Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage

Renee D. Bailey, MD; Robert G. Hart, MD; Oscar Benavente, MD; and Lesly A. Pearce, MS

Article abstract—*Objective:* To characterize the rates of recurrent intracranial hemorrhage (ICH), ischemic stroke, and death in survivors of primary ICH. *Methods:* Systematic review of studies reporting recurrent stroke in survivors of primary ICH, identified at index ICH and followed forward. Studies were identified by computerized search of the literature and review of reference lists. *Results:* Ten studies published between 1982 and 2000 reporting 1,880 survivors of ICH, followed for a total of 6,326 patient-years (mean follow-up, 3.4 patient-years), were included. The aggregate rate of all stroke from five studies was 4.3% per patient-year (95% CI, 3.5% to 5.4%). The rate in the three population-based studies was higher than in the two hospital-based studies, 6.2% versus 4.0% per patient-year ($p = 0.04$). About three fourths of recurrent strokes were ICH. Considering all 10 studies, a total of 147 patients had a recurrent ICH, an aggregate rate of 2.3% per patient-year (95% CI, 1.9% to 2.7%). Based on data from four studies, patients with a primary lobar ICH had a higher rate of recurrent ICH than those with a deep, hemispheric ICH (4.4% versus 2.1% per patient-year; $p = 0.002$). The aggregate rates of subsequent ischemic stroke and mortality were 1.1% per patient-year (95% CI, 0.8% to 1.7%) and 8.8% per patient-year (95% CI, 5.2% to 11.0%). *Conclusions:* Recurrent stroke among survivors of primary ICH occurs at a rate of about 4% per patient-year, and most are recurrent ICH. Survivors of ICH have a higher risk of recurrent ICH than of ischemic stroke, and this has implications for the use of antithrombotic agents in these patients.

NEUROLOGY 2001;56:773–777

Intracranial hemorrhage (ICH) accounts for 10% to 15% of all strokes and carries substantial associated mortality and often permanent disability for those affected.[1] For the estimated 50,000 Americans who survive ICH each year, the risk of recurrent stroke and death are unclear. We undertook a systematic review of this issue, seeking to characterize the occurrence of recurrent ICH, ischemic stroke and death among survivors of primary ICH, as well as to identify predictors of recurrent stroke. We hypothesized a priori that recurrence of ICH would be infrequent and that subsequent stroke more often would be ischemic than hemorrhagic.

Methods. *Types of studies.* Studies of patients identified at the time of a primary ICH, followed longitudinally, and evaluated for recurrent stroke were considered for inclusion. Minimum average follow-up required for a study to be included was 3 months.

Types of participants. We included studies of patients of any age or gender surviving a primary ICH for at least 30 days. When possible, the studies confirmed ICH by CT or MRI and excluded those due to vascular malformation, coagulopathy, trauma, or neoplasm.

Types of interventions. There were no restrictions as to the type of intervention.

Types of outcome measures. The primary outcomes evaluated were recurrent intracranial hemorrhage (any hemorrhage confirmed by CT, MRI, or autopsy and excluding those related to vascular malformation, coagulopathy, trauma, or neoplasm), ischemic stroke (evaluated by CT, MRI, or autopsy), all stroke (ICH, ischemic, plus those of unknown type), and death. Outcomes (except death) in patients with ICH who survived 30 days were counted from the time of the index hemorrhage whenever possible.

Search strategy for identification of studies. Studies following the natural history after primary ICH and published in any language were identified using an electronic search of MEDLINE from 1 January 1966 to 31 January 2000. *Intracranial hemorrhage* and *hypertension* were the primary keywords and textwords employed. Following the electronic searches, the reference lists of the articles collected were reviewed. Contact with other authors in the field was made in order to identify additional studies.

Methods of the review. Selection of studies and data collection. The results of the searches were evaluated and data abstracted by two reviewers (R.D.B. and R.G.H.), and then crosschecked; disagreements were resolved by consensus. Extracted information included age, gender, coexistent vascular disease and vascular risk factors, mean follow-up, use of antithrombotic therapy, ethnicity, outcomes of hemorrhagic and ischemic stroke, and death.

Assessment of methodological quality. Two reviewers evaluated the methodological quality of each selected

From the Department of Medicine (Neurology) (Drs. Bailey, Hart, and Benavente), University of Texas Health Science Center, San Antonio, TX, and the Axioresearch Corporation (L.A. Pearce), Seattle, WA.

