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Conventional vascular and specific risk factors for intracerebral hemorrhage in females

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Summary. Intracerebral hemorrhage (ICH) is responsible for 10 to 15% of all strokes and associated with high mortality and disability. Conventional risk factors for ICH are advancing age, hypertension, cerebral amyloid angiopathy, tobacco and alcohol abuse, oral anticoagulation and reversible cerebral vasoconstriction syndrome (RCVS). Conventional vascular risk factors, as well as female specific risk factors, have not been thoroughly investigated for their possible sex specific roles in the risk of an ICH. This narrative review reports on studies to date that have investigated for sex specific roles in ICH risk. The limited body of research on females to date, however, does suggest that elderly age, pregnancy and RCVS are implicated in the reported higher risks of ICH. Large prospective studies are needed to investigate conventional and sex specific risk factors in ICH and their reciprocal interaction.

Key words: intracerebral hemorrhage, stroke.

Fattori di rischio convenzionali e specifici per emorragia cerebrale nelle donne

Riassunto. L'emorragia cerebrale (ICH) è responsabile del 10-15% di tutti gli ictus ed è associata ad elevata mortalità e disabilità. I fattori di rischio convenzionali per ICH sono età, ipertensione, angiopatia amiloide, abuso di tabacco e alcol, l'anticoagulazione orale e la sindrome cerebrale da vasocostrizione reversibile (RCVS). I fattori di rischio vascolari convenzionali, nonché i fattori di rischio specifici per il sesso, non sono stati ancora adeguatamente valutati nell'ambito degli aspetti di genere nell'ICH. Questa revisione narrativa riporta i dati osservati dagli studi fino ad oggi pubblicati, che hanno indagato lo specifico ruolo del sesso nel rischio di ICH. I dati sulla relazione tra sesso e ICH sono ad oggi limitati. Tuttavia questi suggeriscono che l'età, la gravidanza e la RCVS sono connessi con un maggior rischio nel sesso femminile per ICH. Sono comunque necessari, visto il limitato numero di studi significativi disponibili, grandi studi prospettici per indagare i fattori di rischio convenzionali e specifici per il sesso nell'ICH e la loro reciproca interazione.

Parole chiave: emorragia cerebrale, ictus.

Introduction

Intracerebral hemorrhage (ICH) is a spontaneous extravasation of blood into the brain parenchyma, responsible for 10 to 15% of all strokes and associated with poor outcome, including mortality and disability. According to the location, ICH is classified into either ganglionic (putamen, caudate and thalamus), lobar, cerebellar or pontine. ICH location correlates with causes, outcomes and potential treatments (Figure 1). Conventional risk factors for ICH are advancing age, hypertension, cerebral amyloid angiopathy (CAA), tobacco and alcohol abuse and oral anticoagulation.

These conventional vascular risk factors, as well as female specific risk factors, have not been thoroughly investigated for their possible sex specific roles in the risk of an ICH event[1-3] (Figure 2). This narrative review reports on studies to date that have investigated for sex specific roles in ICH risk.

Epidemiology

In a meta-analysis, carried out in 2010, ICH incidence was not significantly lower for either females or males[1], whereas the Dijon Stroke Registry, between 1987 and 2012, recorded crude ICH incidence rates per 100,000 of 8 and 12.9 for females and males, respectively. While for subarachnoid hemorrhage (SAH), these percentages were 3.9 and 3.5, respectively[4].

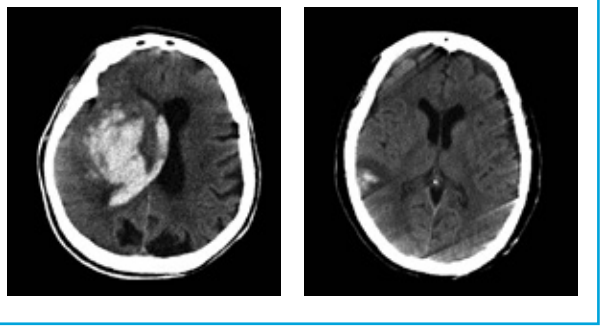

Figure 1. Intracerebral hemorrhage.

