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CADASIL

Pathogenesis, clinical and radiological findings and treatment

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common genetic cause of ischemic strokes and a most important model for the study of subcortical vascular dementia. This unrelentlessly progressive disease affects many hundreds of families all over the world but is not well studied in Brazil. This manuscript reviews pathogenetic, clinical, radiological and therapeutic features of CADASIL. The causal mutations are now very well known, but the same can not be said about its intimate pathogenetic mechanisms. The variable clinical presentation should lead physicians to actively pursue the diagnosis in many settings and to more thouroughly investigate family history in first degree relatives. A rational approach to genetic testing is however needed. Treatment of CADASIL is still largely empiric. High-quality therapeutic studies involving medications and cognitive interventions are strongly needed in CADASIL.

Key words: CADASIL, etiology, genetics, diagnosis, therapeutics.

CADASIL: patogênese, achados clínicos e radiológicos e tratamento

RESUMO

CADASIL é a causa genética mais freqüente de infartos cerebrais e constitui modelo importante de estudo de demências vasculares subcorticais. De natureza inexoravelmente progressiva, afeta milhares de pessoas em todo o mundo. Sua importância é pouco reconhecida entre nós, o que nos levou à presente revisão dos principais aspectos patogenéticos, clínicos, neuroradiológicos e terapêuticos da doença. As mutações causais são hoje bem conhecidas, mas os mecanismos patogenéticos íntimos ainda permanecem misteriosos. A apresentação clínica variável deve fazer com que os médicos considerem o diagnóstico em vários contextos clínicos e investiguem de forma mais extensa que o usual a história familial deparentes de primeiro grau. Além disso, uma abordagem racional é necessária para reduzir custos e aumentar a eficiência do diagnóstico genético. O tratamento atual de pacientes com CADASIL é basicamente empírico. Estudos clínicos sobre medicamentos e intervenções cognitivas de alto nível metodológico constituem uma necessidade urgente.

Palavras-chave: CADASIL, etiologia, genética, diagnóstico, terapêutica.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disease with high penetrance in which occlusion of small arteries in the brain of adults results in small deep brain infarcts and progressive accumulation of demyelination areas in the brain. Its manifestations are diverse and in most individuals include recurrent headache of migraine pattern, focal deficits secondary to brain infarction (more rarely bleeding) and, in later stages, progressive neuropsychiatric disorders including dementia.

This article reviews the main aspects of this puzzling disease, which constitutes

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the main genetic cause of stroke. Emphasis is given to cognitive and neuropsychiatric symptoms.

Definitions

CADASIL is an autosomal dominant disease resulting from mutations of the gene encoding the transmembrane receptor Notch 3, located on chromosome 19. Regarded as a prototype of subcortical vascular dementia related to subcortical microangiopathy, it also results in additional psychiatric disorders, particularly mood changes, usually in association with the development of cognitive impairment.

The disease is reported in several countries from all continents. Its frequency is probably underestimated and CADASIL may be one of the most common inherited neurological conditions. The prevalence of Notch 3 gene mutations has been estimated as more than 4 per 100,000 adults.

The disease appears in adult life. Its manifestations are virtually restricted to the central nervous system, especially the brain, and are caused by the progressive development of disseminated white matter lesions in association with small infarcts - lacunes - in subcortical areas. Migraine with aura and focal neurologic deficits caused by these lacunar infarctions are characteristic forms of presentation in young or middle age. Over the years, mood disorders, diverse neurological deficits and cognitive disturbances add up. To the extent that the total volume of lesions increases and cerebral atrophy develops, the frequency and severity of motor difficulties and cognitive dysfunction also increase.

The cognitive disorder is progressive, and typically reflects accumulating injury resulting from subcortical microvascular disease. Initially, difficulties in information processing and slowing of cognitive processes are most evident; later, changes in memory and other high order cognitive functions lead to the development of dementia. Depression is the commonest mood disorder, occurring in 20% of individuals. In the final stages, individuals are beddriden, apathetic and totally dependent. Death usually results from medical complications, especially malnutrition and infectious diseases such as aspiration pneumonia.