Received September 8, 2000. Accepted in final form November 21, 2000.

Address correspondence and reprint requests to Dr. Renee D. Bailey, Department of Medicine (Neurology), University of Texas Health Science Center, 7703 Floyd Curl Dr, MSN 7883, San Antonio, TX 78229-3900; e-mail: baileyr@uthscsa.edu

Table 1 *Description of included studies*

Location	Year	Participants, n	Quality score*	Mean age, y	Men, %	CT/MRI confirmed, %	Hypertension, %
Population-based studies							
Australia[2]	1998	36	ad	—	—	—	—
United Kingdom[3]	1995	32	ade	69	—	78	—
Finland[4]	1992	78	abcd	—	49	100	46
Hospital-based studies							
Canada[5]	2000	172	ab	62	56	—	56
South Korea[6]	1999	670	abc	—	40	100	61
Mexico[7]	1998	359	abc	—	—	—	—
Portugal[8]	1997	302	d	—	—	—	—
Siena, Italy[9]	1995	112	abcde	64	65	100	62
Rome, Italy[10]	1988	77	abcde	62	54	100	41
United States[11]	1982	42	abcd	—	69	100	>80

* Quality scores a through e defined in text.

study, including type of population enrolled, definition of outcomes, duration and frequency of follow-up, and number of patients lost to follow-up. The design and execution of each study were independently rated according to five criteria below by two of the authors. If information was not provided to allow a criterion to be assessed, it was assumed not met. The criteria were a cohort of unselected survivors of ICH, identified at the time of their index ICH and followed forward (a); exclusion of patients with secondary causes of ICH, such as arteriovenous malformations, aneurysms, trauma, tumor, anticoagulant use, or bleeding disorders (b); confirmation of the index ICH by neuroimaging in >80% of study patients (c); follow-up of >90% of study patients until death or end of the study (d); and neuroimaging or autopsy in >80% of study patients with subsequent strokes (e) (table 1).

For the purposes of this review, studies were considered "high quality" if they met at least four of the five criteria.

Statistical methods. Total patient follow-up for each individual study was calculated from the mean patient exposure or, if not provided, from the event rates and number of events reported. Comparison of the relative frequency of hemorrhagic versus ischemic stroke was restricted to studies reporting both outcomes.

Annualized event rates (events per person-years of observation) for individual trials were computed using a Poisson regression model, with a value of 0.5 events assumed when no relevant events were reported. An aggregate event rate across trials was then computed by taking the anti-ln of the average model coefficient (weighted by relative number of patient-years of observation). The estimated variance for the aggregate event rate coefficient estimate was calculated as the inverse of the total number of events observed. Event rates were compared between groups using a Poisson regression model. Significance was accepted at the 0.05 level and all tests were two-sided.

Results. Of 109 studies reviewed, 10 published between 1982 and 2000 met our criteria for inclusion in these analyses (see table 1). An additional study that included only patients with lobar ICH is considered separately below.[12] The most common reasons for exclusion were that the study involved retrospective chart review, did not report ICH recurrences, or did not follow patients for longer than 30 days. The studies involved follow-up of 1,880 survivors of ICH. The weighted mean quality score for the studies was 3.0 (range, 1 to 5). Three studies were population-based (146 participants), while the remainder were hospital-based (1,734 participants). Five studies were from Europe (601 participants, 32%), with one each from Korea (n = 670, 36%), Australia (n = 36, 2%), Mexico (n = 359, 19%), Canada (n = 172, 9%), and the United States (n = 42, 2%).

Patient features of survivors of ICH often were not provided. Based on four studies, the mean age was about 65 years, about half of the patients were men, and about two-thirds had hypertension.[3,5,9,10] No studies reported the frequency of antiplatelet therapy or its relationship to stroke recurrence. In two studies, the cohort was restricted to those with first-ever strokes.[2,3]

These 10 studies included 1,880 survivors of ICH (range in individual studies, 32 to 670) followed for about 6,326 patient-years (range, 77 to 2,092), for a mean follow-up of 3.4 years per patient (range, 1.0 to 7.0) (table 2).

