Incidence of Convexal Subarachnoid Hemorrhage in the Elderly: The Mayo Clinic Study of Aging

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Objectives: Nontraumatic convexal subarachnoid hemorrhages in the elderly can be a manifestation of cerebral amyloid angiopathy associated with a high risk of future intracerebral hemorrhage. The incidence in the elderly population is unknown. Our objectives were to: 1) determine the incidence of convexal subarachnoid hemorrhage in a population-based study, and, 2) to compare apopolipoprotein-E genotype and amyloid positron emission tomographic (PET) imaging for those with versus without hemorrhage. *Methods:* Between 11/29/2004 and 3/11/2017, 4462 individuals without hemorrhage at baseline participated in the population-based Mayo Clinic Study of Aging. We used the Rochester Epidemiology Project medical records-linkage system to identify intracerebral hemorrhages. Records and images were reviewed to identify convexal subarachnoid hemorrhage. Neuroimaging characteristics, demographics, medications, and apopolipoprotein-E genotype were recorded. *Results:* Four cases were identified. The incidence of convexal subarachnoid hemorrhage was 14.1 per 100,000 person years. Three occurred in women, median age, 79 (range: 71-84). One patient had coexisting cerebral microbleeds. Two participants developed a subsequent lobar intracerebral hemorrhage at a median of 4.75 years after convexal subarachnoid hemorrhage. The apopolipoprotein-E -allele combinations of the 4 were: 3/3, 3/3, 2/2, and 2/3. On Pittsburgh Compound B-PET imaging, median standardized uptake value ratio with convexal subarachnoid hemorrhage was 1.86 (range: 1.38-2.34).

Conclusions: Convexal subarachnoid hemorrhage is rare in the older population, occurring with an incidence of about 14 per 100,000 person years. Yet, when present, it may be associated with a high risk of future intracerebral hemorrhage.

Key Words: Convexal subarachnoid hemorrhage—convexity subarachnoid hemorrhage—cerebral amyloid angiopathy—apopolipoprotein-E (APOE) e2—amyloid PiB PET

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Introduction

Nontraumatic convexal subarachnoid hemorrhage (cSAH) represents 5% to 6% of all SAH and is most commonly caused by reversible cerebral vasoconstriction and cerebral amyloid angiopathy (CAA). After age 60, CAA is the most common cause of cSAH.[1-3] Individuals presenting with cSAH related to CAA have a high risk of future intracerebral hemorrhage (ICH).[4,5] Despite the clinical and prognostic significance of cSAH, studies to date have primarily been clinical series and the population incidence of cSAH remains unknown.

Cerebral amyloid angiopathy can have several clinical presentations, and these phenotypes have been associated with *APOE* genotype.[6-8] Both cSAH and cortical superficial siderosis (cSS), which is thought to be along the same continuum as cSAH,[9] have been associated with the *APOE* e2 allele.[5,10]

Recently, amyloid positron emission tomographic (PET) imaging has been shown to distinguish hypertensive ICH from ICH related to CAA,[11,12] and be positive in cSAH.[13] We hypothesized that cSAH would be associated with the *APOE* e2 allele and with increased amyloid deposition on PET in the general population.

The objectives of this study were to determine the incidence of cSAH in a population-based study and to compare the *APOE* genotype and amyloid PET scan findings of participants with and without cSAH.

Materials and Methods

Study Design

We performed a retrospective descriptive study. The Mayo Clinic Study of Aging (MCSA) is a population-based study of Olmsted County, MN, residents. Details on this study have been reported previously.[10,14-17] Between 11/29/2004 and 3/11/2017, 4462 MCSA participants (median age 75.2 years; range 60-91) without known hemorrhage had a baseline visit. We used the Rochester Epidemiology Project's medical records linkage system to identify MCSA participants who came to medical attention for intracerebral hemorrhage.[17] The hemorrhages were classified by hemorrhage type. The clinical images (MRI or CT) of participants with nontraumatic cSAH were reviewed (MY, CAF) and confirmed by a vascular neurologist (JG-R). Imaging characteristics, demographics, medications, presence of cSS or cerebral microbleeds, and ICH were recorded from the electronic medical record.

Participants without contraindication were invited to undergo imaging including MRI and Pittsburgh compound B (PiB) PET scans. PiB-PET findings were classified as PiB positive if the standardized uptake value ratio (SUVR) was greater than 1.42.[18] *APOE* genotype and PiB PET scans were reviewed if available.

The Mayo Clinic Institutional Review Board and the Olmsted Medical Center Institutional Review Board approved all study protocols. Written informed consent was obtained from all participants.

