Published in final edited form as:

J Stroke Cerebrovasc Dis. 2005 ; 14(6): 267–271.

Perimesencephalic Subarachnoid Hemorrhage: Incidence, Risk Factors, and Outcome

Matthew L. Flaherty, MD, Mary Haverbusch, BSN, Brett Kissela, MD, Dawn Kleindorfer, MD, Alexander Schneider, MD, Padmini Sekar, MS, Charles J. Moomaw, PhD, Laura Sauerbeck, RN, MS, Joseph P. Broderick, MD, and Daniel Woo, MD

Departments of Neurology (M.L.F., M.H., B.K., D.K., A.S., C.J.M., L.S., J.P.B., D.W.) and Environment Health (P.S.), University of Cincinnati Medical Center.

Abstract

Background—Nonaneurysmal perimesencephalic subarachnoid hemorrhage (PMSAH) appears to have an etiology and natural history distinct from aneurysm rupture. Referral-based studies suggest that 15% of SAH patients have no discernable cause of bleeding, but the incidence of PMSAH is unknown. We describe the first population-based study of PMSAH and place it in the context of all non-traumatic SAH, with presentation of incidence rates, patient demographics, and clinical outcomes.

Methods—All patients age ≥ 18 hospitalized with first-ever, non-traumatic SAH in the Greater Cincinnati area were identified from 5/98–7/01 and 8/02–4/04. PMSAH was defined as hemorrhage restricted to the cisterns surrounding the brainstem and suprasellar cistern and a negative cerebral angiogram. Incidence rates were age, race, and sex adjusted to the 2000 US population.

Results—There were 431 SAHs identified. Cases in Asian-Americans (2) were excluded, leaving 429 SAHs for analysis. Of these patients, 77 did not have angiograms. Among remaining cases, 285 had aneurysm rupture, 43 had nonaneurysmal hemorrhage not of the PMSAH pattern, and 24 had PMSAH. The overall annual incidence rates for SAH and PMSAH were 8.7 (95% CI 7.9–9.5) and 0.5 (95% CI 0.3–0.7) per 100,000 persons age ≥ 18 . Patients with PMSAH were younger ($p = 0.018$) and less likely to be female ($p = 0.020$) or hypertensive ($p = 0.005$) than other SAH patients. There was one death among PMSAH patients during 14 months mean follow-up.

Conclusions—PMSAH represents approximately 5% of all SAH. Its risk factors and outcome differ from other forms of SAH.

Non-traumatic subarachnoid hemorrhage (SAH) has an estimated annual incidence of 6 cases per 100,000 persons in the United States, with higher rates in other parts of the world.^{1–4} Ruptured saccular aneurysms account for the majority of SAH and are often clinically devastating, with case fatality rates of 30–50%.^{3–5} Nonaneurysmal perimesencephalic subarachnoid hemorrhage (PMSAH) appears to have an etiology and natural history distinct from aneurysm rupture, with good clinical outcomes.^{6–8} The radiographic pattern of PMSAH is relatively distinct, with hemorrhage centered anterior to the midbrain or pons, with or without extension of blood around the brainstem, into the suprasellar cistern, or into the proximal Sylvian fissures.⁹ Referral-based studies suggest that approximately 15% of SAH patients have no discernable cause of bleeding but the incidence of PMSAH, its risk factors, and its

Corresponding Author: Matthew L. Flaherty, MD., 231 Albert Sabin Way, MSB Room 5161B, University of Cincinnati Medical Center, Cincinnati, OH, 45267-0525, Telephone (513) 558-6609. Fax (513) 558-4305. Email:matthew.flaherty@uc.edu.

Disclosures: Dr. Flaherty has received speaking honoraria from Boehringer Ingelheim; Dr. Kissela has received speaking honoraria from Boehringer Ingelheim and Sanofi/Bristol Myers Squibb. Dr. Broderick has received compensation as a consultant to Ono Pharmaceuticals and Novo Nordisk, has received speaking honoraria from Boehringer Ingelheim, and has received financial support for clinical research from EKOS corporation, AstraZeneca, and Genentech. The remaining authors have no disclosures.

epidemiologic relation to other forms of SAH are not well defined.^{7, 9–11} We present the first population-based study of PMSAH with goals of calculating PMSAH incidence rates, presenting PMSAH patient demographics, and placing PMSAH within the context of all non-traumatic SAH.

