

CADASIL

Hugues Chabriat*, Anne Joutel*, Martin Dichgans*, Elizabeth Tournier-Lasserre, Marie-Germaine Bousser

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common heritable cause of stroke and vascular dementia in adults. Clinical and neuroimaging features resemble those of sporadic small-artery disease, although patients with CADASIL have an earlier age at onset of stroke events, an increased frequency of migraine with aura, and a slightly variable pattern of ischaemic white-matter lesions on brain MRI. *NOTCH3* (*Notch homolog 3*), the gene involved in CADASIL, encodes a transmembrane receptor primarily expressed in systemic arterial smooth-muscle cells. Pathogenetic mutations alter the number of cysteine residues in the extracellular domain of NOTCH3, which accumulates in small arteries of affected individuals. Functional and imaging studies in cultured cells, genetically engineered mice, and patients with CADASIL have all provided insights into the molecular and vascular mechanisms underlying this disease. A recent multicentre trial in patients with cognitive impairment emphasises the feasibility of randomised trials in patients with CADASIL. In this Review, we summarise the current understanding of CADASIL, a devastating disorder that also serves as a model for the more common forms of subcortical ischaemic strokes and pure vascular dementia.

Introduction

CADASIL is the acronym for cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy suggested in 1993 to designate and characterise a hereditary disease of small cerebral arteries that affects middle-aged adults and leads to disability and dementia.^{1,2} CADASIL was possibly first described by van Bogaert in 1955 as “Binswanger’s disease with a rapid course in two sisters”.³ Before 1993, six additional families with similar patterns of presentation were reported under various terms.^{4–12}

In 1976, one of us (M-GB) saw a 50-year-old man with a lacunar infarct and extensive leucoencephalopathy. The tentative diagnosis was Binswanger’s disease, but the absence of hypertension was atypical and led us to undertake a systematic study of his family. The data were reported under three different names^{13–15} until the relevant gene on chromosome 19 could be mapped.¹ Linkage studies in other families enabled further refinement of this genetic interval^{16,17} and identification of the mutated gene as *NOTCH3* (*Notch homolog 3*).¹⁸

Since then, CADASIL has been reported in more than 500 families worldwide, but its overall prevalence is unknown. A small study from Scotland, UK, provided an estimate of 4·15 cases per 100 000.¹⁹ However, the actual prevalence could be much higher because sporadic cases occur.²⁰ CADASIL has been reported to account for 2% of cases of lacunar stroke with leucoaraiosis in patients younger than 65 years and for 11% of cases in those younger than 50 years.²¹

In this Review, we present the main clinical, neuroimaging, pathological, and therapeutic features of CADASIL, and discuss the molecular, genetics, and pathophysiological features of this disorder.

Clinical presentation

Although the clinical presentation of CADASIL varies substantially between and within families, this disease is essentially characterised by five main symptoms—migraine with aura, subcortical ischaemic events, mood

disturbances, apathy, and cognitive impairment. These symptoms vary in frequency with age and duration of disease.^{22–25}

Migraine with aura

20–40% of patients with CADASIL have migraine with aura, a proportion that is five times greater than in the general population. By contrast, migraine without aura has the same frequency in patients with CADASIL and the general population. When present, migraine with aura is usually the first symptom, with an average age at onset of 30 years (range from 6 to 48 years of age; mean age in women is 26 years; mean age in men is 36 years).^{26,27} In one study, an early age of onset correlated with a high serum concentration of homocysteine.²⁸ Most attacks are typical with visual or sensory aura symptoms lasting 20–30 min followed by a headache lasting a few hours; however, 50% of patients also have atypical attacks with basilar, hemiplegic, or prolonged aura, and some patients have very severe attacks with confusion, fever, meningitis, or coma.^{29,30} The frequency of attacks varies widely, and triggering factors are the same as those typical for migraine.²⁷ In some families, migraine with aura is the prominent symptom of CADASIL.^{22,26,27,31}

Subcortical ischaemic events

Transient ischaemic attacks and ischaemic strokes are the most frequent manifestations in CADASIL, occurring in 60–85% of patients^{22,23,32,33} with an estimated incidence of 10·4 per 100 patient-years.³³ These events occur at a mean age of 49 years (range from 20 to 70 years of age), in most cases in the absence of conventional vascular risk factors.^{1,2,22–24} However, in one series, hypertension was present in 20% of patients^{28,33} and the risk factors of high cholesterol concentrations and smoking were present in 50%, with an association between current smoking and earlier stroke onset.²⁸ Ischaemic events are almost invariably subcortical and present in 67% of patients as lacunar syndromes (eg, pure motor or sensory

Lancet Neurol 2009; 8: 643–53

*Contributed equally

Service de Neurologie (H Chabriat MD, M-G Bousser MD) and Laboratoire de Génétique (A Joutel MD, E Tournier-Lasserre MD), Groupe Hospitalier Lariboisière-Fernand-Widal, Assistance Publique Hôpitaux de Paris, Paris, France; INSERM, U740, Paris, France (H Chabriat, A Joutel, E Tournier-Lasserre, M-G Bousser); Université Paris 7-Denis Diderot, Faculté de Médecine, Site Villemin, Paris, France (H Chabriat, A Joutel, E Tournier-Lasserre); and Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, Germany (M Dichgans MD)

Correspondence to: Marie-Germaine Bousser, Service de Neurologie, Hôpital Lariboisière, 2 Rue A Paré, F-75010, Paris, France mg.bousser@lrb.aphp.fr

deficit, ataxic hemiparesis, sensory-motor deficit, dysarthria–clumsy hand syndrome). Most patients have two to five recurrent strokes over several years, progressively leading to gait difficulties, urinary urgency with or without incontinence, and pseudobulbar palsy.^{22,23,34}

Mood disturbances and apathy

Mood disturbances are present in 20% of patients with CADASIL and generally present as severe depressive episodes. These episodes sometimes alternate with manic episodes that could be mistaken for bipolar mood disorder until the typical CADASIL abnormalities are seen on MRI.^{15,22–24,35} Apathy, characterised by absence of motivation associated with decreased voluntary behaviour, has been recognised as a major clinical manifestation that is present in about 40% of patients, and that is independent from depression.²⁵

Cognitive impairment and dementia

Cognitive impairment is the second most frequent clinical manifestation of CADASIL. The earliest sign in most cases is impairment in executive function and processing speed, detectable with dedicated tests such as the Wisconsin card-sorting and the trail-making tests.^{36,37} Executive dysfunction was present in all individuals aged 35–50 years in a series of 42 symptomatic patients,³⁸ and is commonly associated with alterations in attention and memory.^{36,38} Cognitive decline becomes more extensive with ageing, with a progressive appearance of alterations in instrumental activities, verbal or visual memory, language, reasoning, and visuospatial abilities.³⁸ There is, however, some preservation of recognition and semantic memory, and severe aphasia, apraxia, or agnosia is rare.^{38,39} Although cognitive decline is progressive and isolated in up to 10% of patients, it most commonly

worsens with recurrent strokes and, in the years preceding death, dementia is invariably associated with motor impairment, gait disturbances, and, later, pseudobulbar palsy.^{22,33,34}

Other clinical manifestations

Other clinical manifestations are uncommon in CADASIL and include seizures in 5–10% of patients,^{15,22–24} intracerebral haemorrhages reported in a few cases (mostly in hypertensive patients),^{15,40} and, even more rarely, territorial infarcts (possibly coincidental),⁴¹ deafness,¹⁴ and parkinsonism.⁴² One feature of CADASIL is the absence of clinical manifestations indicative of organs other than the brain. An apparent exception is myocardial infarction reported in ten of 41 Dutch patients,⁴³ although this feature was not reported in previous larger series or in a case–control study.^{22,23,44}

The temporal profile of clinical manifestations is shown in figure 1. Although each of the five main manifestations can appear in isolation, they mostly occur in succession. Migraine with aura first starts at around 30 years, ischaemic events and mood disturbances between 40 and 60 years, and dementia between 50 and 60 years.^{2,22,23,27} Patients have difficulties in walking at around 60 years, are bedridden at around 65 years, and have a life expectancy of about 65 years in men and 71 years in women.³⁴ A few cases differ widely from this typical pattern with a very rapid or very slow progression or with a late age (>60 years) of clinical onset.^{34,45} Overall, CADASIL is a severe disease affecting young or middle-aged adults leading to a dramatic terminal stage within a mean of 25 years, when patients are fully bedridden and mute, and have dementia.

