

Potential Biological Markers for Cerebrovascular Disease

ALEXANDER KURZ, MATTHIAS RIEMENSCHNEIDER, AND ANDERS WALLIN

ABSTRACT. Cerebrovascular diseases can cause cognitive impairment and dementia by loss of neurons and synaptic connections, destruction of axons, and demyelination. Biological markers including genetic tests, brain imaging techniques, and biochemical assays in the CSF are valuable for the identification and quantification of cerebrovascular diseases. Genetic tests may be used to detect mutations that cause hereditary cerebral amyloid angiopathies or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Structural CT and MR imaging is routinely used to visualize and quantify infarcts and white-matter changes. Functional SPET and PET imaging can demonstrate focal and remote effects of vascular lesions on cerebral blood flow and metabolism. Biochemical imaging using proton MRS is a nonspecific marker for neuronal and axonal damage. Among biochemical markers in the CSF, tau protein, phospho-tau, and beta amyloid protein are helpful to differentiate vascular dementia from Alzheimer's disease.

KEYWORDS: Cerebrovascular disease; biological markers; mutations; tau; amyloid

MAJOR TYPES OF VASCULAR DEMENTIA

The term vascular dementia implies that vascular changes are a necessary and sufficient cause of dementia. With regard to etiology, three major forms of cerebrovascular pathology can be distinguished. Large-vessel (or focal) cerebrovascular disease is caused by artery-to-artery or cardiogenic embolism and results in large cortical and subcortical infarcts but

is rarely associated with dementia. Small-vessel (or diffuse) cerebrovascular disease is due to hypertensive lipohyalinosis of deep penetrating arteries of the brain, which leads to multiple lacunar infarcts, usually in combination with white-matter changes, including demyelination and loss of axons. In small-vessel disease, loosening, vacuolation, and gliosis of the neuropil surrounding the small arteries is often present. Small-vessel cerebrovascular is a much more frequent cause of

From the Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany (A. Kurz, MD; and M. Riemenschneider, MD), and the Institute of Clinical Neuroscience, Göteborg University, Mölndal, Sweden (A. Wallin, MD).

Offprints. Requests for offprints should be directed to Alexander Kurz, Technische Universität München, Moehlstrasse 26, D-81675 Munich, Germany. email: alexander.kurz@lrz.tum.de

dementia than is large-vessel disease (Vinters et al., 2000). In rare cases, it is caused by hereditary disorders, including cerebral amyloid angiopathies and cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). A third type of cerebrovascular pathology that can cause dementia consists of singular infarcts in strategic areas in the cortex or, more commonly, in subcortical areas. In large-vessel cerebrovascular disease, dementia is probably associated with the number, volume, and localization of brain infarcts. Small-vessel cerebrovascular disease, including lacunes, extensive white-matter lesions, and hemorrhages, can affect cognitive function by disconnecting cortical from subcortical or other cortical areas. The available evidence suggests that loss of neurons and synaptic connections, interruption of neuronal pathways, demyelination, and loss of axons all may contribute to the emergence of dementia in cerebrovascular disease (Morris, 1997).

ROLE OF BIOLOGICAL MARKERS IN Cerebrovascular Disease

Biological markers may be defined as peripheral indicators of brain pathology that are used to demonstrate the presence of diseases independently of their clinical symptoms. They fall into two major categories: brain imaging techniques and biochemical assays in body fluids. Genes associated with diseases are present before brain pathology evolves but sometimes are also considered as biological markers. Biological markers have value for early identification and differential diagnosis. In progressive neurodegenerative diseases,

