Incidence, treatment, and case-fatality of non-traumatic subarachnoid haemorrhage in the Netherlands

R. Risseladaa,∗, L.M. de Vriesb,c,1, D.W.J. Dippeld, F. van Kootend, A. van der Lugte, W.J. Niessena,e,f, A. Firouzan,a,e, B.H.Ch. Strickerab,∗, M.C.J.M. Sturkenbooma,c

a Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands
b Department of Pharmaceutical Affairs and Medical Technology, Inspectorate for Health Care, The Hague, The Netherlands
c Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
d Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands
e Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands
f Faculty of Applied Sciences, Delft University of Technology, The Netherlands

ABSTRACT

Background: Non-traumatic subarachnoid haemorrhage (SAH) is a devastating disorder and in the majority of cases it is caused by rupture of an intracranial aneurysm. No actual data are available on the incidence of non-traumatic SAH and aneurysmal SAH (aSAH) in the Netherlands and little is known about treatment patterns of aSAH. Our purpose was therefore to assess the incidence, treatment patterns, and case-fatality of non-traumatic (a)SAH within the Dutch general population.

Methods: Two population based data sources were used for this retrospective cohort study. One was the nationwide hospital discharge registry (National Medical Registration, LMR). Cases were patients hospitalized for SAH (ICD-9-code 430) in 2001–2005. The second source was the Integrated Primary Care Information (IPCI) database, a medical record database allowing for case validation. Cases were patients hospitalized for SAH (ICD-9-code 430) in 1996–2006. Incidence, treatment, and case-fatality were assessed.

Results: The incidence rate (IR) of non-traumatic SAH was 7.12 per 100,000 PY (95%CI: 6.94–7.31) and increased with age. The IR of aSAH was 3.78 (95%CI: 2.98–4.72). Women had a twofold increased risk of non-traumatic SAH; this difference appeared after the fourth decade. Non-traumatic SAH fatality was 30% (95%CI: 29–31%). Of aSAH patients 64% (95%CI: 53–74%) were treated with a clipping procedure, and 26% (95%CI: 17–37%) with coiling.

Conclusion: Non-traumatic SAH is a rare disease with substantial case-fatality; rates in the Netherlands are similar to other countries. Case-fatality is also similar as well as age and sex patterns in incidence.

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1. Introduction

Non-traumatic subarachnoid haemorrhage (SAH) is a devastating event, with a case-fatality of around 30% [1,2]. Incidence rates have been assessed in many countries and two patterns can be distinguished: countries with high incidence of around 20 per 100,000 person years (PY), such as Finland and Japan, and countries with low incidence of approximately 5–10 per 100,000 PY [3].

Approximately 85% of non-traumatic SAH is a result of rupture of an intracranial aneurysm (IA), although it is not clear whether this percentage is the same over different age and sex categories [1]. Causes of spontaneous SAH from other origins include other vascular lesions, inflammatory and non-inflammatory lesions, tumours, and drug or substance use [1,4].

The diagnosis of SAH is primarily based on CT imaging and lumbar puncture, eventually followed by angiography; not only to identify an aneurysm as potential cause of the haemorrhage, but also to study the anatomical and morphological configuration of the aneurysm in relation to adjoining arteries, which allows for optimal treatment selection [1]. Treatment of aneurysmal SAH (aSAH) consists mainly of either neurosurgical clipping or endovascular coiling. Other less frequently used treatment modalities comprise wrapping, stenting, or balloon occlusion [5–7].

Given the fact that no recent data on age and sex specific incidence of non-traumatic SAH and aSAH in the Netherlands are available, we assessed the incidence of both conditions in the general Dutch population. Moreover, we studied case-fatality, and
treatment modalities applied to aSAH patients. This was done in two population based databases; a national discharge database and a smaller medical record database which allowed for assessment of the presence of an aneurysm and treatment modality.

2. Materials and methods

2.1. LMR database

Hospital discharge diagnoses were obtained from the national registry of hospital admissions, the National Medical Registration (LMR), containing information on all admissions in general and academic hospitals throughout the Netherlands (base population: approximately 16.5 million subjects). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to classify hospital admissions in the Netherlands during the study period. Data used include hospital code, patient sex and age, ICD-9-CM coded discharge diagnosis, up to 9 diagnostic or therapeutic procedures (coded according to the LMR Classification of Diagnostic, Therapeutic, and Surgical Acts), and discharge destination (‘home’, ‘old people’s home’, ‘nursing home’, or ‘died in hospital’).

Non-traumatic SAH cases were all admissions with a primary discharge diagnoses (ICD-9-CM) 430 (non-traumatic subarachnoid haemorrhage) during the years 2001 through 2005. Case-fatality was defined as dying in the hospital during hospitalization for SAH.

