Subarachnoid haemorrhage of unknown cause: a long term follow-up

T D HAWKINS, C SIMS, R HANKA

From the Department of Radiology, Addenbrooke's Hospital, Cambridge and Department of Community Medicine, University of Cambridge, UK

SUMMARY Three hundred and sixteen patients who suffered a subarachnoid haemorrhage of unknown cause were followed up by questionnaire after 2 to 23 years, the average interval being 10 years. Two hundred and fifty one (79.5%) are known to be alive, 49 (15.5%) had died, and 16 (5%) patients were untraceable. The cumulative survival for the whole group after 22 years was 69%, the expected survival being 89%. The certified cause of death of 30 patients was from diseases of the circulatory system, mainly myocardial infarction and cerebrovascular disease, the expected number being 21.8. The results of this survey show a reduced life expectancy for both males and females and suggest that a more guarded view should be taken than is presently the case about the long term prognosis of these patients.

As the most common cause of spontaneous subarachnoid haemorrhage is a ruptured intracranial aneurysm, the potential accuracy of angiography in demonstrating cerebral aneurysms has been the subject of a number of studies. These have shown that a false negative rate of less than 3.8% can be achieved and that unless further bleeding occurs repeat angiography is seldom justified.¹⁻³ It has been suggested that in patients in whom angiography is negative, the cause may be a small aneurysm that undergoes thrombosis or is destroyed at the time of rupture.⁴⁻⁶ The evidence to support this is the similarity of the clinical presentation, sex ratio, age and immediate clinical course of patients with and without demonstrable aneurysms and the frequency with which small aneurysms are found at necropsy in patients who have died from other causes.^{6,7} Whatever the underlying cause may be, it is known that the outcome for patients who have suffered a subarachnoid haemorrhage due to a ruptured intracranial aneurysm treated conservatively is very different from that expected for patients in whom no cause is found.⁸ The study by Winn and colleagues⁹ of 364 patients with anterior or posterior communicating artery aneurysms treated conservatively and followed for periods of up to 21 years, demonstrated the gravity of the outcome for these

patients. This contrasts with the findings of a number of retrospective studies in which the authors have looked at the morbidity and mortality of smaller groups of patients who have suffered a spontaneous subarachnoid haemorrhage of unknown cause and have attempted to identify features of prognostic value in determining outcome.^{6,10-12}

The possibility that bloodstained cerebrospinal fluid (CSF) may be due to rupture of an intracerebral haemorrhage into the ventricles or subarachnoid space must always be considered, especially in patients who are known to be hypertensive. The now almost routine use of cranial computed tomography (CT) has made easy their identification, has shown that a haemorrhage too small to be detected by angiography is uncommon¹³ and has confirmed, among other things, that in a significant minority of patients with blood visible in the subarachnoid space, no underlying cause is found by angiography. The object of this retrospective study of subarachnoid haemorrhage of unknown cause was not merely to confirm the work of others but to look at survival rates and the certified cause of death of a larger group of patients over a longer period than had previously been attempted and compare them with those for the general population, matched for age and sex, derived from the national statistics.

Material and methods

The Departments of Neurological Surgery and Radiology at

Address for reprint requests: Dr T D Hawkins, Dept of Radiology, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.

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Addenbrooke's Hospital provide a service for a population of some 1.5 to 1.75 million in East Anglia, where the residents are rather less mobile than in many other regions.

The records of all patients with a proven subarachnoid haemorrhage investigated by angiography between 1962 and 1984 were reviewed. Patients in whom the bloodstained CSF was considered at the time or on review to have been due to a head injury or primary intracerebral haemorrhage were excluded from the study (table 1). A questionnaire was sent to the last known general practitioner of each of the remaining patients seeking information about their previous and present state of health or the date and cause of death. This provided information on approximately 80% of the patients under review. The Office of Population Censuses and Surveys (OPCS) and the Department of Health and Social Security (DHSS) Central Register provided information on all but 16 of the remaining patients and the date and certified cause of death of those who had died.

