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Gender Differences in Incidence, Pathophysiology, and Outcome of Primary Intracerebral Hemorrhage

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1. Introduction

While ongoing clinical trials are directly assessing ethnic/racial differences in incidence and outcome of ICH, it is clear that individuals of certain ethnic groups (Asian, African American, etc.) more commonly experience ICH [1,2]. However, few published studies comprehensively assess the role of gender differences in incidence, clinical presentation, etiology, or outcome after ICH. This knowledge is important for understanding putative pathophysiological mechanisms, improving research models, and developing effective treatment options for patients with ICH.

2. Incidence

While epidemiological observations on gender differences in the incidence of ischemic stroke are abundant [3], relatively few have been published assessing gender differences in incidence of ICH [4,5]. Over the course of the last several years, the incidence of primary ICH in the developed world seems to be same or decreasing [4,5]. Presumably this is attributed to better public awareness of preventive measures, such as control of hypertension, regular physical activity, and healthy lifestyle. This observation is supported by population-based studies by Islam et al. [6] in Perth, Australia as well by Lovelock et al. [5] in Oxfordshire, UK. On the other hand, the incidence of ICH was reported to be nearly the same in studies done in France and Finland [7,8]. In a systematic meta-analysis involving 36 studies over last 2 decades, Charlotte et al. [4], found no significant difference in incidence of ICH over time.

3. Influence of gender on incidence of ICH

Observations differ regarding the existence of gender differences in incidence of ICH. Further, ethnic/racial background and age may interact with gender to influence ICH incidence. For example, gender differences in ICH incidence are difficult to find in populations composed largely of Caucasian individuals, such as Europe and Australia. In contrast, data from multiethnic/racial populations, such as Northern America, suggest gender differences do exist. Interestingly, there is a relative paucity of data from African, Southeast Asian, and Middle Eastern populations about gender differences in incidence of ICH.

Below observations from major stroke registries and epidemiological studies are summarized in Table 1. Statistical significance is reported wherever available (p values and confidence intervals). All the incidence values for ICH are reported as per 100,000 people per year, unless otherwise stated.

3.1. Studies from Europe

In a community-based study in Oxfordshire, UK, Bamford et al. [9] reported no gender difference in overall incidence of ICH for men compared to women. Out of 66 patients with ICH presenting over 5 years (1981-1986), 29 were men and 37 were women. Out of 37 women with ICH, 23 (62%) were more than 75 years old, as compared to only 6 out of 29 men (21%). In a population-based observational study during the years 1985-1989 in Dijon, France, involving a town with 140,000 subjects, no gender differences were found in 87 cases of ICH from a total of 984 cases of new strokes [10].

Fogelholm et al. [11] studied the epidemiology of ICH in central Finland during the years 1985-1989. From a total of 158 patients with ICH, they noted that 80 were women and 78 were men. The incidence rates were similar in men (32) as compared to women (31) over this time period. There was no difference in age of presentation between men and women with ICH.

These results were similar in a community-based study over the year 1989 in Italy. Researchers in this study did not find any gender difference in annual incidence of ICH [12].

In a similar population-based study in Italy in 1992, it was noted that incidence of ICH was similar in men and in women [13]. The incidence was 47 (95% CI=35-61) in women as compared to 39 (95% CI=27-53) in men. In addition, there was no significant difference in the age of presentation with the majority of patients being 65-75 years old at the time of presentation.

In the FINSTROKE study, Sivenius et al. [8] looked at the incidence of various types of strokes across ages and genders from 1983-1997. This was a large comprehensive study to evaluate incidence and types of various strokes, in addition to outcomes in Finland, over a span of 15 years. The investigators evaluated 5650 new cases of stroke. In their study, the incidence of ICH did not change as opposed to incidence of ischemic stroke, which showed a decreasing trend. Further the incidence of ICH was similar in men and women during course of the study (p=0.6).

The incidence of ICH was similar between men and women in an observational study conducted at Vibo Valentia, Italy. This was a population-based study involving 97 subjects with primary ICH in southern Italy conducted in 1996. The investigators found that the incidence of ICH was 35. The incidence ratio in women to men was 0.92 (95% CI=0.56-1.51). This was similar to another observation in 1989 from Valle d'Aosta, Italy. The investigators noted an annual incidence of primary ICH of 22 in men and 30 in women (95% CI=0.85-3.49) [12,14,15].

