Familial Subarachnoid Hemorrhage: Distinctive Features and Patterns of Inheritance

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To delineate the distinctive features of familial subarachnoid hemorrhage, we compared gender and age at the time of subarachnoid hemorrhage, as well as site and number of aneurysms, in patients with familial subarachnoid hemorrhage (at least 1 first-degree relative with subarachnoid hemorrhage) and patients with sporadic subarachnoid hemorrhage (no subarachnoid hemorrhage in first- or second-degree relatives), in a prospective, hospital-based series of patients. In addition we studied the pattern of inheritance in 17 families with familial subarachnoid hemorrhage. Mean age at the time of hemorrhage in patients with the familial form was 6.8 years lower than that in those with the sporadic form, and middle cerebral artery aneurysms occurred more often in patients with familial disease. Sex distribution and number of aneurysms were similar in the two groups. Inheritance was compatible with autosomal dominant transmission in some families, and with autosomal recessive or multifactorial transmission in others. In our 5 families as well as in all 18 previously reported families with two affected generations, the age at the time of subarachnoid hemorrhage was invariably lower in later generations, which is suggestive of anticipation. We conclude that familial subarachnoid hemorrhage is a separate entity with occurrence at a young age, predilection for aneurysms of the middle cerebral artery, and variable modes of inheritance, including autosomal dominant inheritance with possible anticipation.

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The existence of familial subarachnoid hemorrhage (familial SAH) as a separate entity has been postulated on the basis of numerous case reports and a few retrospective studies [1–3]. In these reports familial SAH is loosely defined as the occurrence of SAH in 2 or more relatives, irrespective of the degree of kin [1]. Moreover, with the exception of two retrospective studies [3, 4], clinical characteristics have always been compared with those of series of patients with SAH from which familial SAH patients were not excluded, though these comprise 5 to 10% of all cases [3–5]. The imprecise definition and the presence of familial SAH patients in the control groups may have obscured differences between familial and sporadic SAH. A difference in the biological features is, however, suggested by our recent finding that familial SAH carries a worse prognosis than does sporadic SAH [6]. The concept of familial SAH may be further clarified by determination of genetic features such as the pattern of inheritance.

To assess whether familial SAH is characterized in ways other than by familial clustering alone, we conducted a prospective study to compare biological features (age at onset, sex distribution, number and location of aneurysms) of patients with familial SAH, defined as SAH in at least 2 first-degree relatives, with those of patients with sporadic SAH. To determine the mode of inheritance we studied the pattern of inheritance and the ages at the time of SAH in families with familial SAH.

Materials and Methods

From September 1991 to October 1992 we prospectively collected a series of 148 patients with computed tomography (CT)–proved SAH admitted to three centers: the Academic Medical Centre in Amsterdam, and the University hospitals of Rotterdam and Utrecht. In the same period 65 other patients with SAH were admitted and excluded for the following reasons: 15 patients because they had perimesencephalic, nonaneurysmal hemorrhage; 3 patients because a cause other than a ruptured aneurysm was found for the SAH; 36 pa-

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Table 1. Criteria for the Diagnosis of Subarachnoid Hemorrhage (SAH) in Relatives

Medical documents
Clinical features
and blood in basal cisterns on CT
or aneurysm on angiogram or autopsy
Sudden severe headache
and normal neurological findings on examination
and hemorrhagic CSF
and sudden deterioration and death within 4 weeks
History
In first 4 weeks after "stroke," second ictus followed by death
and age <70[a]

[a]The upper limit for age is based on data by Broderick and colleagues [7].

CT = computed tomography; CSF = cerebrospinal fluid.