Methods

The Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) study is an ongoing, population-based study of SAH and intracerebral hemorrhage (ICH) in the Greater Cincinnati/Northern Kentucky (GCNK) region. The methodology of the GERFHS study has been previously described.^{12, 13} All patients ≥ 18 years of age who reside within a 50-mile radius of the University of Cincinnati and are admitted to one of 16 local hospitals with SAH or ICH are identified and their charts abstracted by a trained nurse. Study nurses currently maintain active surveillance (“hot pursuit”) at several hospitals which treat most SAH and ICH in the city by reviewing neurosurgery logs and patient rosters several times each week. They also screen primary and secondary ICD-9 codes (430–432 through 10/1999, 430–438.9 thereafter) at all regional hospitals. Study physicians review each abstracted file to determine whether or not it qualifies as a case. Among qualifying cases, a subset of patients are interviewed and enrolled in a case-control study which includes genetic analyses.

The present study includes all cases of SAH in persons age ≥ 18 occurring within the five metropolitan counties of the GCNK region from 5/98–7/01 and 8/02–4/04. The dates 8/01–7/02 were not included due to an interruption of study funding during that period. Residents of the five county GCNK region seek care almost exclusively at one of the sixteen participating metropolitan hospitals¹. Patients living within the 50-mile radius required by the GERFHS study but outside of the five counties of interest were excluded by zip code of residence. Traumatic SAH was excluded. SAH associated with vascular malformations or anticoagulation was included. PMSAH was defined as hemorrhage restricted to the cisterns surrounding the brainstem and suprasellar cistern (with scant blood allowed in the ventricles and proximal Sylvian fissures) and a negative cerebral angiogram.^{6, 9} For any case possibly consistent with PMSAH (ie excluding cases of cerebral convexity SAH or SAH with large intraventricular hemorrhage), CT or MRI films were personally reviewed by a study neurologist (M.L.F.).

For the calculation of incidence rates, the entire population age ≥ 18 of the five GCNK counties was considered at risk. Denominator age-, race- and sex-specific populations for each year were obtained from published census estimates.¹⁴ Population denominators from 2003 were used for the first four months of 2004. Overall incidence rates were age, race, and sex-adjusted to the 2000 United States population and are presented with 95% confidence intervals. To place our data in the context of other studies, SAH incidence for all ages was estimated using SAH cases ascertained among children < 18 during a comprehensive epidemiologic survey of all stroke subtypes in the GCNK region in 1999, and assuming a stable rate over five years. The methodology of this study was similar to a prior, published study in 1993.⁴ PMSAH is exceedingly rare among children, and so an incidence of zero was assumed for persons < 18 .¹⁵ Mortality following PMSAH was assessed via study records, the Social Security Death Index, and the Ohio and Kentucky death registers. Clinical and demographic characteristics of PMSAH patients were compared to all other SAH patients using Fisher’s exact test for categorical variables and Student’s t-test for continuous variables. Heavy drinking was defined as the consumption of > 2 alcoholic beverages per day; current smoking was defined as any smoking within the previous 6 months; the diagnoses of diabetes and hypertension were based upon chart review. The institutional review board for each participating hospital system approved the GERFHS study.

Results

There were 431 SAHs identified over 5 calendar years. Cases in Asian-Americans (2, both aneurysmal) were excluded, leaving 429 SAHs for analysis. Of these, 77 did not have angiograms. Among the remaining cases, 285 had aneurysm rupture, 43 had nonaneurysmal hemorrhage not of the PMSAH pattern, and 24 had PMSAH. In the group of SAH patients without an angiogram, 2 had hemorrhages possibly consistent with PMSAH by radiographic standards, but were not considered PMSAH for this analysis. A breakdown of SAH cases and corresponding incidence rates are presented in Table 1. The overall annual incidence rates for all SAH and for PMSAH were 8.7 (95% CI 7.9–9.5) and 0.5 (95% CI 0.3–0.7) cases per 100,000 persons age ≥ 18 . After extrapolating incidence rates of SAH among persons age < 18 from our prior epidemiologic studies, the incidence of all SAH fell to 6.6 (95% CI 6.0–7.3) cases per 100,000 persons. Assuming no cases of PMSAH among persons < 18 , its annual incidence fell to 0.4 (95% CI 0.2–0.5) cases per 100,000 persons. Patient demographics among SAH categories are presented in Table 2, while Table 3 compares the frequency of demographic characteristics among PMSAH patients and all other SAH patients. Compared to all other SAH patients, those with PMSAH were younger ($p = 0.018$) and less likely to be female ($p = 0.020$) or hypertensive ($p = 0.005$), with a trend toward less smoking ($p = 0.091$).

One death was recorded among PMSAH patients during a mean follow-up of 14 months. This occurred after a prolonged hospitalization in a woman with multiple medical comorbidities including end-stage renal failure and failed kidney and pancreatic transplants. During hospitalization she suffered several ischemic strokes unrelated to cerebral vasospasm.