Neuroimaging and other investigations

Subcortical infarcts and leucoencephalopathy are best detected by use of MRI. Their presence is crucial for the diagnosis of CADASIL, particularly in patients with misleading presentations such as epilepsy, depression, hemiplegic migraine, progressive cognitive decline, or psychiatric manifestations.

MRI

Except for very rare cases of early migraine with aura and normal MRI at onset,⁴⁶ MRI changes precede the onset of other symptoms by 10–15 years. These MRI changes appear at a mean age of 30 years, increase with age, and are present in all individuals carrying the mutation after the age of 35 years.^{1,2,14,47,48} The earliest and most frequent abnormalities are areas of increased signal on T2-weighted imaging or fluid-attenuated inversion recovery (figure 2). First appearing as punctiform or nodular, predominating in periventricular areas and in the centrum semiovale, these abnormalities later become more diffuse, mostly symmetrical, and mostly occur in the external capsule and the anterior part of the temporal lobes—a location highly suggestive of CADASIL (figure 3).^{49–51} The basal

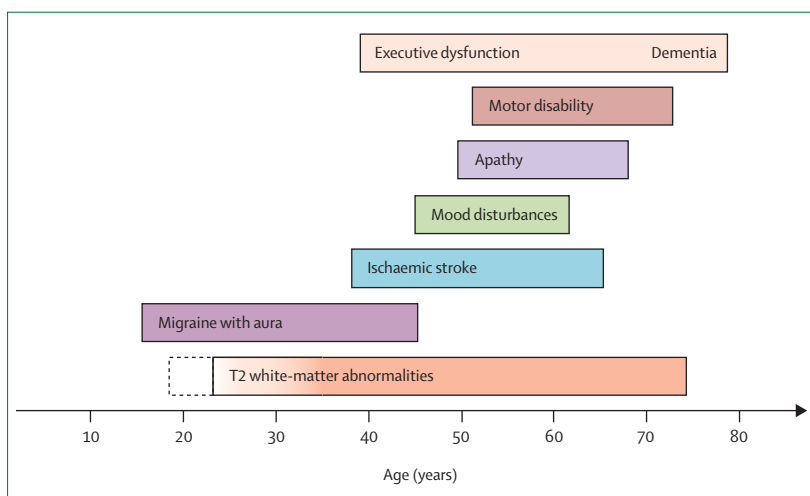


Figure 1: Natural history of the main clinical manifestations of CADASIL

The exact age at earliest onset or of first MRI abnormalities is uncertain (dotted line). The frequency of T2 white-matter abnormalities increases progressively and becomes constant by around 35 years in all patients. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

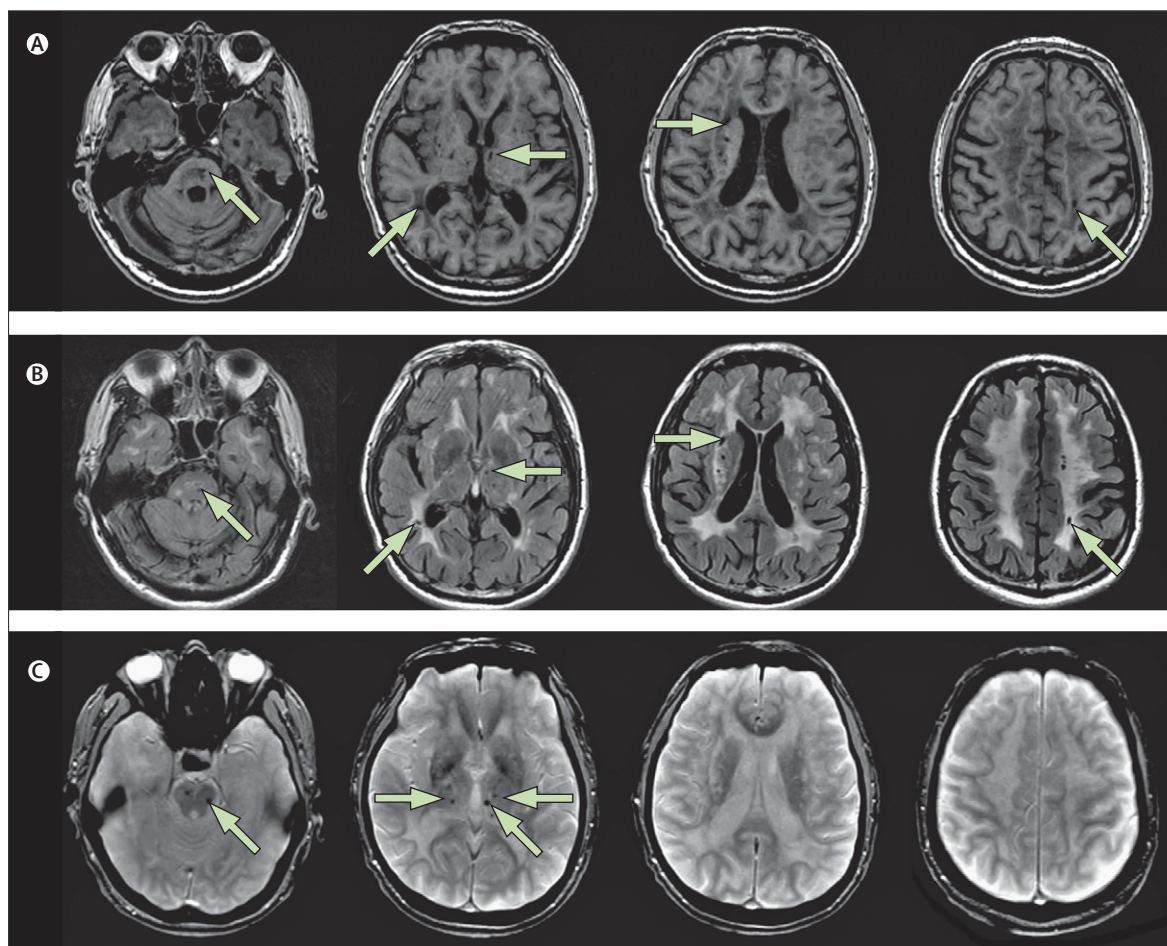


Figure 2: Main MRI changes in CADASIL

(A) Lacunar infarcts shown on T1-weighted imaging are mainly located in the brainstem (pons), thalamus, and lentiform nuclei in a 61-year-old man with a history of stroke, gait difficulties, and executive dysfunction with memory deficits. (B) Small deep infarcts are shown on fluid-attenuated inversion recovery images in association with diffuse and confluent white-matter hyperintensities involving the anterior part of the temporal lobes. (C) Microbleeds are visible on T2* or gradient-echo images as small hypointense foci in the thalamus and brainstem. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

ganglia and thalamus are also affected (a crucial difference from multiple sclerosis, a frequent mimic of CADASIL), as, on occasion, are the brainstem and corpus callosum.⁵²

Lacunar infarcts of variable shape, size, and number appear on T1-weighted imaging as punctiform or larger areas of decreased signal. These infarcts essentially occur within the same areas as T2 changes but occur later in life (figure 2).^{47,53} Diffusion-weighted MRI can show small areas of increased signal, suggestive of recent, sometimes multiple, infarcts.⁵⁴ Other magnetic resonance findings include dilated perivascular spaces, sometimes with a typical “état criblé” (or status cribrosum) predominating in the basal ganglia,⁵⁵ and microbleeds detected on gradient echo images (T2*) in 25–69% of patients; the frequency of microbleeds increases with age,^{56,57} blood pressure, haemoglobin A_{1c} concentration, and extent of leucoencephalopathy (figure 2).⁵⁸