the typical brain pathology is present many years before the onset of dementia and before the development of gross structural changes that can easily be identified on computed tomography or magnetic resonance scans. Alzheimer's disease (AD) and frontotemporal dementia (FTD) have a typical topographical pattern that can be demonstrated at a predementia stage by positron emission tomography (PET). In addition, many neurodegenerative diseases are associated with specific proteins, for example, hyperphosphorylated tau and beta amyloid 1-42 in AD or alpha synuclein in Lewy body and Parkinson's diseases, which may be identified by sensitive biochemical assays in the cerebrospinal fluid (CSF) or other body fluids. CSF markers for neuronal and axonal degeneration, and PET and magnetic resonance spectroscopy (MRS) also have a potential for following neurodegenerative diseases over time. In cerebrovascular disorders, some but not all aspects of the pathology can be visualized by high-resolution structural brain imaging. Other biological markers including CSF proteins and functional or biochemical imaging may not be needed to demonstrate the presence of ischemic changes but may contribute to identify their precise nature. More specifically, biological markers may be used to map the extent of ischemic brain damage beyond visible structural lesions, to monitor the progression of these lesions, and to improve differential diagnosis. Our definition of biological markers does not include risk factors for cerebrovascular disease including hyperlipidemia, diabetes mellitus, or arterial hypertension.

Hyperhomocysteinemia is another important risk factor for atherosclerosis in peripheral, coronary, and cerebral

vessels (Bertsch et al., 2001) but is not a biological marker. Elevated plasma levels of homocysteine have been found in patients with Alzheimer's disease and in patients with cerebral vascular disease (Lebihuber et al., 2000), particularly in those with subcortical vascular encephalopathy (small-vessel disease) (Fassbender et al., 1999).

POTENTIAL BIOLOGICAL MARKERS FOR CEREBROVASCULAR DISEASE

Genetic Markers

Hereditary cerebral amyloid angiopathies (CAA) are rare, occurring in fewer than 200 families worldwide. The causes involve mutations in the genes for cystatin-C, amyloid precursor protein, gelsolin, transthyretin, prion protein, and BRI. Vascular pathology in familial CAA comprises intense deposition of fibrillar amyloidogenic proteins in the walls of small vessels, in addition to focal deposits of amyloid peptide in capillaries, causing hemorrhages and ischemic infarcts. CADASIL is the most common hereditary form of stroke leading to progressive dementia. It is caused by mutations in the gene for Notch 3 (chromosome 19) and is characterized histopathologically by narrowing of microvessels via intimal thickening and expansion of the extracellular matrix. Vascular abnormalities are also present in peripheral tissues. In the brain, they result in extensive white-matter changes and recurrent infarction but not in hemorrhages (Kalaria, 2001).

Structural Imaging

In clinical practice, techniques of structural brain imaging including computed tomography (CT) and magnetic

resonance tomography (MRT) are routinely used to demonstrate cerebrovascular diseases. These methods help to visualize and quantify focal lesions (infarcts, lacunes) and diffuse white-matter changes. The knowledge that has been gained from structural imaging on pathogenetic mechanisms is limited. It has been shown that the probability of dementia after stroke increases with the number of infarcts and with the cumulative infarct volume (Rockwood et al., 1999). Furthermore, left-hemispheric infarcts are associated with an increased likelihood of dementia after stroke (Pohjasvaara et al., 2000).

Functional Imaging

PET studies have demonstrated that lacunar infarcts, most of which are clinically silent, can produce cognitive impairment by remote effects that occur by interruption of subcortico-frontal and thalamo-cortical connections (Reed et al., 2000). Lacunar infarcts are associated with a reduced brain perfusion in the cortex, most frequently in the frontal lobes, which are correlated with cognitive impairment (Baron et al., 1992). Infarcts in the thalamus or internal capsule lead to reduced brain metabolism (Clarke et al., 1994; Kwan et al., 1999; Pappata et al., 1990) or perfusion (Mori et al., 1999) in ipsilateral cortical areas. In paramedian thalamic infarcts, the associated metabolic or blood flow deficit may involve the whole cortex (Levasseur et al., 1992; Mori et al., 1999). The degree of neuropsychological impairment is associated with the findings in functional brain imaging (Baron et al., 1992). Depending on localization, thalamic infarcts can also lead to an ipsilateral metabolic deficit in the frontal lobe, which is expressed in pronounced executive dysfunction (Mori,

1999; Van Der Werf, 1999). Remote effects have also been demonstrated for extensive white-matter changes. There is reduced perfusion and metabolism in the periventricular white matter itself (De-Cristofaro et al., 1990), but also in the frontal, temporal, and parietal cortex in the absence of any structural lesions (Yao et al., 1992).

