Risk factors in patients with perimesencephalic hemorrhage

L. A. Mensing\textsuperscript{a}, Y. M. Ruigrok\textsuperscript{a}, P. Greebe\textsuperscript{a}, M. H. M. Vlak\textsuperscript{a,b}, A. Algra\textsuperscript{a,c} and G. J. E. Rinkel\textsuperscript{a}

\textsuperscript{a}Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht; \textsuperscript{b}Department of Neurology, Slotervaart Hospital Amsterdam, Amsterdam; and \textsuperscript{c}Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Keywords: alcohol, hypertension, perimesencephalic hemorrhage, risk factor, smoking

Received 30 December 2013
Accepted 7 February 2014

Background and purpose: Smoking and hypertension are risk factors for aneurysmal subarachnoid hemorrhage (aSAH), whilst excessive alcohol consumption is less consistently linked with aSAH. Perimesencephalic hemorrhage (PMH) is a benign subset of non-aneurysmal subarachnoid hemorrhage. The exact cause of PMH is unknown, and its risk factor profile may help to elucidate the pathogenesis. The influence of smoking, hypertension and excessive alcohol consumption on the occurrence of PMH was studied.

Methods: Seventy-nine patients admitted with a PMH to the University Medical Center Utrecht were studied. As controls 574 persons were selected from five different general practices in the referral region of the University Medical Center Utrecht. All participants filled in a questionnaire about smoking habits, the presence of hypertension and alcohol consumption before their hemorrhage. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to assess the association of risk factors and PMH, and multivariable logistic regression was used to adjust for possible confounding by age and sex.

Results: Adjusted ORs for the occurrence of PMH were 1.7 (95% CI 1.0–2.8) for smoking cigarettes, cigars, pipes or any combination of these, 1.1 (95% CI 0.6–2.0) for hypertension and 1.1 (95% CI 0.5–2.1) for excessive alcohol consumption.

Conclusions: Similar to aSAH, smoking is a risk factor for PMH and excessive alcohol consumption is not. In contrast to aSAH, hypertension is not a risk factor for PMH. This implies that the pathophysiological mechanisms causing PMH might be slightly different from those causing aSAH.

Introduction

Smoking and hypertension are modifiable risk factors for aneurysmal subarachnoid hemorrhage (aSAH); recent studies found no relation between excessive alcohol consumption and the occurrence of aSAH [1–5]. Perimesencephalic hemorrhage (PMH) is a benign subset of non-aneurysmal subarachnoid hemorrhage, with an overall annual incidence rate of 0.5 [95% confidence interval (CI) 0.3–0.7] per 100 000 persons [6]. The cause of PMH is unknown and its risk factor profile may help to elucidate the pathogenesis.

Subjects and methods

Study population

From a prospectively collected database of consecutive SAH patients admitted to the University Medical Center Utrecht, all patients with PMH who were admitted from January 2005 until August 2011 were retrieved (n = 100). The diagnosis of PMH was based on MRI/MRA imaging findings and clinical presentation.
on the following criteria: computed tomography (CT) scan performed within 72 h after the onset of the headache showing a perimesencephalic pattern of hemorrhage and absence of an aneurysm on CT angiography or conventional angiography [8]. As controls, a series of 574 persons recruited from five different general practices in the referral region of the University Medical Center Utrecht between January 2009 and January 2010 were used [2,7]. These controls had also served as controls in a recent case–control study for which they had been matched for age and sex with a cohort of patients with aSAH [7]. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study protocol.

**Data collection**

All patients with PMH who were still alive and had not moved abroad were invited to participate in our study and received a structured questionnaire by mail about their smoking habits, the presence of hypertension and their alcohol consumption in the year before their hemorrhage. Patients who gave informed consent and returned the questionnaire were included in the study. The controls received the same questionnaire about their smoking habits, the presence of hypertension and their alcohol consumption in the past year. Patients were divided into non-smokers or smokers of cigarettes, cigars, pipes or any combination of these. Hypertension was defined as a history of hypertension as diagnosed by physicians or the use of antihypertensive drug(s). The presence of hypertension was checked against medical records to confirm that the diagnosis was made prior to the hemorrhage. Excessive alcohol consumption was defined as consumption of ≥18 units/week.

**Data analysis**

Crude odds ratios (ORs) with 95% CIs were calculated to assess the association of smoking (of cigarettes, cigars, pipes or any combination of these), hypertension and excessive alcohol consumption (≥18 units/week) with PMH, and multivariable logistic regression analyses were used to adjust for possible confounding by age and sex.

**Results**

Of our group of 100 patients with PMH four had moved abroad and one had died. The remaining 95 patients received a questionnaire of whom 79 (83%) returned it. The baseline demographic data and risk factor data of the 79 patients with PMH and 574 controls are summarized in Table 1.

For smokers of cigarettes, cigars, pipes or any combination of these the OR for the occurrence of PMH was 1.9 (95% CI 1.2–3.2) (Table 2). The association of smoking with PMH did not change after adjusting for age and sex (Table 2). ORs for the occurrence of PMH were 1.0 (95% CI 0.6–1.8) for hypertension and 0.8 (95% CI 0.4–1.6) for excessive alcohol consumption (Table 2).

