

Original Research Article

Subarachnoid haemorrhage and intracranial aneurysms in Greenland in the period 2018–2021: incidence, outcome and familial disposition

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ABSTRACT

Subarachnoid haemorrhages (SAH) caused by rupture of intracranial aneurysms (IA) are a severe condition. Earlier studies found a higher incidence of SAH in Greenlandic patients compared to Danish patients, with familial aggregation also higher in Greenland. However, updated data is lacking. To investigate the contemporary incidence, outcome, and familial disposition of SAH/IA in Greenlandic patients in 2018–2021. Greenlandic patients diagnosed with ruptured or unruptured IA (UIA) during 2018–2021 were included. Data was obtained from patient files, x-ray department, and discharge registry. Incidence rates were estimated as cases/100,000/year. Direct age-standardised incidence rates were calculated using WHO 2000–2025 as standards. Of 30 SAH patients, 20 (66.7%) were females, 10 (33.3%) males. Of 36 UIA patients, 27 (75.0%) were females, 9 (25.0%) males. For SAH, crude incidence was 13.4/100,000/year, age-standardised incidence was 10.8/100,000/year. Familial history was observed in 30.0% of SAH patients. 5 patients (16.7%) died before treatment, 28-day case-fatality rate (CFR) for all patients was 23.3%. Overall and age-standardised incidence rates were similar to previous studies but higher among females and compared to neighbouring countries. A high occurrence of familial history was reported. SAH remains a serious condition in Greenland, as evidenced by five fatalities before treatment was administered.

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Introduction

A subarachnoid haemorrhage (SAH) caused by the rupture of an intracranial aneurysm (IA) is a type of haemorrhagic stroke accounting for 5% of the strokes globally [1] and 6.4% of the strokes in Greenland [1,2].

It is a condition with high morbidity and mortality, often leaving survivors with disability or incomplete recovery (50%) [1,3–8]. If diagnosed, specialised care and immediate surgical or endovascular treatment is required to avoid rebleeding and limit complications [1,5,7–14]

Risk factors for IA development include smoking, hypertension, excessive alcohol consumption, family history and certain genetic disorders [1,8,15–19]. Risk factors for rupture are related to aneurysm size and location [20–22]. Familial occurrence is well described and first-degree relatives have up to seven-fold increased risk of having SAH, indicating a genetic influence [1,8,13,15,23–25]

While the global incidence of SAH has declined from 1 0.2/100,000 in 1980 to 6.1/100,000 per population in 2010, considerable geographical variation persists [1,8,26]. The

incidence of SAH in Greenland has been reported to be approximately 1 0.0/year/100,000 in previous studies [2,27]. When compared to neighbouring countries, the incidence rate of SAH has been reported higher in Greenlandic Inuit compared to Caucasian Danes. In 30–40-year-old studies, the annual incidence rate of SAH for all ages was 9.1 for Inuits versus 3.1 for Danes per 100,000 person-years [23,27]. The incidence rate of SAH in Denmark is currently 5.1/year/100,000 [28], while the current incidence of SAH in Greenland is unknown.

A 2003 study reported the proportion of patients having a family history of UIA or SAH in Greenland to be 23.1% amongst SAH cases and 9.6% for UIA cases, as compared to 4.3% and 1.6% in Danish patients [23].

Given the previously reported high incidence rates of SAH, evidence of familial aggregation in Greenland along with the current challenges of smoking and hypertension as major public health challenges in Greenland [29–32], this study aims to investigate the contemporary incidence, outcome and familial disposition to UIA and SAH in Greenland.

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Material and methods

Study design and period

The study was performed as a retrospective case series and incidence study. All patients admitted to Queen Ingrid's Hospital (QIH) in Nuuk and diagnosed with ruptured (SAH) or unruptured IA (UIA) during the period between 1 January 2018, to 31 December 2021, were included.