These findings are similar to Arcadia Stroke Study from Greece. Vemmos et al. [16] studied 555 patients with stroke during 1993-1995 from a population-based stroke registry database study. The age-adjusted incidence was 50.9, similar to other European studies. The incidence of ICH was 64.4 (95% CI=41-88) in men as compared 38.2 (95% CI=20-56) in women. Thus, there was no gender difference in incidence of ICH in this cohort.

The incidence of ICH over a 2-year period was found to be 24 in the German study, ESPro [17]. This was a prospective population-based study to evaluate the incidence of various types of strokes. The incidence of ICH was 29 in women and 18 in men.

3.2. Studies from Asia

In the population-based Hisayama study from Japan, Kubo et al. [18] analyzed patients with various types of strokes from 1961-2000, breaking down patient populations into 3 time-based cohorts (1961-1973, 1974-1986, 1986-2000). They observed differences in the incidence of ICH in men as compared to women. Incidence in men was higher (321, 125, and 130 over the 3 time periods) as compared to women (63, 73, and 70, respectively) over the course of these cohorts. Notably, there was a drop in incidence of ICH in men from 321 to 125 between the first and second time periods ($p=0.01$), whereas the incidence in women remained the same across 40 years of observation.

In a large population-based retrospective observational study involving 32,859 inhabitants of rural Japan, Morikawa et al. [19] found the incidence of ICH was lower in women as compared to men. The researchers analyzed the incidence of various types of strokes over the years 1977-1991, divided into 3 time periods (1977-1981, 1982-1986 and 1986-1991). There were 410 cases of ICH [175 (97 men, 78 women), 120 (70 men, 50 women) and 115 (67 men, 48 women) during three sub-periods]. The incidence of ICH in each time period for men was 605, 455, and 417 as compared to 476, 322, and 329 for women. Further, in their study they did not notice any difference in the age of presentation between the genders.

In another hospital-based study by Inagawa et al. [20], the incidence of ICH was similar in men and women. They studied 350 patients with first-ever primary ICH who were treated during the 8-year period 1991 to 1998 in Izumo City, Japan. The incidence of ICH in men was 93 as compared to 57 in women. ($p=0.938$). Inagawa et al carried out a population-based retrospective study of 267 patients with primary ICH in Izumo City, Japan, during the time period 1991-1996. The investigators noted similar incidence of ICH in men and women. The incidence of ICH in age groups 50-59, 60-69, 70-79 and 80-89 in men versus women was: (36/13, 55/27, 40/41, 20/33). The study did not have enough power to assess for statistical significance. The

slightly higher incidence of ICH in older women was attributable to higher life expectancy in women and increasing incidence of amyloid angiopathy with age. In another population-based study in Shibata province of Japan, the investigators studied 97 patients with primary ICH during the time period 1976-1978. The investigators noted incidence in men of 80 as compared to 44 in women. [18,19,21-23].

In a large multicenter study conducted across 10 different provinces in China during the years 1991-2000, the investigators identified a total of 16,031 cases of new onset stroke. Out of these cases, 23.9 percent were ICH. The investigators found no difference in incidence of ICH across gender. [24]

3.3. Studies from North America

In the Northern Manhattan Stroke study [25,26] the investigators found that the annual incidence of ICH in the urban population of New York City was 30.9. Incidence was the same in men (81) as compared to 74 in women. Risk of ICH in men was higher than in women overall with a relative risk of 1.5 (95% CI=1.2-1.8) for ICH in men as compared to women. Below age 65, men were at significantly greater risk than women (RR=3.4, 95% CI=2.7-4.3) but age 65 and above men and women had a similar risk (RR=0.8, 95% CI=0.5-1.2). Men were at significantly greater risk of deep ICH than women (RR=1.8, 95% CI=1.4-2.3) but there was no difference in risk of lobar ICH (RR=1, 95% CI=0.8-1.2).

Kissela et al. [27] conducted a hospital-based observational study of 3136 stroke patients during the time period of January 1, 1993, to June 30, 1994, to evaluate racial differences in clinical features of strokes. The investigators noted that the incidence of primary ICH was 37 (95 CI, 28-46) in blacks as compared to 18 (95 CI, 16-20) in whites. Further, the incidence of ICH was higher in black men in age group 65-74, (225) as compared to black women in the same age group (100). There was no significant gender difference in the incidence of ICH in white population.

