Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: from stroke to vessel wall physiology

Ischaemic stroke, which accounts for 85% of all strokes is characterised by its remarkable aetiopathogenic diversity, with three main varieties: atherothrombotic brain infarction, cardiac emboli, and small artery diseases, and with up to 40% of undetermined cause. Small artery disease of the brain has long been thought to be restricted to hypertension related lipohyalinosis resulting in lacunar infarcts and eventually inBinswanger’s encephalopathy, the archetype of subcortical vascular dementia.

From 1976 onwards we were able to study a large French family, some members of whom were affected by a small artery disease of the brain reminiscent of Binswanger’s disease but remarkable by the absence of hypertension and of other vascular risk factors. This familial cerebral arteriopathy was strikingly similar to eight others reported under various eponyms from 1955 to 1992. The extensive study of 57 members of this French family led us in 1993 to identify this small artery disease of the brain as a specific entity, to describe its main clinical and MRI features, to propose the acronym CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and, using a positional cloning approach, to locate the responsible gene on chromosome 19. Linkage was later confirmed in many families, which allowed us in 1996 to refine the genetic mapping within a 2 cM interval. The next crucial step was the identification of the mutated gene as Notch 3, a gene previously unknown in humans which encodes for a large transmembrane receptor belonging to the Notch/lin 12 gene family which is known to be involved in cell fate specification during development. Genetic analysis of more than 120 CADASIL unrelated families allowed us to show that these mutations are highly stereotyped, and affect only the extracellular domain of the protein. On the basis of these data, a molecular diagnostic test has been set up which is now widely used and has allowed us to show that CADASIL could also occur in patients who have no affected relatives, due to the existence of Notch 3 de novo mutations. Sporadic cases are thus now expanding the range of this disease, which nevertheless remains the most frequent variety of hereditary ischaemic stroke.

The clinical presentation of CADASIL is highly variable between families and even within families. It is characterised by four main symptoms: ischaemic stroke, dementia, migraine with aura, and mood disturbances. Ischaemic events, transient or completed, are the most frequent manifestations, occurring in 85% of patients. They are almost invariably subcortical and often present as classic lacunar syndromes: pure motor or pure sensory stroke, ataxic hemiparesis, and sensorimotor stroke, with or without dysarthria. They are often recurrent over the years leading to gait difficulties, pseudobulbar palsy, and urinary incontinence. Dementia is the second most frequent sign, present in 40% of patients. It usually occurs late in the disease and it is preceded for years by a cognitive decline predominating in frontal functions. Dementia is invariably of the subcortical type with apraxia, apathy, and memory impairment. Migraine with aura is the third leading symptom, present in 20%-30% of affected subjects. The aura is that of “usual” migraine with predominant visual and sensory symptoms but the frequency of basilar, hemiplegic, or prolonged aura is noticeably high. The frequency of attacks is highly variable from one attack in life to several a month. The aura is that of “usual” migraine with predominant visual and sensory symptoms but the frequency of basilar, hemiplegic, or prolonged aura is noticeably high. The frequency of attacks is highly variable from one attack in life to several a month. Mood disturbances, usually a severe depression of the melancholic type sometimes alternating with manic episodes, are present in 20% of cases. Other manifestations include seizures (5%), spinal cord signs, deafness, and intracerebral haemorrhage. No involvement of peripheral nerves, muscles, or other organs has so far been reported.

Each of the main manifestations can occur in isolation, leading to great diagnostic difficulties but most often they occur in succession over the years. Migraine with aura starts first, usually between 20 and 30 years. Ischaemic events and eventually mood disturbances mostly occur between 40 and 50 years, dementia between 50 and 60 years, and death around 65 years. The progression of the disease can be continuous or stepwise and the total duration is highly variable, from a few years to 30 years, with a mean of 20 years. On the whole, CADASIL is a severe disease of midadulthood leading to a dramatic terminal stage which can last for years with a bedridden and mutic state. There are, however, a few affected people who can remain asymptomatic after 70 years.

Subcortical signal abnormalities on MRI are the hallmarks of CADASIL. They can be detected as early as 20 years of age and they are always present after 35 in affected people. The earliest and most frequent abnormalities are hypersignals on T2 weighted images. They are first punctuate or nodular, predominating in
periventricular areas and in the centrum semiovale. Later in life they become diffuse, mostly symmetric, and they tend to involve the whole white matter. They also involve the basal ganglia (a crucial difference from multiple sclerosis, a frequent mimick of CADASIL) and the pons. T1 weighted images show punctiform or nodular areas of hypointensity in the basal ganglia and white matter, suggestive of small infarcts. Diffusion tensor imaging shows T2 hyperintensities and a parallel loss of diffusion anisotropy which seem correlated with the severity of clinical disability. Brain MRI is thus at present a crucial tool for the diagnosis of CADASIL and it may become a promising technique to monitor disease progression or eventually regression. The pathology of the brain in CADASIL is typical of small artery diseases with a diffuse white matter rarefaction and numerous small deep infarcts. The cortex is essentially normal and there are no large artery territorial infarcts. Diffusion tensor imaging shows T2 hyperintensities and, to a lesser extent in the apparently normal white matter, an increase in water diffusivity and a prompt alteration of smooth muscle cells which eventually disappear. Ultrastructural analysis, characteristic rounded granular osmiophilic deposits of yet unknown nature are seen, located in close vicinity to the basement membrane of smooth muscle cells. A simple skin biopsy with electromicroscopic study thus allows the diagnosis of CADASIL when it shows this typical granular osmiophilic material. It has recently been shown that Notch 3 expression in normal subjects is strictly restricted to vascular smooth muscle cells and that in the brains of patients with CADASIL there is a dramatic and selective accumulation of the extracellular domain of the Notch 3 receptor at the cytoplasmic membrane of the smooth muscle cells, in close vicinity but not within the granular osmiophilic material. This accumulation of Notch 3 cleavage product leads to a characteristic immunostaining pattern with Notch 3 antibodies. Next important steps will be to determine whether mutations lead to inhibition or activation of the Notch 3 signalling pathway and whether Notch 3 accumulation in a ligand dependent or independent context. This will require, as a first step, identification of Notch 3 ligands that are so far unknown. These approaches should provide important clues to the mechanism of CADASIL and possibly to those of other varieties of subcortical vascular dementia, of migraine with aura, and even of some forms of depression.

Thus the story of CADASIL, through a constant collaboration between clinicians and geneticists, has led us from one family with a non-hypertensive small artery disease of the brain to the unexpected discovery of the crucial role of Notch 3 and its signalling pathway in the physiology of vascular smooth muscle cells. So far, over 400 families and the first sporadic cases have been identified worldwide, suggesting that the condition is still underdiagnosed. Together with the elucidation of the mechanism of the arterial and cerebral lesions, the next and most important challenge in CADASIL is obviously to find an effective treatment for this dramatic condition.
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