Other magnetic resonance techniques have no diagnostic value in practice but are useful to study the clinical significance of MRI lesions. In the thalamus and areas of abnormal, but also of normal, white matter, use of diffusion tensor imaging can show an increase in water diffusion, which is better correlated with severity of executive dysfunction and clinical disability than are T2 hyperintensities.^{59–61} Follow-up studies of whole-brain diffusion have shown detectable changes over 1 or 2 years that correlated with clinical worsening, which suggests that diffusion histograms could be used as a predictor of disease progression and as a surrogate marker in future treatment trials.^{62–64} Measures of brain volume have shown brain atrophy, the extent of which is correlated with cognitive and disability scales.^{65,66} Brain atrophy progresses three times more rapidly in patients with CADASIL than in normal ageing and is independently associated with the mean apparent diffusion coefficient and the volume of lacunar lesions.^{65,66}

Other investigations

Apart from mutational screening and skin biopsy, which are used to confirm the diagnosis (see below), other

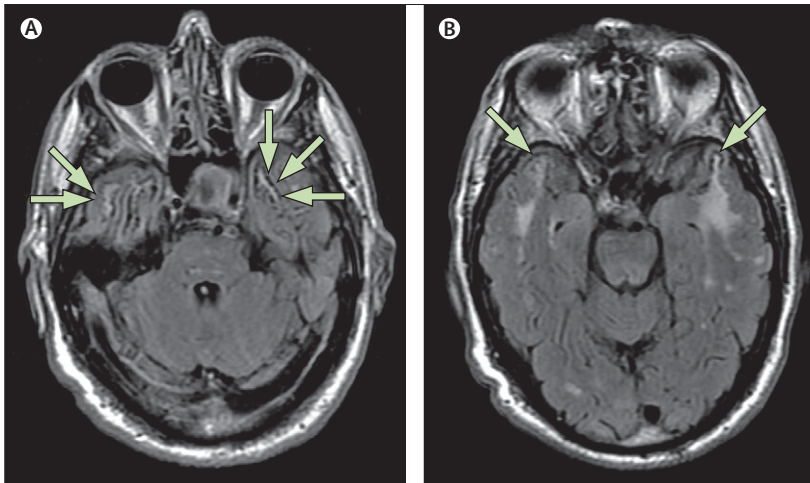


Figure 3: Specific MRI features in CADASIL
MRI (fluid-attenuated inversion recovery) scans (A and B) showing multiple hypointense lesions (lacunes related to dilated perivascular spaces) at the cortico-subcortical junction (arrows). These lesions are the most specific feature seen in CADASIL, are present in about 67% of patients, and are associated with confluent white-matter hyperintensities in the anterior part of the temporal lobes. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

investigations are not helpful for this purpose, although could be useful to exclude other disorders. The results of examination of cerebrospinal fluid, usual blood tests, electromyography, ultrasound studies, electrocardiography, and conventional spinal cord MRI are normal in most patients.^{67,68} Echocardiography results are also generally normal, although a high frequency of patent foramen ovale (47%) has been reported in an Italian series.⁶⁹ Conventional cerebral angiography occasionally shows intracranial stenosis,⁴¹ but should not be undertaken because of a high rate of complications.⁷⁰ Although patients with CADASIL have no ocular symptoms, various retinal abnormalities are common, such as arteriolar sheathing and narrowing, nerve fibre loss, and cotton-wool spots.^{71,72}

Pathology, genetics, and pathogenesis

Pathology

Macroscopic examination of the brain shows changes typical of chronic small-artery diseases of the brain: diffuse myelin pallor and rarefaction of the hemispheric white matter predominating in periventricular areas and centrum semiovale; lacunar infarcts located in white matter and basal ganglia; and dilated Virchow-Robin spaces. In the cortex, which was thought to be unaffected,

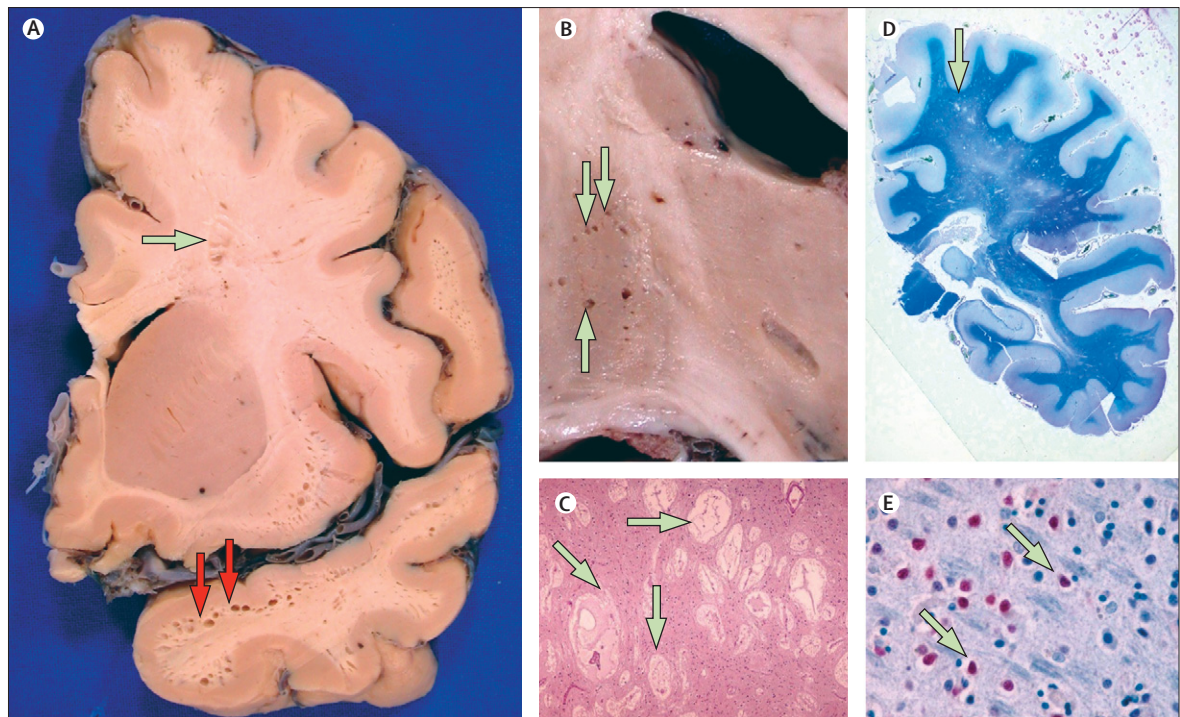


Figure 4: Pathological features of cerebral lesions in CADASIL

(A) Coronal section of the right hemisphere at the level of the caudate nucleus. Multiple subcortical lacunes (small infarcts) corresponding to dilated perivascular spaces are detected at the cortico-subcortical junction in the temporal lobe and insula (red arrows). Other lacunes are present in the centrum semi-ovale (green arrow). (B) Macroscopic section of the striatum and thalamus showing a notable area of status cribrusosus (arrows) with (C) microscopy (haematoxylin and eosin, $\times 40$) confirming accumulation of dilated perivascular spaces (arrows). (D) Coronal section of the right hemisphere at the level of the pulvinar nucleus. Klüver-Barrera stain (luxol cresyl violet) shows myelin loss in the centrum semi-ovale and small lacunes in the white matter (arrow). Note the relative sparing of the cortex by ischaemic lesions. (E) Neuronal apoptosis in layer 3 of the occipital cortex (TUNEL technique). Several neurons are positively stained, some of which have pyknotic nucleus ($\times 400$; arrows). CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

there is widespread neuronal apoptosis (particularly in layers three and five) that is more extensive in the presence of a large subcortical ischaemic lesion load (figure 4).⁷³

Microscopic and ultrastructural investigations (figure 5) show a specific arteriopathy affecting mainly the small penetrating cerebral and leptomeningeal arteries. This arteriopathy is characterised by a thickening of the arterial wall leading to lumen stenosis,⁷⁴ a largely normal endothelium, the presence of a non-amyloid granular osmiophilic material within the media extending into the adventitia, and prominent morphological alterations of smooth-muscle cells.^{15,73,75,76} These cells can eventually disappear from the vessel wall. The granular osmiophilic material, a specific ultrastructural feature of CADASIL, is extracellular, located close to the cell surface of smooth-muscle cells, but it can also be occasionally found in capillaries (figure 5).