Statistical Analysis

Descriptive statistics were used to summarize participant characteristics. When comparing participants with and without cSAH, Kruskal–Wallis tests were performed for continuous measures whereas Fisher exact tests were performed for categorical measures. Incidence of cSAH was calculated directly by dividing the number of incidental cases by the sum of observation time (in years) for the entire cohort studied. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Among the 4462 MCSA participants without known hemorrhage at baseline, the cumulative follow-up for all MCSA participants was 28,436.0 years (ranging: 0.9 to 12.2 years, mean: 4.88, SD = 2.83). 1523 participants underwent amyloid-PET imaging and 4318 had *APOE* genotyping. Ten patients had nontraumatic SAH, 4 of whom had cSAH. Four had aneurysmal SAH and 2 had perimesencephalic SAH. The incidence of cSAH was estimated to be 14.1 cases per 100,000 person years of follow-up.

Clinical Presentation/Location of Hemorrhage

The median age at cSAH was 79 years (range: 71-84), and 3 of the 4 cSAHs occurred in women. Three of the 4 cSAH were symptomatic, with paresthesias and dysarthria being the most common symptoms. The fourth cSAH was found incidentally during a routine scan performed as part of the MCSA. The cSAH occurred 1, 3, 4, and 10 years after entry into the MCSA, respectively. All underwent MRI scans as part of their evaluation. Three cSAHs occurred in the right frontal lobe and one in the right parieto-occipital lobe. Two participants were on antithrombotic medications at the time of SAH detection: one on warfarin (INR 2.9) and one on aspirin 81 mg. Cerebral angiogram was performed in one patient and did not reveal a cause for cSAH. All 4 participants had follow-up imaging as part of the clinical work-up after their cSAH. Three cSAH participants who had follow-up MRI with hemosiderin-sensitive sequences were found to have cSS which had not been noted previously. The fourth participant with cSAH had follow-up MRI after the cSAH, but the scan did not include a hemosiderin-sensitive sequence available to evaluate for cSS. Two participants developed symptomatic lobar ICH which occurred 4 and 5.5 years after the cSAH, one of these 2 was on aspirin at that time. One of these 2 had new cerebral microbeeds first documented one year prior to the lobar ICH. No other participant with cSAH had cerebral microbleeds.

The APOE allele combinations of the 4 participants were 3/3, 3/3, 2/2, and 2/3. Half of participants with cSAH had an *APOE* e2 allele compared to 15.8% of participants without cSAH (P = .062). The incidence of cSAH in *APOE* e2 positive and negative participants was 45.0 and

8.5 per 100,000 person years, respectively. All 4 participants with cSAH had amyloid-PET imaging performed in the MCSA, and 2 of the 4 participants (50%) had elevated brain amyloid, compared to 38.4% of participants without cSAH (P = .64). On amyloid-PET imaging, the median SUVR for participants with cSAH was 1.86 (range: 1.38-2.34). Table 1 describes characteristics for participants with and without cSAH.

Discussion

The incidence of cSAH was 14.1 per 100,000 person years in the older general population (median age 75.2 years; range 60-91). Despite the low rate of occurrence, identification and recognition of cSAH has prognostic significance. Our findings were consistent with previous studies, suggesting that patients with cSAH are at increased risk for subsequent ICH—2 of the 4 participants with cSAH suffered a lobar ICH roughly 5 years after the cSAH.[5,9,19]

Additionally, the risk of ICH has been suggested to be increased in individuals with a history of cSAH independent of microbleed burden.[9] In our study, 1 of the 2 participants with subsequent ICH did not have preceding microbleeds. Three of the 4 participants with cSAH in our study were subsequently confirmed to have cSS supporting the concept that cSS and cSAH occur along a continuum.[9]

Previous work has suggested that the pattern of amyloid deposition in CAA may be related to *APOE* genotype and that different genotypes may correspond to different phenotypic presentations. CAA associated with cSAH may be related to an APOE e2 genotype, whereas cerebral microbleeds may be more associated with APOE e4.[19,20] The proportion of participants with APOE e2 allele in our study was greater among participants with cSAH (50%) than among the rest of the population (16%), although this difference cannot be interpreted with certainty due to the low number of participants with cSAH.

Half of participants with cSAH had abnormal amyloid-PET scans with a median SUVR of 1.86. This proportion with elevated brain amyloid was only slightly higher than in the overall cohort (38%). Amyloid-PET needs to be tested in a larger number of cSAH cases to determine whether this technique can be used for early recognition of CAA in patients with this presentation and whether the amyloid load might predict future risk of bleeding in these cases.

Our study has several limitations. The frequency of cSAH was low and consequently our study lacked the power to establish a definite relationship among cSAH, APOE genotype, and amyloid PET imaging results and to determine the frequency of future ICH among those with cSAH. Another potential limitation of the study is that some asymptomatic hemorrhages may have been missed if the patient did not undergo imaging after the hemorrhage, since the presentation can be transient sensorymotor symptoms, which may not prompt all individuals to seek care.[1,2]

Summary

cSAH is rare in the older general population, but its recognition is prognostically important as it may identify patients at a high future risk of lobar ICH. The association of cSAH in older patients with APOE e2 genotype and elevated amyloid on PET scan requires further investigation.