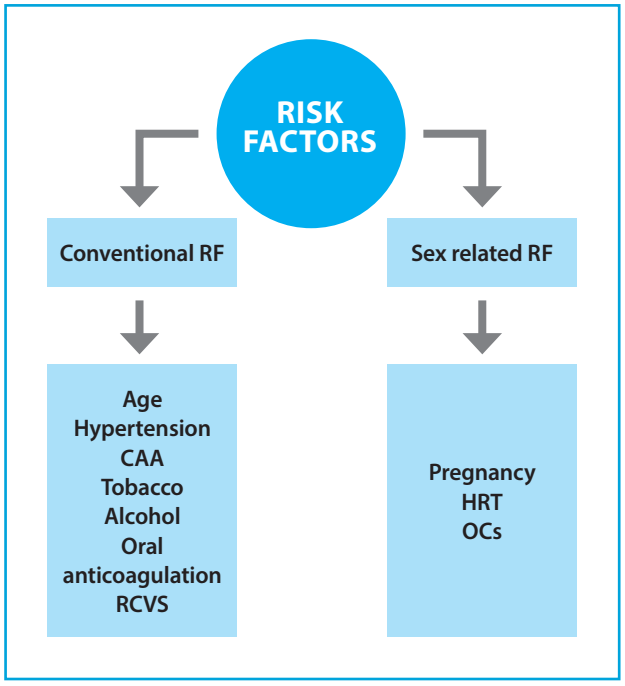

Figure 2. Conventional and sex-specific risk factors for intracerebral hemorrhage in females.

RF, risk factors; CAA, cerebral amyloid angiopathy; RCVS, reversible cerebral vasoconstriction syndrome; HRT, hormone replacement therapy; OCs, oral contraceptives.

Age

The risk of ICH in females has been reported to increase exponentially with age and sharply increase after age 55, doubling for each successive decade[5]. Moreover, in a large cohort of ICH patients, males had a higher risk of ICH than females for all groups under 80 years of age, but this risk was significantly increased in females over 80[5]. Likewise, the BasicMar hospital-based registry observed that females were on average older than males at ICH onset[2]. Furthermore, a systematic review reported that the age-adjusted male/female incidence ratio for ICH had two peaks: between 65-74 years and ≥85 years, with 1.74 and 1.75 of rate ratios, respectively[6]. Finally, a population-based incidence study has reported that at age below 65, males were at a significantly greater risk of having ICH than females (risk ratio 3.4, 95% CI 2.7-4.3) but ≥65 years, males and females had similar risks (risk ratio 0.8, 95% CI 0.5-1.2)[7].

Locations

Numerous studies investigating for sex differences have failed to detect any differences regarding lobar location[7]. Regarding deep hematomas, a 43% occurrence rate was reported for females in the Northern Manhattan Study[7]. A similar result has also been reported by Roquer et al., in the BasicMar hospital-based registry for ICH patients[2].

Cerebral amyloid angiopathy

CAA is characterized by cerebrovascular amyloid deposition, which is known to significantly increase the risks of both ICH and dementia. Age is the most powerful risk factor for CAA-related ICH[8]. To this regard, a recent Japanese pathology based study has reported a corrected female-to-male ratio (F/M) of 2.2, with significant female predominance, particularly in the 65-74-year age group (F/M = 3.7). Moreover, non-significant female predominance has also been reported for a small patient series investigating for the presence of CAA[9].

Hypertension

The BasicMar hospital-based registry, including more than 500 primary ICH patients, reported hypertension to be the most common risk factor (77.0%), without sex differences ($p = 0.471$)[2]. Likewise, an Italian prospective multicenter observational study, including 470 consecutive primary ICH patients, reported no sex differences in hypertension rates[10].

Alcohol and tobacco abuse

A meta-analysis including 19 cohort studies and 16 case-control studies, with a total of 259,257 patients, reported heavy alcohol consumption (>60 g of ethanol/day) to be significantly associated with increased relative risk (RR) of both ischemic (RR 1.7) and hemorrhagic strokes (RR 2.2) for both males and females[11,12]. According to a previous meta-analysis, females were reported to have a protective effect from moderate drinking, defined as up to 36 g of pure alcohol. In the same study, heavy alcohol consumption, defined as 96 g, was seen to significantly increase the risk of ICH in females[12]. Cigarette smoking has been reported in 28% of ICH patients both males and females over a 3-year follow-up[13].