Although clinical manifestations are only cerebral, arteriopathy is also present in other organs, such as the spleen, liver, kidneys, muscle, aorta, and skin.^{77–80} The presence of granular osmiophilic material on electron-microscopic study of skin biopsy samples thus indicates a diagnosis of CADASIL,^{77–79,81,82} but the sensitivity of this test is variable.⁵¹ Immunostaining of skin samples with a NOTCH3 monoclonal antibody, which can reveal the accumulation of NOTCH3 protein in the vessel wall, is highly sensitive (85–95%) and specific (95–100%).^{80,83}

Molecular genetics

CADASIL is an autosomal dominant disease caused by mutations in *NOTCH3*. This gene encodes a single-pass transmembrane receptor of 2321 amino acids with an extracellular domain containing 34 epidermal growth factor repeats (EGFR), each including six cysteine residues, three Notch/Lin12 repeats, a single transmembrane domain, and an intracellular domain (containing seven ankyrin repeats;^{18,84} figure 6). More than 150 mutations have been reported in at least 500 pedigrees. *NOTCH3* has 33 exons but all CADASIL mutations occur in exons 2–24, which encode the 34 EGFR, with strong clustering in exons 3 and 4, which encode EGFR 2–5 (>40% of mutations in >70% of families occur in these exons). Over 95% of mutations are missense mutations; others are small in-frame deletions or splice-site mutations.^{85–89} All mutations lead to an odd number of cysteine residues within a given EGFR (figure 6).^{84–86,88–91} De novo mutations have been reported but their exact frequency is unknown.^{20,92} Two homozygous patients have so far been described.^{93,94}

Genetic testing is the gold standard for the diagnosis of CADASIL. Screening of the 23 exons that encode the 34 EGFR has 100% specificity when a mutation leading to an odd number of cysteine residues within an EGFR is detected, and the sensitivity is close to 100%.^{89,91,95} Ultrastructural examination of a skin biopsy should be restricted to two rare situations: a negative molecular test

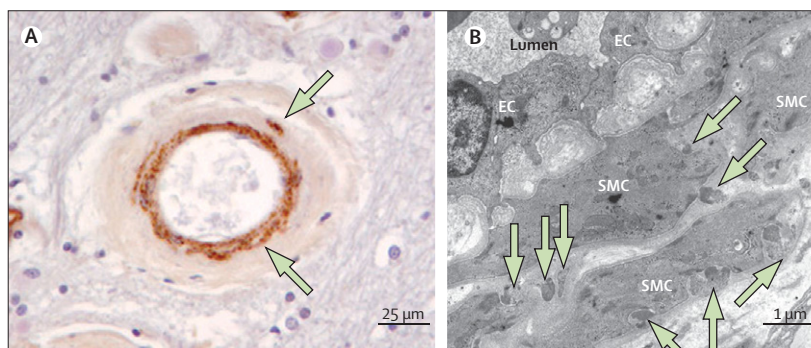


Figure 5: The characteristic arterial lesions in CADASIL

(A) Section of a small artery from the cerebral white matter immunostained with the 1E4 antibody raised against the extracellular domain of NOTCH3. Note the thickening of the vessel wall, degeneration of SMCs, and aggregates of NOTCH3 around the residual SMCs (arrows). (B) Electron micrograph of a dermal artery showing irregular SMCs and many deposits of granular osmiophilic material (arrows) located in the basement membrane of SMCs. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. EC=endothelial cell. NOTCH3=Notch homolog 3. SMC=smooth-muscle cell.

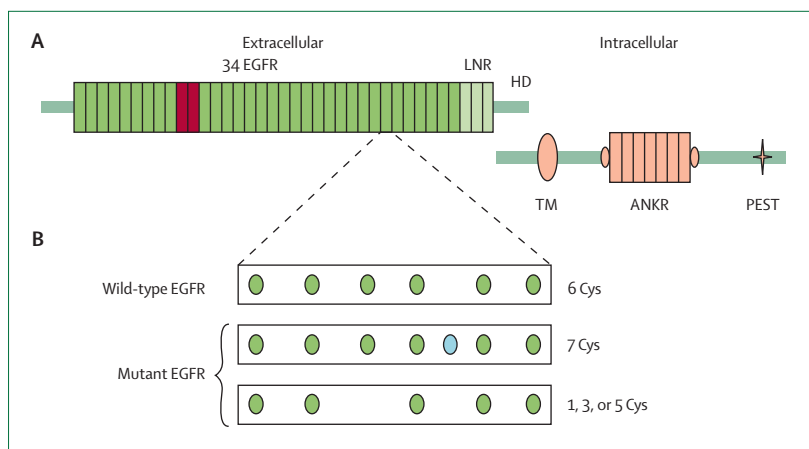


Figure 6: Schematic drawing of the NOTCH3 receptor and CADASIL mutations

(A) The different domains of the NOTCH3 receptor are shown. The mature protein is a heterodimer made of an extracellular part containing 34 EGFR, three LNR, and a HD, as well as a transmembrane–intracellular part containing a short TM, seven ANKR, and a PEST domain. EGFR 10 and 11, required for binding to the ligand, are shown in red. (B) Normal EGFR with its six cysteine residues (top) and mutated EGFR (bottom). Additional Cys residue shown in blue. CADASIL-causing mutations to the NOTCH3 receptor lead to an odd number of cysteine residues in the EGFR. ANKR=ankyrin repeats. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. EGFR=epidermal growth factor-like repeat. HD=heterodimerisation domain. LNR=Lin12 repeats. NOTCH3=Notch homolog 3. PEST=sequence that is rich in proline (P), glutamic acid (E), serine (S), and threonine (T). TM=transmembrane domain.

(screening of the 23 exons) in a patient with clinical and MRI features highly suggestive of CADASIL; and the identification of a sequence variant of unknown significance not involving a cysteine residue.

Genetic testing is indicated if the patient has a characteristic clinical syndrome in combination with characteristic neuroimaging features or a positive family history, particularly if there is no history of hypertension. The need is more debatable if a patient without a family history has only migraine with aura and a few hypersignals on T2-weighted imaging. Unless there is a specific request from the patient, genetic testing is not done at our institution in such cases for the following reasons: white-matter abnormalities are common in migraine

(particularly migraine with aura); up to 30 years can elapse in CADASIL between the onset of migraine with aura and the first stroke or onset of cognitive decline; and there is no treatment for CADASIL at present. In asymptomatic adult relatives of patients with CADASIL, genetic testing raises the same psychological and ethical concerns as in other adult-onset neurological autosomal dominant disorders leading to dementia and premature death, such as Huntington's disease.⁹⁶ Screening has no benefit for asymptomatic children and is therefore not indicated. In the experience of the authors of this Review, requests for prenatal testing are rare.

Mechanisms underlying symptoms

Various studies with single photon emission computed tomography, PET, or MRI bolus tracking methods have shown an early decrease in cerebral blood flow and metabolism, which suggests chronic subcortical ischaemia.^{97–100} Compromised cerebral haemodynamics probably arises from both structural and functional changes in brain arteries. Autopsy studies in patients with CADASIL have shown stenosis of arterioles in the white matter^{15,75,76} but not in the basal ganglia, another common site of lacunar infarcts.⁷⁶ Additionally, vasoreactivity of small penetrating arteries is likely to be compromised by both vascular fibrosis and degeneration of smooth-muscle cells. Moreover, functional studies have indicated a blunted increase in cerebral blood flow response to carbon dioxide inhalation or acetazolamide infusion in patients with CADASIL.^{101,102} Reactivity is also altered in the skin microcirculation, with a delayed post-occlusive hyperaemia response.¹⁰³

Vascular alterations in CADASIL have been partly modelled in transgenic mice, in which the regulatory sequences of *transgelin* (*TAGLN*; *SM22 α*) drive the expression of a human NOTCH3 protein with an archetypal CADASIL mutation (Arg90Cys) in smooth-muscle cells. These mice have impaired cerebral blood flow autoregulation and increased myogenic tone before the appearance of structural vascular abnormalities such as loss of smooth-muscle cells.^{104–106} This observation suggests that cerebrovascular dysfunction might contribute to disease initiation, although it is probably not the cause of the pathology, because these mice do not develop parenchymal lesions.

