Journal of Clinical Neuroscience 22 (2015) 1867–1870

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Review

The role of age in intracerebral hemorrhages

Elvis Camacho [1], Melissa A. LoPresti [1], Sam Bruce, Derek Lin, Mickey Abraham, Geoff Appelboom *, Blake Taylor, Michael McDowell, Byron DuBois, Mihika Sathe, E. Sander Connolly

Department of Neurological Surgery, Cerebrovascular Laboratory, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 9 December 2014
Accepted 11 April 2015

Keywords:
Age
Comorbidities
Intracerebral hemorrhage
Outcome
Predictor

ABSTRACT

We aimed to identify the role of age in intracerebral hemorrhage (ICH), as well as characterize the most commonly used age cut off points in the literature, with the hope of understanding and guiding treatment. Strokes are one of the leading causes of death in the USA, and ICH is the deadliest type. Age is a strong risk factor, but it also affects the body in numerous ways, including changes to the cardiovascular and central nervous systems that interplay with the multiple risk factors for ICH. Understanding the role of age in risk and outcomes of ICH can guide treatment and future clinical trials. A current review of the literature suggests that the age cut offs for increased rates of mortality and morbidity vary from 60–80 years of age, with the most common age cut offs being at 65 or 70 years of age. In addition to age as a determinant of ICH outcomes, age has its own effects on the maturing body in terms of changes in physiology, while also increasing the risk of multiple chronic health conditions and comorbidities, including hypertension, diabetes, and anticoagulant treatment for atrial fibrillation, all of which contribute to the pathology of ICH. The interaction of these chronic conditions, changes in physiology, age, and ICH is evident. However, the exact mechanism and extent of the impacts remains unclear. The ambiguity of these connections may be further obscured by individual patient preferences, and there are limitations in the literature which guides the current recommendations for aging patients.

1. Introduction

In the USA, stroke is the fourth leading cause of death and one of the leading causes of long term disability [1,2]. Intracerebral hemorrhages (ICH) account for approximately 10–15% of all strokes, and are considered to have the highest mortality rate [3]. Unlike other types of strokes, ICH does not have an effective treatment, making the understanding of the risks factors and predictors of ICH imperative for proper risk stratification and management.

One common risk factor associated with stroke is advancing age. Hemphill et al. created one of the first widely accepted ICH scores, and in their univariate analysis, age $\geqslant$ 80 years was a significant independent predictor of 30 day mortality, with an odds ratio of 9.55 [4]. The natural and pathological changes that occur with aging carry numerous implications for the body, including changes to the cardiovascular and central nervous systems that interact with many other risk factors for ICH. Although there has been a recent decrease in ICH rates among patients younger than 75 years, the rates have increased in those 75 years or older [5]. Moreover, with the trend of an aging population, there is an increase in incidence rates for many of the comorbidities that occur with advanced age, and with the associated increase in stroke incidence, the potential risk of ICH among the elderly is vast.

With the severity and prevalence of ICH in the aging population, understanding the effects of age on the body, the increasing number of comorbidities in that population, and the specific changes to the nervous system with age, can enhance our knowledge of age as a risk factor for disease. Similarly, exploring the outcomes that are associated with age and ICH can further guide therapy. Therefore, it is the aim of this review to characterize and examine age as a predictor of ICH risk and outcomes, and identify significant markers for intervention and treatment.

2. Aging and the increasing prevalence of comorbidities

Advanced age is associated with worse clinical outcomes in many conditions. For ICH, this association may be independent or directly related to the pathology of the multiple risk factors of stroke. Many common chronic conditions, including essential hypertension, coronary artery disease, atrial fibrillation, cardiovascular disease, and diabetes mellitus, have a higher prevalence with increasing age [6], and as a result, may confound the attributable

* Corresponding author. Tel.: +1 6467098708.
E-mail address: ga2294@columbia.edu (G. Appelboom).

[1] These authors have contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.jocn.2015.04.020
0967-5868/

risks of age in regards to the odds of having an ICH and the outcomes in patients who survive. Hypertension is a widely identified risk factor for ICH [7–10], which has been shown to increase the risk of ICH two-fold [11], and is estimated to be present in 83% of ICH patients [12]. In addition to hypertension, atrial fibrillation is a primary risk factor for cardioembolic stroke [13], and this patient population is routinely anticoagulated with agents such as warfarin, which may increase the risk of ICH by two to five-fold in a dose-dependent manner [14–16]. In studies of ICH survivors, those with comorbidities, such as diabetes and peripheral vascular disease, have a higher 30 day and 1 year mortality, as well as worse functional outcomes [17,18]. Moreover, pooled data from case-control studies has shown that diabetic individuals are 1.3 times more likely to develop ICH than non-diabetics [7]. While diabetes has been identified as only a weak risk factor, the pathogenesis of the disease, with both microvascular and macrovascular changes developing over time, perhaps increases susceptibility to ICH.