Settings

Greenland, with approximately 56.000 residents as of 1 January 2020 [33], is primarily inhabited in the five largest towns, including the capital Nuuk [33]. The national hospital, QIH, located in Nuuk, has additional functions and specialties compared to the regional hospitals and is home to the only CT- and MR-scanner in Greenland. If a patient is suspected to suffer from SAH, evacuation to QIH, Nuuk is necessary for diagnosis and initial treatment [9,10] before further transport to Denmark for specialised care. Healthcare in Greenland is free, but access can be problematic as great distances and rugged terrain separate populated areas. Often patients are transported by boat, plane, or helicopter which depends on weather conditions. Medical evacuations from the coast to QIH can therefore be impeded [34]. In recent years, screening for IAs has been offered to patients >30 years with a positive family history. They are referred to QIH, Nuuk for a computed-tomography angiography of the cerebrum (CT-C-angio) [10]. If an aneurysm is discovered, the patient is discussed with neurosurgeons and interventional radiologists at Copenhagen University Hospital, Rigshospitalet (RH), Denmark to suggest either treatment or radiological follow-up. This follow-up can be done as a CT-angio or magnetic resonance angiography (MR-angio) in QIH, Nuuk, Greenland. However, treatment of the UIA is performed at RH in Denmark.

Study population

All Greenlandic patients diagnosed with the International Classification of Diseases (ICD-10) of SAH (I60), or cerebral aneurysm, non-ruptured (I671) [35] were retrieved through the Greenlandic Patient Discharge Registry. In addition, we included all patients with one or more CT-C-angio verified aneurysms at QIH in the 4-year study period.

Data sources

Data were obtained from the X-ray department with a list of all completed CT-C-angio. All patients discharged from the hospital with the mentioned ICD-10 and a list of patients admitted to the Department of Neurosurgery in Denmark were retrieved through the digital surgical work board at the department.

Data on symptoms, risk factors, gender, date of admission, location and number of aneurysms, clinical representation, examination results, and outcome were obtained from patient files.

Data on the background population was extracted from Greenland Statistics [33] and The Greenland population health survey 2018 [36].

Definition of variables

SAH was defined as blood in the subarachnoid space, verified on CT.

UIA were identified on a CT-C-angio and described by a radiologist. If a patient had multiple control scans during the study time, data was retrieved from the most recent. For patients undergoing treatment of the UIA within the study period, data were retrieved from the date of surgery.

Multiple aneurysms were defined as more than one.

Familial disposition was defined as having at least two first-degree relatives with SAH or UIA [37] or one first-degree relative and multiple (≥ 2) affected family members. In this study, patients with reports of familial history mentioned in patient files were included. If there was missing data of familial history in the patient file, the patient was categorised as not having familial disposition.

Only current smoking at the time of admission was defined as a risk factor. Smoking cessation was not accounted for.

Hypertension was based on data from patient files and was defined as the history of a relevant diagnosis code or the use of antihypertensive medication at the time of admission [38].

Outcome was measured as death before treatment, 28 days mortality and 1 year mortality, or dependent or independent outcome. Mortality was calculated as case-fatality rate (CFR) for survivors who received treatment and overall, for SAH patients.

Dependent outcome was defined as a state of condition that did not allow the patient to return to their baseline health before the diagnosis (such as concentration and memory problems, neurological deficits).

Independent outcome included patients who did not suffer from sequelae.

Other variables recorded were location and number of aneurysms, clinical representation (headache/vomiting, seizures, neurological deficits, loss of consciousness), treatment performed (clipping or endovascular treatment), and postoperative complications (hydrocephalus, infections, re-bleeding, infarcts, vasospasms) if mentioned in the discharge journal from the Department of Neurosurgery, Denmark.

Statistics

Age and gender-specific incidence rates were calculated using the Greenlandic population aged 20–79 years as per 1 January 2020 [33] as background population. Age was described using medians and interquartile range (IQR).

A confidence interval of 95% was used in the study and a p -value <0.05 was used as the level of significance. Direct age-standardised incidence rate was calculated using the WHO 2000–2025 as the standard [39]. Chi-square tests and Fisher's Exact test were used to compare frequencies. Statistical analyses were performed using IBM SPSS statistics version 28.

Ethics:

The study was approved by The Ethics Committee in Greenland (reference no. 2022–14) and by The Agency for Health and Prevention in Greenland.