There is thus good evidence of chronic subcortical ischaemia in CADASIL, the risk of which increases with age. This ischaemia can cause recurrent lacunar infarcts and microstructural alterations that correlate with cognitive decline and motor disability and finally lead to cortical atrophy and neuronal apoptosis. By contrast, the pathophysiology of the two other main symptoms—mood disorders and migraine with aura—is mostly unknown. Strategic lesions in the basal ganglia and frontal white matter might affect mood disorders and other psychiatric disturbances,^{107,108} but this effect remains to be proven in CADASIL. Similarly, the early occurrence

of migraine with aura in some patients might be affected by the distribution and extent of white-matter hyperintensities on MRI,²⁷ but this hypothesis is far from being established. The cortical spreading depression that underlies the migrainous aura is known to be triggered by ischaemia. However, migraine with aura can present before changes on MRI are detectable and generally starts long before the first ischaemic events. Furthermore, infarcts are subcortical and migraine with aura is not seen in chronic hypertension-related small-artery diseases of the brain, which suggests a specific mechanism for migraine with aura in CADASIL. Studies of cortical spreading depression in transgenic mice with CADASIL might help to elucidate how mutations in *NOTCH3* decrease the threshold for this event. Because CADASIL-linked migraine with aura is one of the best examples of symptomatic migraine, an understanding of this symptom might also prove crucial for migraine in general.

NOTCH3 function and association with disease pathogenesis

The Notch signalling pathway has a central role in the development of most vertebrate organs, with pleiotropic effects depending on dose and cellular context.¹⁰⁹ Expression studies of late embryos and adult tissues of mice and human beings have shown that Notch3/NOTCH3 is predominantly expressed in vascular smooth-muscle cells, preferentially in small arteries.^{110,111} Genetically engineered mice without Notch3 have prominent structural defects of small arteries because of impaired differentiation and maturation of arterial smooth-muscle cells. Additionally, Notch3-null mice have strongly defective autoregulation of cerebral blood flow and vascular myogenic tone.^{112,113} However, total loss of Notch3 does not cause CADASIL pathology.

As with all NOTCH receptors, full-length NOTCH3 is initially synthesised as a single polypeptide chain, which subsequently undergoes constitutive proteolytic processing.^{110,114} NOTCH3 functions at the cell surface as a heterodimer composed of its extracellular domain (NOTCH3^{ECD}) non-covalently attached to the membrane-tethered intracellular domain (NOTCH3^{TMC}). Ligand binding initiates a series of proteolytic cleavages that release the NOTCH intracellular domain, which then translocates to the nucleus. Here, the NOTCH intracellular domain interacts with the transcription factor RBPJ κ and co-activators and activates the transcription of target genes.¹¹⁵

CADASIL mutations cause gradual accumulation of NOTCH3^{ECD}, without associated accumulation of NOTCH3^{TMC}. NOTCH3^{ECD} forms microscopic aggregates around vascular smooth-muscle cells and pericytes of brain arteries and capillaries, in close proximity to deposits of granular osmiophilic material. However, whether NOTCH3^{ECD} is part of the granular osmiophilic material is much debated.^{80,110,116}

Recent work strongly suggests that CADASIL mutations act through neomorphic (gain of novel function) mechanisms rather than compromised canonical NOTCH3 function. Reporter gene assays in cultured cells have shown that most CADASIL-associated NOTCH3 mutant alleles can activate RBP-J κ transcription at wild-type levels.^{117–121} Moreover, genetic studies in a mouse model of CADASIL expressing a representative mutation in EGFR2 (Arg90Cys) indicated that the mutant receptor retains normal function in brain arteries despite accumulation of Notch3^{EC95}. By contrast, some naturally occurring mutations in the ligand-binding domain (EGFR 10 and 11)^{118,119} are predicted to result in a loss of functional Notch3 receptor. The in vivo relevance and functional importance of this observation with regard to clinical disease expression remain to be investigated. The current data indicate that the change in the number of cysteine residues, and not the effect of the mutation on signalling, is the common denominator in CADASIL. At present, the hypothesis is that gain of novel function for the mutant protein, which could arise from novel protein–protein interactions, is a likely mechanism for the CADASIL mutations. Thus, the unpaired cysteine residues within mutant NOTCH3 receptors might titrate key factors for viability and function of vascular smooth-muscle cells within the deposits of granular osmiophilic material; however, other mechanisms have been suggested.¹²²

Treatment

At present, there is no treatment of proven efficacy for CADASIL, either for the disease or for the main symptoms. Treatment is thus entirely pragmatic.

Migraine with aura rarely requires prophylactic treatment as the frequency of attacks is low in most patients. If required, the usual prophylactic drugs such as antiepileptic drugs or β blockers can be used. According to anecdotal reports, acetazolamide has been found to be effective.^{123,124} For acute treatment, we avoid vasoconstrictors such as ergot derivatives and triptans, and we prefer conventional analgesics and non-steroidal anti-inflammatory drugs.⁶⁷

Prevention of ischaemic attacks is based on the usual preventive measures for non-cardioembolic ischaemic stroke: use of antiplatelet drugs rather than anticoagulants (because of the increased risk of intracerebral haemorrhage)^{15,40} and treatment of vascular risk factors. Antihypertensive drugs are used when there is hypertension, although the putative risk of making the chronic hypoperfusion worse is not known. In patients with hypercholesterolaemia, we use statins because of their well-established preventive effects in arterial diseases and because data from animals indicate that these drugs increase cerebral blood flow.¹²⁵

The only randomised controlled trial to be done in CADASIL¹²⁶ tested the efficacy of donepezil in patients with cognitive impairment. Inclusion criteria included

a mini-mental state examination score of 10–27 or a trail-making test part B time score that is at least 1.5 SD below the mean, after adjustment for age and education. 168 patients were included and the follow-up was 18 weeks. Donepezil showed no effect on the primary endpoint (the cognitive subscale of the vascular Alzheimer's disease assessment scale), whereas improvements were found on several measures of executive functions. However, the clinical relevance of this finding is not clear. Although essentially negative, this study is important because it shows the feasibility of multicentre trials in CADASIL and because it has implications for the design of future trials in subcortical vascular cognitive impairment. The limitations of the global cognitive scales originally designed for Alzheimer's disease are highlighted, as is the need to use executive function tests as outcome measures, particularly those that measure processing speed such as the trail-making test.¹²⁶

The wide variability in the natural history of CADASIL hampers the design of any preventive trial. 602 patients would be needed in an interventional 2-year study with an assumed treatment effect of 40% and stroke occurrence as the outcome measure.³³ Thus, the use of quantitative MRI measures as surrogate markers or for stratification could be necessary in future trials.^{62–64}

Rehabilitation, physiotherapy, psychological support, and nursing care are important in this severe chronic, debilitating disease, as well as genetic counselling, particularly for asymptomatic members at risk of carrying the mutation.

Conclusions and future directions

CADASIL has gained great interest as a model for the more common forms of ischaemic cerebral small-artery diseases and subcortical ischaemic vascular dementia.¹²⁷ The clinical presentation, profile of neuropsychological deficits, and neuroimaging abnormalities of CADASIL closely resemble those of sporadic small-artery diseases with subcortical ischaemic vascular dementia. The main difference is, however, the absence in CADASIL of Alzheimer's-type pathological changes that are common in elderly patients with sporadic small-artery diseases. CADASIL is thus a model of pure subcortical ischaemic vascular dementia, which was the rationale for a proof-of-concept trial in CADASIL that tested the efficacy of donepezil in subcortical ischaemic vascular dementia¹²⁶ and that might also help to refine the criteria for vascular dementia.^{128,129}

Evidence is accumulating of other autosomal dominant small-artery diseases that closely resemble CADASIL but are unlinked to *NOTCH3*—as is the case for both the Swedish family reported by Sourander and Walinder^{4,12} and a large Portuguese and French family previously reported by Verreault and colleagues.¹³⁰ These families showed no granular osmiophilic material in small arteries, thus indicating distinct arteriopathies.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed between January, 1975, and March, 2009, with combinations of the search terms “familial” or “hereditary” and “vascular dementia” or “stroke” (before 1993) and “CADASIL” (after 1993). Only papers published in English and that included a substantial number of patients or original results were reviewed. Reports of isolated cases or of newly described mutations in *NOTCH3* were not included.