The angiographic studies of these patients were reviewed by one of us (TDH), all but 10 examinations being retrieved from the archives. Two hundred and seventy patients had all the intracranial arteries examined, 52 patients, mostly over 65 years of age, had had bilateral carotid angiography and in 11 patients only a single carotid angiogram had been performed. The latter and five patients shown to have small aneurysms of uncertain significance were excluded from the study as was one patient with progressive obliterative arterial disease who presented with a subarachnoid haemorrhage. It was decided to include for statistical purposes the 10 patients whose examinations were missing from the archives, all of which had been reported on by an experienced observer (table 2). Those angiograms with all the necessary projections including subtraction films were classified as good and those with sufficient projections but without subtraction films were classified as satisfactory. No examination was found to be insufficient for diagnostic purposes. Those with evidence of localised narrowing of one or more arteries due to spasm were graded (+) and those with more widespread spasm (+ +). Because improvements in equipment and in technique during the period of the survey might have had some bearing on the frequency with which an aneurysm was demonstrated, the number of negative examinations and the total number performed each year was recorded.

Twenty three patients underwent a second angiographic examination because of their failure to improve clinically or due to the demonstration of arterial spasm at the first examination. Nine patients are known to have suffered a further subarachnoid haemorrhage, investigated by angiography, during the period of the survey.

The medical records of all patients were reviewed by one of

Table 1 Cerebral angiography for subarachnoid haemorrhage

1962-1984	Population 1.5-1.75 million
Total patients	1,569
Aneurysm demonstrated	1,106
No aneurysm demonstrated	463
Post traumatic & primary intracranial haemorrhage	114
S.A.H. No cause found	349
Negative rate overall	29%
Negative rate excluding post traumatic and primary intraactive haemorrhage	22%

Table 2 Review of angiograms

Angiographic studies reviewed	323 (350*)
Angiographic studies not reviewed	10
3/4 Vessel angiogram	270
Bilateral carotid	52
Unilateral carotid	11
Probable aneurysms	5
Moya moya	1
Patients remaining in study	316

*Includes repeat angiograms and recurrent SAH.

us (CS): the clinical state, graded on the Hunt and Hess scale¹⁴ and the blood pressure on admission and on discharge were recorded. The analysis of the data was carried out by one of us (RH) on an IBM 3081 computer using the SPSSX Statistical Package.

Results

Of 1569 patients admitted to the Department of Neurological Surgery with a proven subarachnoid haemorrhage between 1962 and 1984 who were fit for angiography no cause was found in 463 (29%). One hundred and fourteen of these patients were considered at the time or on review to have had a traumatic subarachnoid haemorrhage or primary intracerebral haemorrhage, leaving 349 (22%) patients for analysis (table 1). The distribution of negative to positive examinations showed there to be no significant difference by year ($X^2_{22} = 25.28$), nor by sex and decade (males $X^2_3 = 5.72$, females $X^2_3 = 5.81$) (figs 1 & 2). The 16 patients lost to follow up were included in these analyses as their angiograms were available for review and were confirmed to be negative. Of the 316 patients in the survey, 256 (81%) were Grade 1, 51 patients (16%) were Grade 2, and 9 patients (3%) were Grade 2/3 on the Hunt and Hess scale on admission. Patients were judged to be hypertensive if the diastolic pressure was more than 90 mm HHg or the systolic pressure was more than 120 mm Hg plus the age of the patient, or both. Using these criteria 108 patients (34%) were hypertensive on admission and 43 (14%) were hypertensive on discharge (table 3).

The angiograms of 213 (67%) patients were of good diagnostic quality and 103 (33%) were satisfactory. In 215 (68%) there was no arterial spasm, in 65 (21%) there was localised spasm (+) and in 36 (11%) the

Table 3 Subarachnoid haemorrhage—clinical grade and B.P. on admission

Patients	316
Clinical Grade ¹⁴	
Grade 1	256 (81%)
Grade 2	51 (16%)
Grade 3	9 (3%)
Hypertensive on admission	108 (34%)
Hypertensive on discharge	43 (14%)

Fig 1 Subarachnoid haemorrhage: number of negative and positive examinations by year.

changes were more widespread (+ +). No unreported aneurysms were identified (table 4). Of the 23 patients without evidence of a further subarachnoid haemorrhage who had repeat angiography, 18 were Grade 1, four Grade 2 and one Grade 2/3 on the Hunt and Hess scale. Fifteen of these patients had arterial spasm (11 had (+) and four had (+ +) of spasm) on the first angiogram (table 5). There was no previously undetected aneurysm.