All strokes. Five studies involving a total of 561 patients followed their participants for the endpoint of all strokes.[2-4,8,9] A total of 82 patients had a recurrent stroke during a mean follow-up period of 3.2 patient-years, an aggregate rate of 4.3% per patient-year (95% CI, 3.5% to 5.4%). The aggregate rate from the three population-based studies (6.2% per patient-year) was higher than from the two hospital-based studies (4.0% per patient-year; $p = 0.04$; rate ratio = 1.6).

Ratio of recurrent ICH to ischemic stroke. Of the 82 first recurrent strokes observed in these five studies, 69 were confirmed as hemorrhagic or ischemic by CT or autopsy, and 13 were categorized as unknown. Excluding strokes of unknown type and weighting studies by relative amount of exposure-years, the aggregate ratio of recurrent ICH to ischemic stroke during follow-up was 2.9:1. The ratio was lower in population-based studies compared with hospital-based studies (1.1:1 versus 3.4:1; χ^2 test, $p = 0.04$).

Table 2 *Outcomes of included studies**

Location	Participants, n	Total follow-up, y	All stroke, n	Hemorrhagic stroke, n	Ischemic stroke, n	Deaths, n
Australia[2]	36	140	10	3 (+3)*	3 (+1)	—
United Kingdom[3]	32	100	8	2 (+3)	2 (+1)	11
Finland[4]	78	211	11	6	5	23
Canada[5]	172	654	—	15	—	—
South Korea[6]	670	2092	—	53	—	—
Mexico[7]	359	1616	—	31	—	—
Portugal[8]	302	550	21	11 (+4)	5 (+1)	—
Siena, Italy[9]	112	784	32	26	6	—
Rome, Italy[10]	77	77	—	0	—	4
United States[11]	42	102	—	0	—	7
Aggregate	1880	6326	—	147 (+10)	—	—

* Unknown strokes are reported in parentheses, where three fourths of unknown strokes are considered hemorrhagic and one fourth ischemic, based on the weighted ratio.

Recurrent intracranial hemorrhage. Based on results from all 10 studies, 147 patients had a confirmed recurrent ICH during a mean follow-up of 3.4 years. Excluding results from three studies in which the total 13 strokes of an unknown type occurred, the aggregate rate of recurrent ICH was 2.3% per patient-year (95% CI, 1.9% to 2.7%).[2,3,8] Including all studies and assuming that three fourths of 13 unknown strokes were ICH (n = 10), the aggregate rate of recurrent ICH was similar at 2.4% per patient-year (95% CI, 2.0% to 2.8%).

Continuing to consider three fourths of unknown strokes as ICH, the aggregate rate of recurrent ICH in the three population-based studies was 3.7% per patient-year, (95% CI, 2.3% to 5.9%) compared with 2.3% (95% CI, 2.0% to 2.8%) in the hospital-based studies ($p = 0.1$; rate ratio 1.6). Recurrent ICH was 2.3% per patient-year (95% CI, 1.7% to 3.3%) for the four highest-rated studies, compared with 2.4% per patient-year in the remainder (95% CI, 2.0% to 2.8%). The aggregate rate of recurrent ICH from the five European studies was 2.9% per patient-year (95% CI, 2.2% to 3.9%).

Three studies provided information about the rate of recurrent stroke over time, but the results were difficult to interpret.[3,6,9] The rate of recurrent ICH was higher during the initial year following the index ICH in one study.[9]

Ischemic stroke. Again considering only the five studies that followed patients for all strokes, a total of 21 confirmed ischemic strokes occurred. Counting these plus one fourth of the unknown strokes in these studies as ischemic (n = 3), the aggregate rate was 1.1% per patient-year (95% CI, 0.8% to 1.7%) during a mean follow-up of 3.2 years per patient.

Deaths. Four studies involving 229 survivors of ICH reported late mortality rates (30 days or more after the index ICH).[3,4,10,11] Aggregate mortality rate was 8.8% per patient-year (95% CI, 6.6% to 11.8%) during a mean follow-up of 2.1 years per patient. In each study and in aggregate, deaths (n = 45) exceeded recurrent stroke (n = 19).