**Discussion**

Smoking is a risk factor for PMH, but hypertension and excessive alcohol consumption are not associated with the occurrence of PMH. In a study on risk factors for aSAH using patients from the same hospital and the same controls, the same method of data retrieval and similar data analysis, both smoking and hypertension were found as independent risk factors for aSAH [2]. The finding that smoking, but not hypertension, is a risk factor for PMH could imply that the pathogenesis of PHM is different from the pathogenesis of aSAH.

The pathogenesis of PMH has not been elucidated yet. The most common assumption is that PMH has a venous instead of an arterial origin. Apart from the invariably good clinical condition on admission and the limited extension of the hemorrhage, other

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Univariable analysis</th>
<th>Age-and sex-adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>1.9 (1.2–3.2)</td>
<td>1.7 (1.0–2.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0 (0.6–1.8)</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>0.7 (0.4–1.2)</td>
<td>0.5 (0.3–1.0)</td>
</tr>
<tr>
<td>Alcohol ≥18 units/week</td>
<td>0.8 (0.4–1.6)</td>
<td>1.1 (0.5–2.1)</td>
</tr>
</tbody>
</table>

PMH, perimesencephalic hemorrhage; OR, odds ratio; 95% CI, 95% confidence interval.
arguments for a venous source are the higher presence of a primitive variant of venous drainage compared with controls and a higher cerebral blood flow on admission head CT perfusion in patients with PMH compared with patients with aSAH [9,10].

Since the pathogenesis of PMH is not known yet, it is only possible to speculate on the pathophysiological mechanism underlying the relation between smoking and the emergence of a PMH. Smoking induces multiple pathological effects in the endothelium as a result of vascular inflammation, oxidative stress and increased wall shear stress through increased blood viscosity and volume. As endothelium is part of arteries and veins, smoking could have a damaging effect on both of them [11,12]. Since hypertension has comparable pathological effects on the endothelium, it remains unclear why smoking and not hypertension is a risk factor for PMH [13].

Our study has some limitations. To demonstrate causality between a risk factor and a disease the ideal design for a study is a prospective population-based cohort study. However, given the low incidence of PMH such a study is almost impossible [6]. Secondly, the case-control design may lead to selection bias. This bias was minimized by recruiting controls from the referral region of our hospital. Compared with the patient group the control group includes more women (46% vs. 69%), which potentially may lead to confounding. However, the preponderance of women in the control group did not influence our study to a large extent since after adjustment for sex our results remained the same. Thirdly, our control group was previously matched for age and sex to a cohort of patients with aSAH [2], which may influence the efficiency of subgroup analysis on the association of risk factors per sex and/or age category. Therefore such subgroup analyses were not performed. Fourthly, there could be recall bias because a retrospective study design was used in which the patients had to report about their lifestyle up to 5 years before filling in the questionnaire, whereas controls had to report on their current situation. This may have led to under-reporting of risk factors in patients, consequently leading to a weaker association of smoking with PMH and a missed association of alcohol use or hypertension with PMH. However, it was not thought that in the analysis on hypertension under-reporting plays an important role since the presence of hypertension in the questionnaire was cross-checked with the presence of this diagnosis in the medical record and an agreement of more than 90% was found between the two. Lastly, it should be taken into account that the patients who completed our questionnaire could have under-reported their alcohol consumption or smoking habits, which would mean that the actual association between smoking and PMH is even stronger than was found.

A strong point of our study is the relatively large number of patients with PMH. Furthermore, PMH patients were compared with controls from the general population instead of with patients with aSAH as was done in most previous studies investigating potential risk factors for PMH [6,14,15]. These studies showed that patients with PMH are less likely to be hypertensive than patients with aSAH, and showed a trend towards less smoking amongst patients with PMH compared with patients with aSAH [6,14,15]. Thus far, only one other case-control study has compared risk factors in 40 patients with PMH to 120 controls selected from a general practice [16]. That study found hypertension to be an independent risk factor for PMH for both sexes, and smoking as a risk factor in women but not in men. These findings are partly in contrast with our study, as it was shown here that smoking is a significant risk factor for PMH adjusted for age and sex whilst hypertension is not. The substantially higher number of patients and controls in our study could explain this difference, by increasing the statistical power.

Our study shows that smoking, but not hypertension or excessive alcohol consumption, is a risk factor for PMH. Ideally one would like to perform histopathological studies comparing intracranial vessels from patients with PMH with those from patients with aSAH to further elucidate the pathogenesis of PMH in relation to that of aSAH. But given the invariably good outcome of PMH, intracranial vessels of these patients cannot be obtained. Improved imaging techniques such as 7T magnetic resonance or positron emission tomography studies looking for inflammatory responses in the vessel wall will shed further light on the pathogenesis of PMH.

Acknowledgement

Y.M. Ruigrok was supported by a NWO-VENI grant by the Netherlands Organisation for Scientific Research (NWO) (project no. 91610016).

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References