3.4. Studies from South America

There have been few studies from South America in this regard. The PISCIS stroke project, a community-based prospective study in Iquique, Chile noted that the incidence of ICH was higher in men as compared to women with nearly two thirds of the total study cohort being men. Minelli et al. [28] in a population-based study in Brazil noted similar findings. They studied overall incidence of various types of strokes in the assigned population and found the overall incidence of ICH was 14.7. Incidence in men (18.7) was nearly twice as much in women (10.7). The majority of women were older (above 75 years of age) at presentation as compared to men who most commonly were between 55-74 years of age.

3.5. Studies from Australia and New Zealand

In STROMA study, slightly higher incidence of ICH in men was found as compared to women [29]. These findings are similar to the Australian study, NEMESIS, completed over

period of 2 years [30]. A higher incidence of ICH was observed in men compared to women (30 vs. 18) [30,31].

There was no significant gender difference in incidence of ICH in Auckland Regional Community Stroke Study [32-34]. The adjusted incidence for ICH was 29, with an incidence of 33 in men and 26 in women. There was uniform increase in the incidence of ICH in the older age groups in both genders.

4. Gender differences in pathophysiology and outcome

While gender differences in clinical features of aneurismal subarachnoid hemorrhage has been studied [35,36], a relative paucity of data exists regarding gender difference in similar characteristics after ICH.

In the Northern Manhattan study [25,26], the incidence of ICH in men was 81 as compared to 74 in women (RR=1.5, 95% CI=1.2-1.8). The incidence of deep ICH was 58 in men as compared to 43 in women (RR=1.8, 95% CI=1.4-2.3). On the other hand, the incidence of lobar ICH was 21 in men as compared to 28 in women (RR=1, 95% CI 0.7-1.4).

Inagawa et al. [20] evaluated incidence of ICH across gender and anatomical location during 8-year period 1991 to 1998 in Izumo City, Japan. Though ICH occurred more commonly in men as opposed to women, the investigators did not find any significant difference regards to the anatomical hematoma location across genders. Taken together, these findings suggest a potential interaction between gender and race/ethnicity in determining the site of ICH.

Mean arterial pressure (MAP) may be associated with mortality in first 24 hours after presentation of ICH. Qureshi et al. [37] carried out a retrospective chart review of 105 patients with a diagnosis of primary ICH, and looked at the effect of rapid lowering of MAP on mortality in the first 24 hours after ICH. The rate of decline in MAP (slope) was independently associated with increased mortality ($p=0.04$), i.e., a faster rate of MAP decline was associated with higher mortality. This effect was independent of other known predictors of mortality, i.e., hematoma volume, presence of ventricular blood, and initial GCS score. While not powered to examine gender-specific interaction, MAP lowering effects on mortality were nearly greater in men as compared to women. ($p=0.08$). These findings may highlight gender differences in susceptibility to changes in MAP and its potential contribution to mortality.

Gender differences may exist in formation of deep venous thrombosis (DVT) in patients with primary ICH. Kawase et al. [38] prospectively evaluated 81 patients with primary ICH for risk of developing DVT. After adjustment for age and relevant confounders, female sex was the only independent predictor for DVT (odds ratio 6.89, 95% confidence interval, CI, 1.56-36.34, $p=0.014$). Female patients with an initial NIHSS score ≥ 12 had 19 times the risk for DVT compared to men with an NIHSS score <12 (95% CI 2.61-213.77, $p=0.007$). Development of DVT could add significantly to the mortality and morbidity, especially in patients with ICH, as these patients are not routine candidates for anticoagulation in the acute phase.

Perihematomal edema (PHE) formation after ICH may affect mortality and long-term neurological function in this patient population. Wagner et al. [39] looked at the role of gender in perihematomal edema in cases of primary ICH. PHE development was assessed over a 14-day period on follow-up CT scans in 387 subjects and was compared between men and women. The investigators found that starting at days 2-4, women showed lower PHE values ($P < 0.05$; days 2-4 and 8-11). The mechanism and ultimate effect on outcome of these findings is unclear.