Predictors of recurrent ICH. Patient features associated with recurrent ICH were assessed in two studies.[3,7] No trends relating recurrence to age or gender were apparent. Diabetes was associated with recurrent ICH by univariate analysis in one study.[2]

Lobar location of the index ICH appeared to confer a higher risk of recurrent ICH compared with deep, hemispheric ICH (table 3; rate ratio 2.2; $p = 0.002$) based on data from four studies.[6,8,9,11] The aggregate rate of recurrent ICH in the 192 patients with initial lobar ICH was 4.4% per patient-year (95% CI, 3.1% to 6.3%) versus 2.1% per patient-year (95% CI, 1.6% to 2.7%) among the 823 patients whose index event was a deep, hemispheric ICH.

Table 3 *Site of initial bleed versus recurrent ICH*

Location	Participants, n	Total follow-up, y	Recurrent ICH, n (% per patient–year)
Lobar ICH			
South Korea[6]	77	235	10 (4.3)
Portugal[8]	60	109	4 (3.7)
Siena, Italy[9]	42	294	16 (5.4)
Jackson, MS, USA[11]	13	31	0 (0.0)
Boston, MA, USA[12]	71	141	19 (13.5)
Aggregate	263	810	49*
Deep hemispheric ICH			
South Korea[6]	493	1541	37 (2.4)
Portugal[8]	242	441	7 (1.6)
Siena, Italy[9]	61	427	8 (1.9)
Jackson, MS, USA[11]	27	65	0 (0.0)
Aggregate	823	2474	52 (2.1)†

* Including all five studies: 5.4% (95% CI, 4.1–7.1); excluding Boston[12]: 4.4% (95% CI, 3.1–6.3).
† 95% CI 1.6–2.1.

ICH = intracranial hemorrhage.

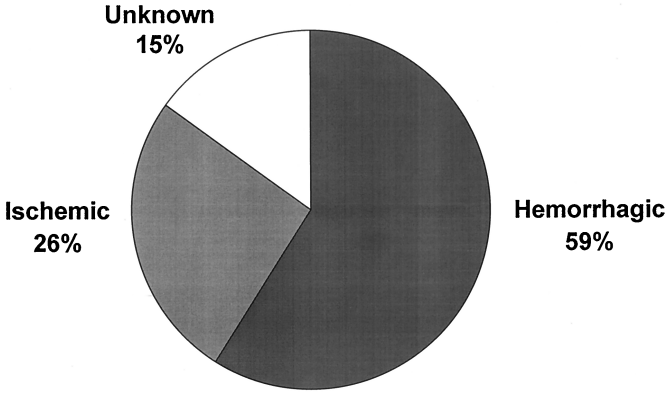

Figure. Distribution of stroke recurrence (as raw percentages) among the survivors of primary intracranial hemorrhage in five studies.[2-4,8,9]

When data from an additional trial that was restricted to survivors of primary lobar ICH were added to the analysis, the rate of ICH recurrence in patients surviving primary lobar ICH was 5.4% per patient-year (95% CI, 4.1% to 7.1%).[12] Apolipoprotein ε genotype was independently associated with the risk of recurrent ICH among those with lobar hemorrhage in one study.

Discussion. From systematic review of the available data, particularly the studies with additional data on ischemic stroke and death, recurrent ICH is not rare and occurs at twice the rate of ischemic stroke in survivors of primary ICH (figure). This result challenges the paradigm that small artery disease, likely related to hypertension, is the common precursor for both ischemic and hemorrhagic stroke. The prominently accelerated rate of recurrent ICH and the relatively low rate of subsequent ischemic stroke suggest that vascular mechanisms are different between these stroke subtypes.

The aggregate rates of all stroke was higher in the population-based studies than in the hospital-based studies, likely due to a higher rate of recurrent ICH rather than ischemic stroke. Possible explanations include different patient characteristics or possibly more complete follow-up in the population-based studies. More information about the study patients than is available from the publications is needed to investigate these possibilities.

Several studies, including case-control studies ineligible for inclusion in this analysis, suggest that lobar hemorrhages have a higher risk for recurrent hemorrhage, which is also usually lobar.[13,14] In patients in whom the site of primary ICH was lobar, the rate of recurrent ICH was twice as great as for those with a primary deep, hemispheric ICH. The ratio of recurrent ICH versus recurrent ischemic stroke may be different for survivors of lobar ICH versus deep, hemispheric ICH, but available data were inadequate to assess this directly.