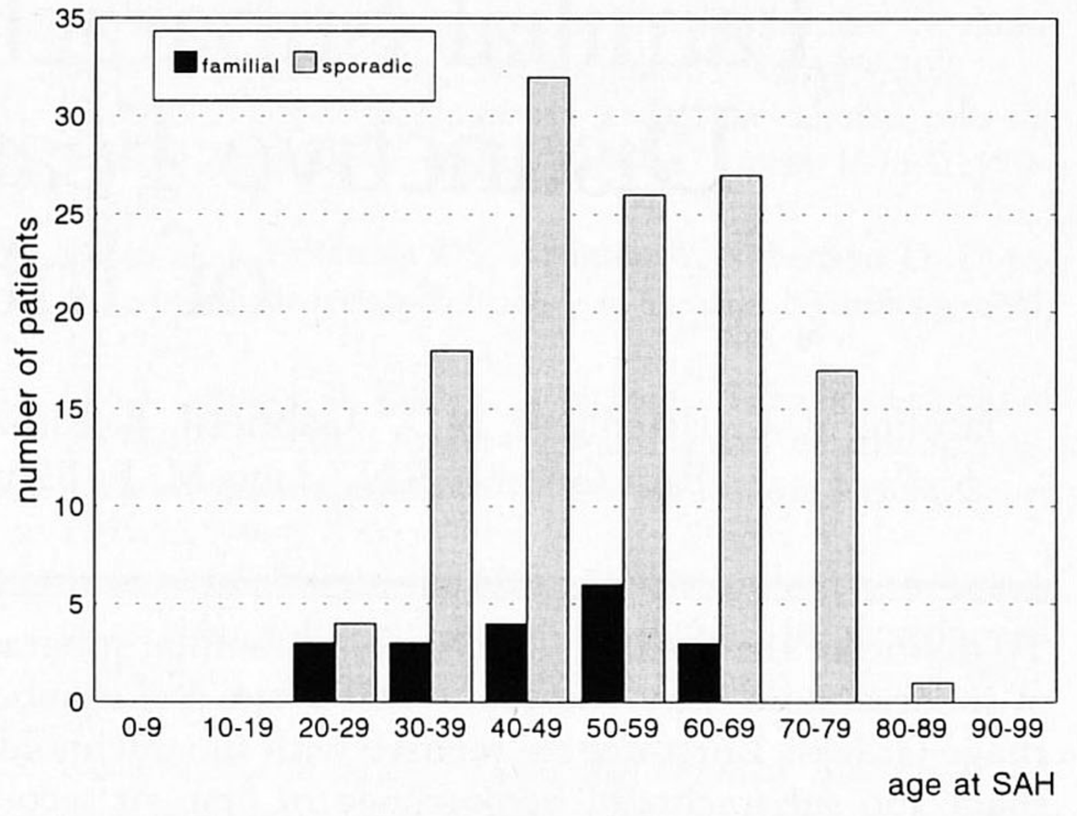

Fig 1. Age distribution of patients with familial and sporadic subarachnoid hemorrhage (SAH).

tients because the patient or the next of kin refused participation; 10 patients because most relatives lived outside Europe; and 1 patient because she was adopted and knew nothing of her biological relatives. Informed consent for approaching relatives was obtained from the patient or a next of kin. A pedigree was drawn up for each family. All living relatives were interviewed by telephone, by means of a standard questionnaire. For deceased relatives a next of kin was interviewed about the cause of death. When stroke or any other brain disease was reported, medical documents were retrieved if available. Nine patients had 1 or more first-degree relatives (parents, children, or sibs) with SAH, according to criteria defined in advance (Table 1). These 9 patients had ten first-degree relatives with SAH and were designated as having familial SAH. Patients who had no relatives with SAH (125) served as control subjects for the comparison of biological features. The remaining 14 patients were excluded from the study: 9 because they had only second-degree relatives (grandparents, grandchildren, aunts, uncles, nephews, or nieces) with SAH, and 5 because they had relatives in whom the diagnosis was suspected but could not be proved (possible SAH). In 115 of the 144 included patients and relatives with SAH, one or more aneurysms were proved by angiography or autopsy. The results of angiography were negative in 5 patients and it was not performed in 24; these patients were not included in the analysis of the aneurysms. Intra-arterial digital subtraction angiography (IA-DSA) techniques with variable magnification factors were used, and precluded comparison of aneurysm size.