Results

Study population

During the study period, a total of 48 patients with SAH and 68 patients with UIA were identified with a relevant discharge diagnosis or CT-C-angio. Of these, 18 patients with SAH were excluded as the date of incident was prior to the study period. Of UIA patients, 32 were diagnosed outside of the study period and excluded, however they were monitored regularly with control scans.

Characteristics SAH

Thirty patients suffered from SAH, 20 (66.7%) females and 10 (33.3%) males. The median age was 51.5 (IQR = 15) with the youngest being 28 years old and the oldest 68 years old.

The clinical presentations included headache/vomiting (74.2%), seizures (25.8%), focal neurological deficits (9.7%), loss of consciousness (22.6%) or a combination of two or more symptoms (32.3%).

Risk factors included hypertension $n = 8$ (26.7%), smoking $n = 18$ (60.0%), none or unknown $n = 9$

(30.0%). Nine (30.0%) of the patients had reports of familial history. Amongst patients with familial history, there were significantly more patients with multiple aneurysms ($p = 0.032$) compared to non-familial cases. The aneurysm was also more often ($p = 0.35$) located on the middle cerebral artery (MCA) amongst familial cases. In total, the rate of multiple aneurysms was 40.0% and the rate of MCA aneurysms was 36.7%.

Five patients died before receiving initial neurosurgical treatment, while 25 were admitted to the Department of Neurosurgery in Denmark for treatment where 15 patients received surgical treatment and 10 received endovascular treatment. See Table 1, 2 & 3.

Characteristics UIA

Of the 36 patients diagnosed with UIA, 27 (75.0%) were females and 9 (25.0%) males. The median age was 53 (IQR = 16). Twenty-four (66.7%) were reported smokers, 12 (33.3%) had hypertension and 10 (27.8%) had no reports of or no risk factors stated. 19 (52.8%) of the UIA patients did not require intervention while 13 (36.1%) received surgical treatment and 4 (11.1%) received endovascular treatment. More than half (52.8%) of the patients had reports of familial history. Amongst patients with familial history, there were significantly more with hypertension ($p = 0.011$) compared to non-familial cases. The location of the aneurysm did not differ between familial and non-familial cases nor did the number of patients with multiple aneurysms. However, the rate of MCA aneurysms was 66.7% for both familial and non-familial cases and the rate of multiple aneurysms was 33.3% across familial and non-familial cases and 42.1% for familial cases. See Table 1 and Table 2.

Incidence of SAH and UIA

The overall estimated crude incidence rate of SAH was 13.8/100,000/year (95% CI, 9.3–18.3) and 16.0 (95% CI, 11.2–20.9) for UIA. Age-standardised incidence rate was 1 0.8/100,000/year and 13.5/100,000/year for SAH and UIA respectively. Results can be seen in Table 1.

The incidence rate of SAH for all ages (20–79) was significantly higher for women than men ($p = 0.03$, OR = 0.44, 95% CI 0.2–0.93). The same was true for UIA ($p < 0.001$, OR = 0.29, 95% CI 0.14–0.62). See Table 1.

Outcome SAH

Of all 30 patients, 5 (16.7%) died before receiving treatment. The 28-day CFR for all patients, whether they

Table 1. Characteristics of patients.