Cigarette smokers, defined as smoking at least one cigarette, cigar, or pipe per day for the previous year, of both sexes, had a 3-fold greater risk of SAH, compared with non-smokers, whereas it was reported that female smokers had a 20% risk of aneurysmal SAH[14].

Table 1. Intracerebral bleedings reported in clinical trials of new oral anticoagulants.

	Intracerebral bleeding n. of events or/and %/y		
	Males	**Females**	**P–value**
Dabigatran 110 mg	n.r.	n.r.	
Dabigatran 150 mg	n.r.	n.r.	
Warfarin	n.r.	n.r.	
Rivaroxaban ROCKET AF (ITT) *Secondary prevention*			
Rivaroxaban	970 (22.6)	505 (17.9)	0.004
Warfarin	898 (20.9)	551 (19.5)	
Apixaban AVERROES *Primary and secondary prevention*			
Apixaban	25 (1.4)	19 (1.5)	0.97
Acetylsalicylic acid	22 (1.2)	17 (1.3)	
Apixaban ARISTOTLE Primary *and secondary* prevention			
Apixaban	225 (2.3)	102 (1.9)	0.08
Warfarin	294 (3.0)	168 (3.3)	
Edoxaban ENGAGE AF-TIMI 48 *Primary and secondary prevention*			
Edoxaban 60 mg	n.r.	n.r.	
Edoxaban 30 mg	n.r.	n.r.	
Warfarin	n.r.	n.r.	

n.r.: not reported.

Anticoagulant and antithrombotic treatment

Intracerebral bleeding is the most serious complication associated with oral anticoagulant and antithrombotic drugs, as they increase the risk of hematoma enlargement, therein more than often severely compromising functional outcome[15]. According to results from several large multicenter studies, about 20% of all patients prior to ICH had been prescribed anticoagulant treatment, and up to 30% were prescribed platelet inhibitors[16-18].

A large, multicenter observational study including 4,093 patients over 80 years of age receiving treatment with vitamin K antagonists (VKA), reported no significant sex differences in ICH rates[19]. The age-standardized relative risk (RR) of hemorrhagic stroke during oral anticoagulant treatment has been reported to be 10.9 (95% CI 6.7-17.6) for males and 9.3 (95% CI 5.7-15.0) for females[20].

Regarding the prescription of the new oral anticoagulants (NOACs), female sex has not been reported to be a risk factor for ICH in randomized clinical trials (Table 1). According to the Danish National Patient Registry on major bleeding complications and NOAC use in patients with nonvalvular atrial fibrillation, apixaban had a lower adjusted major bleeding risk compared with rivaroxaban, dabigatran, and warfarin in women compared to men[21].

Female specific risk factors

Pregnancy

Pre-eclampsia and eclampsia are known to induce hypertensive disorders, which in turn can lead to ischemic stroke or ICH onset in up to 36% of patients,

with an estimated incidence from 0.4 to 38.9 per 100,000 pregnancies[22]. It is well-recognized (or similar) that stroke is the main cause of maternal death (almost 12%)[23-25].

Pre-eclampsia-eclampsia has been reported to be associated with 24.7-fold increased risk of hemorrhagic stroke up to 12 months post-partum[26]. A Swedish population-based study observed that the highest risk of stroke for pregnant females was in the peripartum period (2 days prior to and 1 day after delivery; RR for cerebral infarction 33.8, 95% CI 10.5-84.0; RR for ICH 95.0, 95% CI 42.1-194.8), although excess risk also persisted during the puerperium period (2 days to 6 weeks postpartum) and the age and race-adjusted attributable risks of either cerebral infarction or ICH during or within 6 weeks after pregnancy was 8.1 per 100,000 pregnancies[23]. A US inpatient sample from 2000 to 2001, reported an ICH rate of 8.5/100,000 pregnancies[26]. In this study, an RR 2.5-fold higher risk of ICH during pregnancy increased to 28.3-fold during the first 6 weeks postpartum[27].