For the part of our study concerned with patterns of inheritance, we added 8 families that were referred to the outpatient clinic in Utrecht because of familial SAH or familial intracranial aneurysms, defined as families with at least 2 first-degree relatives with proved SAH or intracranial aneurysm. In these families also, medical documents were reviewed to verify the information. Since these patients were subject to referral bias, the families were not included in the analysis of biological features. Thus, together with the 9 families from our prospective series, 17 families with proved familial SAH were available for analysis of the mode of inheritance. None of the families were known to suffer from connective tissue disorders, autosomal dominant polycystic kidney disease, or hereditary amyloid angiopathy of the Dutch type. We calculated the percentages of affected siblings with exclusion of the proband, to correct for ascertainment bias. If the proband was a parent, all children were included in the calculations. Siblings with "possible SAH" were excluded from the calculations.

In families with two affected generations, the ages at onset were compared in parent-child pairs. To compare our data on parent-child pairs with data in the literature, we performed a Medline search for all indexed articles in English over the years 1983 to 1993, and we also scanned the reference lists of these articles for other reports of families with multiple instances of SAH. In all reported parent-child pairs we compared ages at the time of the SAH.

In the comparison of biological features between patients with familial and those with sporadic SAH, we used relative risks with matching 95% confidence intervals (95% CIs) based on logarithmic transformation of the data [8]. For parent-child pairs with SAH, the ages at occurrence of SAH were compared by the Wilcoxon test for nonparametric comparison of paired samples.

Results

Biological Features

The distribution of age is shown in Figure 1. The mean age of the 19 patients with familial SAH was 46.6 years (standard deviation, 13.2); that of the 125 patients with sporadic SAH was 53.4 years (standard deviation, 13.0). Thus, patients with familial SAH were on average 6.8 years younger (95% CI, 0.4–13.1; $p = 0.04$) than patients with sporadic SAH. The sex distribution was similar in the familial and the sporadic groups: 12 (63.2%) of 19 patients with familial SAH and 77 (61.6%) of 125 patients with sporadic SAH were women.

The 115 patients and relatives for whom the presence of one or more aneurysms was proved by angiography or autopsy had 136 aneurysms. The proportion

Table 2. Number of Aneurysms on Angiography, Operation, or Autopsy[a]

No. of Aneurysms/ Patient	Familial SAH (14/19 Patients)	Sporadic SAH (101/125 Patients)
1	11 (79%)	87 (86%)
2	3 (21%)	11 (11%)
3		2 (2%)
4		1 (1%)
Patients with multiple aneurysms	3 (21%)	14 (14%)
Relative risk for multiple aneurysms	1.6 (95% CI, 0.5–4.7)	1

[a]The 29 patients for whom angiography demonstrated negative results or was not performed are not included in the table.

SAH = subarachnoid hemorrhage; CI = confidence interval.

of patients with multiple aneurysms did not differ significantly between patients with familial and those with sporadic SAH (Table 2). Patients with familial SAH more often had aneurysms of the middle cerebral artery (57%) compared to patients with sporadic SAH (24%) (relative risk, 2.4; 95% CI, 1.4–4.3; Table 3). For the other main sites differences were not statistically significant.

Genetic Features

The family trees of our 17 families with familial SAH or familial intracranial aneurysms are shown in Figure 2. In some families (Families 3, 4, 5, 9, 11, 12, and 17) the pattern of inheritance appeared to be autosomal dominant, especially in the 2 families in which half-brothers or half-sisters were affected (Families 9 and 17). In 1 of these families (Family 9) the 2 affected siblings were half-brother and sister from the same mother and different fathers. In the other family (Family 17) a sister and a half-sister of a patient with SAH had asymptomatic aneurysms and the father they had in common had died of recurrent "brainstem hemorrhage" at the age of 56.

