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. Morbidity for this condition is often high, with mean lengths of hospital stay longer than those for brain tumors, and a 1-year mortality of approximately 30%. Brain atrophy, increasing age, and alcoholism all predispose a patient to the development of cSDH. Preceding trauma is often denied or noted to be unremarkable. Loss of consciousness is
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.16,23,28,51,32 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.3 A 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 ($\mu_{ICC}$) of the scans to the corrected volumes. These equations are as follows:

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

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

$$ICC-V = BV + CSF-V$$

$$nBV = \frac{BV}{ICC-V}$$

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), $\mu_{ICC}$, 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), $\mu_{ICC}$, 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.
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), μICC, 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
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**

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

* 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.
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.\(^6\) Chronic SDH is characterized by an oxidative burst of neutrophils surrounding the hematoma membrane.\(^28\) 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

### 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.\(^6\) Chronic SDH is characterized by an oxidative burst of neutrophils surrounding the hematoma membrane.\(^28\) Local inflammatory and oxidative products in cases of intracerebral and subdural hemorrhage probably contribute to surrounding tissue damage and the resulting atrophy.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BV Loss (ml/yr)</th>
<th>Atrophy Rates</th>
<th>Normalized Rate (% of ICC/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
</tr>
<tr>
<td>Intercept</td>
<td>1517.63</td>
<td>1441.29</td>
<td>1593.97</td>
</tr>
<tr>
<td>Baseline age*</td>
<td>-2.32</td>
<td>-3.66</td>
<td>-0.99</td>
</tr>
<tr>
<td>Dementia</td>
<td>-6.61</td>
<td>-8.47</td>
<td>-4.74</td>
</tr>
<tr>
<td>Post-SDH</td>
<td>-16.32</td>
<td>-19.66</td>
<td>-12.97</td>
</tr>
<tr>
<td>Pre-SDH</td>
<td>-3.57</td>
<td>-7.09</td>
<td>-0.05</td>
</tr>
<tr>
<td>Nondementia</td>
<td>-5.33</td>
<td>-6.74</td>
<td>-3.93</td>
</tr>
</tbody>
</table>

* 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.
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, 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. Global cortical atrophy has been linked to increased risk of dementia diagnosis and the rate of clinical progression of dementia. 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). 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. The rate of ventricular expansion in a healthy aging population without dementia is known to be 1.3 ml/year, 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).

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. 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. 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, 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. 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-
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. 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

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References

26. Mori K, Maeda M: Surgical treatment of chronic subdural hematoma in 500 consecutive cases: clinical characteristics,


**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.

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