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Neurodegenerative and Vascular Involvement in Post Stroke Dementia

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Abstract

Cognitive Impairment and Dementia are not rare conditions in patients with stroke. The close link between cerebrovascular disease and dementia appears a clear public health problem. With an ischemic stroke, the onset of vascular dementia could be triggered, mostly in those patients with a pre-existing cognitive decline. The underlying mechanisms of post-stroke cognitive impairment are not known in detail. Neurodegeneration and vascular factors are activated, with coexistence, when also overlap, of these two pathological mechanisms within the neuro-vascular unit. Several works have found that acute stroke can cause changes in brain volume affecting cognitive abilities frequently, but not constantly, as found in Alzheimer's disease patients. This review analyzes previous data on the role of stroke in initiating or promoting neurodegenerative dementia.

Keywords: Stroke; Cerebrovascular disease; Dementia; Neurodegenerative disorders; Neuroimaging

Introduction

Stroke is the second most frequent cause of death in the world after ischemic heart disease [1] and represents the principal cause of acquired disability [2], with patients remaining physically dependent in the 50% of the cases and approximately two-thirds having different neurological impairment after 5 years from stroke [3]. In addition, the close link between stroke and dementia is well-defined, with a prevalence of one patient in 10 with a pre-stroke dementia condition, and one in 10 who develop dementia after a first cerebrovascular event and on in three who develop dementia with the recurrence of stroke events [4]. Several factors have been associated with post-stroke cognitive deficits. Pendlebury and Rothwell reviewed 73 cohort studies on post-stroke dementia including a total of 7511 patients and founded that most predictors of post-stroke dementia were related to the stroke itself (hemorrhagic stroke, left hemisphere stroke, dysphasia, stroke severity and infarct volume), the number of strokes (previous stroke, multiple infarcts and recurrent stroke) and the complications of stroke (incontinence, early seizures, acute confusion, hypoxic ischemic episodes and hypotension) [5]. Other factors included demographic features (older age, low educational attainment, previous cognitive decline and premorbid disability) [5]. Dementia syndromes diagnosed after a stroke are usually considered to be vascular in origin. However, stroke and degenerative dementia are probably strictly dependent, especially Alzheimer's disease (AD), more than expected by chance: in some cases, patients with post-stroke dementia show a progressive onset and course, which suggests an underlying degenerative process [6]. Therefore, dementia occurring after stroke may be the consequence of the effects of stroke on already existing degenerative processes: when a stroke occurs at a pre-clinical stage of AD, the period of time required for its clinical expression may be shortened by the stroke itself. Some studies demonstrated that changes in brain volume and cognitive performance could be connected with a stroke event, although generally with a different pattern (site and function involved) seen in Alzheimer's disease [7-10].

Pre-Stroke Dementia

Cognitive impairment is not easily detected before stroke. Previous studies found a Pre-Stroke Dementia prevalence of 14% in hospital based setting and 9% in population based studies. Nonetheless, the underlying mechanism has not yet been clearly defined [5]. The majority of studies on Pre- and Post-stroke cognitive impairment are commonly based on cohorts of patients affected by ischemic stroke or mixed clinical pictures, while just a minority of them involves patients affected by hemorrhagic stroke. However, Pre-Stroke cognitive impairment and dementia were demonstrated to be more frequent in intra-cerebral hemorrhage (ICH) patients compared to a simultaneously evaluated cohort of patients with ischemic stroke and TIA. Cordonnier et al. described higher rates of pre-ICH cognitive impairment in patients affected by lobar ICH. Lobar hemorrhages are associated with cerebral amyloid angiopathy and cerebral microvascular amyloid β protein deposition is a common pathological feature of Alzheimer's disease, both supporting the evidence of higher frequencies of pre-ICH cognitive impairment in lobar ICH compared to deep ICH [11].

Several longitudinal studies have also investigated whether cognitive decline is linked with the exposure at cerebrovascular risk factors. A meta-analysis study found a relation with worst neuropsychological performance in cognitive tests and higher risk of stroke (almost 15%) [12]. Furthermore, people with a story of rapid cognitive impairment in a short period of time have themselves a greater risk to have stroke.

How to Assess Pre Stroke Dementia

When evaluating stroke effects on cognition, the Pre-stroke cognitive abilities should be considered. The assessment of Pre-Stroke cognitive status through a multidimensional neuropsychological evaluation, that keep in mind the appropriate time interval between Pre-Stroke cognitive evaluation and the occurrence of stroke and then, between incident stroke and the following Post-stroke dementia assessment, is essential [13].

Brief cognitive screening tests for dementia, such as the Mini-

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mental State Examination (MMSE), are widely used both in research and clinical practice. However, informant-based screening tests can suggest an additional way to assess patients [14]. Indeed, informant-based methods can be useful when combined with screening tests to improve screening accuracy, or to evaluate pre- morbid cognitive impairment, where present. A large number of informant instruments are available [15], however most of them have not yet come into widespread use. The IQCODE was developed as a way of measuring cognitive decline from a pre-morbid level using informant reports.

