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Impact of spontaneous intracerebral hemorrhage on cognitive functioning: An update

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ABSTRACT

Intracerebral hemorrhage (ICH) accounts for 15% of all strokes and approximately 50% of stroke-related mortality and disability worldwide. Patients who have experienced ICH are at high risk of negative outcome, including stroke and cognitive disorders. Vascular cognitive impairment are frequently seen after brain hemorrhage, yet little is known about them, as most studies have focused on neuropsychological outcome in ischemic stroke survivors, using well-documented acute and chronic cognitive scores. However, recent evidence supports the notion that ICH and dementia are closely related and each increases the risk of the other. The location of the lesion also plays a significant role as regards the neuropsychological profile, while the pathophysiology of ICH can indicate a specific pattern of dysfunction. Several cognitive domains may be affected, such as language, memory, executive function, processing speed and gnosis.

1. Introduction

The low frequency (10–15% of all strokes) [1] and high mortality rate (up to 60% in the first year) [2] of intracerebral hemorrhage (ICH) may explain the lack of cognitive data for that patient population. The two main classes of ICH – traumatic and spontaneous (primitive) – are usually dissociated. Spontaneous ICH accounts for approximately 70–80% of cases and is due to the rupture of small arteries in the brain afflicted by two main pathologies: hypertensive arteriopathy and cerebral amyloid angiopathy (CAA) [3]. The present report focuses on spontaneous ICH without vascular malformation.

The question of the origin of cognitive disorders after ICH is a complex topic linked to the presence of hemorrhage itself, but also to the pathophysiological mechanisms that evolve silently and are present well before stroke happens. Furthermore, while ischemic stroke research commonly uses a specific topographical system of organization, most ICH studies are focused on the differences between lobar and non-lobar hemorrhages. This simple distinction would certainly mask the influence of an individual cause of disease.

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The present study focuses on studies performed in either an ICH or general stroke population where, in the latter, a distinction is made between ischemic and hemorrhagic stroke. The neuropsychological outcome is also described and the data compared with that of ischemic stroke survivors if available. Severity markers of small-vessel disease are also reported with descriptions of their relationship to cognitive function.

2. Vascular cognitive disorders (VCDs)

2.1. *Definition and criteria for VCD diagnosis*

When patients present with vascular cognitive impairment (VCI) following spontaneous ICH, they then meet the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) criteria, published by Sachdev et al. [4] in 2014. This society aimed to establish working groups to develop common minimal standards for the entire spectrum of cognitive impairment by introducing new terminology and quantitative criteria for defining the severity of vascular cognitive disorders (VCDs). VASCOG has identified seven categories of cognitive disorders: attentional and processing speed; frontal/executive function; learning and memory; language; visuoconstructional–perceptual ability; praxis–gnosis–body schema; and social recognition; it has also listed pathologies that may be responsible for cognitive decline. The term 'dementia' is no longer used, but has instead been replaced by major VCDs, as described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Diagnosing major VCDs is based on objectively measured acquired declines in one or more cognitive domains in cases where a patient, relative or clinician is worried about the level of decline compared with previous levels of cognitive function [test performance of at least 2 standard deviations (SD) below the mean (or below the third percentile)] and where there is interference with daily life. When test performance are between 1 and 2 SD (between the 16th and third percentiles) with no interference on daily life, mild VCDs is diagnosed. However, the use of a cut-off of –1 SD (or 16th percentile) to consider a test performance mildly altered, as defined by the DSM-5, can lead to false positives and should therefore be discussed [5]. This issue should be borne in mind for future studies assessing the sensitivity and specificity of each criterion. In addition, VASCOG criteria have been established under the same schema as those of the US National Institute of Neurological Disorders and Stroke (NINDS) – *Association internationale pour la recherche et l'enseignement en neurosciences* (AIREN), where there must be a relationship between neuropsychological disorders and vascular lesions.

2.2. *Prevalence of VCDs*

2.2.1. *Pre-existing VCDs*

Previous cognitive changes are usually estimated via the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [6], which is rated by a relative who estimates the degree of change over the previous 10 years. This is a powerful tool and easy to administer, and has a short and long version (16 and 26 questions, respectively). The cut-off differs between studies, but most use a score > 3.6 to diagnose pre-existing major VCDs (such as dementia). Diagnostic accuracy of the IQCODE across cut-off points (3.3–4.1) was evaluated by a Cochrane review of 13 studies involving data from 2745 subjects (51% with dementia) [7]. Pooled analysis of all these studies showed that a cut-off of 3.3 indicated a sensitivity of 0.91 [95% confidence interval (CI): 0.86–0.94] and a specificity of 0.66 (95% CI: 0.56–0.75). Notably, no difference in accuracy was found between the short and long versions of the IQCODE. This questionnaire is widely used in clinical and research studies to overcome the lack of premorbid cognitive testing.

In 2012, Pendlebury et al. [8] showed that the prevalence of prestroke dementia was 15% in cohorts of patients with multiple stroke, with comparable rates for patients presenting with ischemic stroke or ICH. Two years earlier, Cordonnier et al. [9] had found the prevalence of dementia before ICH to be 16% (IQCODE score > 4) and 14% for mild cognitive impairment (IQCODE score > 3.31 but < 3.94) in 417 ICH survivors [median age: 72 years, interquartile range (IQR): 58–79]. The authors also observed a greater prevalence within the lobar group, with a rate of pre-existing dementia of 23%, which was 12% in the deep ICH group and 9% in the fossa ICH group. More recently, Laible et al. [10], in a cohort of 89 patients (median age: 70 years, IQR: 58–78) recruited during the acute phase of ICH, found pre-ICH cognitive impairment in 16 of 89 patients (18%, IQCODE score ≥ 3.44). Of these, pre-ICH dementia was detected in 8 of 89 patients (9.0%, IQCODE score ≥ 4). These clinical data question the common comorbidity of VCI and Alzheimer's disease (AD), especially in lobar ICH in the elderly, in which AD pathology is known to make significant contributions to cases of dementia after stroke. Indeed, autopsy studies have shown that about 50% of dementia cases can be attributed to either the association of VCI and AD or to mixed dementia [11].

2.2.2. *Post-ICH VCDs*

Post-stroke dementia is highly prevalent. The risk of dementia is greatest in the immediate post-stroke period [12], and the risk of delayed dementia increases over time [13]. Despite this, there are very few studies of longitudinal cognitive outcome in ICH survivors.

In 2012, Garcia et al. [14] were the first to evaluate the frequency and pattern of cognitive dysfunction in an ICH cohort ($n = 48$, mean age: 60.8 ± 14.2 years) in a cross-sectional retrospective study. They classified 71% of hematomas as primitive. Dementia was observed in 23% (95% CI: 13–32%) of cases according to the DSM-IV, and cognitive impairment without dementia was observed in 77% (95% CI: 65–89%) of patients. This work supports the need to assess cognition with one major limitation: a 40-month post-ICH cognitive assessment, making the culpability of VCDs tricky. In 2016, Moulin et al. [13], in a prospective study of 218 ICH survivors (median age: 67.5, IQR: 55–76 years), described the risk factors and prevalence of dementia during a median follow-up of 6 years. Dementia diagnosis was based on the US National Institute on Aging/Alzheimer's Association criteria for all-cause dementia. The authors showed that 14.2% of patients developed new-onset dementia by 1 year of ICH, and the rate increased over