Long-term risk of aneurysmal subarachnoid hemorrhage after a negative aneurysm screen

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ABSTRACT

Objective: The objective was to assess the risk of aneurysmal subarachnoid hemorrhage (aSAH) in the initial 15 years after negative aneurysm screening in persons with one first-degree relative with aSAH.

Methods: From a cohort of first-degree relatives of patients with aSAH who underwent screening between 1995 and 1997 (n = 626), we included those with a negative screening (n = 601). We retrieved all causes of death and sent a questionnaire to screenees who were still alive. If aSAH was reported, we reviewed all medical data. We assessed the incidence of aSAH in this cohort with survival analysis and calculated an incidence ratio by dividing the observed incidence with the age- and sex-adjusted incidence in the general population.

Results: Of the 601 screenees, 3 had aSAH during 8,938 follow-up patient-years (mean 14.9 years). After 15 years, the cumulative incidence was 0.50% (95% confidence interval: 0.00%–1.06%) with an incidence rate of 33.6 per 100,000 person-years; the incidence rate ratio was 1.7 (95% confidence interval: 0.3–5.7).

Conclusions: In the first 15 years after a negative screening, the risk of aSAH in persons with one first-degree relative with aSAH is not nil, but in the range of that in the general population, or even higher. Whether this finding justifies serial aneurysm screening in this population requires further study. *Neurology*® 2015;84:912–917

GLOSSARY

aSAH = aneurysmal subarachnoid hemorrhage; **CI** = confidence interval; **MRA** = magnetic resonance angiography.

A familial preponderance is a strong risk factor for the development of intracranial aneurysms. Persons with 2 or more affected first-degree relatives have a 50 times higher risk of having an aneurysmal subarachnoid hemorrhage (aSAH) during life,¹ and in such relatives, repeated screening is cost-effective.² Persons with only one affected first-degree relative have a 2-times-higher risk of aSAH compared with the general population.¹ There is some evidence that familial intracranial aneurysms have a greater rupture risk compared with sporadic aneurysms.³ In a Markov model based on observational data from screening 626 first-degree relatives of a consecutive series of patients with aSAH between 1995 and 1997, we found that a single magnetic resonance angiographic (MRA) screening for intracranial aneurysms increased life expectancy slightly. However, this increase was at the cost of a reduced number of life years in good health because of complications of preventive treatment and thus screening was not effective. On average, screening and preventive treatment increased estimated life expectancy by 0.9 months per person screened, at the expense of 19 years of impaired functional health per person.⁴ Also, screening was not considered to be efficient because 149 relatives would need to be screened to prevent a subarachnoid hemorrhage in one person on a lifetime basis.

However, in the model, it was assumed that persons with a negative screen were no longer at risk of aSAH, but empirical data supporting this assumption are lacking.

We therefore performed a follow-up study in this cohort of persons with one first-degree relative with an aSAH to determine the risk of aSAH in the first 15 years after a negative screening for intracranial aneurysms.

METHODS Patient selection. We performed a follow-up study of a cohort of asymptomatic first-degree relatives of patients with aSAH who underwent MRA screening for intracranial aneurysms in the context of a study on the efficiency and effectiveness of screening such relatives.⁴ None of the original index patients with aSAH were found to have a disorder with higher risk of intracranial aneurysm, such as connective tissue disorders or autosomal dominant polycystic kidney disease. The initial cohort consisted of 626 first-degree relatives of 160 consecutive patients with aSAH screened with MRA between 1995 and 1997. The number of relatives of these patients with aSAH who were originally screened per family in that cohort ranged from 1 to 11. The 25 relatives in whom an aneurysm was found on this screening were excluded from the present follow-up study.

Standard protocol approvals, registrations, and patient consents. The current study was approved by the medical ethical review committee and all participants provided informed consent.

Data extraction. We first consulted the Municipal Personal Records Database to check whether the 601 eligible screenees were still alive. All screenees who were still alive were invited to participate in the follow-up study and received a standardized questionnaire. If a screenee reported an aSAH or other type of stroke, all medical data including imaging studies were retrieved and reviewed to assess the cause of stroke. New episodes of aSAH were defined as aSAH proven by lumbar puncture and an intracranial aneurysm on imaging or autopsy. In case of aSAH, the initial MRA was reviewed by 2 neuroradiologists (B.K.V., T.D.W.) independently from each other to see whether in retrospect the aneurysm was visible at the time of screening.

