Cognitive Impairment and Seizures in Patients with Lacunar Strokes

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Abstract

Lacunar strokes are mainly related to cerebral microangiopathy and to the presence of leukoaraiosis. Cognitive impairment is frequently linked to the presence of lacunes and white matter changes. The cognitive impairment consists mainly of disturbances of executive functions sometimes leading to dementia. It is mainly due to interruption of the frontal-subcortical neuronal circuits. Seizures are also observed in patients with lacunes and white matter changes. Although lacunes cannot be considered as the cause of the seizures, there is a relationship between the occurrence of cognitive impairment and seizures. Repeated seizures promote further cognitive decline. However, the development of dementia in patients with late-onset epilepsy is most probably not directly due to the lacunes but rather due to Alzheimer's disease or to cortical cerebrovascular lesions. The development of lacunes should only be the aggravating factor for the cognitive decline as demonstrated in the Nun study.

Keywords

Lacunar stroke, leukoaraiosis, cognitive impairment, seizures, vascular dementia, Alzheimer's disease, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy, Binswanger's disease

Lacunes are defined as small deep infarcts and are generally considered as the hallmark of small-vessel disease.[1] They are mostly asymptomatic[2] or give rise to a specific[3] or a less specific lacunar syndrome.[4] The short-term outcome is considered to be better than in those with a territorial infarct,[5] but on the long-term mortality rate is approximately the same.[6]

Mild cognitive impairment defines a transitional state between normal ageing and dementia. Progression relates mostly to subcortical lesions but determinants of such progression are unknown.[7] Lacunar infarcts and white matter changes have been linked to cognitive impairment,[8] although patients presenting a lacunar syndrome as a first ever stroke event, had not an elevated risk of developing mild cognitive impairment 12 months post-stroke.[9]

Cerebral microbleeds, detected on gradient-echo T2*-weighted magnetic resonance imaging (MRI) are another manifestation of small-vessel disease and related to lacunar infarcts and white matter lesions. Deep frontal and temporal located microbleeds correlate with cognitive performance in non-demented elderly patients.[10]

Seizures have also been described to occur in patients with lacunar strokes and white matter changes.[11] However, the relationship between seizures and lacunar infarcts is uncertain.[12]

Epidemiology

Silent thalamic and basal ganglia lacunes observed on computed tomography (CT) or MRI of the brain are independent predictors of cognitive decline in elderly individuals without concomitant dementing processes such as Alzheimer's disease.[13] The presence of lacunes in the thalamus is associated with lower scores of Mini Mental State Examination (MMSE) and worse compound scores for speed and motor control and executive functions.[14]

The overall prevalence of cognitive impairment 3 months after any kind of stroke and at annual follow-up remains relatively unchanged at 22 %. The prevalence ratio of cognitive impairment increases with older age (2 % for each year of age), ethnicity (2.2-fold higher among black people) and socioeconomic status (42 % increased among manual workers). The effect of education on the cognitive reserve is most pronounced in patients with mild and moderate degrees of brain pathology, whereas there is no influence in patients with severe MRI changes.[15] A progressive trend of cognitive impairment is observed among patients with small-vessel occlusion and lacunar infarction, with an average annual percentage change of 10 and 2 % respectively, up to 5 years after stroke.[16]

In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial 47 % of patients with lacunar strokes are found to have cognitive impairment on neuropsychological testing at baseline.[17] Patients with frontal subcortical ischaemia, from acute lacunar infarcts and chronic white matter disease, are 1.5 times more at risk of cognitive impairment.[18]

Clinical Spectrum

In patients with cognitive impairment and lacunar strokes the prominent deficits are seen on tests of episodic memory, verbal fluency and motor dexterity. Pure amnestic deficits are present in 36 %, amnestic multi-domain in 37 % and non-amnestic in 28 %.[17] Additional 'focal' circumscribed impairments of specialised functions such language, intentional gesture or categorical recognition may be present as result from strokes.[19] Parkinsonism can also be found associated by the presence of more severe ischaemic lesions in the striatum, interrupting the basal ganglia-thalamic-cortical 'motor' circuits.[20]

The only clinical predictors of mild cognitive impairment are higher depression scores and fewer years of education.[21] Depressive symptoms associated to poorer memory are present in 17 % of stroke patients and related to lacunar infarcts in deep white-matter tracts.[22]

In another study executive dysfunction and gait disturbances are observed in respectively 90 and 75 % of patients with lacunar state. Onset of cognitive impairment without clinical strokes is observed in approximately 45 % of patients with small-vessel disease.[23] On MMSE, patients with a lacunar stroke had an average decline of 1.7 points after 1 year, whilst patients with other stroke types had an average increase of 1.8 points.[24]