Genetics and pathogenesis

The genetics of CADASIL is directly linked to that of the Notch receptor family. These surface receptors mediate signal transduction with ligands (such as Jagged [Jag] and Delta [D]) in neighboring cells, which are also type I transmembrane receptors. Notch 3 mutations are responsible for CADASIL, whose main characteristic is a vascular degeneration, indicating that this system plays an important role in maintaining structural stability and function of vascular smooth muscle cells (VSMC).

Studying two large French families in 1993, Tournier-Lasserve and cols. found that the gene responsible for CADASIL should be located on chromosome 19 in a 14-cM centimorgans) segment between D19S221 and D19S222[1]. As two other autosomal dominant diseases - familial hemiplegic migraine and episodic hereditary cerebellar ataxia - were also mapped on chromosome 19 in close proximity with CADASIL, the question of allelism in these three conditions soon arised[2,3].

The 14-cM segment on chromosome 19q12 was progressively reduced in successive studies, until Joutel et al. were able to reduce it to a critical 800 kb interval that would probably contain the gene for CADASIL, now in 19p13.1[4]. Among several genes in this region, there was one that exhibited strong homology with Notch 3 gene encoding region 5 in mice. Further studies showed that the human homologue of the Notch 3 gene actually was located in that critical 800 Kb region[5].

In the last decade, more than 80 Notch 3 mutations were identified in more than 400 families with CADASIL. These mutations are distributed across 34 repetitions of the epidermal growth factor (EGFR) that comprise the extracellular domain of Notch 3[6]. All mutations responsible for CADASIL lead to an odd number of cysteine residues.

The Notch 3 gene encodes a single pass transmembrane receptor comprising 2,321 amino acids with an extracellular domain containing 34 epidermal growth factor (EGF)-like repeats (with 6 cysteine residues in each) and 3 Lin-12 repeats related to the transmembrane and intracellular domains . It consists of 33 exons (23 extracellular)[5,7,8] (Fig 1A). All mutations occur in extracellular domains, more specifically the epidermal growth-like factor-repeats (EGF-repeats), from a non-paired cysteine[4,7]. Most mutations occur in codons of exon 4, followed by exons 3, 5, 6 and 11[7,9,10] (Fig 1B). The exon 3 seems to be the second most commonly affected site in French, English and German families[7,9]; exon 11 could, however, be the second most prevalent in Dutch families[11].

The Notch proteins constitute a family of surface receptors that promote transduction of signals between neighboring cells. Their interaction with ligands leads to cleavage of its intracellular portion, which translocates to the nucleus and activates transcription of specific factors, thus regulating subsequent gene expression (Fig 1).

This signaling pathway has been highly preserved throughout phylogeny, and seems to exert a central role in determining cell fate during embryonic development, including various aspects of vascular development such as vasculogenesis, angiogenesis, vascular remodeling, and differentiation of VSMC[12,13]. In humans, mutations in one Notch ligand system cause congenital abnormalities (Alagille syndrome - OMIM # 118450). In adults, evidence of involvement of abnormalities in the regulation of Notch signaling system accumulates, even in cancer[8].

