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Intracerebral hemorrhage and cognitive impairment☆

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ABSTRACT

Vascular cognitive impairment and vascular dementia are composed of cognitive deficits resulted from a range of vascular lesions and pathologies, including both ischemic and hemorrhagic. However the contribution of spontaneous intracerebral hemorrhage presumed due to small vessel diseases on cognitive impairment is underestimated, in contrast to the numerous studies about the role of ischemic vascular disorders on cognition. In this review we summarize recent findings from clinical studies and appropriate basic science research to better elucidate the role and possible mechanisms of intracerebral hemorrhage in cognitive impairment and dementia. This article is part of a Special Issue entitled: Vascular Contributions to Cognitive Impairment and Dementia edited by M. Paul Murphy, Roderick A. Corriveau and Donna M. Wilcock.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) results from bleeding into the brain parenchyma because of rupturing small vessel, typically affected by sporadic microangiopathies. While ICH represents only 10–15% of all strokes, it carries a higher risk of morbidity and mortality compared to the more common ischemic forms of stroke [1,2]. Previous studies have established that different underlying pathologies are associated with the specific location of hemorrhage in the brain [3]. ICH located in deep brain regions (deep ICH) is a result of rupture of small arterioles most commonly in the putamen or thalamus [4–6], while ICH in lobar locations (lobar ICH), results from rupture of small and medium-sized arterial perforators in the cortex and subcortical white matter [7]. While deep perforating vasculopathy (including arteriolosclerosis, lipohyalinosis and fibrinoid necrosis, mainly driven by traditional cardiovascular risk factors) appears to underlie deep ICH [3], cerebral amyloid angiopathy (CAA), resulting from progressive cerebrovascular β-amyloid (Aβ) deposition within small cortical and leptomeningeal small vessel walls, accounts for the majority of lobar ICH in the elderly [8–11]. In both forms of ICH, high rates of daily living dysfunction were reported [12–16].

However, not much attention has been focused on the cognitive impairment after ICH and the mechanisms involved in cognitive dysfunction in these patients, despite the reported high prevalence of dementia after hemorrhagic stroke (ranging from 5% to 44%) [17]. Moreover, studies have suggested that dementia may be a predictor of mortality in ICH survivors [18]. Therefore, a better understanding of the association between ICH and cognition would be important to help guide the clinical management of ICH survivors. The cognitive impairment after ICH may consist of both the immediate cognitive deficits resulting from the acute hemorrhagic lesion, and also progressive cognitive deterioration driven by slowly accumulating diffuse vascular and non-vascular pathology.

Beyond symptomatic ICH, subclinical or even asymptomatic bleeding events are frequently detected on neuroimaging in population-based studies [19]. These small bleeding events, commonly termed cerebral microbleeds (CMBs), have also been seen in patients with hypertension [20], ischemic stroke [21] and CAA [22]. Since the implication of CMBs on cognition has been widely studied and summarized [23–25], this review will focus on macrohemorrhage only.

Small vessel disease (SVD) is the common underlying pathology in patients with spontaneous ICH. The association between SVD related neuroimaging markers, including white matter hyperintensities, brain atrophy, lacunar infarcts, perivascular spaces, and cognitive impairment has been extensively established and has been reviewed elsewhere [26–29]. This narrative review aims to highlight the link between ICH and cognition, and to explore the underlying mechanisms of hemorrhage-related cognitive impairment. We discuss results from

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patient cohorts in an attempt to define the incidence and prognostic factors for ICH-related cognitive impairment. In addition, we include a discussion of data from animal models to define the possible mechanisms underlying these associations. In writing this review, it is our intention that it may serve as a roadmap for future research in this relatively understudied, yet important area in stroke and cognition research.

2. ICH and cognition: insights from clinical studies

2.1. Pre-existing cognitive impairment in patients with ICH

There are only a few studies examining the incidence of pre-existing cognitive impairment or dementia in ICH [14,30–32]. Fig. 1 provides pooled estimates of the incidence of pre-ICH cognitive impairment based on these studies published to date. Two large studies examining this question in patients with primary ICH in any location have shown that cognitive impairment prior to ICH is common [14,30]. In one study, pre-existing cognitive impairment was defined as a history of cognitive impairment based on family interview and medical record review supplemented by the Informant Questionnaire on Cognitive Declines in the Elderly (IQCODE). The incidence of pre-existing cognitive impairment was reported in 15% of 629 ICH patients [14]. In the second study including 417 ICH patients, cognitive status before ICH was evaluated with the short version of IQCODE and the cut-off values used were 53 for cognitive impairment without dementia and 64 for pre-existing dementia. The authors showed that 14% of patients had pre-existing cognitive impairment without dementia while 16% had pre-existing dementia [30]. Among patients with strictly lobar ICH the incidence of pre-existing dementia was as high as 23% (95% CI 17%–31%) vs. 12% in deep ICH (95% CI 8%–17%). The investigators showed that factors associated with pre-ICH dementia in this group were increasing age, lower education level (<8 years) and cortical atrophy. It is possible that the higher rates of pre-existing dementia in lobar ICH patients could result from underlying amyloid-based pathologies, including Alzheimer's disease (AD) and CAA, and their interplay. Available postmortem data from 5 patients in this study with lobar hemorrhage confirmed both AD and CAA pathology. In the same study, risk factors for pre-ICH dementia in patients with deep ICH included presence of previous large-artery infarctions and severity of white matter hyperintensities (WMH). The autopsy results of one patient in this category showed SVD without AD pathology [30]. In line with these post-mortem results, pathological results from another retrospective study demonstrated that in 109 ICH subjects, AD pathology was found in 68% of CAA-related ICH patients versus 9% of non-CAA-related ICH patients. By contrast, autopsy evidence of hypertension-related small vessel disease (SVD) was detected in 36% of CAA-related ICH patients versus 75% of non-CAA-related ICH [33]. These pathological findings suggest that both SVD-related pathology and neurodegenerative pathology are common in ICH patients. However, lobar ICH (CAA) patients appear to have more underlying neurodegenerative disease, while deep ICH patients (non-CAA) have more SVD related pathology.