In patients with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL), a genetic small-vessel disease causing pure vascular cognitive impairment, an exploratory functional MRI analysis identified a network of five imaging variables as the best determinant of processing speed: the left anterior thalamic radiation, the left cingulum, the left forceps minor, the left parahippocampal white matter and the left cortical-spinal tract.[25]

Vascular Cognitive Impairment and Seizures

Stroke-related seizures occur predominantly in patients with infarcts in the temporal and parietal cortex.[26] Repeated seizures or epilepsy, following any kind of ischaemic stroke, leads to a significantly lower mean MMSE score.[27] Also in patients with late-onset cryptogenic seizures positron emission tomography (PET) examination suggests that they could represent the premonitory signs of a progressive encephalopathy leading to cognitive impairment.[28]

However, the use of anti-epileptic drugs can also increase the cognitive impairment.[29] On the other hand, severe seizures or status epilepticus, induces additional cytotoxic oedema around the infarct on MRI,[30] leading to increase in the infarct size and a worse outcome.[31]

In our series a history of seizures was found in 15 % of patients with lacunar strokes. The National Institutes of Health Stroke Scale score at stroke onset was on average 3.7 in the seizure patients and 5.5 in the non-seizure ones, with an independence rate at 1 year on modified Rankin of 55 % in the former and of 73 % in the latter group. On the other hand the MMSE score was on average 21 points in the seizure group and 25 points in the non-seizure group.[32]

Vascular Cognitive Impairment in Alzheimer's Disease

The Nun study has clearly demonstrated that among patients who met the neuropathological criteria for Alzheimer's disease, those with additional lacunar infarcts in the basal ganglia, thalamus and deep white matter had an especially higher prevalence of dementia, compared to those without infarcts.[33]

In the CERAD study the clinicopathological correlations also indicated that the presence of cerebral infarction in patients with Alzheimer's disease was associated with greater overall severity of clinical dementia, despite semi-quantitative measures of frequency of neuritic plaques and neurofibrillary tangles showed no differences with those without infarction.[34]

Vascular risk factors increase the risk of incident Alzheimer's dementia. Treatment of these risk factors is associated with a reduced risk of incident of Alzheimer's disease conversion.[35] Common susceptibility genes leading to shared risk factors may be one of the reasons for a higher coincidence of Alzheimer's disease and vascular dementia than can be expected by chance.[36]

One has also to take into account the existence of pre-existing cognitive impairment in stroke patients. In an overall cohort of patients with ischaemic and haemorrhagic accidents 16.3 % were already demented before stroke.[37] Post-stroke dementia occurred in 28.5 %. One-third of the patients met the criteria for Alzheimer dementia and two-thirds of those for vascular dementia.[38]

Cerebral amyloid angiopathy occurs in 40 % of patients with Alzheimer's disease and can also cause severe cerebrovascular lesions such as lobar haematomas, cortical microbleeds and microinfarcts, and white matter changes, leading to increased cognitive decline.[39]

Neuropathology

Lacunar infarcts are largely confined to striatum, internal capsule, thalamus, corona radiata and brain stem. They are due to occlusion of small perforating arteries affected by arteriolosclerosis and lipohyalinosis.[40] These perforating arteries have tree-like ramifications and are end-branches, without mutual anastomoses. The longest ones end in the periventricular white matter, representing the periventricular arterial border zones with the long medullary branches, issued from the leptomeningeal arteries.[41] The size of the occluded deep perforating branch determines the size of the lacunar infarct. Most lacunar infarcts have a haemorrhagic component and contain siderophages and haemosiderin deposits.[42]

White matter lesions are found in up to 65 % of subjects over the age of 65 years of age. They generally consist of loosing of the white matter, with loss of myelin and axons, mild reactive gliosis and the occasional presence of macrophages. The subcortical arcuate fibres are generally spared.[43] Recently neuropathological criteria and staging of cerebrovascular pathology in vascular cognitive decline and vascular dementia have been proposed.[44]

However, in a large majority of *post mortem* brains of demented patients a mixture of neurodegenerative changes, mainly of the Alzheimer type, and of different types of cerebrovascular lesions including, cortical microinfarcts and small and large bleeds are observed together with lacunes.[45] Also, not all cerebrovascular lesions are due to arteriolosclerosis and lipohyalinosis, but also to cerebral amyloid angiopathy, which is frequently associated to Alzheimer's disease.[46]

Brain Metabolism

PET studies have demonstrated that leukoaraiosis is due to chronic ischaemia and that the severity of the white matter changes contributes to the cognitive decline, leading to dementia.[47,48]

