Poststroke Dementia among Older Adults

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Stroke and dementia are major health problems affecting older people. Cerebrovascular disease is the second-leading cause of dementia after Alzheimer's disease, the third-leading cause of death, and one of 10 leading causes of physical disability. In parallel with the increased prevalence of stroke in aging populations and the decline in mortality from stroke, the rate of diagnosed poststroke dementia has increased, causing a growing financial burden for health care systems. This article discusses the epidemiology, etiology, and determinants of poststroke dementia and outlines the search for a suitable treatment.

Key words: *dementia, stroke, cognition, risk factors, cognitive impairment*

Introduction

Stroke and dementia are major health problems affecting older people. Cerebrovascular disease is the second leading cause of dementia after Alzheimer's disease (AD), the third leading cause of death, and one of 10 leading causes of physical disability.[1] In parallel with the increased prevalence of stroke in aging populations and the decline in mortality from stroke, the rate of diagnosed poststroke dementia (PSD) has increased, causing a growing financial burden for health care systems.

Dementia occurring after a stroke is PSD irrespective of its possible cause: vascular, degenerative, or mixed. Vascular dementia (VaD), a direct consequence of ischemic or hemorrhagic stroke, is not a synonym for PSD but is one of its possible causes.

Epidemiology

The prevalence of dementia in population-based studies is about 30% among persons with history of stroke: this is 3.5–5.8 times higher than among those without stroke.[2,3] In hospital-based studies, the prevalence of PSD ranges from 6 to 31.8%. So there is a great discrepancy in the data, which is a consequence of different methodologies of published studies. The biggest impact on PSD prevalence has been the choice of diagnostic criteria for dementia. Rasqiun *et al.*[4] showed that in one stroke population the prevalence of PSD 1 month after a stroke varied depending upon the diagnostic criteria for dementia that was used, ranging from 11.3% using criteria from the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) to 15.5% using criteria from Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R), 16% using criteria from Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), 18.0% using criteria from DSM-IV, 19.6% with DSM-III, and 20.1% using criteria from the International Classification of Diseases, 10th Revision: Neurological Adaptation (ICD-10 NA).

Another factor affecting PSD prevalence is the time from onset of stroke to neuropsychological evaluation. According to published data, 5.9–31.8% of individuals have dementia 3 months after stroke,[5,6] 8.5–22.8% 6 months after stroke.[7,8] 10–21.4% 1 year after stroke,[7,8] and 21.6%8 and 19.2%[8] 2 and 3 years after stroke, respectively.

The prevalence of PSD is also affected by a lack of homogeneity of studied populations (e.g., variety in ethnicity, age range, exclusion or inclusion of patients with aphasia, presence of prestroke dementia, or impairment too severe to allow for neuropsychological evaluation after stroke). Evaluating prestroke dementia is very important in the proper estimation of PSD prevalence: according to different studies, 9.2–16.3% of patients admitted to hospital with stroke already have prestroke dementia,[9,10] usually unrecognized previously. The inclusion of individuals with prestroke dementia can increase the frequencies of PSD. On the other hand, the exclusion of patients too severely impaired to undergo neuropsychological examination or patients with aphasia can artificially decrease the prevalence of PSD.

In population-based studies examining the incidence of PSD 10 years after a stroke, patients with stroke had a twofold increased risk for dementia compared with stroke-free controls.[11] In a cohort from Rochester, Minnesota, the incidence of PSD was 7% at 1 year, 10% at 3 years, 15% at 5 years, 23% at 10 years, and 48% at 25 years of observation. In comparison with stroke-free individuals, the risk of dementia was 8.8 at 1 year after a stroke, 4.5 at 3 years, 3.5 at 5 years, 2.5 at 10 years, and 2.0 at 25 years.[12]

In hospital-based cohorts, the risk for dementia associated with stroke in a dementia-free sample of patients 3 months after stroke compared with controls was 5.5, and the incidence rate was 33.3% after 52 months of observation.[13] In other studies conducted among stroke survivors >75 years without dementia 3 months after stroke, PSD was found in 9% 1 year later[14] and in 21.5% within 4 years after the stroke.[15]

In spite of wide differences in the various studies, they all show that the risk of PSD is high for persons with stroke, especially in the first months after the event, and is still highly elevated in following years when compared with a stroke-free population.