Of the nine patients known to have had a further subarachnoid haemorrhage 10 days to 16 years after the first, five were males and four were females aged between 38 and 59 years. Six patients were Grade 1, one Grade 1/2, one Grade 2 and one Grade 2/3 and four had arterial spasm on the second occasion. No aneurysm was demonstrated. Five of the nine patients were hypertensive on discharge. All were alive at the

end of the survey (table 6).

Two hundred and fifty one patients (79.5%) are known to be alive, the length of survival ranging from 2 to 23 years; 16 (5%) were untraceable owing to emigration or membership of the Armed Forces and 49 (15.5%) had died, the date and certified cause of death being known for all of them. Thirty patients died of diseases of the circulatory system, mainly myocardial infarction and cerebrovascular disease, compared with the expected number 21.82, derived from the death rates for England and Wales in 1978, matched for age and sex. Nineteen patients died of other causes as compared with the expected number 27.18. The year 1978 was chosen as a compromise between the slightly different death rates applicable between the years 1961 and 1984. The log-odds ratio (-0.2197) of the expected numbers of deaths in the two groups lies outside the 95% confidence interval of the log-odds ratio (0.4568 , $SD\ 0.5747$) of the observed deaths. The difference between the expected and observed ratios is therefore significant at 5% level. The actuarially adjusted cumulative proportion of survivors was calculated and plotted (fig 3). The cumulative proportional survival after 22 years was 69% as compared with an expected survival of 89%. In figure 4 survival functions are plotted separately for

Fig 2 Subarachnoid haemorrhage: number of negative and positive examinations by sex and age in decades.

Table 4 Review of angiograms—diagnostic quality and the presence of spasm

Angiograms	316		
Diagnostic quality	GOOD	SATISFACTORY	
	213 (67%)	103 (33%)	
Arterial spasm	None	+	++
	215 (68%)	65 (21%)	36 (11%)
		(32%)	

+ = localised arterial spasm
++ = widespread arterial spasm

Table 5 Repeat angiography. Clinical grade and presence of spasm on original angiogram. (No evidence of further subarachnoid haemorrhage)

Patients—23			
Clinical grade (Hunt & Hess)	1	2	2/3
Arterial spasm	18	4	1
	None	+	++
	8	11	4
No aneurysm demonstrated.			

patients who were normotensive and those who were hypertensive on discharge. The cumulative proportional survival of the normotensive patients at the end of the period was 76% as compared with 48% for patients who were hypertensive on discharge. The differences are statistically significant ($p < 0.05$). Separate survival functions were plotted for clinical grade on admission (fig 5). There was no statistically significant difference between them.

The age at the time of subarachnoid haemorrhage and the age at death of the 29 males and 20 females were plotted and life expectancy curves derived from the OPCS Life Tables for England and Wales were superimposed upon these plots for comparison (fig 6). The results show a reduced life expectancy for both males and females whether dying from circulatory disorders or other causes.

Discussion

The percentage of patients who present with a subarachnoid haemorrhage and in whom no underlying cause is found by cerebral angiography is reported to vary between 15% and 27%. If cases due to trauma or primary intracerebral haemorrhage are excluded, 20% is likely to be a more realistic figure. The negative rate of 22% in the present series is compatible with this. The inclusion of the 51 patients who had bilateral carotid angiography only may have introduced a number of false negative examinations since they could have been harbouring aneurysms on the posterior circulation: none of these patients had a further subarachnoid haemorrhage during the period of the

Table 6 Recurrent subarachnoid haemorrhage

Sex	Age	Grade	B.P.	Spasm	Interval/SAH	Alive
F	38	1	150/100	+	10 days	+
F	48	1/2	150/100	++	17 days	+
M	52	2	160/110	—	6 months	+
M	51	2/3	155/95	—	6 months	+
M	54	1	160/110	+	10 months	+
M	41	1	110/70	—	2 years	+
F	59	1	130/90	—	9 years	+
F	59	1	150/90	+	9 years	+
*M	49	1	160/90	—	16 years	+

No aneurysm demonstrated.

*CT—intracranial haemorrhage on second occasion.