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Table 1. *Distribution of relevant variables in patients with and without cSAH*

Variable‡	No cSAH (n = 4458)	cSAH (n = 4)	Total (n = 4462)	*P* Value
Age	75.2 (70.7, 81.6)	73.4 (70.0, 78.2)	75.2 (70.7, 81.6)	.68†
Male	2267 (50.9%)	1 (25.0%)	2268 (50.8%)	.30*
Education, years	14 (12.0, 16.0)	14 (13.0, 14.5)	14 (12.00, 16.00)	.91†
Presence of APOE e2 allele	683 (15.8%)	2 (50.0%)	685 (15.9%)	.062*
Global PiB ratio	1.37 (1.31, 1.60)	1.86 (1.38, 2.34)	1.37 (1.31, 1.61)	.11†
PiB positive	584 (38.4%)	2 (50.0%)	586 (38.5%)	.64*

Abbreviations: APOE, apolipoprotein E; cSAH,convexity subarachnoid hemorrhage; PiB, Pittsburgh compound B.
*Fischer exact test.
†Kruskal Wallis.
‡Data are presented as n (%), except for age, education, and global PiB ratio, which are presented as median (Q1, Q3).Standardized uptake value ratio (SUVR) determined by voxel size–weighted average, gray matter + white matter sharpening, no partial volume correction, and cerebellar crus reference.Positive PiB defined as PiB ratio greater than 1.42; information unavailable in 171 participants with negative cSAH.

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References

1. Beitzke M, Gattringer T, Enzinger C, et al. Clinical presentation, etiology, and long-term prognosis in patients with nontraumatic convexal subarachnoid hemorrhage. Stroke 2011;42:3055-3060.
2. Khurram A, Kleinig T, Leyden J. Clinical associations and causes of convexity subarachnoid hemorrhage. Stroke 2014;45:1151-1153.
3. Kumar S, Goddeau Jr. RP, Selim MH, et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology 2010;74:893-899.
4. Graff-Radford J, Fugate JE, Klaas J, et al. Distinguishing clinical and radiological features of non-traumatic convexal subarachnoid hemorrhage. Eur J Neurol 2016;23:839-846.
5. Martinez-Lizana E, Carmona-Iragui M, Alcolea D, et al. Cerebral amyloid angiopathy-related atraumatic convexal subarachnoid hemorrhage: an ARIA before the tsunami. J Cereb Blood Flow Metab 2015;35:710-717.
6. Greenberg SM, Vonsattel JP, Segal AZ, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology 1998;50:961-965.
7. Biffi A, Anderson CD, Jagiella JM, et al. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol 2011;10:702-709.
8. Charidimou A, Martinez-Ramirez S, Shoamanesh A, et al. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. Neurology 2015;84:1206-1212.
9. Ni J, Auriel E, Jindal J, et al. The characteristics of superficial siderosis and convexity subarachnoid hemorrhage and clinical relevance in suspected cerebral amyloid angiopathy. Cerebrovasc Dis 2015;39:278-286.
10. Pichler M, Vemuri P, Rabinstein AA, et al. Prevalence and natural history of superficial siderosis: a population-based study. Stroke 2017;48:3210-3214.
11. Gurol ME, Becker JA, Fotiadis P, et al. Florbetapir-PET to diagnose cerebral amyloid angiopathy: a prospective study. Neurology 2016;87:2043-2049.
12. Gurol ME, Dierksen G, Betensky R, et al. Predicting sites of new hemorrhage with amyloid imaging in cerebral amyloid angiopathy. Neurology 2012;79:320-326.
13. Ly JV, Singhal S, Rowe CC, et al. Convexity subarachnoid hemorrhage with PiB positive pet scans: clinical features and prognosis. J Neuroimaging 2015;25:420-429.
14. Roberts RO, Geda YE, Knopman DS, et al. The mayo clinic study of aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology 2008;30:58-69.
15. Rocca WA, Yawn BP, St Sauver JL, et al. History of the Rochester epidemiology project: half a century of medical records linkage in a US population. Mayo Clin Proc 2012;87:1202-1213.
16. St Sauver JL, Grossardt BR, Leibson CL, et al. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester epidemiology project. Mayo Clin Proc 2012;87:151-160.
17. St Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. Am J Epidemiol 2011;173:1059-1068.
18. Jack Jr. CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement 2017;13:205-216.
19. Wilson D, Hostettler IC, Ambler G, et al. Convexity subarachnoid haemorrhage has a high risk of intracerebral haemorrhage in suspected cerebral amyloid angiopathy. J Neurol 2017;264:664-673.
20. Calviere L, Cuvinciuc V, Raposo N, et al. Acute convexity subarachnoid hemorrhage related to cerebral amyloid angiopathy: clinicoradiological features and outcome. J Stroke Cerebrovasc Dis 2016;25:1009-1016.