Table 1: Strategic Cerebral Locations Responsible for Dementia Secondary to Single Vascular Lesion

Cortical localization	Subcortical localization
Left and right angular gyri (middle cerebral artery lower division)	Thalamus (paramedian arteries or polar artery)
Inferomedial temporal lobe (posterior cerebral artery)	Genu of the left internal capsule (middle cerebral artery)
Mesial frontal lobe (anterior cerebral artery)	Caudate nucleus (anterior and posterior cerebral artery)

Sources: Leys D, et al., 1999[16]; Tatemichi TK, et al., 1995.[17]

Etiology

Most data concerning the etiology of PSD suggest that its origin is complex. First, stroke of any cause can directly effect dementia. In these cases, the disease is classified as vascular dementia (VaD) or multi-infarct dementia (where multiple lesions have a synergistic effect on mental functions, resulting in dementia irrespective of the specific brain location or tissue volume lost). However, there are only a few circumstances when this direct connection can be recognized: among young people who are unlikely to have associated Alzheimer pathology; among individuals with normal cognitive functioning before stroke who become demented immediately and do not worsen over time; when the lesion is located in the so-called strategic area; and when a well-defined vasculopathy known to cause dementia is proven.[16] Strategic areas in which damage interrupts critical pathways for cognition and is responsible for dementia are listed in Table 1.

The clinical manifestation of VaD is abrupt, and there is no progression of symptoms over time. Vasculopathies responsible for dementia are listed in Table 2.

Second, some patients with dementia after stroke have a progressive course, suggesting an underlying degenerative disorder. It is possible that a single stroke may lower the threshold for future clinical expression of pre-existent neurodegenerative disease. Data from epidemiological and clinicopathological studies suggest overlaps between AD and cerebrovascular lesions. Vascular changes may magnify the effect of cognitive decline due to AD pathology, promote its progression,[22,23] and lower the threshold of AD pathology required for the clinical expression of dementia.[24]

Autopsy evidence reveals that large vessel infarcts or small striatal infarcts are larger in the presence of amyloid. Individuals with minor cerebral infarcts and moderate AD pathology develop the clinical manifestations of dementia.[25]

Stroke and neurodegenerative dementia share common environmental and genetic factors predisposing their co-occurrence. Among them are increasing age, hypertension, smoking, increased intima-media thickness of the common carotid artery, and apolipoprotein E gene.[26] White matter changes are related to stroke by increasing the risks of stroke recurrence of any type and PSD.[27] In AD, white matter lesions are found often and the extent of damage has a strong correlation with the cognitive function, reflecting selective impairment of the corticocortical and corticosubcortical disconnections in the pathomechanism of disease.[28] The risk of AD is increased among individuals with adult-onset diabetes mellitus, hypertension, atherosclerotic disease, and atrial fibrillation. Experimentally, small striatal infarcts in the presence of high levels of amyloid in the brain exhibit a progression in infarct size over time with an enhanced degree of cognitive impairment, AD-type pathology, and neuroinflammation compared with striatal infarcts or high amyloid levels alone.[25]

Third, even if the vascular lesion in the brain, white matter changes, or Alzheimer's degenerative lesions do not lead to dementia alone, they may have an additive effect and reach the threshold of lesions required to produce dementia.[29]

Determinants

Many studies have assessed risk factors for PSD, but their results are not unequivocal. Only data showing increasing age as a risk factor are unanimous.[5,7,8,10,11,13,15,31–33] Other demographic risk factors determined by some studies but not confirmed by others are gender,[5,6,8,9,11,32,33] low education level,[8,9,18,32,33]

Table 2: Vasculopathies Responsible for Secondary Dementia due to Multiple Deep Infarcts and Leukoencephalopathy

Binswanger's disease
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Subcortical arteriosclerotic encephalopathy (Binswanger's type) with cortical infarcts without arterial hypertension
Subcortical arteriosclerotic leukoencephalopathy with alopecia and lumbago without arterial hypertension
Cerebroretinal vasculopathy
Hereditary cystatin C amyloid angiopathy

Sources: Loizou D, et al., 1982[18]; Fukutake T, et al., 1995[19]; Grand MG, et al., 1988[20]; Blondal H, et al., 1989.[21]

Key Points

- Poststroke dementia (PSD) is defined as dementia occurring after stroke irrespective of its possible cause.
- PSD is common complication of stroke: it affects about one-third of stroke patients.
- The etiology of PSD is complex: stroke and neurodegenerative dementia share common environmental and genetic factors predisposing their co-occurence.
- Age is the most powerful risk factor for PSD.
- PSD increases risk of mortality and recurrence of stroke.
- Primary and secondary prevention of stroke is the most effective strategy to reduce the risk of PSD.

prestroke cognitive decline,[8,32] and dependency before stroke.[33]

