:1355–1365, 2009
- Jack CR Jr, Weigand SD, Shiung MM, Przybelski SA, O'Brien PC, Gunter JL, et al: Atrophy rates accelerate in amnesic mild cognitive impairment. *Neurology* 70:1740–1752, 2008
- Jeong EO, Choi SW, Lim JW, Kwon HJ, Kim SH, Koh HS, et al: Effectiveness of cortical atrophy scale and indirect indices of brain atrophy to predict chronic subdural hematoma in older patients. *Korean J Neurotrauma* 12:112–117, 2016
- Ju MW, Kim SH, Kwon HJ, Choi SW, Koh HS, Youm JY, et al: Comparison between brain atrophy and subdural volume to predict chronic subdural hematoma: volumetric CT imaging analysis. *Korean J Neurotrauma* 11:87–92, 2015
- Lee KS: History of chronic subdural hematoma. *Korean J Neurotrauma* 11:27–34, 2015
- Martin RM, Wright MJ, Lutkenhoff ES, Ellingson BM, Van Horn JD, Tubi M, et al: Traumatic hemorrhagic brain injury: impact of location and resorption on cognitive outcome. *J Neurosurg* 126:796–804, 2017
- Mills E, Dong XP, Wang F, Xu H: Mechanisms of brain iron transport: insight into neurodegeneration and CNS disorders. *Future Med Chem* 2:51–64, 2010
- Miranda LB, Braxton E, Hobbs J, Quigley MR: Chronic subdural hematoma in the elderly: not a benign disease. *J Neurosurg* 114:72–76, 2011
- Mori K, Maeda M: Surgical treatment of chronic subdural hematoma in 500 consecutive cases: clinical characteristics,

- surgical outcome, complications, and recurrence rate. **Neurol Med Chir (Tokyo)** **41**:371–381, 2001
27. Sim YW, Min KS, Lee MS, Kim YG, Kim DH: Recent changes in risk factors of chronic subdural hematoma. **J Korean Neurosurg Soc** **52**:234–239, 2012
 28. Suzuki K, Takano S, Nose T, Doi M, Ohashi N: Increased concentration of vascular endothelial growth factor (VEGF) in chronic subdural hematoma. **J Trauma** **46**:532–533, 1999
 29. Tao Z, Lin Y, Hu M, Ding S, Li J, Qiu Y: Mechanism of subdural effusion evolves into chronic subdural hematoma: IL-8 inducing neutrophil oxidative burst. **Med Hypotheses** **86**:43–46, 2016
 30. Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, et al: Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. **Alzheimers Res Ther** **8**:18, 2016
 31. Weigel R, Schilling L, Schmiedek P: Specific pattern of growth factor distribution in chronic subdural hematoma (CSH): evidence for an angiogenic disease. **Acta Neurochir (Wien)** **143**:811–819, 2001
 32. Weigel R, Schmiedek P, Krauss JK: Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. **J Neurol Neurosurg Psychiatry** **74**:937–943, 2003
 33. Xi G, Keep RF, Hoff JT: Mechanisms of brain injury after intracerebral haemorrhage. **Lancet Neurol** **5**:53–63, 2006

Disclosures

Drs. Bin Zahid and Samadani have submitted a patent related to the segmentation algorithm used in this study.

Author Contributions

Conception and design: Samadani, Bin Zahid, Balser, Mahan, Hubbard. Acquisition of data: Bin Zahid, Balser, Thomas, Hubbard. Analysis and interpretation of data: all authors. Drafting the article: Samadani, Bin Zahid, Balser, Thomas. Critically revising the article: Samadani, Bin Zahid, Balser, Mahan, Hubbard. Reviewed submitted version of manuscript: Samadani, Bin Zahid, Balser, Mahan, Hubbard. Approved the final version of the manuscript on behalf of all authors: Samadani. Statistical analysis: Bin Zahid, Mahan. Administrative/technical/material support: Samadani. Study supervision: Samadani.

Correspondence

Uzma Samadani: Hennepin County Medical Center, Minneapolis, MN. uzma.samadani@hcmcmed.org.