Study population	SAH <i>n</i> = 30(%)	Familial SAH <i>n</i> = 9(%)	UIA <i>n</i> = 36(%)	Familial UIA <i>n</i> = 19(%)
2018	4 (13.3)	-	5 (13.9)	-
2019	14 (46.7)	-	10 (27.8)	-
2020	7 (23.3)	-	11 (30.6)	-
2021	5 (16.7)	-	10 (27.8)	-
Total	30 (100)	9 (100)	36 (100)	19 (100)
Gender (%)				
Female	20 (66.7)	6 (66.7)	27 (75.0)	15 (78.9)
Male	10 (33.3)	3 (33.3)	9 (25.0)	4 (21.1)
Multiple aneurysms (%)				
Yes	12 (40.0)	4 (44.4)	12 (33.3)	8 (42.1)
No	14 (46.7)	5 (55.6)	24 (66.7)	11 (57.9)
Unknown	4 (13.3)	-	-	-
Risk factors (%)				
Smoking	18 (60.0)	8 (88.9)	24 (66.7)	10 (52.5)
Hypertension	8 (26.7)	3 (33.3)	12 (33.3)	6 (31.6)
None/unknown	9 (30.0)	1 (11.1)	10 (27.8)	6 (31.6)
Familial disposition (%)				
Yes	9 (30.0)	9 (100)	19 (52.8)	19 (100)
No	21 (70.0)	0 (0)	17 (47.2)	0 (0)
Treatment (%)				
Surgical	15 (50.0)	7 (77.8)	13 (36.1)	5 (26.3)
Endovascular	10 (33.3)	2 (22.2)	4 (11.1)	2 (10.5)
None	5 (16.7)	0 (0)	19 (52.8)	12 (63.2)
Median age (IQR)				
Females	51.5 (19)	-	-	-
Males	51.5 (18)	-	-	-
All	51.5 (15)	50 (14)	46 (10)	46 (11)
Crude incidence n/100.000 person-years/year (95% CI)				
All	13.4 (8.9–17.8)	-	16.0 (11.2–20.9)	-
Females	18.8 (11.5–29.1, <i>p</i> = 0.03*)	-	25.4 (16.8–37.0, <i>p</i> < 0.0006*)	-
Males	8.5 (4.1–15.6)	-	7.6 (3.5–14.5)	-
Age-standardised incidence n/100.000 person-years/year	10.8	-	13.5	-

* Level of significance *p* < 0.05, when comparing female and male frequencies. Background population were age-groups 20–79.

Table 2. Aneurysm characteristics.

Location of aneurysm (%)	SAH (%) <i>n</i> = 30	Familial SAH (%) <i>n</i> = 9	UIA (%) <i>n</i> = 36	Familial UIA (%) <i>n</i> = 19
MCA – Middle cerebral artery	11 (36.7)	5 (55.6)	24 (66.7)	13 (68)
Posterior cerebral artery	1 (3.3)	1 (11.1)	2 (5.6)	0 (0)
ACOM – Anterior communicating artery	12 (40.0)	2 (22.2)	0 (0)	0 (0)
PCOM –posterior communicating artery	3 (10.0)	1 (11.1)	0 (0)	0 (0)
ICA – interna carotid artery	0 (0)	0 (0)	7 (19.4)	2 (11)
ACA – anterior cerebral artery	0 (0)	0 (0)	2 (5.6)	2 (11)
Pericallosa	0 (0)	0 (0)	0 (0)	1 (5)
Basilaris	0 (0)	0 (0)	2 (5.6)	2 (11)
Anterior choroidea artery	0 (0)	0 (0)	0 (0)	1 (5)
Unknown	5 (16.7)	1 (11.1)	4 (11.1)	2 (11)

Table 3. Clinical features and complications for SAH patients.

Clinical features (%) <i>N</i> = 30	<i>n</i>	%
Headache/vomiting	23	76.7
Seizures	8	26.7
Loss of consciousness	7	23.3
Focal deficits	3	10.0
Combination of two or more	10	33.3
Complications (%) <i>n</i> = 25		
Post OP* complications	14	56.0
No complications	8	32.0
Unknown	3	12.0

*Post operative complications.

received treatment or not, was 23.3% while 28-day CFR when only looking at patients who received treatment was 8.0%. One-year CFR was 12.0% for patients who

received treatment and 26.7% for all SAH patients. Of the 25/30 patients who received treatment, 13/30 (52%) of the patients were dependent afterwards while 9/30 (36%) were independent. See Table 4.

Discussion

Incidence rates for SAH and UIA

The crude incidence rates for SAH and UIA per 100,000/year were 13.8 (95% CI, 9.3–18.3) and 16.0 (95% CI, 11.2–20.9), respectively, with age-

Table 4. Outcome.