Patients with cognitive decline and lacunar infarcts have on PET examination in addition decreased cerebral blood flow and oxygen consumption in the frontal, temporal and parietal cortex.[49] The PET pattern suggests a state of misery perfusion not only in the deep structures but also in the whole cerebral cortex.[50] Also the vasoreactivity, after acetazolamide administration, is globally lost in all cerebral regions of patients with lacunes and severe cognitive impairment, compared to those without or with mild cognitive impairment in which exhausted metabolic reserve is only observed in the thalamus.[51]

Cerebral blood flow and oxygen consumption are more decreased in non-demented patients with leukoaraiosis and late-onset seizures compared to a normal age-matched control group, to a group of late-onset seizures without leukoaraiosis and to a group of mentally normal persons with leukoaraiosis.[52]

Neuroimaging

Microbleeds are increasingly recognised on T2*-weighted gradient-echo MRI of patients with arterial hypertension, lacunar strokes and small-vessel disease.[53] Microbleeds observed in the frontal regions and in the basal ganglia are moderately correlated to cognitive dysfunction.[54] Brain atrophy and white matter lesions are independently related to longitudinal cognitive decline in small vessel disease.[55]

In a voxel-based morphometric study, patients with mild cognitive impairment after lacunar infarction showed more atrophy bilaterally in the middle temporal gyrus, right and left frontal and posterior bilateral occipital-parietal regions including the posterior cingulate as well as the cerebellum. Further bilateral parahippocampal gyrus and right hippocampus volume reductions were also observed.[56] In a prospective follow-up study, progression of mild cognitive impairment was associated to increase of regional grey matter atrophy in the frontal and temporal cortex and in subcortical regions, such as in the pons, cerebellum and caudate nuclei.[57]

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy

This is an inherited microangiopathy with subcortical lacunar and white matter lesions, caused by mutations in the *Notch3* gene. The clinical presentation is variable between and within affected families and is characterised by symptoms including migraine with aura, subcortical ischaemic events, mood disturbances, apathy and cognitive impairment. The mean age at onset of symptoms is 45 years with variable duration of the disease ranging from 10 to 40 years. MRI shows on T2-weighted or fluid attenuation inversion recovery sequence, widespread areas of decreased signal in the white matter associated with focal hypointensities in basal ganglia, thalamus and brainstem.[58]

It represents the pure vascular form of cognitive impairment and supports the central role of frontal-subcortical circuits in this disease.[59] Migraine with aura is more frequent in women while stroke is more frequent in men before the age of the menopause.[60]

The pathological hallmark of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy is the presence of electron-dense granules in the media of arterioles that can be identified by electron microscopic evaluation of skin biopsies.[61] Also genetic variants of the *Notch3* gene in the elderly could play a role in age-related cerebral small vessel disease and vascular cognitive impairment.[62]

Binswanger's Disease

The main question remains whether this cerebrovascular disease, presenting clinically as a pure form of vascular dementia, is different from that caused by the frequent occurrence of leukoaraiosis and lacunar infarcts on neuroimaging in elderly patients with cognitive decline.[63]

Although the initial description by Binswanger himself was poor the neuropathological characteristics have been clearly described afterwards. They consist of enlarged ventricles, diffuse myelin loss in the deep white matter, sparing the subcortical arcuate fibres and the presence of many lacunar infarcts in the white matter and in the basal ganglia. A main characteristic is the fact that the cerebral cortex is completely spared.[64,65]

Also a PET study has confirmed that blood flow and oxygen consumption are only decreased in the deep structures and preserved in the cerebral cortex of a patient with an afterwards neuropathologically confirmed Binswanger's disease. These findings are different from the global decrease of blood flow and oxygen metabolism, involving as well cerebral cortex as subcortical structures, in brains of cognitive impaired patients with lacunar infarcts and white matter lesions on MRI or CT.[49] However Binswanger's disease remains a rare cause of pure vascular dementia.[66]

Conclusions

Cognitive decline in patients with lacunar infarcts is mostly due to a combination of different factors. Mild cognitive decline can be explained by the progression of the ischaemic changes in the white matter and increase of lacunes.[8,13] However, in patients with more severe and progressive mental deterioration, lacunar infarcts and white matter lesions must be associated to other changes mainly involving the cerebral cortex. The combination of Alzheimer disease and lacunes aggravates the cognitive decline.[33–35] In addition, Alzheimer's disease is frequently associated to cerebral amyloid angiopathy, responsible for additional cerebrovascular lesions such as cortical microinfarcts and microbleeds.[39,46] Also, repeated seizures and status epilepticus promote further cognitive damage.[31]

Despite the high prevalence of vascular cognitive impairment the therapeutical possibilities are still limited. Stroke and dementia share the same cluster of modifiable risk factors. Lifestyle interventions and strict adherence to medication can not only decrease the risk of stroke but also the risk of vascular cognitive decline.[67] ■

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