The prevalence of multimorbidities, namely vascular diseases, greatly increases with age and has been found to be present in most people aged 65 or older, contributing to higher mortality and reduced functional status, and possibly worsening the outcomes of ICH [19–22]. In effect, comorbidities likely have varying degrees of influence on the risk of having an ICH and on the functional outcome. However, it is the potential, and likely culmination that when acting together in the elderly population, the comorbidities greatly account for the higher ICH incidence and mortality rates that are seen in this population.

3. Effects of aging on the nervous system

There are numerous effects of aging on the body, and the most significant to ICH are age-related changes in the cerebrovascular system and the brain. The effect of aging on the brain microvasculature is well-recognized, and includes decreased vascular density, microembolic brain injury, vessel basement membrane thickening, endothelial dysfunction, and increased blood–brain barrier permeability. In addition, cerebral white matter lesions known as leukoaraiosis, characterized by spongiosis, gliosis, demyelination, and capillary degeneration [23], are seen with vascular risk factors and/or vascular dementia in the elderly population, and are thought to be related to cerebrovascular disease in this population. Systemic conditions, such as hypertension and diabetes mellitus, may also contribute to these changes of the cerebrovasculature. These structural changes to the brain vasculature make the parenchyma more susceptible to injury, which increases the risk of stroke. Pathologies involving further endothelial damage, changes in vessel elasticity, or fluctuations in blood flow and pressure, implicate chronic diseases such as hypertension, atherosclerosis, diabetes, and atrial fibrillation in worsening the risks of neurologic injury.

Age-related changes of gross brain volume are also well documented, with an annual loss of volume ranging from 0.2–0.5% [4], especially in regions such as the prefrontal cortex [3], and are thought to be the result of neuronal atrophy. In a study by Gottesman et al., the authors suggested that since the elderly tend to have anatomically smaller brains than their younger counterparts, a given stroke volume in the elderly would affect a greater proportion of brain parenchyma, which may be a factor in the poorer neurological outcome [24]. Older populations also have a higher probability of having a history of prior strokes, which could impair their ability to recover, and make them more susceptible to additional injuries [25]. Additionally, several animal studies have shown that white matter vulnerability increases with age [26–28], perhaps leading to changes in the cerebral architecture that impact ICH.

4. General physiological changes with aging

Aging is not only characterized by changes in the cardiovascular and nervous systems. The weakened physiologic reserve, higher mortality rates, poor healing, worse long term functional outcomes, and greater rates of debilitation with less insult, are more often seen in comparison to younger cohorts [29]. The physiologic reserve is the additional capacity of the body's organ systems to overcome challenges. Therefore, a reduction in this in the elderly population increases their susceptibility to injury, disease, and loss of function. In the review by Pisani et al., many physiological changes associated with treating elderly populations are elucidated [30]. For instance, as individuals age, their ability to respond to sympathetic stimulation declines, leading to a failure of compensatory mechanisms such as increased maximal heart rate, ejection fraction and cardiac output. This puts them at an increased risk for vascular complications. An up to 50% decrease in pulmonary function can also be seen with older patients. Likewise, the kidneys also experience declining function due to the fact that approximately 40% of nephrons become sclerotic between the ages of 25 and 85 years. Furthermore, renal blood flow decreases by half, and the glomerular filtration rate declines to about 45% by the time an individual reaches 80 years of age. Medications will also have different physiological effects. Hepatic blood flow diminishes by 30% between the ages of 30 and 75 years, and this alters the absorption, distribution, metabolism and excretion of medication.

These factors culminate in an age-related decline of organ system functions, causing an increased vulnerability to sepsis, changes in pharmacodynamics, and cognitive decline [30], all of which contribute to disproportionate rates of complications, extended inpatient hospitalizations and intensive care unit admissions in older cohorts compared to their younger counterparts. While a determined age at which these changes occur is still uncertain, the literature suggests that age does impact certain complication rates during inpatient hospitalizations after stroke [31]. These changes, as general deteriorations in physiologic status and function, can contribute to the increasing frailty and overall weakness of the elderly, increasing their propensity for stroke, and causing variations in recovery rates post stroke.

5. Counselling the elderly: A self-fulfilling prophecy?

Hospital management may also play a role in the differences in mortality and outcomes between older and younger patients. Elderly patients tend to engage in more end of life care, including do not resuscitate (DNR) orders, advanced care plans, and living wills. The subtleties of patient care and advanced care planning may impact the management decisions, often dictating the decisions between conservative and aggressive management. As a result, it is possible that the nuances in ICH management are providing a selection bias, in that elderly patients with worse outcomes are less likely to receive interventions due to the premeditated goals of care [32].

A recent study showed that patients who were treated more aggressively and were transferred to specialist centers had better outcomes. Similarly, the younger patients had higher transfer rates [33]. In this study, the odds of a patient being transferred decreased by 50% for every 10 years of age. After adjusting for prognostic factors, including age, the authors found that neurosurgical care remained strongly associated with a lower hazard of death, while a DNR was associated with a higher hazard of death. The role of DNR in the mortality and morbidity of elderly patients is controversial. Some studies suggest that a DNR order could negatively impact the management and care [34], others have not found any such association [35]. Moreover, patients holding DNR orders tend to be associated with more severe strokes and