Other smaller studies focusing in lobar ICH patients have demonstrated similar prevalence of pre-existing cognitive impairment. In a cohort of 182 lobar ICH patients aged 55 years and above, 23% patients had pre-ICH cognitive impairment and it was independently associated with more severe CT-based white matter disease after adjustment for age and the degree of cortical atrophy [31]. A similar prevalence of pre-ICH cognitive impairment was reported in a smaller cohort of ICH patients meeting the Boston criteria for probable or possible CAA (20%, 10 out of 49 patients) [9,32]. In this study, global mean apparent diffusion coefficient (ADC) was measured to assess microstructural tissue damage. The elevated mean ADC, rather than volume of WMH and number of microbleeds, was the only variable associated with pre-ICH cognitive impairment [32]. This difference may be explained by the fact that mean ADC is a more sensitive marker of white matter damage compared to WMH volumes or CT-based measures [34].

These data suggest that pre-existing cognitive impairment is not uncommon in patients with ICH. Interestingly, the associated factors of pre-ICH cognitive impairment may differ between patients with lobar versus deep ICH, which may be related to differences in the underlying pathology (i.e. CAA versus deep perforating vasculopathy). While these few (and likely underpowered) studies suggest that pre-existing cognitive impairment is an important consideration in patients with ICH, further research is needed to better define the precise mechanisms involved. For example, future community-based studies could investigate the neuropsychological profile of pre-existing cognitive impairment in subjects who eventually develop ICH. Moreover, advanced neuroimaging studies in this population-based cohort will help define network disruption or underlying pathology that could be associated with pre-existing cognitive impairment. Case–control studies can be conducted to examine MRI markers to see differences between groups of patients with and without pre-existing cognitive impairment. This may help to confirm the relationship between the underlying pathology and cognitive impairment in these patients.

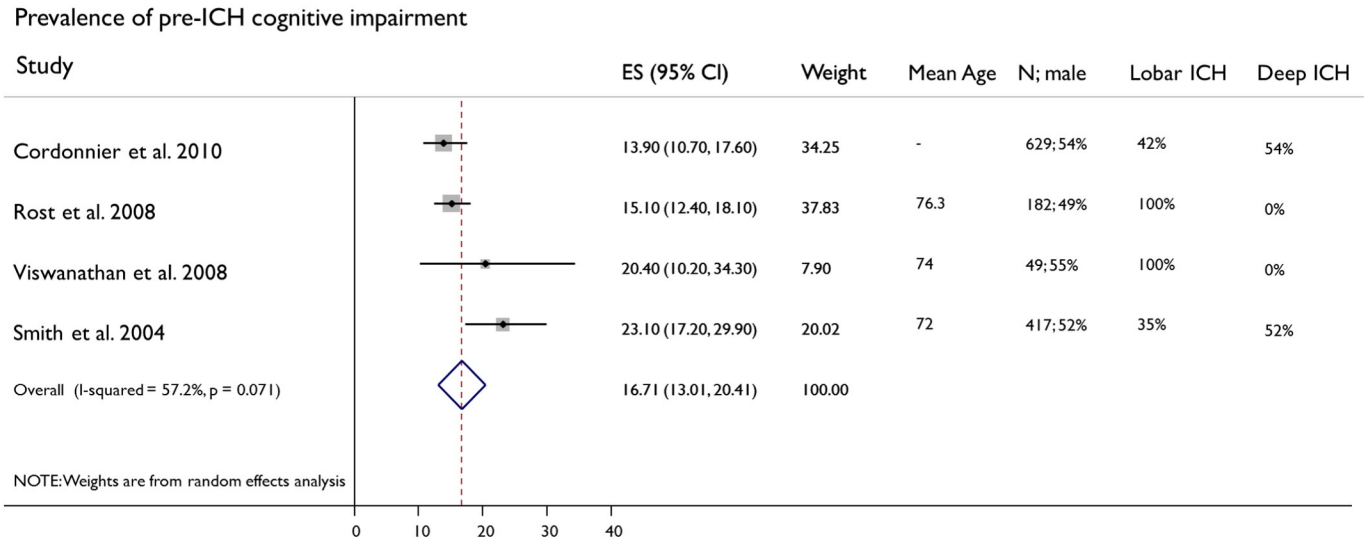

Fig. 1. Pooled incidence of pre-ICH cognitive impairment based on the studies published to date. There was some evidence of statistical heterogeneity in the pooled estimate, likely reflecting the different characteristics of the ICH patients included in these studies.

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