In at least 1 family (Family 10), in which the parents were cousins, inheritance appears to be autosomal recessive. Three of the 19 children had a SAH, a fourth probably had a SAH, and 2 additional children had an asymptomatic aneurysm, documented by magnetic resonance (MR) angiography and confirmed by conventional angiography. The father had died at age 62 of an unrelated illness; the mother, aged 80 years, had negative findings by MR angiography; and all 9 grandchildren who were older than 20 years and had affected parents had negative findings by MR angiography. In the remaining 9 families it was difficult to determine the mode of inheritance from the pedigree.

Table 3. Site of Aneurysms[a]

Aneurysm Site	Familial SAH (14 Patients)	Sporadic SAH (101 Patients)	RR (for Familial Patients)
AcoA/ pericall.A	3 (21%)	52 (52%)	0.4 (95% CI, 0.2–1.2)
MCA	8 (57%)	24 (24%)	2.4 (95% CI, 1.4–4.3)
ICA	2 (14%)	25 (25%)	0.5 (95% CI, 0.1–2.1)
Posterior circulation	1 (7%)	16 (16%)	0.5 (95% CI, 0.1–3.1)

[a]Two patients with familial SAH and 1 patient with sporadic SAH had two carotid artery aneurysms; 1 patient with familial SAH and 2 patients with sporadic SAH had two middle cerebral artery aneurysms.

SAH = subarachnoid hemorrhage; RR = relative risk; AcoA/pericall.A = aneurysms of anterior communicating artery, pericallosal artery, or marginal callosal artery; MCA = aneurysms of middle cerebral artery; ICA = aneurysms of internal carotid artery, including posterior communicating artery; posterior circulation = aneurysms of basilar or vertebral arteries; CI = confidence interval.

In the 17 families with familial SAH, 40 of 116 sibs, including the proband, were affected with SAH or were known to have unruptured intracranial aneurysms: 25 of 66 females and 15 of 50 males. Twelve families had affected members in one generation only, and 5 families had affected members in two generations. In 2 of these last 5 families the parent was the proband and had a SAH after the child did. If we excluded the proband child, in families with affected relatives in two generations, 7 (44%) of 16 sibs were affected compared to only 18 (21%) of 85 sibs in families with affected relatives in one generation. The relative risk for siblings in families with two affected generations compared with families with one affected generation is 2.1 (95% CI, 1.0–4.1).

The ages of all parent-child pairs at the time of their SAH are shown in Table 4. In the families with two affected generations, the mean age of the parent at the time of SAH was 52.4 years, whereas the mean age of the child when his or her SAH occurred was 35.8 years (mean of the differences, 16.6; standard deviation, 12.0). When the ages of these parent-child pairs are compared with the Wilcoxon test for paired samples, the difference is significant (two-tailed, $p = 0.01$).

In our literature search for families with familial SAH, we found 18 families in which two or more first-degree relatives in two or more generations had suffered SAH according to the criteria in Table 1, and for whom age at time of rupture was given [9–24]. In these 18 families, 21 parent-child pairs with SAH were