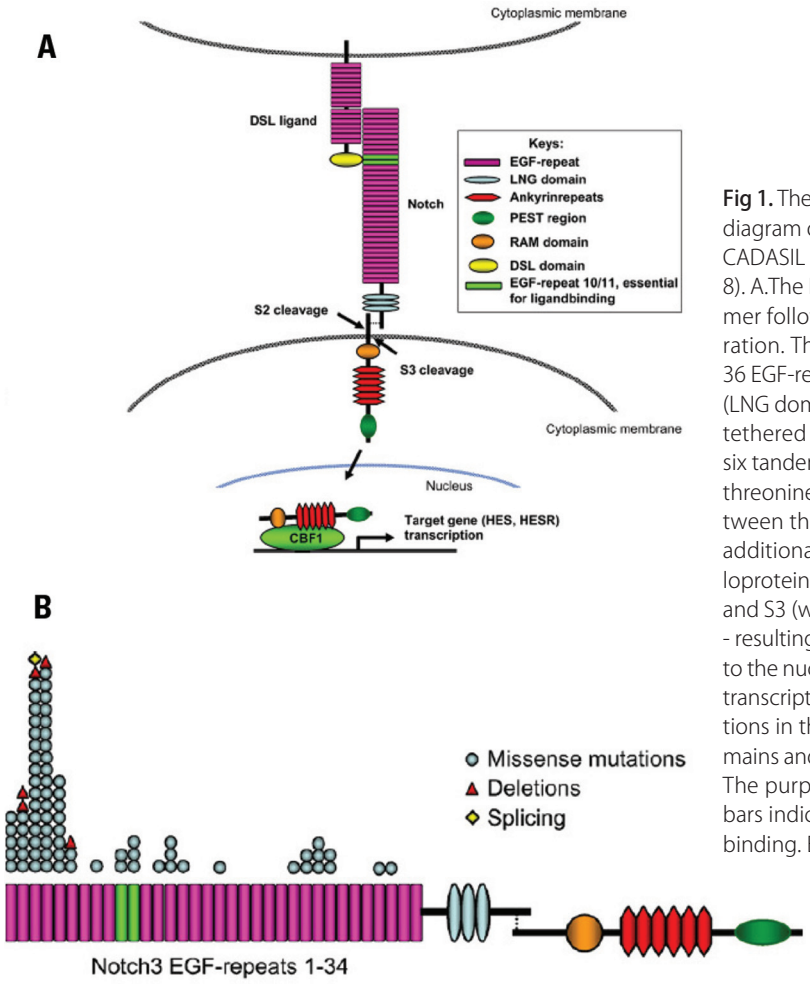

Fig 1. The classic NOTCH signaling pathway (a) and schematic diagram of the Notch 3 mutations identified in patients with CADASIL (b) (compressed and adapted from Wang T et al. ref. 8). A.The Notch receptor locates at cell surface as a heterodimer following protease cleavage (S1) during protein maturation. The extracellular domain (NECD) - containing up to 36 EGF-repeats and three cysteine-rich Notch/LIN-12 repeats (LNG domain) - associates non-covalently with a membrane-tethered intracellular domain (NICD) - with a RAM domain, six tandem ankyrin repeats and a praline-, glutamate-, serine, threonine-rich sequence (PEST domain). The interaction between the DSL-ligand and the Notch receptor leads to two additional proteolytic cleavages - S2 (mediated by a metalloproteinase family protein TNFa-converting enzyme, TACE) and S3 (within the transmembrane domain,by a g-secretase) - resulting in the release of the NICD, which then translocates to the nucleus, where it interacts with CBF1/RBP-Jk to activate transcription of target genes HES and HESR (or HRT). B. Mutations in the protein Notch 3 are only present in the EGF-domains and clustered in the N-terminus of the Notch3 protein. The purple bars indicate EGF-repeats 1–34, and two green bars indicate EGF-repeats 10/11 that are essential for ligand binding. Each dot indicates a recurrence mutation.

In mammals, there are four Notch receptors. While other genes of the Notch group are ubiquitous, the Notch 3 gene is restricted to VSMC of arterial walls[14].

The Notch 3 protein, when activated, undergoes serial cleavage by proteolysis, producing extracellular and transmembrane domain spliting. After cleavage, these two fragments form a heterodimer on the cell surface of VSCM. Mutations and deletions of the Notch 3 gene responsible for CADASIL promote accumulation of the Notch receptor ectodomain 3 in the vascular wall, probably by reducing their clearance efficiency[15]. This accumulation occurs near but not within granules of osmeophylic material characteristic of the disease in electron microscopy studies.