Some studies attempted to restrict analysis to hypertension-associated ICH. One study reported a cohort restricted to hypertensive ICH, but inclusion criteria included blood pressure measured after hospital admission for ICH. This study also reported 10% lobar hemorrhages, but did not provide data about additional, excluded patients with lobar ICH who did not meet criteria for hypertension. This series did not appear to represent purely hypertension-related ICH, but rather primary ICH, much like the other studies.[6] Another study attempted to exclude ICH not associated with hypertension, but this exclusion was not clearly defined, as the authors did not provide data on the number of patients with primary ICH who failed to meet criteria for hypertension and were excluded from the study. In addition, relatively short follow-up and a small patient population make difficult any determination as to whether the lack of observed recurrence reflected a real difference between hypertension-related ICH and the play of chance.[11] An additional study did not report the relationship between hypertension and lobar or nonlobar hemorrhage, neither at index event nor with recurrence. However, these authors also conclude that lobar ICH is more likely to recur.[9] Overall, these studies do seem to suggest an association between index lobar ICH and recurrent lobar ICH.

This systematic review demonstrates the limitations of currently available data and the need for further research, pertinent to the management of hundreds of thousands of survivors of ICH. Among the studies included in this analysis, the data are based on clinically diagnosed, symptomatic strokes during follow-up. Lacunar infarcts occurring during follow-up are less likely to be identified than recurrent ICH. For this reason minor ischemic strokes and ICH may have been underdetected, and hence the rates of occurrence may be underestimated. Better data about the timing and severity of recurrent vascular events, influence of hypertension control, use of antiplatelet agents, and identification of high-risk subgroups are needed. Available studies of recurrent stroke in survivors of primary ICH suggest that recurrent ICH occurs more frequently than ischemic stroke, that ICH recurs at a rate of about 2.4% per year, and that those with lobar hemorrhage may be at higher risk.

References

1. Thrift A, Donnan G, McNeil J. Epidemiology of intracerebral hemorrhage. Epidemiol Rev 1995;17:361–381.
2. Hankey G, Jamorozik K, Broadhurst R, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke 1998;29:2491–2500.
3. Counsell C, Boonyakarnkul S, Dennis M, et al. Primary intracerebral haemorrhage in the Oxfordshire Community Stroke Project. Cerebrovasc Dis 1995;5:26–34.
4. Fogelholm R, Nuutila M, Vuorela A-L. Primary intracerebral haemorrhage in the Jyväskylä region, Central Finland, 1985–89: incidence, case fatality rate, and functional outcome. J Neurol Neurosurg Psychiatry 1992;55:546–552.
5. Hill M, Silver F, Austin P, Tu J. Rate of stroke recurrence in patients with primary intracerebral hemorrhage. Stroke 2000; 31:123–127.
6. Bae H, Jeong D, Doh J, et al. Recurrence of bleeding in patients with hypertensive intracerebral hemorrhage. Cerebrovasc Dis 1999;9:102–108.

7. González-Duarte A, Cantú C, Ruíz-Sandoval J, Barinagarrementeria F. Recurrent primary cerebral hemorrhage. Stroke 1998;29:1802–1805.
8. Melo T, Guerreiro S, Pinto A, et al. Recurrence of stroke in patients with spontaneous intracranial hemorrhage. Cerebrovasc Dis 1997;7(suppl 4):3.
9. Passero S, Burgalassi L, D'Andrea P, et al. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke 1995;26:1189–1192.
10. Fieschi C, Carolei A, Fiorelli M, et al. Changing prognosis of primary intracerebral hemorrhage: results of a clinical and computed tomographic follow-up study of 104 patients. Stroke 1988;19:192–195.
11. Douglas M, Haerer A. Long-term prognosis of hypertensive intracerebral hemorrhage. Stroke 1982;13:488–491.
12. O'Donnell H, Rosand J, Knudsen K, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000;342:240–245.
13. Neau J-P, Ingrand P, Couderq C, et al. Recurrent intracerebral hemorrhage. Neurology 1997;49:106–113.
14. Lee KS, Bae HG, Yun IG. Recurrent intracerebral hemorrhage due to hypertension. Neurosurgery 1990;26:586–590.