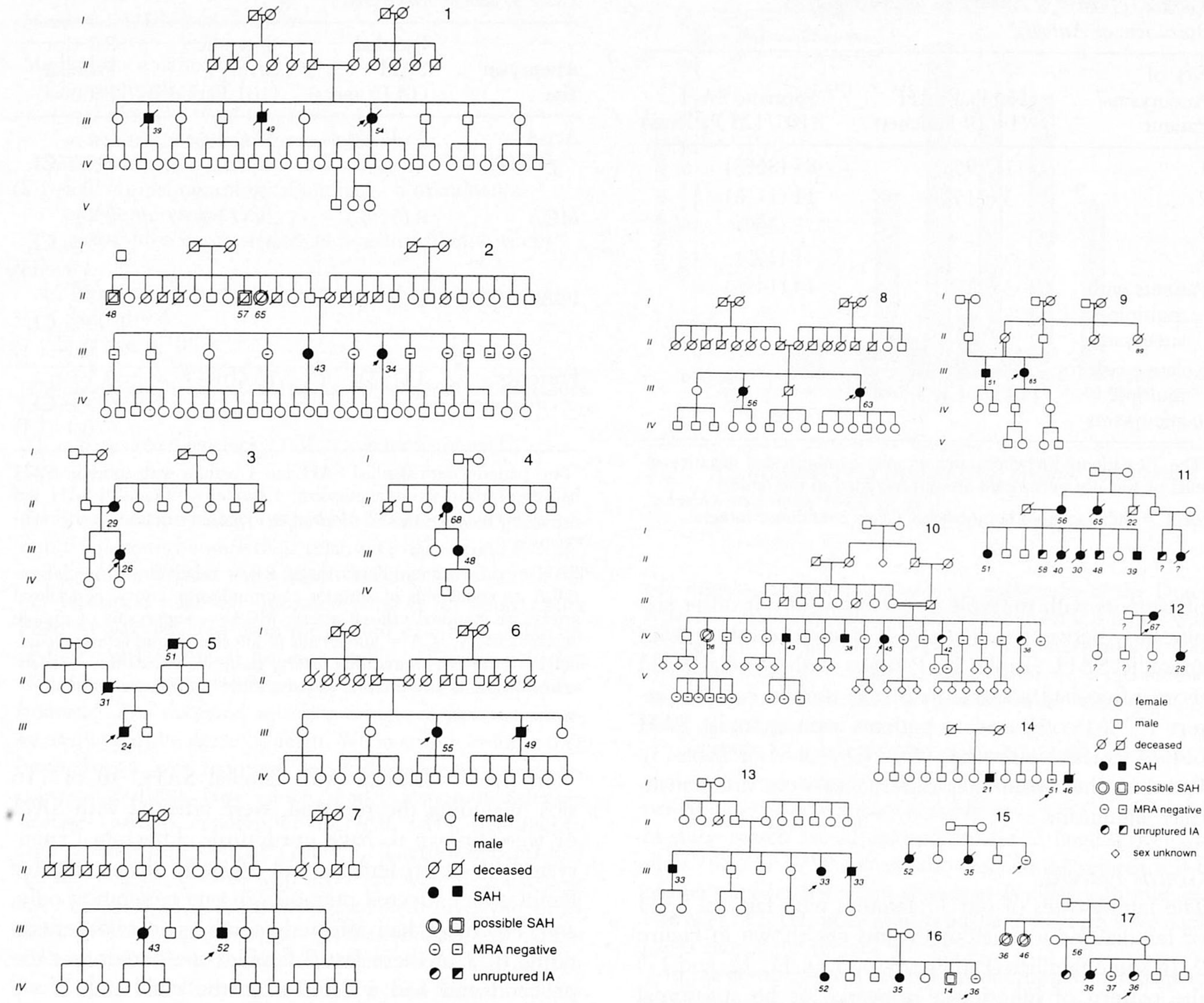

Fig 2. Family trees of all families with at least 2 first-degree relatives with subarachnoid hemorrhage (SAH). *MRA = magnetic resonance angiography; IA = intracranial aneurysm.*

Table 4. Ages at Time of Subarachnoid Hemorrhage in Parent-Child Pairs in Families with Two Affected Generations

Family No.	Age of Parent (yr)	Age of Child (yr)
3	29	29
4	68	48
5	31	24
11	56	51
		40
		39
		30
12	67	28
Mean	52.4	35.8

found. The mean age of the parent at the time of SAH was 49.7 years, versus 26.8 years for the child (mean of the differences, 22.9; standard deviation, 10.9). No family was found in which the parent was younger than the child at the time of SAH. When the ages of these parent-child pairs are compared with the Wilcoxon test, the difference is again significant (two-tailed, $p = 0.0001$).