Biochemical Imaging

Proton MRS provides noninvasive biochemical measurements in living tissues. In the brain, the most frequently used target compounds are N-acetylaspartate (NAA), a marker of neuroaxonal integrity, and myo-inositol (MI), a marker of membrane turnover predominantly in glial cells. In AD and other neurodegenerative diseases, a decrease of NAA and an increase of MI have been reported, showing that MRS measurements are nonspecific indicators of cellular and axonal pathology (Blennow et al., 1995).

Markers of Axonal, Neuronal, and Synaptic Loss

Tau is a small protein that promotes the assembly and stability of microtubules by binding to tubulin. CSF tau is consistently increased in AD and in other neurodegenerative diseases, including Creutzfeldt-Jakob disease (CJD). Since tau is present in the neuron and in axons, it may be considered as a marker for neuronal and axonal degeneration. Tau protein is the most frequently studied biological marker in subjects with cerebrovascular dementias. Several studies have found normal values in patients with unspecified vascular dementia (Arai et al., 1998; Mecocci et al., 1998; Mori et al., 1995) and in patients with subcortical white-matter dementia (Sjögren et al.,

2000; Wallin & Sjögren, 2001), whereas others have reported increased CSF tau levels in vascular dementias (Andreasen et al., 2001; Andreasen et al., 1998; Blennow et al., 1995; Skoog et al., 1995; Tarkowski et al., 2001). Most probably, CSF tau levels are elevated several months after acute ischemic events but return to normal afterwards. Part of the inconsistency may also be due to the heterogeneity within cerebrovascular dementias or to comorbid AD pathology. Tau is hyperphosphorylated in AD and in some forms of frontotemporal degeneration. Measurement of phospho-tau could therefore be of particular value for the differentiation between cerebrovascular and neurodegenerative diseases (Sjögren, personal communication, 2002).

Neuron-specific enolase (NSE), also called 14-3-2 protein, is a specific biochemical marker for neurons and neuroendocrine cells. An elevated CSF level of NSE is regarded as a biochemical marker of neuronal damage. Increased CSF levels of NSE have been found in acute stroke and in CJD. Neuron-specific enolase was increased in patients with subcortical vascular dementia (Blennow, 1994).

N(epsilon)(gamma-glutamyl)lysine isopeptide is released from the breakdown of proteins which are cross-linked by transglutaminase enzymes. Transglutaminase activation is a marker of apoptosis, and CSF levels of the isopeptide are increased in AD. The apoptosis marker N-lysine isodipeptide was significantly increased in a small group of patients with vascular-type dementia but also in patients with AD (Nemes, 2001).

Growth-associated protein 43 (GAP 43), also called neuromodulin, is a nervous-tissue-specific protein that is

primarily localized in presynaptic terminals and axons. It is thought to play a major role in neuronal growth and neuritic formation as well as in regeneration and neuronal sprouting after injury. GAP 43 was not changed in the CSF of patients with subcortical white-matter dementia (Sjögren, 2000).

The neurofilament is a major structural element of neurons particularly abundant in myelinated axons but also found to some extent in cell bodies and dendrites. It has an important function in maintaining the size and shape of axons. It is composed of a triplet protein, of which the light neurofilament subunit (NFL) is the essential component. Increased levels of NFL have been found in diseases with white-matter degeneration, for example, multiple sclerosis or normal pressure hydrocephalus (NPH) but also in nonvascular neurodegenerative diseases including frontotemporal degeneration (FTD). In small groups of patients with subcortical vascular dementia, increased CSF levels of NFL were found (Rosengren, 1999; Wallin & Sjögren, 2001).