Outcome	Case-fatality (%) for 25 patients receiving treatment (95% CI)	n/N	Case-fatality (%) for all 30 patients	n/N
Dead before treatment	–	–	16.7 (5.4–38.9)	5/30
<28 days mortality	8.0 (1.0–28.9)	2/25	23.3 (9.4–48.1)	7/30
<1 year mortality	12.0 (2.5–35.1)	3/25	26.7 (11.5–52.5)	8/30
Survivors – dependent	52.0 (27.7–88.9)	13/25	43.3 (23.1–74.1)	13/30
Survivors – independent	36.0 (16.5–68.3)	9/25	30.0 (13.7–56.9)	9/30

standardised incidence rates at 10.8 for SAH and 13.5 for UIA cases.

More than two-thirds of SAH and UIA cases were females ($p = 0.03$), consistent with findings of high incidences of SAH in postmenopausal females [40], suggesting a potential sex-specific hormonal influence or influence from genes localised to the X chromosome [1,41–43].

The incidence rate, while high in a global context, was consistent with previous findings in Greenland [2,27]. The results were based on patients who made it to the hospital, possibly underestimating the already high incidence. Geographical differences in SAH incidence exist within Europe, with rates per 100,000/year, ranging from 6.3 overall, 8.0 in Iceland, 5.7 in Norway, 16.6 for southern Finland and 5.1 in the Capital Region of Denmark [26–28,40,44,45]. The global incidence of SAH over time has seen a decrease [1,26] associated with a decrease in blood pressure [26] and smoking rates [46]. In Greenland, 52% of the population are daily smokers and hypertension prevalence in 2021 was 17.5% for patients >20 years of age [30,31,36]. In this study, 18/30 (60.0%) and 24/36 (66.7%) of patients with SAH and UIA, respectively, were smokers while 8/30 (26.7%) and 12/36 (33.3%) of patients with SAH and UIA had hypertension. Smoking cessation was not accounted for, a limitation given its risk factor status. Excessive alcohol consumption is another risk factor [1,8,47]. Despite a slight decrease over the past few years, the prevalence of alcohol misuse in Greenland remains high [29,32,36]. Data on alcohol consumption would have been a strength to include, but it was not feasible due to missing data. Most SAH patients were young with limited healthcare contact prior to the incidence.

The incidence rate of SAH has remained somewhat constant in Greenland over the past 40 years, despite fewer daily smokers and more hypertension cases [36]. Regardless of the slightly elevated prevalence of smoking and hypertension within the study population, along with potential familial lifestyle factors [48], these risk factors alone cannot fully explain the high incidence rate observed in Greenland.

Familial disposition

Familial disposition was observed amongst 9/30 (30.0%) of SAH patients and 19/36 (52.8%) of UIA patients. However, assessing familial history imposed a challenge due to missing data. Questions regarding familial disposition and risk factors may not have been prioritised in the acute phase. The reported high familial history among UIA patients likely reflects selection bias as most IAs were discovered through patient-requested screening rather than incidental findings.

A 2003 study by Lindgaard et al. [23] found a higher rate of familial history in Greenlandic patients; 21.1% for SAH and 9.6% for UIA compared to 4.3% and 1.6%, respectively, for Danish patients. The high report of familial history in our study might be overestimated due to classification bias, as not all mentions in patient files adhere to correct definitions. However, the 2003 study defined familial history as having at least one first- or second degree relative [23], while our study had a stricter definition. Family history was not verified by healthcare personnel, which is a limitation.

More than 40.0% of the patients with familial UIA and SAH had multiple aneurysms, with higher prevalence in females, consistent with other studies [13,23,41,49]. SAH patients with familial occurrence had a higher likelihood of having multiple aneurysms, and the 2003 study found that Inuits had a higher rate of multiple aneurysms compared to Danish patients [23]. The high overall proportion of patients with multiple aneurysms is noteworthy, as multiple aneurysms usually are found in approximately 20.0% of the patients [1,50]. Smoking and hypertension rates were higher amongst familial SAH cases (not significant). Conversely, UIA patients with familial history exhibited a lower prevalence of smoking compared to those with no familial history. Familial aneurysms were most often located at the MCA, and the rate of MCA aneurysms in Greenlandic patients was also higher compared to other studies [23,49,50]. The onset age of SAH did not differ from non-familial cases. This could be due to the small sample size. Despite possible biases, the observed familial occurrence was higher compared to earlier studies, and the results are consistent with a high rate of familial aggregation [23].