The role of arterial hypertension, a risk factor for stroke, VaD, and AD, is not clearly identified in the case of PSD. Some studies showed a high risk for PSD in those with hypertension, but others did not. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS), the lowering of hypertension among persons with prior stroke or transient ischemic attack was associated with a lower risk of "dementia or cognitive decline with recurrent stroke" but no reduction in the risk of "other dementia or other cognitive decline."[30] Therefore, the benefit of treatment was rather a consequence of stroke prevention than a direct effect on dementia or cognitive decline.[28]

In other studies, atrial fibrillation,[9,15,32] diabetes mellitus,[5,6,31–33] myocardial infarction,[6,32,33] cardiac arrhythmias,[32] congestive heart failure,[32] epileptic assures,[32] and sepsis[32] were found as independent determinants for PSD. Stroke features associated with PSD include a variety of factors. Among them are stroke recurrence,[10,32,33] more severe neurological deficit on admission to the hospital,[8,32] left hemisphere lesions,[32,33] supratentorial lesions,[32] anterior and posterior cerebral artery territory infarcts,[3,32] strategic infarcts,[34] and multiple brain lesions.[9,15] Characteristics seen on neuroimaging such as silent infarcts,[8,33] global cerebral atrophy,[15,32] medial temporal lobe atrophy,[35] and white matter changes[36] independently influence PSD development.

Risk for Mortality and Stroke Recurrence

Poststroke dementia increases the risk of mortality.[13,37,38] Individuals with stroke and dementia are also at an elevated risk of long-term stroke recurrence compared with nondemented stroke patients;[39] however, not all studies confirm this association.[40] One may assume that increased mortality and stroke recurrence among persons with PSD is a consequence of different therapeutic approaches in demented patients (less aggressive treatment of vascular risk factors) or/and worse compliance with treatment regime.

Diagnosis

Three months after the stroke, the patient should be referred for the first neuropsychological evaluation. It is assumed that at that time cognitive functioning of the patient is relatively stable. Clinical identification of the underlying cause of dementia is rather difficult and presumed types of underlying disease can only be confirmed definitively by autopsy. However, young age and no cognitive deficit before stroke as well as strategic localization of vascular lesion, stable cognitive deficit, or even a small improvement over time could be evidence for VaD. Progressive onset and course of dementia, as well as pre-stroke cognitive decline, suggest a degenerative rather than vascular process. Neuropsychological patterns of dysfunction can be helpful to establish the differential diagnosis but only in some cases. In autopsy-defined Alzheimer's disease and cerebrovascular disease cases, Reed *et al.*, found that predominant verbal and nonverbal memory loss and preserved executive function can differentiate AD from pure VaD.[41] Patients with mixed pathology of PSD perform on neuropsychological examination similar to patients with AD. In pure VaD executive dysfunction predominated memory dysfunction.[41] Follow-up of demented patients should be long enough to allow detection of possible cognitive improvement (mainly in memory and language).

Treatment

At present, primary and secondary prevention of stroke is the most effective strategy to reduce the risk of PSD. Proper control of arterial hypertension, lipid abnormalities, atrial fibrillation, myocardial infarction, coronary heart disease, smoking, obesity, carotid stenosis, diabetes mellitus, and hyperhomocysteinemia should be emphasized in primary prevention. The Systolic Hypertension in Europe (Syst-Eur) study demonstrated that treatment of isolated systolic hypertension in older adults with a calcium channel blocker decreased the incidence of dementia significantly.[42] Early diagnosis and appropriate treatment of acute stroke, prevention of stroke recurrence, and the slowing of progression of brain changes associated with VaD by intensive management of existing risk factors are crucial for secondary prevention.

Currently, no drugs are approved for the treatment of PSD. Because cholinergic deficits have been found in individuals with both AD and VaD, cholinergic therapy might be considered. A large number of clinical trials in AD and VaD of donepezil, galantamine, and rivastigmine have become available. Large-scale prospective studies in VaD have been reported for only donepezil.[43,44] Donepezil showed a small benefit in cognition of uncertain clinical significance in patients with mild to moderate VaD. The N-methyl-d-aspartate receptor antagonist memantine also showed moderate benefit. However, among persons with

mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with VaD.[45] So far, the data are insufficient to support the widespread use of these drugs in PSD.

Conclusion

Poststroke dementia is a common complication of stroke. Individuals with PSD have an increased risk of mortality and stoke recurrence. All persons who have experienced stroke should have a neuropsychological evaluation performed at least once, in order to identify and properly care for those with dementia.

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