Neuroscience and Biobehavioral Reviews 67 (2016) 119–124

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The impact of gender on stroke pathology and treatment

Claire L. Gibson*, Luke Attwood

Department of Neuroscience, Psychology & Behaviour, University of Leicester, Lancaster Road, Leicester LE1 9HN, UK

ARTICLE INFO

Article history:
Received 21 July 2015
Received in revised form 13 August 2015
Accepted 25 August 2015
Available online 2 December 2015

Keywords:
Gender
Ischemia
Stroke
Apoptosis

ABSTRACT

Cerebral ischemic stroke is a leading cause of mortality and functional disability. However, unfortunately few effective treatments exist to counteract the deleterious pathological mechanisms triggered following an ischemic event. Epidemiological and experimental studies have revealed a significant difference in the vulnerability of males versus females to both the incidence of stroke and amount of resulting pathology following an ischemic stroke which is also dependent on the stage of lifespan. Here we review the evidence for gender differences in both the overall pathology and cellular mechanisms of injury following ischemic stroke. In addition, we discuss the evidence for any gender differences that may occur in the effectiveness of treatments and how this supports the need for the investigation and development of gender-specific therapies.

Contents

1. Introduction

Cerebral stroke continues to kill over 5 million people worldwide per annum and is the leading cause of long-term adult disability in many developed countries including the UK and USA. Among those surviving a stroke, it is estimated that work capacity is compromised in 70% stroke victims and 30% need assistance with self-care. The majority of cerebral strokes are ischemic and occur as a result of occlusion in a major cerebral artery by a thrombus or an embolism leading to compromised blood flow and loss of tissue perfused by that vessel. Although the introduction of specialised intensive stroke care units over the last 10–20 years has improved the functional outcome of stroke patients, limited advances have been made in developing therapies to counteract the deleterious effects of ischemic stroke. The only current pharmacological treatment available is thrombolysis with tissue plasminogen activator (tPA) but due to its narrow therapeutic window (<4.5 h) and risk of symptomatic intracerebral haemorrhage only about 20% of stroke patients receive tPA and in those patients, recanalisation rate can be less than 50% (Wardlaw et al., 2003). Thus, there is an urgent need for the development of safe and effective treatments for treatment of acute stroke.

In terms of stroke incidence up until the age of 45 men experience higher incidence of ischemic stroke (Rosamond et al., 2008) and poorer functional recovery (Thorvaldsen et al., 1995) compared to age-matched women. However, between the ages of 45–54 years the incidence of ischemic stroke in females begins to increase which coincides with the onset of female menopause and a subsequent decline in circulating levels of sex steroid hormones. This also coincides with a surge in obesity and metabolic syndrome which must also contribute to increased stroke risk (Towfighi et al., 2007). From the age of 55 upwards the incidence of stroke in male and females is generally comparable until beyond the age of 85 years when females represent the group at highest risk of suffering an ischemic stroke (Rosamond et al., 2008). In terms of stroke recurrence studies indicate that females experience a higher five year recurrence

* Corresponding author.
E-mail address: cg95@le.ac.uk (C.L. Gibson).

http://dx.doi.org/10.1016/j.neubiorev.2015.08.020
0149-7634/

Table 1
Prevalence of stroke by age and sex (National Health and Nutrition Examination Survey, American Heart Assocation, 2009–2012.

	Age (years)			
	20–39 (%)	40–59 (%)	60–79 (%)	80+ (%)
Males	0.2	1.9	6.1	15.8
Females	0.7	2.2	5.2	14.0

Percent of population.

of cerebral events than males (Wang et al., 2013). However, such an effect is not sustained when controlling for other factors including age, comorbidities (e.g. hypertension, obesity) and other relevant risk factors (Fukuda et al., 2009).

Epidemiological studies show that both stroke risk and outcome following ischemic stroke are sexually dimorphic—although the direction of such dimorphism is variable depending on the stage of life span being compared. Table 1 shows the incidence rates of stroke according to age and gender although some variation in stroke incidence occurs according to population studied (Appelros et al., 2009). In addition to stroke incidence there also seems to be gender differences in the pathology produced following ischemic stroke with experimental studies beginning to provide evidence that the actual mechanisms of cell death initiated following ischemic injury may differ between the genders. Here we review the evidence that gender does in fact influence pathology following ischemic stroke and assess what this may mean for the development of effective treatments.