The denominator for the incidence calculation was the annual mid-year population size as obtained from Statistics Netherlands (CBS, accessed through http://www.cbs.nl, as of June 7th, 2010).

2.2. IPCI database

The Integrated Primary Care Information (IPCI) database is a general practice research database with electronic medical record data currently comprising more than one million patients throughout the Netherlands. The patient population is representative of the Dutch population regarding age and sex [8]. Details of the database have been described elsewhere [9]. The system complies with the European Union guidelines on the use of medical data for research and has been proven valid for epidemiological studies [9]. The Scientific and Ethical Advisory Group of the IPCI project approved the study (Project No. 07/02). The database allows for validation of disease by requesting additional information from the general practitioner by questionnaire and copies of original specialist letters.

Potential cases of non-traumatic SAH and aSAH were identified from the IPCI database using an extensive narrative search; we identified potential cases in the computerized records by searching for International Classification of Primary Care (ICPC) codes of ‘cerebrovascular accident’ (K90), ‘other diseases of peripheral arteries’ (K92), or ‘other diseases of the circulatory tract’ (K99), and by free text searches on ‘intracranial’, ‘aneurysm’, ‘subarachnoid’, ‘haemorrhage’, or ‘nimodipine’. In the Netherlands, nimodipine is exclusively prescribed as prophylaxis for delayed cerebral ischemia after aSAH.

To further validate the diagnosis of SAH, a short questionnaire was mailed to the GPs. The questionnaire was used to confirm whether the person, according to the GP’s judgment, indeed suffered from (aneurysmal) SAH, and whether the patient had been seen and diagnosed by a specialist. Copies of all specialist letters were requested. Specialist letters usually provide information about history, physical examination, lumbar puncture, and reports on imaging of the patient.

All cases were validated by manual review of the electronic medical record and subsequently by review of the questionnaires and specialist letters that were obtained from the GP for each case. The validity of the diagnosis was judged by a medical doctor (R.R.) and a neurologist (D.W.J.D. or F.K.). The judgment of the neurologist was decisive. Case-fatality was defined as dying within a period of 30 days after the date of onset of SAH (index date).

The denominator for the incidence calculation was the number of person years in the IPCI database during the study period (January 1996–September 2006).

2.3. Statistical analysis

The incidence rate of non-traumatic SAH and aSAH was calculated by dividing the number of incident cases (numerator), by the total number of accrued person years (IPCI) or persons (LMR) in the study population (denominator). Incidence rates (IR) were calculated in age and sex categories. Confidence intervals (95% CI) for each estimate were based on the Poisson distribution. To estimate case-fatality of aSAH in the IPCI database, Kaplan–Meier survival analysis was used. Incidence rates were used to calculate rate ratios of non-traumatic SAH and aSAH between females and males. All analyses were performed using SPSS software version 15.0 (Chicago, Ill., USA).

2.4. Literature review

To compare our Dutch findings with the existing literature on this topic, we performed a systematic review of the literature from October 2005 onwards, adding to the review of De Rooij and co-workers on the same topic, which ended in October 2005 [3]. A similar Medline search was used: (“Stroke”[Mesh] OR “Subarachnoid Haemorrhage”[Mesh]) AND (“Epidemiology”[Mesh] OR “Population”[Mesh] OR “Incidence”[Mesh]) for the time period from October 2005 to May 2009. The papers thus obtained were abstracted manually by one researcher (R.R.). Our inclusion criteria were: (1) study population is representative of the population in general; and (2) for studies about stroke in general, SAH should be considered as a separate entity. We excluded papers reporting incidence rates in Finnish and Japanese populations, since these rates are consistently higher than in other populations and therefore add little to the comparison with our findings [1].

3. Results

3.1. LMR: non-traumatic SAH

In the period 2001–2005 a total of 5769 patients (64% female) were admitted to Dutch hospitals with discharge diagnosis ‘non-traumatic subarachnoid haemorrhage’. The overall nationwide incidence rate of non-traumatic SAH was 7.12 per 100,000 person years (PY) (95% CI: 6.94–7.31) (Table 1). The incidence rate increased rapidly with age (Table 1, Fig. 1). The overall incidence rate of non-traumatic SAH was 7.12 per 100,000 person years (PY) (95% CI: 6.94–7.31) (Table 1). The incidence rate was 1.72 (95% CI: 1.63–1.81). This differential risk occurred gradually and was most pronounced in the fourth and fifth decade (Table 1, Fig. 1). Case-fatality for non-traumatic SAH during hospitalization was 30% (95% CI: 29–31%), and increased with age, but did not differ between males and females (Table 1).