Neuro*Images*

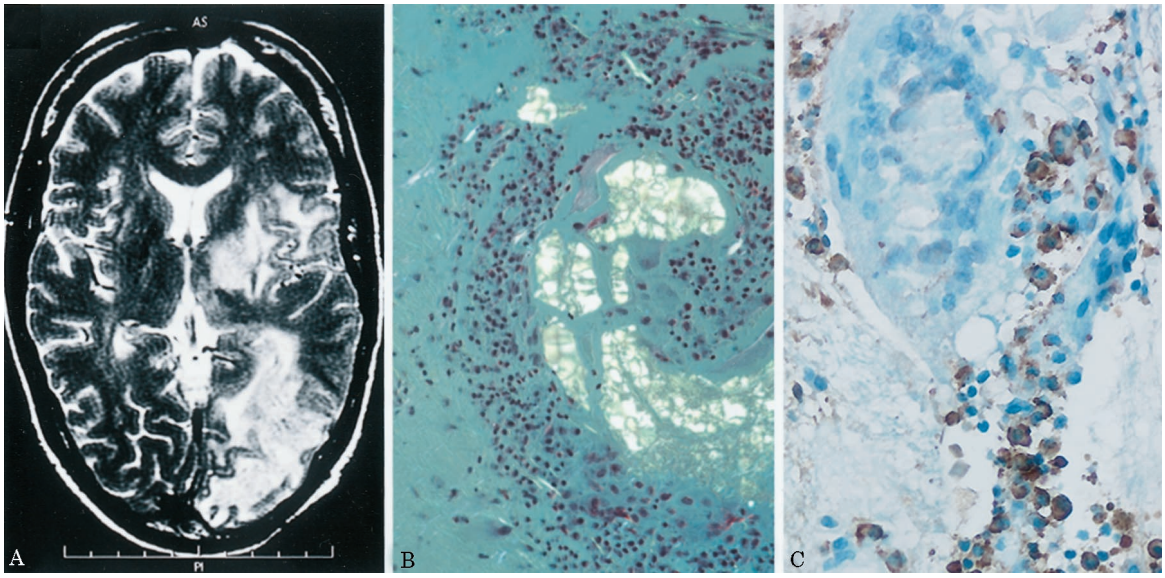

Figure. (A) T2-weighted MRI at first admission. (B) Brain biopsy reveals amyloid deposition in the white matter surrounded by lymphocytes, plasma cells, epithelioid cells, and multinucleated giant cells. Apple green birefringence of amyloid upon polarization, Congo red stain. (C) Immunohistochemical stain for lambda light chains shows high content of lambda light chain expressing plasma cells (brown reaction product), but no immunoreactivity of the amyloid.

Primary cerebral amyloidoma

Thomas Blattler, MD, Adrian M. Siegel, MD, Wolfram Jochum, MD, Adriano Aguzzi, MD, Klaus Hess, MD, Zürich, Switzerland

A 26-year-old-woman was admitted to our hospital because of paresis of her right hand and dysarthria. MRI showed large contrast enhancing white matter lesions in the parieto-occipital region and in the corona radiata of the left and several small lesions in the right hemisphere (figure, A). CSF analysis showed normal cell count and protein, and oligoclonal bands. Results of routine laboratory testing and thoracic x-ray were normal. Stereotactic brain biopsy revealed lymphocytic and plasma cellular infiltrates around small vessels and diffuse deposition of amorphous material in the white matter. The material was stained with Congo red and surrounded by epithelioid cells and a few multinucleated giant cells (figure, B). Three-fourths of the plasma cells expressed lambda light chains, and one-fourth kappa light chains. Immunohistochemically, the amyloid could not be further characterized (figure, C). The diagnosis of cerebral amyloidoma was made.[1-2] There was no evidence of plasmacytoma, multiple myeloma, or systemic amyloidosis.

Five years later, the patient was readmitted because of a seizure. The paresis of her right hand had progressed to mild hemiparesis and dysarthria was more pronounced. MRI showed slight enlargement of the lesions and patchy calcification. Again, there was no evidence of systemic disease.

1. Eriksson L, Sletten K, Benson L, Westermark P. Tumor-like localized amyloid of the brain is derived from immunoglobulin light chain. Scand J Immunol 1993;37:623–626.
2. Vidal RG, Ghiso J, Gallo G, Cohen M, Gambetti PL, Frangione B. Amyloidoma of the CNS II. Immunohistochemical and biochemical study. Neurology 1992;42:2024–2028.

Primary cerebral amyloidoma

Thomas Blattler, Adrian M. Siegel, Wolfram Jochum, et al.

Neurology 2001;56;777
DOI 10.1212/WNL.56.6.777