2. Presentation of clinical symptoms following ischemic stroke

It would appear that gender differences are present in some clinical aspects of ischemic stroke. Upon hospital admission, prospective observational studies suggest that men are more likely to present with the classical symptoms of stroke, i.e. hemi body paraesthesia, hemiparesis, ataxia, speech/language disturbance, visual impairment, facial weakness, dizziness and problems with coordination. In contrast, women are more likely to present with the non-classical symptoms of stroke which includes mental status change, migraine, pain, general neurological symptoms (e.g. nausea, hiccups, non-facial weakness) and non-neurological symptoms such as chest pain, palpitations and shortness of breath (Lisabeth et al., 2009). Although such gender difference in symptoms are not supported by all studies (e.g. Labiche et al., 2002) they may occur as a consequence of underlying differences in pathology (see below) or differences in lateralisation of brain functions according to gender. For example, certain brain functions such as language (Kansaku and Kitazawa, 2001) and specific types of memories (Persson et al., 2013) have been shown to be differentially lateralised in males compared to females. However, such variance in presentation of symptoms may also be a consequence of time at which males and females are likely to seek medical attention as studies have found that women may experience up to three times longer delay in seeking treatment for suspected cerebral incidents (Mandelzweig et al., 2006).

Establishing the relationship between gender and symptomatic presentation has important implications for the rapid diagnosis and treatment of ischemic stroke. In particular, identifying differences between presentation of classical and non-classical symptoms according to gender could help facilitate access to emergency treatment for women. Moreover, public health campaigns such as 'FAST' (facial weakness, arm weakness, slurring of speech, time to call emergency assistance) in the UK which focus on recognising the classical symptoms of stroke may need to become more gender-specific to ensure the classical and non-classical symptoms of stroke are recognised appropriately and timely (Kleindorfer et al., 2007).

Table 2
Incidence rates of thrombolytic vs. embolic strokes in men and women from a European population-based study, 1994–1998 (Kolominsky-Rabas et al., 2001).

Gender	Large vessel thrombotic stroke	Small vessel thrombotic stroke	Embolic stroke
Males	22.6 per 100,000	32.9 per 100,000	26.2 per 100,000
Females	13.1 per 100,000	27.1 per 100,000	44.5 per 100,000

2.1. Gender differences in pathology—Gross pathology

Cerebral ischemic strokes are caused by an interruption in the cerebral blood flow due to the presence of a thrombus or embolism. Thrombotic strokes are typically triggered by rupture of atherosclerotic plaques leading to the release of pro-thrombotic factors and subsequent clot formation, whereas, embolic strokes most commonly occur when thrombi detach, travel through the vasculature, and obstruct a more distantly located blood vessel (Haast et al., 2012). Studies indicate that the incidence of thrombotic strokes is more frequent in men compared to women with embolic strokes occurring more frequently in women (Table 2; Kolominsky-Rabas et al., 2001). It is well established that oestrogens inhibit the development of atherosclerotic plaques due to their effects on smooth muscle, adhesion molecules and differentiation of monocytes (Haast et al., 2012). Consequently, higher circulating levels of oestrogens may protect females from the development of thrombotic strokes and women are more likely to suffer from atrial fibrillation which is a major risk factor for emboli formation (Bushnell, 2008). Clinically, this difference in terms of whether an ischemic stroke is thrombotic or embolic in nature may affect the symptom presentation of stroke. For example, Takano et al. (1998) report that patients with embolic ischemic strokes typically present with symptoms such as reduced alertness and vomiting which may explain why women are more likely to present with non-classical symptoms of stroke compared to men.

There has been a large amount of experimental research demonstrating the protective properties of female steroid hormones (for review see Gibson, 2013) but results from clinical trials have been disappointing so far (Henderson and Lobo, 2012). Although clinical trials investigating the potential of steroid hormones, i.e. hormone replacement therapy for ischemic stroke, have tended to focus largely on postmenopausal women. When considering gender differences in stroke incidence and pathology it is important to not only consider the potential protective role of female hormones but also whether male hormones have any potential for detrimental effects. In males, the levels of circulating change throughout the lifespan and such changes may impact upon the vulnerability of the male brain to an ischemic event. Studies have reported a correlation between testosterone and stroke incidence with lower levels of testosterone in ageing men being associated with an increased risk factor for cerebral stroke whereas higher levels of testosterone in younger men tends to increase the stroke risk (Quillinan et al., 2014).

In terms of gross pathology, it is relevant to consider the cerebral hemisphere which is predominantly affected following an ischemic stroke and whether this has any clinical implications. Strokes occurring predominantly in the left hemisphere tend to result in language and motor disturbances which are synonymous with the classical symptoms of stroke whereas strokes predominantly in the right hemisphere are associated with symptoms of neglect and other non-classical symptoms (Foerch et al., 2005). Overall consensus appears to be that more ischemic strokes typically occur in the left hemisphere compared to the right (Neau et al., 1998; Naess et al., 2006). This may be due to a