In case a screenee had died, the general practitioner was contacted to determine the cause of death. If the general practitioner did not know the cause of death, we retrieved on group level the cause of death from the Cause of Death Register of Statistics Netherlands.

Patients with a history suggestive of aneurysmal rupture but without confirmation of the diagnosis because they had died

before reaching hospital were classified as sudden death probably as a result of aSAH. A history suggestive of aneurysmal rupture was suggestive of aneurysmal rupture if an eyewitness reported a sudden severe headache before onset of coma.

Data analysis. Incidence of aSAH during follow-up after initial negative screening was assessed in 3 analyses. In the primary analysis, we considered the total cohort of 601 screenees, assuming that all screenees in whom follow-up data were lacking were still alive at the end of the follow-up period and that none of these screenees had experienced an aSAH. The second analysis included all screenees of whom direct follow-up information was available: those patients who returned their questionnaires themselves and those with a known cause of death. The third analysis consisted of all screenees of whom direct follow-up information was available plus the screenees of whom indirect follow-up information was retrieved using responses of other screenees from the same family.

The incidence rate per 100,000 patient-years and the cumulative incidence at 5, 10, and 15 years with corresponding 95% confidence intervals (CIs) were calculated for episodes of confirmed aSAH and, if applicable, for episodes of confirmed aSAH and sudden death probably as a result of aSAH. We calculated incidence ratios with corresponding 95% CIs by dividing the observed incidence rate in our study population by the expected incidence for the general population, considering the age categories and sex distribution of our study population.⁵

RESULTS First-degree relatives. The baseline characteristics of the 601 first-degree relatives of patients with aSAH who had a negative MRA screening are given in table 1. Of these 601 screenees, 15 had emigrated and 27 had died during follow-up (figure 1). In 15 of the 27 relatives who died during follow-up, the cause of death could be retrieved from the general practitioners: 8 relatives died of malignant neoplasms, 3 of heart diseases, 1 of complications of dementia, 1 of septic shock, 1 committed suicide, and 1 died in a traffic accident.

In the other 12 of the 27 deceased relatives, the cause of death could no longer be retrieved from the general practitioner. The Cause of Death Register of Statistics Netherlands showed that none of these

Table 1 Baseline characteristics of the first-degree relatives with negative screening

Characteristic	Entire group (n = 601)	Group with direct follow-up data (n = 432)	Group with direct or indirect follow-up data (n = 568)
Mean age, ^a y, ±SD	56.3 ± 12.3	56.9 ± 11.9	56.4 ± 12.2
Women, n (%)	309 (51.4)	225 (52.1)	293 (51.6)
aSAH, n (%)	3 (0.5)	3 (0.7)	3 (0.5)
Unruptured intracranial aneurysm, n (%)	1 (0.2)	1 (0.2)	1 (0.2)
Deceased, n (%)	27 (4.5)	27 (6.3)	27 (4.8)
Emigrated, n (%)	15 (2.5)	0 (0.0)	10 (1.8)
Follow-up, y	8,938	6,384	8,436
Mean follow-up, y (range)	14.9 (2-16)	14.8 (2-16)	14.9 (2-16)

Abbreviation: aSAH = aneurysmal subarachnoid hemorrhage.

^aAge at time of questionnaire.

Figure 1 Overview of the relatives eligible for the follow-up study

aSAH = aneurysmal subarachnoid hemorrhage; MRA = magnetic resonance angiography.

12 relatives had died of aSAH (4 died of heart diseases, 4 of malignant neoplasms, 2 of lung disease, 1 of aortal dissection, and 1 relative had committed suicide). In 10 of the 15 screenees who emigrated, follow-up could be retrieved indirectly by the questionnaires of family members. The other 559 screenees received a questionnaire, of which 405 (72.5%) were returned. For 126 of the 154 screenees who did not return the questionnaire, follow-up data could be retrieved from the questionnaires of other screenees from the same family, because several relatives had stated that no episodes of aSAH had occurred in their family. For the entire cohort of 601 screenees, total follow-up time was 8,938 patient-years with a mean period of follow-up of 14.9 years (range 2–16 years).