Markers of Beta Amyloid Pathology

Beta amyloid protein, in particular the larger fragment containing 42 amino acids, is deposited in the brain in patients with AD. As a consequence, CSF levels of the protein are lower than in age-matched controls. Cerebrovascular disease in the absence of coexistent Alzheimer's pathology should not be associated with amyloid deposition. Therefore, measurements of CSF beta amyloid could be helpful for the differential diagnosis. According to a recent community-based autopsy study, however, mixed Alzheimer's plus cerebrovascular pathologies are more likely

than "pure" disease entities in elderly patients with dementia (Neuropathology-Group-of-the-Medical-Research-Council-Cognitive-Function-and-Ageing-Study, 2001). The concentrations of soluble amyloid precursor protein and beta amyloid(1-42) can be normal in patients with vascular dementia (Sjögren et al., 2001). On the other hand, decreased levels have been reported in subcortical white-matter dementia (Sjögren et al., 2000), which may suggest that some patients with subcortical white-matter disease have coexisting Alzheimer's pathology. However, disruption of the blood brain barrier that usually accompanies cerebrovascular disease may also affect beta amyloid levels in the CSF.

Markers of Myelin Loss

Sulfatide is the major acidic glycosphingolipid in the oligodendrocytes that form the myelin sheath, but it constitutes only a minor proportion of the membrane lipids in other brain cells. An increased shedding of membrane fragments from myelin might therefore lead to an increased CSF sulfatide concentration. Postmortem findings have indicated significantly reduced levels of glycolipids, cerebroside, and sulfatides in the white matter of patients with vascular dementia (Wallin et al., 1989). This is interpreted as a sign of demyelination in the periventricular white matter. Increased CSF levels of the myelin sheet component glycosphingolipid (sulfatide) were found in patients with subcortical vascular dementia (Fredman et al., 1992). In patients with subcortical arteriosclerotic encephalopathy, CSF levels of this molecule were significantly higher than in patients with normal pressure hydrocephalus (Tullberg et al., 2000). In contrast, sulfatide CSF con-

centration was normal in patients with leukoaraiosis who were less severely demented (Tarvonen-Schröder et al., 1997).

Markers of Microglia Activation

The interleukin IL6 is a proinflammatory parameter. Hypoxia and trauma are associated with IL6 release. According to most studies, CSF levels of this protein are increased in AD. The proinflammatory and trophic cytokine GM is important for the proliferation of microglia. It is also significantly elevated in AD. The cytokine GM was increased in the CSF of patients with vascular dementia (Tarkowski et al., 2001).

Markers of Blood-Brain-Barrier Breakdown

An increased CSF/serum albumin ratio indicates damage to the vessel wall with breakdown of the blood-brain-barrier (BBB), which is a temporary consequence of acute ischemia. Barrier function can be normal in pure AD but is abnormal in AD patients with white-matter changes. Several studies have consistently found an increased CSF/serum albumin ratio, indicating a defective BBB, in patient populations with vascular dementia (Wallin et al., 1990), white-matter changes (Blennow et al., 1991; Pantoni et al., 1993; Skoog et al., 1998), and subcortical white-matter dementia (Yao et al., 1992).

SUMMARY AND CONCLUSION

Many but not all aspects of cerebrovascular diseases, including complete and incomplete infarcts, white-matter changes,

and hemorrhages, can be visualized by high-resolution structural imaging techniques. Other biological markers, such as CSF proteins and functional or biochemical imaging, may not be needed to demonstrate the presence of ischemic changes but may be used to map the extent of ischemic brain damage beyond visible structural lesions, to monitor the progression of these lesions, and to improve differential diagnosis between neurodegenerative and cerebrovascular diseases. Functional brain imaging can be used to demonstrate the impact of cerebrovascular pathology on brain function in terms of perifocal and remote effects. Biochemical markers in the CSF for axonal, neuronal, synaptic, and myelin loss but also for microglia activation can be used to map the extent of ischemic brain damage beyond visible structural lesions. For purposes of differential diagnosis, measurement of beta amyloid (1-42), tau, and phospho-tau is useful. In particular, decreased levels of beta amyloid (1-42) might help to distinguish "pure" cerebrovascular disease and AD with cerebrovascular components, although a defective BBB may bias the results. To date, the potential of biological markers in cerebrovascular cognitive impairment and dementia has not been fully exhausted.

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