Fig 3 Graphs showing actuarially adjusted cumulative proportion of patients surviving up to 22 years as compared with expected survival.

survey. It is possible that in a few patients the subarachnoid haemorrhage may have been due to rupture of an unrecognised spinal angioma. No patient in the survey was subsequently found to have such a lesion. The consistency in the ratio of negative to positive angiograms throughout the period under review is evidence that when satisfactory standards of angiography and interpretation are maintained, neither of these factors will contribute to the negative rate.

The absence of a significant difference between patients with and without an aneurysm when compared by sex and age, in decades, and their similar clinical presentations suggests that they may share some common aetiological factors, although the prognosis for these two groups of patients is profoundly different. This study provides scant evidence to support or refute the hypothesis that in the absence of a demonstrable cause the source of the haemorrhage

Fig 4 Graphs showing actuarially adjusted survival up to 22 years of patients who were normotensive as compared with those who were hypertensive on discharge.

Fig 5 Graphs showing actuarially adjusted survival up to 22 years by clinical grade on admission.

may be small aneurysm which thromboses or is destroyed at the time of rupture.⁴⁷ The small aneurysms of uncertain significance demonstrated in the five patients who were excluded from the series may represent an early stage in the development of the type of aneurysm normally responsible for subarachnoid haemorrhage. In the two patients who came to necropsy no aneurysm was reported to be present at the usual sites.

The grading of the patients shows that in general their clinical state was less grave than those in the Co-operative Study of aneurysmal subarachnoid haemorrhage.¹⁵ Although some 34% of the patients were hypertensive on admission only 14% were so on

discharge, as compared with 19% reported by Brismar and Sundbarg.¹⁰ They, among other things, considered this to be confirmatory evidence that the number of cases of primary intracerebral haemorrhage in their series was small.

Arterial spasm was revealed in 32% of the patients, which is appreciably greater than the four out of 51 reported by Hayward,⁶ is similar to the 50 out of 137 patients (36%) with a ruptured aneurysm reported by Griffith and his colleagues¹⁶ but is less than the 42.8% of patients in the Co-operative Study.¹⁵ The number known to have had a further subarachnoid haemorrhage, nine of 316 (2.8%), may be too few owing to the retrospective nature of the survey. The rebleed rate is nevertheless significantly lower than that of untreated aneurysms, estimated by Winn *et al* to be 3.5% per annum after the first 6 months.⁷

Apart from the few patients who died in the immediate postictal period there was no relationship between the severity of the patients' clinical state on admission and their survival. Of the 49 patients who had died, 29 were male and 20 female, a ratio of 1.45:1 as compared with the sex ratio in the group as a whole of 0.9:1. The prognosis for survival of this group of patients is less than expected, and the difference in cumulative proportional survival compared with that for the general population is statistically significant. The less favourable prognosis for those who were hypertensive on discharge may merely reflect the known increased risk of developing diseases of the circulatory system and of dying from them. The reduced survival of patients who were normotensive

Fig 6 A and B. Age at time of subarachnoid haemorrhage and age and cause of death for males and females. The diagonal superimposed on the graph is a guide linking the ages on the ordinate and the abscissa. The horizontal distance to the right of the diagonal indicates the length of survival following the subarachnoid haemorrhage. The life expectancy curve is derived from the OPCS Life Tables for England and Wales. MI/CV = myocardial infarction/cerebrovascular disease.

on discharge is less easily explained. They too appear to be prone to die from diseases of the circulatory system, either myocardial infarction or cerebrovascular disease. It is thus possible that a subarachnoid haemorrhage of unknown cause may be a harbinger of these diseases.

Conclusions

This retrospective study confirms that in about one fifth of patients who suffer a spontaneous subarachnoid haemorrhage no cause is found by cerebral angiography. There is no support for the belief that repeat angiography is necessary if the first examination is of satisfactory standard, unless the patient has a further haemorrhage. The patients are largely indistinguishable from those known to have an aneurysm but their clinical state on admission is usually less grave. The low rebleed rate confirms the accepted view that subarachnoid haemorrhage of unknown cause is a relatively benign condition. The long term outcome, however, is less favourable than expected and there appears to be an excess of deaths from circulatory disorders, in particular myocardial infarction and cerebrovascular disease. The results of this survey suggest that a more guarded view should be adopted than is presently the case about the long term survival of these patients.

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