The genetic defects underlying these disorders remain to be identified but there are probably more diseases that meet the operational criteria of CADASIL (ie, a cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy). These disorders could be labelled consecutively in accordance with the order of gene identification (ie, CADASIL type 2 and 3).

CADASIL is now recognised as the most common cause of inherited stroke and vascular cognitive impairment in adults. The discovery of mutations in a cell-surface receptor on vascular smooth-muscle cells has facilitated targeted studies in various biological systems. Degenerative and functional abnormalities of small cerebral arteries play a central part in this progressive disorder. The mechanisms underlying stroke, migraine with aura, and vascular cognitive impairment are far from being understood. However, initial studies in patients with CADASIL and transgenic mice hold promise that these questions might eventually be answered. Meanwhile, efforts to investigate novel treatment strategies in randomised controlled trials should continue. Such trials are feasible and could provide insights beyond CADASIL, a disease that is a genetic variant of stroke and vascular dementia.

Contributors

HC, AJ, and MD contributed equally to the acquisition of all the necessary data for this Review and to the writing of the paper. ET-L and M-GB contributed to the idea and drafting of the Review.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

Figure 4 was kindly provided by Françoise Gray, Department of Pathology, Hôpital Lariboisière, Paris, France. Figure 5 was kindly provided by Hannu Kalimo and Saara Tikka, Department of Pathology, Turku University Hospital, Finland.

References

- 1 Tournier-Lasserre E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy maps to chromosome 19q12. *Nat Genet* 1993; **3**: 256–59.
- 2 Bousser MG, Tournier-Lasserre E. Summary of the proceedings of the First International Workshop on CADASIL. Paris, May 19–21, 1993. *Stroke* 1994; **25**: 704–07.
- 3 Van Bogaert L. Encéphalopathie sous-corticale progressive (Binswanger) à évolution rapide chez deux soeurs. *Med Hellen* 1955; **24**: 961–72.
- 4 Sourander P, Walinder J. Hereditary multi-infarct dementia. Morphological and clinical studies of a new disease. *Acta Neuropathol* 1977; **39**: 247–54.
- 5 Stevens DL, Hewlett RH, Brownell B. Chronic familial vascular encephalopathy. *Lancet* 1977; **1**: 1364–65.
- 6 Colmant H. Familiäre zerebrale Gefäßerkrankung. *Zbl Allgemein Pathologie Bd* 1980; **124**: 163.
- 7 Gerhard. Familiäre zerebrale arteriosklerose. *Zbl Allg Path Bd* 1980; **124**: 163.
- 8 Sonninen V, Savontaus ML. Hereditary multi-infarct dementia. *Eur Neurol* 1987; **27**: 209–15.
- 9 Davous P, Fallet-Bianco C. Familial subcortical dementia with arteriopathic leucoencephalopathy. A clinico-pathological case. *Rev Neurol* 1991; **147**: 376–84 (in French).
- 10 Mas JL, Dilouya A, de Recondo J. A familial disorder with subcortical ischemic strokes, dementia, and leucoencephalopathy. *Neurology* 1992; **42**: 1015–19.
- 11 Salvi F, Michelucci R, Plasmati R, et al. Slowly progressive familial dementia with recurrent strokes and white matter hypodensities on CT scan. *Ital J Neurol Sci* 1992; **13**: 135–40.
- 12 Low WC, Junna M, Borjesson-Hanson A, et al. Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL. *Brain* 2007; **130**: 357–67.
- 13 Bousser MG, Tournier-Lasserre E, Aylward EH, et al. Recurrent stroke in a family with diffuse white-matter abnormalities and muscular lipidosis—a new mitochondrial cytopathy. *J Neurol* 1988; **235**: 54–55.
- 14 Tournier-Lasserre E, Iba-Zizen MT, Romero N, Bousser MG. Autosomal dominant syndrome with stroke-like episodes and leucoencephalopathy. *Stroke* 1991; **22**: 1297–302.
- 15 Baudrimont M, Dubas F, Joutel A, Tournier-Lasserre E, Bousser MG. Autosomal dominant leucoencephalopathy and subcortical ischemic stroke. A clinicopathological study. *Stroke* 1993; **24**: 122–25.
- 16 Ducros A, Nagy T, Alamowitch S, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy, genetic homogeneity, and mapping of the locus within a 2-cM interval. *Am J Hum Genet* 1996; **58**: 171–81.
- 17 Dichgans M, Mayer M, Muller-Myhsok B, Straube A, Gasser T. Identification of a key recombinant narrows the CADASIL gene region to 8 cM and argues against allelism of CADASIL and familial hemiplegic migraine. *Genomics* 1996; **32**: 151–54.
- 18 Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996; **383**: 707–10.
- 19 Razvi SS, Davidson R, Bone I, Muir KW. The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland. *J Neurol Neurosurg Psychiatry* 2005; **76**: 739–41.
- 20 Joutel A, Dodick DD, Parisi JE, Cecillon M, Tournier-Lasserre E, Bousser MG. De novo mutation in the Notch3 gene causing CADASIL. *Ann Neurol* 2000; **47**: 388–91.
- 21 Dong Y, Hassan A, Zhang Z, Huber D, Dalageorgou C, Markus HS. Yield of screening for CADASIL mutations in lacunar stroke and leukoaraiosis. *Stroke* 2003; **34**: 203–05.
- 22 Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. *Lancet* 1995; **346**: 934–39.
- 23 Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998; **44**: 731–39.
- 24 Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke* 1999; **30**: 1230–33.
- 25 Reyes S, Viswanathan A, Godin O, et al. Apathy: a major symptom in CADASIL. *Neurology* 2009; **72**: 905–10.
- 26 Chabriat H, Tournier-Lasserre E, Vahedi K, et al. Autosomal dominant migraine with MRI white-matter abnormalities mapping to the CADASIL locus. *Neurology* 1995; **45**: 1086–91.
- 27 Vahedi K, Chabriat H, Levy C, Joutel A, Tournier-Lasserre E, Bousser MG. Migraine with aura and brain magnetic resonance imaging abnormalities in patients with CADASIL. *Arch Neurol* 2004; **61**: 1237–40.