To further support the neuroprotective role of female sex hormones, menopause may alter the risk of primary ICH in women. Feldman et al. [40] carried out a prospective observational study of 1714 patients with a diagnosis of ICH, and evaluated various risk factors for developing primary ICH. The investigators found that post-menopausal women had significantly higher incidence of ICH as compared to premenopausal women. Thus, menopause was significantly associated with development of primary ICH (adjusted OR, 2.50; 95% CI, 1.06 to 5.88). This observation may support role of female sex hormones in modifying the risk of developing ICH. Clearly, more studies are necessary in this regard.

Five studies provide information about the fatality of ICH in both genders. In a cross sectional study done by Kimura et al. [41], investigators found no difference in ICH mortality in men vs. women at 28 days. The case fatality was 17.6% overall, with 18.8% in men and 16.2% in women. These findings were similar to subsequent studies. Data from the Arcadia stroke registry [16] showed a slightly higher rate of case fatality in women (51.8%) as compared to men (44%) at 4 weeks after ICH. There was no difference in the case fatality rates in men as compared to women from the observations in STROMA study. [29] The investigators found that case fatality rate was 23.9% in men and 22.7% in women at 4 weeks after UCG. These findings were supported by a large multicenter study from China, where the case fatality rate was 48.4 percent in men, similar to 50.7 percent in women at 4 weeks after ICH. [24] Strikingly different were the observations made by Thrift et al. [30] from Australia. The investigators found that case fatality was higher in women (50.6%) as compared to men (29.2%). Finally, women had better survival than men after first-ever primary ICH in a prospective stroke register from Sweden, largely explained by a higher 28-day mortality in male patients over 75 years. [42]

5. Preclinical observations of the role of sex in ICH

Data from preclinical models of ICH suggest response to the estrogen therapy. Nakamura et al. [43] studied sex differences in rat model of ICH. They observed that brain edema and neurological deficits at 24 hours after ICH were less in female rats as compared to male rats. The investigators then studied the role of an estrogen derivative on edema as well as functional outcome in male and female rats. They observed that administration of exogenous estrogen decreased edema as well as neurological deficits in male rats, but made no difference in female rats. Other studies support these findings. [44,45] These observations may also extend to pretreatment. Auriat et al. [46] found that estrogen pretreatment significantly reduced hemorrhagic blood volume at 12 hours after ICH in male rats; however estrogen did not lessen

cerebral edema at 2 days after ICH. These observations are supported by work from Gu et al. [47] The investigators evaluated the role of estrogen pretreatment in reducing brain edema and neuronal survival in iron induced injury in murine models of ICH. The investigators found that estrogen pretreatment in male rats reduced brain edema ($p < 0.01$) as well as reduced neuronal death *in vitro* suggesting a broader neuroprotective effect of estrogen.

Further, accumulation of iron and free radicals is proposed as one of the mechanisms of neuronal injury after ICH. Chen et al. [48] evaluated the molecular mechanisms underlying estrogen-mediated neuroprotective effect against iron induced neuronal injury in cases of ICH. The investigators found that ferrous citrate induced greater brain injury in male rats than female rats. Further, they observed that estrogen pretreatment was protective in iron-induced brain injury in both sexes but the effect was more pronounced in female rats as compared to male rats. The protective effect in female rats was attributed to higher concentrations of estrogen receptor alpha in the brain regions involved. These observations suggest a direct receptor mediated neuroprotective effect of estrogens against iron-induced free radical injury in murine models of ICH.

Findings from work with estrogen may be partially extended to other gonadal hormones. Chen et al. [49] evaluated progesterone and testosterone effects on ICH-induced brain injury in male rats. There was significant reduction of PHE in progesterone-treated rats ($p < 0.05$) as well as improved functional outcome following ICH ($p < 0.05$), as compared to vehicle-treated rats. However, testosterone treatment did not affect PHE and was associated with worse functional outcome ($p < 0.05$) as compared to vehicle-treated rats. These observations suggest a differential effect between female and male sex hormones after ICH.

Finally, Lei et al. [50] evaluated the role of sex and APOE polymorphism in modifying outcomes in murine models of ICH. The investigators found that female mice had better functional outcome as compared to male mice after ICH, as measured by neurobehavioral and cognitive tests. Further, female mice showed rapid rates of recovery as compared to male mice after comparable ICH injury. Interestingly, both male and female mice showed functional benefits after administration of apoE mimetic peptide. Thus, sex differences may exist in pharmacogenomic interactions for drug therapy to improve recovery after ICH.