3.2. IPCI database: non-traumatic SAH and aSAH

In the initial source population of 488,118 persons, 107 incident cases of non-traumatic SAH (70% female) were identified after validation (Table 1). Based on these data the observed crude rate of non-traumatic SAH was 5.53 per 100,000 person years (PY) (95% CI: 4.56–6.66) (Table 1), which translates to a rate of 6.48 per 100,000 PY in the Netherlands after standardization to the Dutch age and
Table 1

Incidence rates of SAH by age and sex in the LMR and IPCI databases.

<table>
<thead>
<tr>
<th>Age</th>
<th>LMR SAH cases (n)</th>
<th>IR</th>
<th>95% CI</th>
<th>Fatality&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IPCI SAH cases (n)</th>
<th>IR</th>
<th>95% CI</th>
<th>Fatality&lt;sup&gt;b&lt;/sup&gt;</th>
<th>IPCI aSAH cases (n)</th>
<th>IR</th>
<th>95% CI</th>
<th>Fatality&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>&lt;40</td>
<td>570</td>
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<td>1.23–1.45</td>
<td>19.47</td>
<td>15</td>
<td>1.28</td>
<td>0.75–2.06</td>
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<td>12</td>
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<td>6.96–21.59</td>
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<td>Total</td>
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<td>7.12</td>
<td>6.94–7.31</td>
<td>29.75</td>
<td>107</td>
<td>5.53</td>
<td>4.56–6.66</td>
<td>25.5</td>
<td>73</td>
<td>3.78</td>
<td>2.98–4.72</td>
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</table>

<sup>a</sup> During hospitalization.

<sup>b</sup> Within 30 days, using Kaplan–Meier survival analysis.

sex distribution. The incidence rate increased with age and was similar to the LMR rates up until 64 years; rates were lower that that (Table 1).

In 68% of all IPCI derived non-traumatic SAH cases (n = 73) an aneurysm had been diagnosed (95% CI: 59–76%). In our study, the proportion of aneurysms as a cause of non-traumatic SAH seemed to diminish with age, although the trend is not statistically significant (data not shown).

The crude observed incidence rate of aSAH in IPCI was 3.78 per 100,000 PY (95% CI: 2.98–4.72), which would imply a rate of 4.26 per 100,000 for the Dutch population (age and sex standardized). Of the patients with an aneurysm the majority was treated by means of a neurosurgical clipping procedure (64%, 95% CI: 53–74%) and 26% (95% CI: 17–37%) by means of endovascular coiling. Five patients (7%) did not receive any treatment because of rapid deterioration and death. In the remaining 3% we could not find information on procedures.

Kaplan–Meier survival analysis showed that 26% of SAH patients died within 30 days (95% CI: 17–34%) (Table 1). Case-fatality in aSAH patients was 5.6% (95% CI: 0.31–10.9) (Table 1). Risks could not be estimated in separate treatment groups due to low numbers.

3.3. Literature review

The Medline query yielded 866 papers. After screening on title and abstract 48 studies remained for full text reading and finally 15 studies complied with the inclusion criteria. An overview of the results from the studies is given in Table 2. Incidence rates varied but in general remained below 10 per 100,000 PY. In almost all studies a female preponderance was seen. Case fatality ranged between 20 and 30%.

4. Discussion

We used two different population based databases: a hospital discharge database and an electronic medical record database to assess the occurrence, treatment, and case-fatality of non-traumatic SAH and aSAH in the Netherlands. We used both sources
Table 2
Published incidence rates of SAH, overall and in sex strata.

<table>
<thead>
<tr>
<th>1st author</th>
<th>Year</th>
<th>All IR</th>
<th>All 95% CI</th>
<th>Female IR</th>
<th>Female 95% CI</th>
<th>Male IR</th>
<th>Male 95% CI</th>
<th>All Case-fatality</th>
<th>All 95% CI</th>
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<td>De Rooij</td>
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<td>9.1</td>
<td>8.8–9.5</td>
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<td></td>
<td>2007²</td>
<td>10.5</td>
<td>9.9–11.2</td>
<td>11.5</td>
<td>10.6–12.6</td>
<td>9.2</td>
<td>8.4–10.2</td>
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<td>Benatru</td>
<td>2006</td>
<td>2.1²</td>
<td>1.04–3.21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>26.1</td>
<td>10.6–55.5</td>
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<td>Feigin</td>
<td>2006</td>
<td>10</td>
<td>8.0–12.0</td>
<td>10</td>
<td>7.0–13</td>
<td>10</td>
<td>7.0–13</td>
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<tr>
<td>Jiang</td>
<td>2006</td>
<td>1.6³</td>
<td>0.8–4.1</td>
<td>1.5⁴</td>
<td>0.6–6.7</td>
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<td>9</td>
<td>–</td>
<td>10</td>
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<td>27.5</td>
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<tr>
<td>Labovitz</td>
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<td>Vaartjes</td>
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<td>7.4–8.3⁷</td>
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<td>4.8⁹</td>
<td>1.5–11.4</td>
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<td>Sridharan</td>
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<td>4.2²</td>
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</table>