Discussion

In our study SAH occurred at a younger age in those with the familial form than in those with the sporadic form. This is in accordance with previous reviews [2, 25] which concluded that familial SAH most frequently occurs in the fifth decade, a decade earlier than sporadic SAH [26]. We found that aneurysms of the middle cerebral artery occur more than twice as often in familial SAH as in sporadic SAH. Previous studies also found a higher than usual proportion of patients

with middle cerebral aneurysms but in those cases the difference was not statistically significant [3, 4]. The true difference may be even more pronounced, because even our strict criteria cannot preclude the possibility that some patients in our control group may later turn out to have had familial SAH if SAH develops in a relative.

With regard to the pattern of inheritance, two pieces of evidence suggest that this may be autosomal dominant, at least in some patients. Firstly, in the 5 families in which two generations were affected, 44% of the sibs (excluding the proband) were affected by SAH. Secondly, in 2 families half-brothers and half-sisters were affected with SAH or intracranial aneurysms. In other families, however, the evidence suggested autosomal recessive or multifactorial inheritance. Firstly, in the 12 families in which only one generation was affected, only 21% of sibs had a SAH or an asymptomatic intracranial aneurysm. Secondly, the consanguinity of the parents in Family 10, combined with aneurysms not having been demonstrated in the patients' children, is typical of autosomal recessive inheritance.

Thus it is likely that two or more types of inheritance are involved in familial SAH. In the only previous study on the inheritance of familial SAH, one family and all available literature reports were analyzed. No single mendelian model that fitted all the pedigrees could be found, and the authors suggested genetic heterogeneity [27]. Our findings support and further substantiate this conclusion.

Asymptomatic intracranial aneurysms were found in 6 (25%) of the 24 siblings of patients with SAH who requested investigation by MR angiography. Since not all siblings of all patients with familial SAH and no siblings of patients with sporadic SAH were investigated, inclusion of sibs with asymptomatic aneurysms may have biased the number of affected relatives in the familial kindreds. However, this only slightly influenced the difference in percentages of affected sibs between families with one and families with two affected generations: Including asymptomatic aneurysms, 44% of siblings were affected in families with two affected generations and 21% were affected in families with one affected generation; excluding asymptomatic aneurysms, the percentages were 31% and 16%, respectively.

In families with two affected generations, the parent was always older than the child or children at the time the subarachnoid hemorrhage occurred, and the mean age of affected parents was significantly higher than that of affected children. This age difference has not been recognized before but was confirmed in our review of all previously published families. Genetically this younger age at onset in later generations is compatible with anticipation, caused by an unstable repeat of a DNA sequence, as is the case in myotonic dystrophy [28, 29]. It might be objected that since SAH most frequently occurs in the fifth or sixth decade and since SAH is often fatal, parents of patients with SAH are often no longer alive and their records no longer available. Ascertainment bias may theoretically have prevented us from detecting parents who had SAH at a younger age than their children, as was initially supposed for myotonic dystrophy [30]. However, this is not likely in our study, since the parent was the proband in 2 of our 5 families in which two generations were affected. Furthermore, the younger age at rupture of familial aneurysms, which has frequently been recorded [2, 25], could be partly explained by anticipation in the families with autosomal dominant inheritance. Thus, our data are very suggestive of anticipation; further support should come from elucidation of the molecular genetics of familial intracranial aneurysms.

In conclusion, multiple modes of inheritance are involved in familial SAH: In at least one third of families with familial SAH, inheritance appears to follow an autosomal dominant pattern in which anticipation seems to be involved. In some other families, inheritance seems to be autosomal recessive or multifactorial. Familial SAH is further characterized by a greater proportion of middle cerebral artery aneurysms and by rupture of the aneurysm at a relatively young age. In addition the outcome of familial SAH is, on average, worse than that of sporadic SAH [6]. These characteristics are not sufficiently different from sporadic SAH to allow recognition of familial SAH on clinical grounds alone. The evidence from our clinical and genetic data combined does, however, suggest that familial SAH is an entity separate from sporadic SAH.

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