Discussion

The concept of a benign, nonaneurysmal form of SAH with a distinct radiographic appearance was first crystallized by van Gijn and colleagues in 1985.¹⁶ Since that time multiple referral-based studies have confirmed that the outcome following PMSAH is good, with minimal risk of rebleeding.^{6, 7, 9, 16} Investigators originally believed that most hemorrhages in PMSAH were centered anterior to the midbrain. Improved imaging of the posterior fossa has demonstrated that in many cases hemorrhage is centered anterior to the pons, leading to a proposed alternative title of “pretruncal nonaneurysmal subarachnoid hemorrhage.”^{6, 17} A posterior variant of PMSAH with hemorrhage primarily in the quadrigeminal cistern has also been described.¹⁸ Because aneurysm rupture occasionally produces a PMSAH-like pattern of bleeding, diagnostic cerebral angiography continues to be recommended for these patients.⁹

The incidence of PMSAH has not been previously defined. Within our large, biracial population, the annual rate of PMSAH was 0.5 cases per 100,000 persons age ≥ 18 . This confirms that PMSAH is a rare condition, representing approximately 5% of all SAH. In the present cohort, PMSAH accounted for roughly 1/3 of non-aneurysmal SAH. The remaining cases of non-aneurysmal SAH were heterogeneous, including SAH caused by vascular malformations and vasculopathy, and were not confined to cases of SAH of unknown cause. Our estimated overall SAH incidence rate is consistent with other reports and suggests adequate case ascertainment.³

Prior epidemiologic studies have defined female sex, black race (in the United States), hypertension, smoking, heavy alcohol consumption, the presence of a first degree relative with SAH, and rare hereditary conditions such as autosomal dominant polycystic kidney disease as risk factors for SAH.^{3, 13} Two small case-control studies have attempted to identify risk factors for PMSAH.^{10, 11} Canhao and colleagues found that hypertension was more common among PMSAH patients than controls, but this finding was not substantiated by Kleinpeter and Lehr. When comparing PMSAH patients to their cohort of aneurysmal SAH patients, Kleinpeter and

Lehr found PMSAH patients were less likely to be hypertensive, while there was a trend toward more females in the aneurysm group.¹¹ In our cohort, PMSAH patients were younger and less likely to be female or hypertensive than other SAH patients, with a trend toward fewer smokers among the PMSAH group.

The excess risk of aneurysmal SAH among women has not been explained, and was not seen in our PMSAH patients. Our study and its investigation of PMSAH risk factors is limited by small numbers, despite case ascertainment in a metropolitan area of 1.3 million over 5 years. For this reason we did not undertake a regression analysis when comparing PMSAH and “other” SAH cases. Nonetheless, the variations documented suggest fundamental differences in the risk factor profile and etiology of PMSAH and aneurysmal SAH. Because PMSAH usually causes severe headache, most patients present for urgent medical attention. However, patients not presenting to a hospital would likely have been missed, and our incidence rates may therefore underestimate the true frequency of PMSAH. The cause of PMSAH remains unknown, although a venous source is possible.¹⁹ The good outcome of our PMSAH cases, with only one death (in a patient with multiple medical comorbidities), is in keeping with previous reports.

Acknowledgements

Supported in part by NINDS (R-01-NS 36695)

References

1. Broderick J, Brott T, Tomsick T, et al. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *NEJM* 1992;326:733–736. [PubMed: 1738378]
2. Linn FHH, Rinkel GJE, Algra A, et al. Incidence of subarachnoid hemorrhage. *Stroke* 1996;27:625–629. [PubMed: 8614919]
3. van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: Diagnosis, causes, and management. *Brain* 2001;124:249–278. [PubMed: 11157554]
4. Kissela B, Schneider A, Kleindorfer D, et al. Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke* 2004;35:426–431. [PubMed: 14757893]
5. Brown RD Jr, Whisnant JP, Sicks JD, et al. Stroke incidence, prevalence, and survival: Secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373–380. [PubMed: 8610298]
6. Wijdicks EFM, Schievink WI, Miller GM. Pretruncal nonaneurysmal subarachnoid hemorrhage. *Mayo Clin Proc* 1998;73:745–752. [PubMed: 9703300]
7. Rinkel GJE, Wijdicks EFM, Hasan D, et al. Outcome in patients with subarachnoid haemorrhage and negative angiography according to pattern of haemorrhage on computed tomography. *Lancet* 1991;338:964–968. [PubMed: 1681340]
8. Van Calenbergh F, Plets C, Goffin J, et al. Nonaneurysmal subarachnoid hemorrhage: Prevalence of perimesencephalic hemorrhage in a consecutive series. *Surg Neurol* 1993;39:320–323. [PubMed: 8488453]
9. Schwartz TH, Solomon RA. Perimesencephalic nonaneurysmal subarachnoid hemorrhage: Review of the literature. *Neurosurgery* 1996;39:433–440. [PubMed: 8875472]
10. Canhao P, Falcao F, Pinho e Melo T, et al. Vascular risk factors for perimesencephalic nonaneurysmal subarachnoid hemorrhage. *J Neurol* 1999;246:492–496. [PubMed: 10431777]
11. Kleinpeter G, Lehr S. Characterization of risk factor differences in perimesencephalic subarachnoid hemorrhage. *Minim Invas Neurosurg* 2003;46:142–148.
12. Woo D, Sauerbeck LR, Kissela BM, et al. Genetic and environmental risk factors for intracerebral hemorrhage: Preliminary results of a population-based study. *Stroke* 2002;33:1190–1196. [PubMed: 11988589]
13. Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: A preventable disease with a heritable component. *Stroke* 2002;33:1321–1326. [PubMed: 11988610]