Episodes of subarachnoid hemorrhage. Two of the 405 screenees who returned the questionnaire reported a definite aSAH. An asymptomatic intracranial aneurysm was detected in one other screenee. This screenee was admitted to hospital because of severe headache; on further examination, no signs of aSAH were found, but CT angiography showed an aneurysm at the right middle cerebral artery. Of the 27

screenees who had died during follow-up, one died of proven aSAH caused by a ruptured basilar artery aneurysm (figure 2). One episode of sudden death was reported, but this was considered to be a cardiac cause, because there was no history of sudden headache preceding death.

The 3 episodes of aSAH occurred 12, 14, and 15 years after initial negative screening (table 2). The 3 patients with aSAH came from different families.

In retrospect, both neuroradiologists did not find the aneurysm causing the aSAH on the initial MRAs performed between 1995 and 1997. However, in one screenee, aSAH occurred from the posterior inferior cerebellar artery, which was not depicted on the initial MRA (figure 2). The radiologists rated all 3 original MRA images as good quality.

Incidence of subarachnoid hemorrhage. Assuming that the 33 screenees (5 emigrated and 28 not returning the questionnaire) in whom no direct or indirect follow-up information was available were alive at the time of follow-up and that no aSAH had occurred, the incidence of aSAH in the entire study population is 33.6 per 100,000 person-years (95% CI: 6.9–98.1) (table 3). The incidence in the

(A) Initial negative screen magnetic resonance angiograms of patients 1, 2, and 3. (B) CT angiography showing aneurysms of the anterior communicating artery (B.1), posterior inferior cerebellar artery (B.2), and basilar artery (B.3), indicated by arrows. (C) Corresponding CT scans showing subarachnoid bleeding.

general population for a cohort with a comparable age and sex distribution was 20.0 per 100,000 person-years.⁵ The calculated incidence rate ratio was 1.7 (95% CI: 0.3–5.7) (table 3); the cumulative incidence after 15 years was 0.50% (95% CI: 0.00%–1.06%).

DISCUSSION In our unique cohort of 601 first-degree relatives from a consecutive series of patients with aSAH, we found that a negative screening for aneurysms does not rule out the risk of aSAH in the initial 15 years after the screening. Although one might expect a very low incidence of aSAH in the initial 15 years after the negative screen for aneurysms, the incidence of aSAH in this cohort is in the range of that in the general population without preceding screening or even higher.

Our data seem to suggest that the risk of aSAH is negligible in the first 10 years after negative screening in persons with one affected first-degree relative with aSAH, but we cannot draw definitive conclusions. Although we were able to retrieve follow-up data for 95% of our relatives and thus to collect data on a large number of persons without aSAH in the initial 10 years after negative screening, we have no data in the remaining 5% of persons, and only indirect information through relatives in approximately 20% of the screenees. Thus, in many persons, we cannot exclude the occurrence of aSAH definitely. Consequently, the incidence of aSAH we report here may be an underestimation of the true incidence of aSAH in the initial 15 years, and therefore also in the first 10 years, after negative screening in persons with one affected first-degree relative with aSAH.

Table 2 Characteristics of the screenees with a negative MRA and an aSAH during follow-up

Patient no.	Age at time of aSAH, y	Sex	Aneurysm location	Aneurysm size, mm	Aneurysm in retrospect visible on screen MRA	No. of follow-up y until aSAH	Outcome mRS ^a	Family relation to index patient ^b	Total no. of screened relatives ^b	Smoking ^c	Hypertension ^d
1	60	M	ACA	3	No	12	2	Sibling	3	Yes	Yes
2	56	F	PICA	7	Not visualized	14	3	Sibling	3	Yes	No
3	48	F	BA	3	No	15	Death	Child	4	—	—

Abbreviations: ACA = anterior communicating artery; aSAH = aneurysmal subarachnoid hemorrhage; BA = basilar artery; MRA = magnetic resonance angiography; mRS modified Rankin Scale; PICA = posterior inferior cerebellar artery.