¹ Subset of 18 studies, reporting incidences for men and women separately.
² Calculated from data in the article.
³ Case-fatality within 28 days.
⁴ Case-fatality within 14 days.
⁵ Most recent period only.
⁶ Standardized to EU population.
⁷ White population only.
⁸ Age adjusted.

to profit from the size in the LMR and the quality of information and validation opportunities in the IPCI database. By using these data we revealed various important observations: first, the crude national incidence rate of non-traumatic SAH was between 5 and 7 cases per 100,000 PY, putting the Netherlands in the low incidence countries. Second, about 70% of non-traumatic SAH were of proven aneurysmal origin and this might vary slightly by age (lower in high ages). Third, case-fatality of non-traumatic SAH was high: around 26% within one month and this increased with age. Fourth, a striking age and gender pattern was observed in the incidence rates. The incidence rates increased rapidly after age 40, but mostly so for women. Fifth, the incidence rates for aSAH increased less rapidly with age than for non-traumatic SAH overall, suggesting a difference in the percentage of aneurysms by age. Sixth the majority of persons with an aSAH underwent surgical clipping.

Our findings on the rates and case-fatality were similar to previously published population-based studies from other countries. However, often the rates for aSAH are not available. The assumption that 85% of non-traumatic SAH is based on aneurysms, may therefore not hold true in general and perhaps specifically not for all age categories. Some of the previous studies have investigated sex specific rates and age–gender interaction, and also reported higher rates in women; however the age dependent change in incidence for women compared to men was reported few times. The reasons for the overall higher incidence in women are not clear, but hormonal factors would be a first logical option [10,11]. Our findings that the preponderance of women becomes evident around the menopause, during which changes in oestrogen levels take place, further supports this suggestion. Previously, an increase in cardiovascular risk among women after menopause has been recognized [12], for which declining endogenous oestrogen levels have been held responsible [13]. Declining levels of oestrogen might lead to impaired activation of nitric oxide [14], which is hypothesized to be an important factor in the aetiology of non-traumatic SAH through its effects on the vascular endothelium [15,16].

Being based on observational data the results of our study should be interpreted in the light of potential limitations, such as selection bias and information bias. Selection bias in assessment of rates and case-fatality is negligible in this study since we used population based databases. Selection may have occurred because validation of the discharge diagnoses for the LMR was done only in our hospital. Results of this validation may not be generalizable to all other centres. Thus, the most important limitation is misclassification of the outcome. For a patient to be considered a case in our study, the diagnosis non-traumatic SAH had to be made. Patients who died before reaching medical care were not included in the LMR estimate and it is highly likely that they were also missed in the IPCI database due to lack of a proper diagnosis and specialist information. Previous studies have estimated the percentage of persons dying outside hospitals to be between 11 and 13% [17,18]. This means that the true incidence is potentially 10% higher than in our estimations (up to 8 per 100,000 PY). Another potential limitation is the accuracy of the registered diagnosis in the LMR database. Validation of discharge diagnoses in our own hospital showed that 10% of the cases were false positive; including perimesencephal haemorrhage (data not shown). Inclusion of these false positive cases in incidence estimates would lead to overestimation. In the IPCI database, false positives were unlikely, since cases were validated. In both databases false negative misclassification has not been quantified. We think it is limited in the IPCI database as we applied a very sensitive search on codes and free text to identify potential cases and reviewed all potential cases manually.

Misclassification of mortality was an issue in the LMR database. Since the database only captures data during hospitalizations and is not linked to a death registry, it is not possible to obtain mortality data of patients once they are discharged from the hospital. We therefore chose to report on the mortality during hospital admission only. Nonetheless, the case-fatality is comparable to the case-fatality as estimated from the IPCI database that does capture follow-up and mortality data. This implies that most cases die often within relatively short time and mostly during hospitalization. Case-fatality of aSAH patients is remarkably low and may not represent true fatality of an aneurysmal SAH (Table 1). Severe cases may have died before undergoing imaging; in that case an aneurysm could not be proven. Less severe cases will probably have survived the 30 day period.

The strength of this study is that two separate databases were used to address not only non-traumatic SAH but also aSAH. Both are
observational and our study showed that they can be used complementary. Discharge databases are large which allows for fine stratification, but medical record databases allow for depth and more clinical insight. Together they have provided thorough insight in the occurrence, case-fatality, and rate of non-traumatic (a)SAH.

5. Conclusion

In this study we showed non-traumatic SAH incidence in the Netherlands is in the range of the low-incidence countries. We demonstrated that the incidence for both non-traumatic SAH and the subgroup of aSAH depends highly on age and sex but the patterns for aSAH might be slightly different than for non-traumatic SAH overall.

References