Jorm et al. [15] assessed scores on the IQCODE against change on cognitive tests over the previous 3.5 years and subsequently against change over the previous 7-8 years [16]. IQCODE score was found to correlate 0.48 with change in MMSE score over the 7-8 years, 0.38 with change in episodic memory and 0.34 with change in mental speed. Two studies have compared the Retrospective IQCODE to neuropathological diagnosis [16]. Thomas et al. found a sensitivity of 73% and specificity of 75% for a cut-off of 3.7+ using conventional neuropathological diagnosis of Alzheimer's disease (AD) as the standard and a sensitivity of 68% and specificity of 80% using immunohistochemistry [17]. Rockwood et al. found a sensitivity of 97% and a specificity of 33% for a cut-off of 3.42, using pathological diagnoses of AD, vascular or mixed dementia [18]. Also relevant is the report by Thomas that the IQCODE was significantly correlated (r not reported) with 130 kDa amyloid precursor protein in the blood of AD patients [19].

Post Stroke Dementia - Mechanisms

A clear connection between neurodegeneration and vascular mechanisms has not yet been identified and associated condition may be diagnosed in 20% of subjects with dementia after stroke. The compresence of vascular, degenerative and probably inflammation could represent an overlap between different pathological situations [20]. A link between stroke, Alzheimer's dementia (AD) or Mild Cognitive Impairment has been frequently described [21,22]. In vascular cognitive impairment (VCI), cerebrovascular disorders (most with ischemic pathway) and amyloid protein synergistically impair cognitive performance [23]. The presence of neuro-inflammation after stroke [24,25] was also detected in specific areas of neuronal damage [26]. As well the involvement of microglia in amyloid deposition for Mild Cognitive Impairment patients [27] and the detection of Pittsburgh compound B in imaging of post-stroke dementia patients [28], suggest the hypothesis of a link of these conditions in the development of post-stroke cognitive decline [29].

According with these data stroke could be a trigger to spark a secondary degenerative process, thus accelerating a pre-existing neurodegenerative condition. Otherwise, It's important to keep in mind that Cognitive impairment could be present in patients affected by subclinical forms of cerebrovascular disease, (silent infarcts and leukoaraiosis) [30,31], but also that patients affected by dementia not subsequent to a stroke showed several vascular risk factors [32,33].

Carotid atherosclerosis has been suggested to play a role in cognitive deterioration in the elderly, and several studies have proposed the possible role of atherosclerosis in increasing Alzheimer's pathology [34]. The effect of atherosclerosis on dementia has also been attributed to its relation to cerebral infarction, or to systemic or local factors that underlie both atherosclerosis and cognition [35]. Although intracranial atherosclerosis was related to the presence of cerebral infarcts, this effect additive respect of the effect of atherosclerosis itself on dementia risk.

However, concomitant pathologies are very common in aging brains. In sum, there is a complex but predictable correlation between AD pathologic hallmarks, vascular risk factors and cognitive impairment [35].

Therefore, it is essential to precisely define the burden of cerebrovascular risk factors and the susceptibility profile neurodegenerative disease. This will be one of the goals of the coming years in order to better define the possible role of symptomatic treatments in patients with post-stroke dementia.

Biomarkers of Post Stroke Dementia for Early Detection of Pathology

The principal role in early detection of patients possibly exposed to Post Stroke dementia concern with the focusing of the major risk factors like hypertension and dyslipidemia. According with the research field about the role of the biomarkers, also in Post Stroke Dementia their application let clinicians to make early and accurate diagnosis. There are 3 different kinds of biomarkers: clinical, neuroradiological and CSF- and blood-based analysis.

In particular, CSF biomarkers could reflect underline pathological processes in the brain [36].There are no definitive data coming from multiple studies able to discriminate their use differentiating Post Stroke from Alzheimer dementia. A significant reduction of Ab-42 in patients with AD as well as Post Stroke Dementia suggests a significant overlap making it difficult to distinguish AD total tau and phosphorylated tau (p-tau) have been extensively studied in AD and there are several reports on their utility in diagnosis and prognosis of AD [36]. However, their diagnostic utility is enhanced when used in combination with folate ratio, Ab-42, total tau, or p-tau levels.

Simonsen et al. conducted the first study to establish the status of these candidate biomarkers in lack specificity and need to be validated and investigated in large prospective multicentric trials [37].