^amRS: 2 = slight disability, 3 = moderate disability.

^bIn original screening study.⁴

^cSmoking at time of questionnaire.

^dHypertension at time of questionnaire or history of hypertension.

For the 3 episodes of aSAH identified in our follow-up study, we have definite proof that aSAH had occurred and that it was caused by an aneurysm. In 2 of the 3 patients, the aneurysm had developed after the screening, because also in retrospect, the aneurysm was not visible on the initial MRA. In the third patient, the site of the ruptured aneurysm was not visualized on the screening. Thus, although the screening was negative, this aneurysm may have been present at the time of the screening. Therefore, it is uncertain whether this last aneurysm is also truly de novo.

It would be helpful to identify risk factors associated with the occurrence of aSAH, such as smoking and hypertension, during follow-up after negative screening, but the number of screenees who had aSAH was too small for such an analysis.

The incidence of aSAH in our study was compared with the population-based incidence found in a large systematic review on the incidence of aSAH.⁵ Because this review provided incidence rates per different age and sex categories, we were able to calculate the population-based incidence rate of aSAH, adjusted for the age and sex distribution of our cohort. Therefore, we are confident that we have used a precise estimation of the incidence of aSAH in a healthy population. In the current study, we could only assess the incidence of aSAH after a negative screening for the first 15 years after the screening.

Whether the difference between first-degree relatives of patients with aSAH and the general population becomes larger on long-term follow-up is no more than speculation.

In persons with 2 or more affected first-degree relatives, the reported prevalence of new intracranial aneurysms is 8% at first screening and remains at approximately 5% at every 5-year cycle during the first 20 years after the initial negative screening.^{6–9} In such persons, repeated screening is cost-effective with an optimal screening strategy every 7 years from age 20 until 80.² In contrast, in persons who have only one first-degree relative with aSAH, the prevalence of unruptured intracranial aneurysms at initial screening is approximately 4%, and Markov modeling showed that screening is neither effective nor efficient.⁴ Therefore, screening is currently not recommended for these persons. In that modeling study, relatives with negative screening were assumed to be no longer at risk of aSAH. Our current data show that this assumption no longer holds true. Furthermore, risks of complications of treatment of unruptured aneurysms probably have decreased since 1995, when we performed the modeling study. Thus, with the improved preventive treatment of aneurysms and the continuing risk of aSAH after a negative screening for aneurysms, the question arises whether serial screening is effective and efficient for first-degree relatives of patients with aSAH. The ideal

Table 3 Incidence and incidence rate ratios^a

	Incidence per 100,000 patient-years (95% CI)	Incidence rate ratio (95% CI)
Primary analysis with all relatives (n = 601)	33.6 (6.9–98.1)	1.7 (0.3–5.7)
Analysis relatives with direct follow-up data (n = 432)	47.0 (9.7–137.3)	2.3 (0.3–6.0)
Analysis relatives with direct or indirect follow-up data (n = 568)	35.6 (7.3–103.9)	1.8 (0.4–7.9)

Abbreviation: CI = confidence interval.

^aIncidence ratios were calculated by dividing the observed incidence rate in our study population by the expected incidence for the general population, considering its age categories and sex distribution.

design for a study on the effectiveness of screening would be a randomized trial comparing several screening strategies with no screening, but because the absolute risk is still very small, such a trial would need a follow-up of more than a decade in a very large study group. Instead, an updated decision analysis including long-term follow-up, serial screening, and updated data on risks of aneurysm treatment is warranted to assess the effectiveness and efficiency of screening first-degree relatives of patients with aSAH.¹⁰ Until data from such a study are available, we currently still advise against serial screening in such relatives.

AUTHOR CONTRIBUTIONS

I.R., Y.M.R., P.G., and M.J.H.W. collected the data. I.R., Y.M.R., and M.J.H.W. were responsible for the data management and statistical analysis. B.K.V. and T.D.W. reviewed the MRAs. I.R. interpreted data and wrote the first draft of the article. All authors contributed to a review of the study findings and the writing of the paper.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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