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Review article

Ischemic stroke across sexes: What is the status quo?

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ABSTRACT

Stroke prevalence is expected to increase in the next decades due to the aging of the Western population. Ischemic stroke (IS) shows an age- and sex-dependent distribution in which men represent the most affected population within 65 years of age, being passed by post-menopausal women in older age groups. Furthermore, a sexual dimorphism concerning risk factors, presentation and treatment of IS has been widely recognized. In order to address these phenomena, a number of issue have been raised involving both socio-economical and biological factors. The latter can be either dependent on sex hormones or due to intrinsic factors. Although women have poorer outcomes and are more likely to die after a cerebrovascular event, they are still under-represented in clinical trials and this is mirrored by the lack of sex-tailored therapies. A greater effort is needed in the future to ensure improved treatment and quality of life to both sexes.

1. Introduction

Stroke is defined as a clinical syndrome characterized by the rapid onset of focal (or global, in the case of subarachnoid haemorrhage) cerebral deficit lasting more than 24 h or leading to death due to a vascular cause (Warlow et al., 2003). Among the different stroke subtypes, in Western societies about 80% of strokes occur following the occlusion of a cerebral artery, thus being classified as ischemic strokes (IS). IS are further subdivided into atherothrombotic, cardioembolic and lacunar types, based on the aetiology of the occlusion. Much rarer causes of IS such as vasculitis and arterial dissection are categorized as "stroke of other known causes" according to the "trial of ORG 10172 in acute stroke treatment" (TOAST) classification while an even smaller fraction of patients whose aetiology of IS cannot be determined are classified as cryptogenic (Adams and Biller, 2015).

Stroke is a leading cause of morbidity and mortality and a major public-health burden worldwide. According to the World Health Organization (WHO), stroke accounted for more than 6 million deaths in 2015, then being the second largest global killer just behind ischemic heart disease (http://www.who.int/mediacentre/factsheets/fs310/en/, 2017). With particular reference to Europe, the latest available epidemiological report published in the *European Heart Journal* in 2017 attributes 11% of all deaths (about 1 million) to stroke showing important differences depending on age and sex distribution (Atlas Writing et al., 2017). Although more than 45% of all stroke-related deaths occur in people aged 75 and over, cerebral ischemia accounts for more than 300,000 premature deaths yearly in Europe (Townsend et al., 2016). In terms of morbidity, in 2015 there were 1.6 million new stroke cases leading to a loss of more than 17 million of disability-adjusted life years (DALY) (Wilkins et al., 2017).

Noteworthy, the combined effect of reduced mortality and decreased fertility is currently causing a demographic shift that will lead to a general aging of the population where, accordingly to the United Nations' forecasts, 25% of the total population will be aged over 65 by 2050 (Nations U. World Population Ageing, 2015). Thus, being stroke a well-recognized age-related pathologies (indeed the rate doubles every decade after the age of 55) (Rojas et al., 2007), its prevalence is expected to increase further over the next years. In particular, the American Heart Association/American Stroke Association (AHA/ASA) forecasts a 20.5% increase in stroke prevalence by 2030 (Go et al., 2014).

In light of the above, to cope with the 'stroke pandemic' that will

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Box 1
Epidemiological differences across sexes

- The age-dependent increase in incidence of stroke is more pronounced in women as compared to men from 65 years of age onward (Danesi et al., 2013; Adeloye, 2014)
- Lifetime risk of ischemic stroke is decreasing, the degree of this reduction is greater in men than in women (Carandang et al., 2006; Benjamin et al., 2017)
- Ischemic stroke prevalence increases in older age groups, this is particularly evident in women (Ferri et al., 2011; Jung et al., 2012; Benjamin et al., 2017)
- Several behavioural, social and economical factors impact on sex-related disparities in ischemic stroke distribution (Walker et al., 2010; Wang et al., 2014; Feigin et al., 2009; Benjamin et al., 2017)

challenge health systems over the next decades and in an effort to guarantee the highest quality of life for these frail patients, an improvement in the clinical management of IS will be necessary. In particular, guidelines should become more "personalised" paying special attention to sex and age (Camici and Liberale, 2017). Accordingly, the aim of this narrative review is to analyse the sexual dimorphism of IS epidemiology, risk factor distribution as well as pathophysiology. Then, we will confront IS management and outcome by analysing the results from recently published clinical trials. Finally, based on the above-mentioned findings, we will speculate how preclinical and clinical research could close the gap of knowledge in this field.