Neuroradiology of Pre and Post Stroke Dementia

Imaging of these patients could be analyzed on different ways: structural, functional and metabolic. When full studied in the different aspects role of vascular as well as neurodegenerative mechanisms in the development of post-stroke cognitive dementia is fully analyzed. However, is essential to compare them with changes occurring with normal ageing [38]. Cerebral cortical atrophy, medial temporal lobe atrophy (MTLA), cerebral silent infarcts and subcortical white matter lesions (WMLs) were found to be possible predictors of PSD [39]. Adherence to guidelines for the identification and definition of the abnormalities documented through MRI sequences has allowed to demonstrate the significant effect of WMLs and MTLA in the development of PSD [40,41]. In addition to the size and location of vascular lesion itself [42], the involvement of fiber tracts connecting cognitive centers might be essential for the development of post-stroke dementia, hence the emerging interest in diffusion tensor imaging (DTI) techniques [43]. Post-stroke dementia, is also described by changes in cerebral blood flow and cerebral glucose metabolism, and physiological variables has been used during different ages in the differentiation of different form of dementia [44,45]. The use of the metabolic deficit in specifically area (temporo-mesial, temporo-parietal cortex and posterior cingulum) was one of the applications of the FDG-PET to differentiate from no metabolic changes found in infarcted areas in vascular dementia. Premorbid amyloid level of deposition and the subsequent damage due by inflammation after stroke can be evaluated by the use positron emission tomography (PET) imaging with different

tracers for amyloid deposition and for microglia activation. In this way increasing accumulation of amyloid can be responsible to the development of PSD.

Post Stroke Dementia and Transcranial Magnetic Stimulation

Alzheimer's disease patient reveal deficit in cholinergic neuronal markers and decreased serotonin metabolism. These findings could be defined also in Post Stroke dementia [46,47]. In the last years, research about the involvement of multiple neurotransmission in Post Stroke dementia and Neurodegenerative Dementia (Alzheimer Disease in particular) have led investigators to use transcranial magnetic stimulation (TMS) in order to define their neurophysiological profile. TMS was developed to explore the development of the corticospinal system, the functioning of the healthy brain and to evaluate the involvement of the corticopiramidal tract in a variety of neurological diseases [48]. Data from these studies reveal that degenerative and vascular cognitive changes may share a common electrophysiological platform, thus making similar conditions that are, at least in principle, different both in location and origin. Previous analysis of excitability measures demonstrated similarly enhanced cortical excitability in AD and Vascular Dementia patients with respect to controls. Bridging gaps in our knowledge within this area is mandatory, given that the development of dementia cannot be accurately predicted by conventional investigations [49,50]. Furthermore, studies in patients with VCI-no dementia at risk for clinical deterioration showed the presence of a TMS pattern similar to that observed in those with an overt dementia [51,52]. This was particularly evident if a late-life depressive disorder concomitantly occurred, highlighting the crucial role of post-stroke affective disorders (namely the so called "vascular depression") in the onset and progression of vascular dementia and post-stroke dementia [52].

Therapies

No Pharmacological trials were applied specifically on Post Stroke Dementia Patients. The potential treatment for these patients should include the prevention of further cerebrovascular events (recurrence of stroke), which can be obtained through the treatment of hypertension and other underlying vascular risk factors, as well as the prevention of beta amyloid accumulation [53].

The stroke prophylaxis guidelines suggest the use of antiplatelet drugs (aspirin or aspirin plus dipyridamole or clopidogrel) when also anticoagulation could be needed. The control of cardiovascular pathology and risk factors, such as hypertension, hyperlipidemia, diabetes, smoking, atrial fibrillation and arrhythmias is fundamental, but there are not a big number of study that define the influences of them on the course of cognitive impairment after stroke. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and the PROGRESS magnetic resonance imaging sub-study have underline the important role of antihypertensive treatment in prophylaxis against white matter damage [54,55]. Non significative improvement on cognitive abilities was detected with the use of donepezil, galantamine and memantine [56,57].

Cochrane reviews have reviewed non-pharmacological treatment (as cognitive rehabilitation), but more studies on this aspect are expected [58]. Central nervous system could benefit in structural integrity with Physical activity that could be able to counteract age-related decline [58]. A 4 year clinical trial testing a physical exercise intervention with cognitive function as a secondary outcome is expected to provide more information on the matter in the near future (The Lifestyle Interventions and Independence for Elders Study) [59].

Conclusion

Early detection of milder forms of cognitive decline after stroke needs a stronger work by clinical researcher. Actually, in line with the prevention of general vascular risk factors, no other significative methods to reduce post-stroke dementia impact are found and no therapies were tested on cognitive deterioration when diagnosed. Some specific findings in Post-Stroke Dementia, including clinical manifestations and neuropathological, instrumental and biochemical correlates, need further research to definitively establish their role as conclusive predictors for this condition.

Cerebral cortical atrophy (in particular medial temporal) and white matter involvement are frequently found in patients with cognitive impairment following stroke. The mechanism triggered by an ischemic or hemorrhagic stroke and the possibility of their link for the progressions of symptoms need to be investigated.

Finally, behavioral interventions and the use of drugs able to promote molecular repair processes in the brain should be encouraged and promoted as a potential useful method of rehabilitation for such patients.

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