- 28 Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. *Brain* 2004; **127**: 2031–38.
- 29 Feuerhake F, Volk B, Ostertag CB, et al. Reversible coma with raised intracranial pressure: an unusual clinical manifestation of CADASIL. *Acta Neuropathol* 2002; **103**: 188–92.
- 30 Schon F, Martin RJ, Prevett M, Clough C, Enevoldson TP, Markus HS. “CADASIL coma”: an underdiagnosed acute encephalopathy. *J Neurol Neurosurg Psychiatry* 2003; **74**: 249–52.
- 31 Verin M, Rolland Y, Landgraf F, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. *J Neurol Neurosurg Psychiatry* 1995; **59**: 579–85.
- 32 Bousser M, Tournier-Lasserre E. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: from stroke to vessel wall physiology. *J Neurol Neurosurg Psychiatry* 2001; **70**: 285–87.
- 33 Peters N, Herzog J, Opherck C, Dichgans M. A two-year clinical follow-up study in 80 CADASIL subjects: progression patterns and implications for clinical trials. *Stroke* 2004; **35**: 1603–08.
- 34 Opherck C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. *Brain* 2004; **127**: 2533–39.
- 35 Kumar SK, Mahr G. CADASIL presenting as bipolar disorder. *Psychosomatics* 1997; **38**: 397–98.
- 36 Taillia H, Chabriat H, Kurtz A, et al. Cognitive alterations in non-demented CADASIL patients. *Cerebrovasc Dis* 1998; **8**: 97–101.
- 37 Dichgans M. Cognition in CADASIL. *Stroke* 2009; **40**: S45–47.
- 38 Buffon F, Porcher R, Hernandez K, et al. Cognitive profile in CADASIL. *J Neurol Neurosurg Psychiatry* 2006; **77**: 175–80.
- 39 Peters N, Opherck C, Danek A, Ballard C, Herzog J, Dichgans M. The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. *Am J Psychiatry* 2005; **162**: 2078–85.
- 40 Choi JC, Kang SY, Kang JH, Park JK. Intracerebral hemorrhages in CADASIL. *Neurology* 2006; **67**: 2042–44.
- 41 Choi EJ, Choi CG, Kim JS. Large cerebral artery involvement in CADASIL. *Neurology* 2005; **65**: 1322–24.
- 42 Van Gerpen JA, Ahlskog JE, Petty GW. Progressive supranuclear palsy phenotype secondary to CADASIL. *Parkinsonism Relat Disord* 2003; **9**: 367–69.
- 43 Lesnik Oberstein SA, Jakema JW, Van Duinen SG, et al. Myocardial infarction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Medicine* 2003; **82**: 251–56.
- 44 Cumurciuc R, Henry P, Gobron C, et al. Electrocardiogram in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy patients without any clinical evidence of coronary artery disease: a case-control study. *Stroke* 2006; **37**: 1100–02.
- 45 Mourad A, Levasseur M, Bousser MG, Chabriat H. [CADASIL with minimal symptoms after 60 years]. *Rev Neurol* 2006; **162**: 827–31 (in French).
- 46 Golomb MR, Sokol DK, Walsh LE, Christensen CK, Garg BP. Recurrent hemiplegia, normal MRI, and NOTCH3 mutation in a 14-year-old: is this early CADASIL? *Neurology* 2004; **62**: 2331–32.
- 47 Chabriat H, Levy C, Taillia H, et al. Patterns of MRI lesions in CADASIL. *Neurology* 1998; **51**: 452–57.
- 48 Dichgans M, Filippi M, Bruning R, et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. *Neurology* 1999; **52**: 1361–67.
- 49 Auer DP, Putz B, Gossel C, Elbel G, Gasser T, Dichgans M. Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. *Radiology* 2001; **218**: 443–51.
- 50 O’Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology* 2001; **56**: 628–34.
- 51 Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology* 2002; **59**: 1134–38.
- 52 Chabriat H, Mrissa R, Levy C, et al. Brain stem MRI signal abnormalities in CADASIL. *Stroke* 1999; **30**: 457–59.
- 53 Herve D, Godin O, Dufouil C, et al. Three-dimensional MRI analysis of individual volume of Lacunes in CADASIL. *Stroke* 2009; **40**: 124–28.
- 54 Gobron C, Viswanathan A, Bousser MG, Chabriat H. Multiple simultaneous cerebral infarctions in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Cerebrovasc Dis* 2006; **22**: 445–46.
- 55 Cumurciuc R, Guichard JP, Reizine D, Gray F, Bousser MG, Chabriat H. Dilatation of Virchow-Robin spaces in CADASIL. *Eur J Neurol* 2006; **13**: 187–90.
- 56 Dichgans M, Holtmannspotter M, Herzog J, Peters N, Bergmann M, Yousry TA. Cerebral microbleeds in CADASIL: a gradient-echo magnetic resonance imaging and autopsy study. *Stroke* 2002; **33**: 67–71.
- 57 van den Boom R, Lesnik Oberstein SA, Ferrari MD, Haan J, van Buchem MA. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR imaging findings at different ages—3rd–6th decades. *Radiology* 2003; **229**: 683–90.
- 58 Viswanathan A, Guichard JP, Gschwendtner A, et al. Blood pressure and haemoglobin A1c are associated with microhaemorrhage in CADASIL: a two-centre cohort study. *Brain* 2006; **129**: 2375–83.
- 59 Chabriat H, Pappata S, Poupon C, et al. Clinical severity in CADASIL related to ultrastructural damage in white matter: in vivo study with diffusion tensor MRI. *Stroke* 1999; **30**: 2637–43.
- 60 Molko N, Pappata S, Mangin JF, et al. Diffusion tensor imaging study of subcortical gray matter in CADASIL. *Stroke* 2001; **32**: 2049–54.
- 61 O’Sullivan M, Singhal S, Charlton R, Markus HS. Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. *Neurology* 2004; **62**: 702–07.
- 62 Molko N, Pappata S, Mangin JF, et al. Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: a study with whole brain histogram analysis. *Stroke* 2002; **33**: 2902–08.
- 63 Chabriat H. Diffusion histograms in CADASIL. *Stroke* 2005; **36**: 2526.
- 64 Holtmannspotter M, Peters N, Opherck C, et al. Diffusion magnetic resonance histograms as a surrogate marker and predictor of disease progression in CADASIL: a two-year follow-up study. *Stroke* 2005; **36**: 2559–65.
- 65 Peters N, Holtmannspotter M, Opherck C, et al. Brain volume changes in CADASIL: a serial MRI study in pure subcortical ischemic vascular disease. *Neurology* 2006; **66**: 1517–22.
- 66 Jouvent E, Viswanathan A, Mangin JF, et al. Brain atrophy is related to lacunar lesions and tissue microstructural changes in CADASIL. *Stroke* 2007; **38**: 1786–90.
- 67 Chabriat H, Bousser MG. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Elsevier, 2008.
- 68 Dichgans M, Wick M, Gasser T. Cerebrospinal fluid findings in CADASIL. *Neurology* 1999; **53**: 233.
- 69 Zicari E, Tassi R, Stromillo ML, et al. Right-to-left shunt in CADASIL patients: prevalence and correlation with clinical and MRI findings. *Stroke* 2008; **39**: 2155–57.
- 70 Dichgans M, Petersen D. Angiographic complications in CADASIL. *Lancet* 1997; **349**: 776–77.
- 71 Cumurciuc R, Massin P, Paques M, et al. Retinal abnormalities in CADASIL: a retrospective study of 18 patients. *J Neurol Neurosurg Psychiatry* 2004; **75**: 1058–60.
- 72 Haritoglou C, Rudolph G, Hoops JP, Opherck C, Kampik A, Dichgans M. Retinal vascular abnormalities in CADASIL. *Neurology* 2004; **62**: 1202–05.
- 73 Viswanathan A, Gray F, Bousser MG, Baudrimont M, Chabriat H. Cortical neuronal apoptosis in CADASIL. *Stroke* 2006; **37**: 2690–95.
- 74 Kalimo H, Ruchoux MM, Viitanen M, Kalaria RN. CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. *Brain Pathol* 2002; **12**: 371–84.
- 75 Okeda R, Arima K, Kawai M. Arterial changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in relation to pathogenesis of diffuse myelin loss of cerebral white matter: examination of cerebral medullary arteries by reconstruction of serial sections of an autopsy case. *Stroke* 2002; **33**: 2565–69.