2. Epidemiological differences across sexes (Box 1)

Sex-related differences is an emerging field of research in IS epidemiology and care. In many contexts, sex-related disparities influence pre-clinical management, the access to and timing of IS diagnostics, treatment strategies and ultimately prognosis. Indeed, for several other clinical conditions, the growing awareness of such differences has changed clinical practice (Di Carlo et al., 2003; Smith et al., 2005; Gattringer et al., 2014). Unfortunately, the quality and availability of IS data is highly heterogeneous and a rigorous epidemiological evaluation of differences across sexes is still missing or incomplete in some regions. However, a recent study based on the epidemiological transition theory (Yusuf et al., 2001a, 2001b) attempted to provide a detailed overview (Arnao et al., 2016). Although reliable registries are lacking in developing countries (including sub-Saharan Africa, Arab countries and the most part of Asia), meta-analyses and community-based studies reported a progressive increase of IS incidence in women with aging, which becomes more pronounced compared to men in age groups over 65 years (men/women ratio 1:1.2) (Danesi et al., 2013; Adeloye, 2014). Such a trend is more evident in urban centers, whereas in rural areas the incidence of IS remains very low. Although the lack of healthcare facilities outside larger cities may be a significant confounder, such data might reflect negative impact of unhealthy lifestyles in urban areas (Walker et al., 2010; Wang et al., 2014). The increased burden of IS in women in last decades has also been noted in middle income countries (including Latin America and Eastern-Europe), likely due to an increased consumption of unhealthy food, smoking and a higher prevalence of hypertension (Feigin et al., 2009). Concerning IS prevalence, a positive trend with increasing age was noted in both men and woman in low to middle-income countries (Park et al., 2010; de Jesus et al., 2010; Ferri et al., 2011; Onwuchekwa et al., 2014). Over 80 years of age, however, the prevalence tends to be greater in women with respect to men (Ferri et al., 2011; Jung et al., 2012). In Western countries, on the other hand a 42% decrease in IS incidence has been noted from 1970 to 2008. The IS incidence was higher in men than in women, but this difference became less evident in elderly (Lofmark and Hammarstrom, 2007). Indeed, the degree of lifetime risk reduction was highly dependent on sex and age, being greater in men (19.5–14.5%) than in women (18.0–16.1%) (Carandang et al., 2006; Benjamin et al., 2017). As result, in older patients the prevalence increased in women (Benjamin et al., 2017). Socio-economic factors certainly also play an important role in determining gender-related differences in IS epidemiology. Indeed, in many societies women have limited access to education and healthcare. Therefore, they may be excluded from epidemiological studies due to the low hospitalization rate and/or the lower use of diagnostic examinations compared to men (Barker-Collo et al., 2015). Inadequate insurance coverage and poor awareness among minority groups might further increase gender disparities. As an example, in the US, where IS incidence in women is decreasing, this effect is less evident in African Americans, Hispanics and Indians than among Caucasians. Accordingly, women account for 60% of IS-related deaths in the US, and 80% of these occur in lower social ranks (Benjamin et al., 2017). By contrast, between 1990 and 2015, an increase in the crude number of new IS cases was recorded in EU countries (Townsend et al., 2015). However, the increase in the absolute number of IS cases was paralleled by an increase in the size of the total population and older ages in particular. Indeed, the age-standardized analysis of prevalence, which accounts for these changes in population size and composition, revealed a slight decrease of IS events in EU countries (Atlas Writing et al., 2017). However, the age-stratified analysis also revealed an increased death rate for IS in males, whereas the prevalence was slightly higher in females (Townsend et al., 2015).

As a non-adjustable risk factor, age plays a key role in determining sex-related differences in IS epidemiology. Women have greater life expectancy, and more of females than males live in ages where the risk for IS is increased (Benjamin et al., 2017). Indeed, the mean age of first IS is 68.6 years for men and 72.9 years for women (Appelros et al., 2009). Furthermore, IS-related mortality in women increases with age, likely due to the loss of neuroprotective effects of estrogen in postmenopausal women (Poorthuis et al., 2017). Based on these epidemiological data, gender and sex disparities in IS will have important clinical and socio-economic implications in resource allocation for many healthcare systems worldwide.

3. Risk factor differences (Box 2)

3.1. Sex hormones

Besides aging, other non-modifiable factors determine sex-related differences in IS. Indeed, in women, the relationship between endogenous estrogen exposure and cardiovascular (CV) risk has been investigated extensively (Charalampopoulos et al., 2014; Roeters van Lennep et al., 2016), and the most recent meta-analysis indicate no association between the age at natural menopause and IS (Poorthuis et al., 2017). Moreover, hysterectomy has been identified as protective factor against IS (Ingelsson et al., 2011), whereas a positive association has been demonstrated for exogenous hormones (oral contraceptive use and hormone replacement therapy [HRT]) and for surgical oophorectomy (Ingelsson et al., 2011). Complex interactions of endogenous and exogenous male hormones with IS have been also demonstrated (Poorthuis et al., 2017; Soisson et al., 2013; Holmegard et al., 2016). As such, the risk of IS increases with decreasing testosterone total and free