6. Conclusions

Several general conclusions can be made from the above observations. Gender differences in incidence of ICH appear to exist in Asian and South American populations, where men seem to suffer a higher incidence. Gender differences in incidence of ICH are not as obvious in Northern America, European, or Australian-New Zealand populations. Interestingly, there appears to be an interaction between age and gender in many of these populations, with ICH occurring at a younger age in men. Differences in access to preventative treatment, prevalence of known risk factors (e.g., hypertension, alcohol consumption, use of sympathomimetic drugs), and genetic variance may explain some of these disparities.

Less clear is the existence of gender differences in pathophysiology and outcomes after ICH. While preclinical data support the role of gonadal hormones influencing hemostatic and neuroinflammatory modulation after ICH, their effects on recovery in humans are unknown.

No.	Author	Study details	Year/s	Observations
1	Tanaka (1981) [23]	Shibata, Japan	1976-1978	Higher incidence of ICH in men
2	Bamford (1988) [9,51]	Oxford shire, UK	1981-86	Same incidence of ICH across genders. Women older age of presentation
3	Giroud (1991) [10]	Dijon, France	1985-1989	No difference in incidence of ICH across genders
4	D'Alessandro (1992) [12]	Italy	1989	No difference in incidence of ICH across genders
5	Fogelholm (1992) [11]	Central Finland	1985-1989	No difference in incidence of ICH across genders, women older age of presentation
6	Lauria G (1995) [13]	Italy	1992	Slightly higher incidence of ICH in women
7	Kimura (1998) [41]	Okinawa, Japan	1988-1991	No difference in ICH related mortality at day 30 across genders
8	Kolominsky-Rabas (1998) [17]	Germany	1993-1995	Slightly higher incidence of ICH in women
9	Sacco (1998) [26]	New York, USA	1993-1996	Higher incidence of ICH in men but women older at age of presentation
10	Vemmos (1999) [16]	Greece	1993-1995	Much higher incidence of ICH in older men
11	Morikawa (2000) [19]	Rural Japan	1977-1991	Same incidence and age of presentation of ICH across genders
12	Thrift (2001) [30]	Australia	1996-1997	Incidence of ICH more in men as compared to women
13	Di Carlo (2003) [14]	Calabria, Italy	1996	Slightly higher incidence of ICH in men
14	Inagawa (2003) [20]	Izumo, Japan	1991-1998	Incidence of ICH more in men as compared to women
15	Kubo (2003) [18]	Japan	1961-2000	Significantly higher incidence of ICH in men
16	Zhang (2003) [24]	China	1991- 2000	No difference in mortality in ICH across genders
17	Sivenius (2004) [8]	Finland	1983-1997	Higher incidence of ICH in men

No.	Author	Study details	Year/s	Observations
18	Anderson (2005) [34]	Auckland, NZ	1981-2003	No difference in incidence of ICH across genders
19	Fogelholm (2005) [52]	Finland	1985-1991	Higher incidence of ICH related mortality in men
20	Khan (2005) [29]	Sweden	1989-1999	Higher incidence of ICH in men
21	Labovitz (2005) [25]	Manhattan, USA	1993-1996	Higher incidence of ICH in men of African American ethnicity
22	Lavados (2005) [53]	Iquique, Chile	2000-2002	Higher incidence of ICH in men
23	Benatru (2006) [7]	Dijon, France	1985 to 2004	Same incidence of ICH over years across genders
24	Feigin (2006) [33]	Auckland, NZ	2002-2003	Same incidence of ICH across genders
25	Lovelock (2007) [5]	Oxford shire, UK	1981-2006	Decrease in incidence of ICH across genders over years
26	Minelli (2007) [28]	Matão, Brazil	2003-2004	Higher incidence of ICH in men
27	Islam (2008) [6]	Perth, Australia	1989-2001	Decrease in incidence of ICH across genders over years
28	Thrift (2009) [31]	Melbourne, Australia	1997-1999	Higher incidence of ICH in men
29	Lavados (2010) [54]	Iquique, Chile	2000-2002	The incidence of non-lobar ICH was high, most non-white populations

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