Hormone replacement therapy (HRT)

Study results investigating estrogen therapy in postmenopausal females and stroke risk have been conflicting. The WEST trial (Women's Estrogen for Stroke Trial) carried out in females with cerebrovascular disease, reported that estrogen use increased the risk of stroke (RR for fatal stroke 2.9; 95% CI 0.9-9.0%)[28]. The Women's Health Initiative (WHI), a randomized trial of 16,608 postmenopausal females (95% with no history of cardiovascular disease), reported that estrogen plus progestin was not associated with an increased risk of ICH. The same study, including females following hysterectomy, reported that conjugate equine estrogen was not associated with a risk of ICH[29,30]. In a meta-analysis including WHI, WEST and the Estrogen/progestin Replacement Study, oral estrogen therapy with or without progestin was not associated with an increased ICH risk[31]. In a recent sub-analysis of the study WHI, the rate of SAH was higher among women on HRT, compared to controls (0.14% vs 0.11%, p <0.0001). An unadjusted analysis from the same study revealed that females on HRT were 60% more likely to suffer an SAH[32].

Oral contraceptives (OCs) and parity

The World Health Organization has reported an overall slightly increased risk of ICH with OCs[33], whereas a large prospective study on middle-aged Swedish females reported no such risk[34]. However, this latter study did conclude that the risk of ICH was significantly elevated among those starting and /or using OCs after age 30, those ceasing OCs for medical reasons, and those who were nulliparous[33].

In the observational arm of the WHI, including 93,676 women 50-79 years of age, the risk of SAH continued to be higher among women reporting active use of OCs (RR 1.5, 95% CI 1.0-2.2) after adjusting for age, systolic blood pressure, cigarette smoking, alcohol consumption, body mass index, race/ethnicity, diabetes, and cardiovascular disease[32].

Regarding parity, a Finnish cohort study reported a 4-fold higher risk of mortality following ICH among females with ≥10 live births compared to those with 2 to 4 live births[34]. This finding was later replicated in a Korean study (Acute Brain Bleeding Analysis, ABBA)[35] and a population-based study, carried out in Chinese women, observed that the risk of stroke increased as the number of live births increased[36]. Pregnancy and delivery are considered risk factors for hemorrhagic stroke. Repeated pregnancies and deliveries may induce hypertension, physical and psychological stress that could damage the cardiovascular system in women with high parity[37]. During pregnancy, hemodynamic changes and oxidative stress may impair vascular resistance, and during delivery, vascular tension may also bring to vessel weakening or aneurysms, which may induce hemorrhagic stroke[38].

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches and reversible constriction of cerebral arteries, and has been reported to be associated with increased risks of both ischemic and hemorrhagic strokes. In a single-center retrospective study including 162 patients with RCVS, of which 126 were female, 21 ICH and 62 SAH have been observed. Comparing patients with isolated SAH to those with normal brain imaging, in this last group, a lower percentage of women has been observed and female sex predict ICH (p=0.043)[39].

Racial differences

Race is considered an important risk factor, but only if we take into account the dynamic relationship between race and age in ICH. According to the population-based study REGARDS, ICH risk in American and African participants has been observed to be approximately 5-times greater than in whites at age 45, but only one-third as great at age 85[40]. So, in white subjects only, risk for ICH has been shown to more than double per decade of age. Moreover, male sex was associated with a nearly 3-times higher risk of ICH[37].

Conclusions

Conventional vascular risk factors, as well as sex specific risk factors, have not been thoroughly investigated for their possible sex specific roles in ICH. The limited body of research on females to date, however, does suggest that older age, pregnancy and RCVS are implicated in the reported higher risks of ICH. Being so, large prospective studies are needed to investigate these conventional and sex specific risk factors for their possible roles in ICH, in order to develop prevention and treatment strategies.

Key messages

- Intracerebral hemorrhage is responsible for 10 to 15% of all strokes and associated with high mortality and disability.
- Conventional risk factors for intracerebral hemorrhage are older age, hypertension, cerebral amyloid angiopathy, tobacco and alcohol abuse, oral anticoagulation and reversible cerebral vasoconstriction syndrome.
- Conventional vascular risk factors, as well as female specific risk factors, have not been thoroughly investigated for their possible sex specific roles in the risk of an intracerebral hemorrhage.
- The limited body of research on females to date suggests that older age, pregnancy and reversible cerebral vasoconstriction syndrome are implicated in the higher risks of intracerebral hemorrhage.
- Large prospective studies are needed to investigate conventional and sex specific risk factors in intracerebral hemorrhage and their reciprocal interaction.

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