14. www.census.gov County population figures were accessed at <http://www.census.gov/popest/datasets.html#mrd>, while national figures were accessed at http://factfinder.census.gov/home/saff/main.html?_lang=en
15. Anderson RC, Baskin J, Feldstein NA. Perimesencephalic nonaneurysmal subarachnoid hemorrhage in the pediatric population: Case report and review of the literature. *Pediatr Neurosurg* 2002;37:258–261. [PubMed: 12411718]
16. van Gijn J, van Dongen KJ, Vermeulen M, et al. Perimesencephalic hemorrhage: A nonaneurysmal and benign form of subarachnoid hemorrhage. *Neurology* 1985;35:493–497. [PubMed: 3982634]
17. Schievink WI, Wijdicks EFM. Pretruncal subarachnoid hemorrhage: An anatomically correct description of the perimesencephalic subarachnoid hemorrhage [letter]. *Stroke* 1997;28:2572. [PubMed: 9412654]
18. Schwartz TH, Mayer SA. Quadrigeminal variant of perimesencephalic nonaneurysmal subarachnoid hemorrhage. *Neurosurgery* 2000;46:584–588. [PubMed: 10719854]
19. van der Schaaf IC, Velthuis BK, Gouw A, et al. Venous drainage in perimesencephalic hemorrhage. *Stroke* 2004;35:1614–1618. [PubMed: 15166390]

Table 1

Subarachnoid hemorrhage incidence rates.

	All SAH Cases	SAH Incidence* (95% CI)	PMSAH Cases	PMSAH Incidence* (95% CI)
Total	429	8.7 (7.9–9.5)	24	0.5 (0.3–0.7)
Black	105	14.8 (12.0–17.7)	5	0.7 (0.1–1.4)
White	324	7.8 (6.9–8.6)	19	0.5 (0.3–0.7)
Men	121	5.4 (4.4–6.4)	12	0.5 (0.2–0.8)
Women	308	11.5 (10.2–12.8)	12	0.5 (0.2–0.8)

* For persons age ≥ 18 , age, race, and sex adjusted to the 2000 US population as appropriate.

Table 2

SAH patient demographics.*

	All SAH	SAH, no angiogram	SAH, aneurysmal [†]	SAH, non-aneurysmal, not PMSAH [†]	PMSAH [†]
Total (%)	429	77 (18)	285 (67)	43 (10)	24 (6)
Age, mean	54.3	66.3	52.0	50.4	49.0
(range)	(20–92)	(22–91)	(22–91)	(20–92)	(28–67)
Women	308 (72)	55 (72)	212 (74)	29 (67)	12 (50)
White	324 (76)	63 (82)	211 (74)	31 (72)	19 (79)
Hypertensive	189 (44)	42 (55)	128 (45)	15 (35)	4 (17)
Current smoker	181 (42)	17 (22)	140 (49)	18 (42)	6 (25)
Warfarin use	11 (3)	5 (7)	4 (1)	2 (5)	0 (0)
Heavy drinker	28 (7)	2 (3)	25 (9)	1 (2)	0 (0)

* Percentages rounded to the nearest whole digit. Due to missing data, not all denominators within a given category are equal.

[†] With cerebral angiogram.

SAH = subarachnoid hemorrhage

PMSAH = perimesencephalic subarachnoid hemorrhage

Table 3
Comparison of PMSAH cases and all other SAH cases.*

Variable (%)	PMSAH	All other SAH	p-value
Total cases	24	405	
Age, mean	49.0	54.6	0.018
Female sex	12 (50)	296 (73)	0.020
White race	19 (79)	305 (75)	0.810
Hypertensive	4 (18)	185 (46)	0.005
Current smoker	6 (25)	175 (43)	0.091
Diabetes	3 (14)	36 (9)	0.470
Heavy drinker	0 (0)	28 (7)	0.393
Warfarin use	0 (0)	11 (3)	1.000

* Percentages rounded to the nearest whole number. Because of missing data not all denominators within a given category are equal.

SAH = subarachnoid hemorrhage

PMSAH = perimesencephalic subarachnoid hemorrhage