Outcome

In this study, the 28-days and 1-year CFR for all SAH patients, regardless of treatment status, was 23.3% and 26.7%, respectively, and 8.0% and 12.0% for treated patients. Due to a small sample size, CFR was calculated for patients receiving treatment and all diagnosed SAH cases. The 28-day mortality from 2011 to 2012 in Greenland was previously 30% [2], but it is unknown if this included patients who received treatment or not. Other studies reported CFR for treated patients of 33% at 1 month, 43% at 1 year [51], with the median CFR ranging from 27 to 44% [45,52]. Stauning et al. [14] reported the cumulative mortality for patients after treatment at 30 days, 3 months, and 12 months to be 10.7%, 12.9% and 16.1%, respectively, for Eastern Denmark, Greenland, and The Faroe Islands combined. However, their study included non-saccular SAH, making direct comparison of outcomes challenging. Interestingly, Stauning et al. [14] observed a higher risk of death amongst Greenlandic patients compared to Danes (not significant). This could reflect patient selection, as the time between verified SAH and treatment is longer in Greenland compared to Denmark. Our study found a higher 28-day CFR for all SAH patients compared to Denmark. However, the 28-day CFR for treated patients was lower than Denmark and median rates from other studies. This discrepancy may stem from selection bias and our small sample size. Results were based on survivors of the initial bleed, who were stable enough to be evacuated to Nuuk before final transfer to Denmark for treatment. Five patients of out 30 (16.7%) with poor clinical conditions were not evacuated for treatment. In general, 10–20% of SAH cases result in death before reaching a hospital [53–55]. Delays in transport from remote areas can introduce further challenges in comparing mortality to other studies. In Denmark, access to healthcare is easier and all patients are assessed for treatment regardless of condition and prognosis. Data on functional outcome is scarce and due to missing data, outcome beyond categorisation as independent or dependent was not possible.

Despite the low CFR for patients receiving treatment, SAH remains a serious condition in Greenland, with five patients dying before even receiving treatment. It is unclear how many patients in remote areas suffer from SAH.

Strengths and limitations

A major strength of this study was its coverage of the entire Greenlandic population and all data on

diagnosed cases of SAH and UIA, as all patients who survive the initial haemorrhage go through QIH.

However, if a patient is suspected to suffer from SAH, evacuation to QIH is indicated [10]. If the clinical condition is critical and GCS < 8, the prognosis is poor with marginal benefit of specialised treatment [56] and transfer is then pending for local assessment of recovery until the following day. Not all patients are evacuated to QIH and not all patients admitted to QIH receive treatment. The study population therefore consists of first-round survivors. Additionally, the study was limited by a small sample size, absence of data on potential confounding factors and missing data from patient files.

Conclusion

In conclusion, overall SAH incidence for all ages and age-standardised incidences was high compared to other countries but has remained somewhat constant over the past 40 years, despite changes in prevalence of smoking and hypertension. Incidence rates for both SAH and UIA were significantly higher amongst females, and there was an increase in reported familial history compared to prior studies. Familial cases of SAH were more likely to have multiple aneurysms and aneurysms located on the MCA compared to non-familial cases. This study had a lower CFR than other studies, most likely due to patient selection, as the results were based on patients surviving the initial haemorrhage and transfer to Denmark. SAH is a life-threatening disease, and it is of high importance to identify the population at risk. The high incidence rates of SAH and UIA in Greenland and familial occurrence cannot solely be explained by known risk factors, thus suggesting a genetic influence.

Future perspectives

Future research is necessary to understand why the UIA seem to aggregate in families. It is important to

investigate potential genetic factors within the Greenlandic population that may contribute to the high incidence of SAH and UIA. The mortality rate of the disease is high, and it is important to identify individuals at risk. This could be done by identifying known or new genetic factors.

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