- 76 Miao Q, Paloneva T, Tuominen S, et al. Fibrosis and stenosis of the long penetrating cerebral arteries: the cause of the white matter pathology in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Brain Pathol* 2004; **14**: 358–64.
- 77 Ruchoux MM, Chabriat H, Bousser MG, Baudrimont M, Tournier-Lasserre E. Presence of ultrastructural arterial lesions in muscle and skin vessels of patients with CADASIL. *Stroke* 1994; **25**: 2291–92.
- 78 Ruchoux MM, Guerouaou D, Vandenhautte B, Pruvo JP, Vermersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Acta Neuropathol* 1995; **89**: 500–12.
- 79 Ebke M, Dichgans M, Bergmann M, et al. CADASIL: skin biopsy allows diagnosis in early stages. *Acta Neurol Scand* 1997; **95**: 351–57.
- 80 Joutel A, Favrole P, Labauge P, et al. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet* 2001; **358**: 2049–51.
- 81 Ruchoux MM, Maurice CA. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Neuropathol Exp Neurol* 1997; **56**: 947–64.
- 82 Tikka S, Mykkanen K, Ruchoux MM, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. *Brain* 2009; **132**: 933–39.
- 83 Lesnik Oberstein SA, van Duinen SG, van den Boom R, et al. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. *Acta Neuropathol* 2003; **106**: 107–11.
- 84 Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a mendelian condition causing stroke and vascular dementia. *Ann N Y Acad Sci* 1997; **826**: 213–17.
- 85 Dichgans M, Herzog J, Gasser T. NOTCH3 mutation involving three cysteine residues in a family with typical CADASIL. *Neurology* 2001; **57**: 1714–17.
- 86 Dichgans M, Ludwig H, Muller-Hocker J, Messerschmidt A, Gasser T. Small in-frame deletions and missense mutations in CADASIL: 3D models predict misfolding of Notch3 EGF-like repeat domains. *Eur J Hum Genet* 2000; **8**: 280–85.
- 87 Dotti MT, De Stefano N, Bianchi S, et al. A novel NOTCH3 frameshift deletion and mitochondrial abnormalities in a patient with CADASIL. *Arch Neurol* 2004; **61**: 942–45.
- 88 Joutel A, Chabriat H, Vahedi K, et al. Splice site mutation causing a seven amino acid Notch3 in-frame deletion in CADASIL. *Neurology* 2000; **54**: 1874–75.
- 89 Peters N, Opherck C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. *Arch Neurol* 2005; **62**: 1091–94.
- 90 Federico A, Bianchi S, Dotti MT. The spectrum of mutations for CADASIL diagnosis. *Neurol Sci* 2005; **26**: 117–24.
- 91 Joutel A, Vahedi K, Corpechot C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *Lancet* 1997; **350**: 1511–15.
- 92 Coto E, Menendez M, Navarro R, Garcia-Castro M, Alvarez V. A new de novo Notch3 mutation causing CADASIL. *Eur J Neurol* 2006; **13**: 628–31.
- 93 Tuominen S, Juvonen V, Amberla K, et al. Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch3 mutation. *Stroke* 2001; **32**: 1767–74.
- 94 Liem MK, Lesnik Oberstein SA, Vollebregt MJ, Middelkoop HA, van der Grond J, Helderman-van den Enden AT. Homozygosity for a NOTCH3 mutation in a 65-year-old CADASIL patient with mild symptoms: a family report. *J Neurol* 2008; **255**: 1978–80.
- 95 Monet M, Domenga V, Lemaire B, et al. The archetypal R90C CADASIL-NOTCH3 mutation retains NOTCH3 function in vivo. *Hum Mol Genet* 2007; **16**: 982–92.
- 96 Walker FO. Huntington's disease. *Lancet* 2007; **369**: 218–28.
- 97 Chabriat H, Bousser MG, Pappata S. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a positron emission tomography study in two affected family members. *Stroke* 1995; **26**: 1729–30.
- 98 Mellies JK, Baumer T, Muller JA, et al. SPECT study of a German CADASIL family: a phenotype with migraine and progressive dementia only. *Neurology* 1998; **50**: 1715–21.
- 99 Tuominen S, Miao Q, Kurki T, et al. Positron emission tomography examination of cerebral blood flow and glucose metabolism in young CADASIL patients. *Stroke* 2004; **35**: 1063–67.
- 100 Tatsch K, Koch W, Linke R, et al. Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: an 18F-FDG PET study. *J Nucl Med* 2003; **44**: 862–69.
- 101 Chabriat H, Pappata S, Ostergaard L, et al. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. *Stroke* 2000; **31**: 1904–12.
- 102 Pfefferkorn T, von Stuckrad-Barre S, Herzog J, Gasser T, Hamann GF, Dichgans M. Reduced cerebrovascular CO(2) reactivity in CADASIL: a transcranial Doppler sonography study. *Stroke* 2001; **32**: 17–21.
- 103 Gobron C, Vahedi K, Vicaute E, et al. Characteristic features of in vivo skin microvascular reactivity in CADASIL. *J Cereb Blood Flow Metab* 2007; **27**: 250–57.
- 104 Ruchoux MM, Domenga V, Brulin P, et al. Transgenic mice expressing mutant Notch3 develop vascular alterations characteristic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Am J Pathol* 2003; **162**: 329–42.
- 105 Dubroca C, Lacombe P, Domenga V, et al. Impaired vascular mechanotransduction in a transgenic mouse model of CADASIL arteriopathy. *Stroke* 2005; **36**: 113–17.
- 106 Lacombe P, Oligo C, Domenga V, Tournier-Lasserre E, Joutel A. Impaired cerebral vasoreactivity in a transgenic mouse model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy arteriopathy. *Stroke* 2005; **36**: 1053–58.
- 107 Aylward EH, Roberts-Twillie JV, Barta PE, et al. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am J Psychiatry* 1994; **151**: 687–93.
- 108 Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain* 1994; **117**: 859–76.
- 109 Gridley T. Notch signaling in vascular development and physiology. *Development* 2007; **134**: 2709–18.
- 110 Joutel A, Andreux F, Gaulis S, et al. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. *J Clin Invest* 2000; **105**: 597–605.
- 111 Prakash N, Hansson E, Betsholtz C, Mitsiadis T, Lendahl U. Mouse Notch 3 expression in the pre- and postnatal brain: relationship to the stroke and dementia syndrome CADASIL. *Exp Cell Res* 2002; **278**: 31–44.
- 112 Domenga V, Fardoux P, Lacombe P, et al. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. *Genes Dev* 2004; **18**: 2730–35.
- 113 Belin de Chantemele EJ, Retailleau K, Pinaud F, et al. Notch3 is a major regulator of vascular tone in cerebral and tail resistance arteries. *Arterioscler Thromb Vasc Biol* 2008; **28**: 2216–24.
- 114 Logeat F, Bessia C, Brou C, et al. The Notch1 receptor is cleaved constitutively by a furin-like convertase. *Proc Natl Acad Sci USA* 1998; **95**: 8108–12.
- 115 Schweissguth F. Regulation of notch signaling activity. *Curr Biol* 2004; **14**: R129–38.
- 116 Ishiko A, Shimizu A, Nagata E, Takahashi K, Tabira T, Suzuki N. Notch3 ectodomain is a major component of granular osmiophilic material (GOM) in CADASIL. *Acta Neuropathol* 2006; **112**: 333–39.
- 117 Karlstrom H, Beatus P, Danmaeus K, Chapman G, Lendahl U, Lundkvist J. A CADASIL-mutated Notch 3 receptor exhibits impaired intracellular trafficking and maturation but normal ligand-induced signaling. *Proc Natl Acad Sci USA* 2002; **99**: 17119–24.
- 118 Joutel A, Monet M, Domenga V, Riant F, Tournier-Lasserre E. Pathogenic mutations associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy differentially affect Jagged1 binding and Notch3 activity via the RBP/JK signaling pathway. *Am J Hum Genet* 2004; **74**: 338–47.

- 119 Peters N, Opherck C, Zacherle S, Capell A, Gempel P, Dichgans M. CADASIL-associated Notch3 mutations have differential effects both on ligand binding and ligand-induced Notch3 receptor signaling through RBP-Jk. *Exp Cell Res* 2004; **299**: 454–64.
- 120 Haritunians T, Chow T, De Lange RP, et al. Functional analysis of a recurrent missense mutation in Notch3 in CADASIL. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1242–48.
- 121 Low WC, Santa Y, Takahashi K, Tabira T, Kalaria RN. CADASIL-causing mutations do not alter Notch3 receptor processing and activation. *Neuroreport* 2006; **17**: 945–49.
- 122 Arboleda-Velasquez JF, Rampal R, Fung E, et al. CADASIL mutations impair Notch3 glycosylation by Fringe. *Hum Mol Genet* 2005; **14**: 1631–39.
- 123 Weller M, Dichgans J, Klockgether T. Acetazolamide-responsive migraine in CADASIL. *Neurology* 1998; **50**: 1505.
- 124 Forteza AM, Brozman B, Rabinstein AA, Romano JG, Bradley WG. Acetazolamide for the treatment of migraine with aura in CADASIL. *Neurology* 2001; **57**: 2144–45.
- 125 Endres M, Laufs U, Huang Z, et al. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 1998; **95**: 8880–85.
- 126 Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol* 2008; **7**: 310–18.
- 127 Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurol* 2002; **1**: 426–36.
- 128 Benisty S, Hernandez K, Viswanathan A, et al. Diagnostic criteria of vascular dementia in CADASIL. *Stroke* 2008; **39**: 838–44.
- 129 Hachinski V. The 2005 Thomas Willis Lecture: stroke and vascular cognitive impairment: a transdisciplinary, translational and transactional approach. *Stroke* 2007; **38**: 1396.
- 130 Verreault S, Joutel A, Riant F, et al. A novel hereditary small vessel disease of the brain. *Ann Neurol* 2006; **59**: 353–57.