The mechanisms by which the accumulation of receptor fragments and osmeophylic material in the adventitia and medial layer of brain arterioles correlates with vascular functional changes and the development of brain lesions in CADASIL are discussed. The molecular mechanisms may include changes in the activation of Notch 3, but the classic Notch activation is not changed, hence lesions can not be solely explained by an increase or reduction of the Notch 3-related signaling classical pathway (mediated by CBF1/JBP-Jk). Alternative signaling pathways mediated by Notch 3, or a cross-regulation of Notch 3 with other signaling pathways may thus play a central role in the survival of VSCM. Alternatively, the Notch 3 mutation can gain new functions not yet studied on VSCM, including toxic ones[8].

As mentioned, the Notch3 receptors are found mainly in adult VSMC. Their main function seems to be related to the maintenance of vascular structural and functional stability. The pathogenesis of CADASIL is most likely related to a disturbance in vascular mechanotransduction, with reduced flow-induced vasodilation and increased vascular myogenic tone induced by pressure[16]. Skin vasoreactivity is altered in disease. For instance, the kinetics of reactive hyperemia after cuff occlusion displays a delayed and slow curve[17]. Endothelium-dependent vasodilation is impaired in resistance arteries (not conductive ones) in the forearm of patients[18]. Transgenic mice expressing mutant Notch 3 develop CADASIL typical vascular alterations[19]. These mice exhibit altered autoregulation of cerebral blood flow (CBF): the mutation appears to reduce the relaxation ability or to increase vascular resistance of resistance vessels[20].

This dynamic process is also associated with deposition of granular osmeophylic material (GOM) and degeneration of the middle layer of cerebral arteries (and other organs and territories), and results in reduced CBF in brain white matter. Cerebral and leptomeningeal arteries and arterioles become thickened, with stenosis of penetrating arteries in the white matter and cortex[21-23]. Gradually, diffuse myelin pallor and rarefaction of hemispheric white matter (sparing the U fibers), deep focal lesions, particularly in periventricular areas and *centrum semiovale*, and lacunar infarctions in the white matter, basal ganglia and pons add up[21,24]. Virchow-Robin spaces tend to become dilated, perhaps by changes related to age or the progression of degeneration of penetrating cerebral arteries[25]. Further changes were demonstrated by MR spectroscopy: metabolic reductions in the relationship between mean NAA/Cr, NAA/Cho and Cho/Cr become obvious, especially in anterior (VS. posterior) regions of the *centrum semiovale*[26]. These changes are more severe in symptomatic individuals, suggesting a correlation between them and the also increasing pathological findings.

The dense osmeophylic deposits form granules (10 to 15 nm in diameter) and occupy the middle layer of the vessel, extending to its adventitial layer, but sparing the vascular endothelium[21,27,28]. They are located near the cell membrane of VSMC, and stain positively for PAS (periodic acid Schiff) - suggesting the presence of glycoproteins - and negatively for elastin and amyloid. There is no evidence of deposition of immunoglobulins. The VSMC, separated by granular material, are swollen and degenerated, and sometimes disappear and are replaced by collagen[29].

Vascular abnormalities characteristic of the brain of patients with CADASIL, like the GOM around the smooth muscle cells, are also common in the medial layer of arteries of other organs such as liver, spleen, heart, kidney, retina, muscles and skin, and even in large arteries such as aorta and carotid arteries[27,28]. Vascular lesions and accumulation of GOM may be detected in biopsies of muscle and nerve, and skin biopsies are commonly used for diagnostic purposes. Nevertheless, the clinical manifestations of the disease are almost always restricted to the central nervous system, specifically the brain.

Diagnosis of CADASIL

The diagnosis of CADASIL should be particularly suspected in the presence of (adapted from[30]):

1. Typical clinical picture: one or more subcortical infarcts, especially early (up to 60 years) or with familial history, migraine, usually with aura (including atypical or prolonged); progressive cognitive changes or subcortical-type dementia;

2. Typical neuroradiological findings on magnetic resonance imaging (MRI): multifocal and bilateral FLAIR/T2 hyperintensities in the periventricular and deep white matter, with lesions mainly affecting the anterior temporal pole, frontal and parietal lobes, external capsule, pons

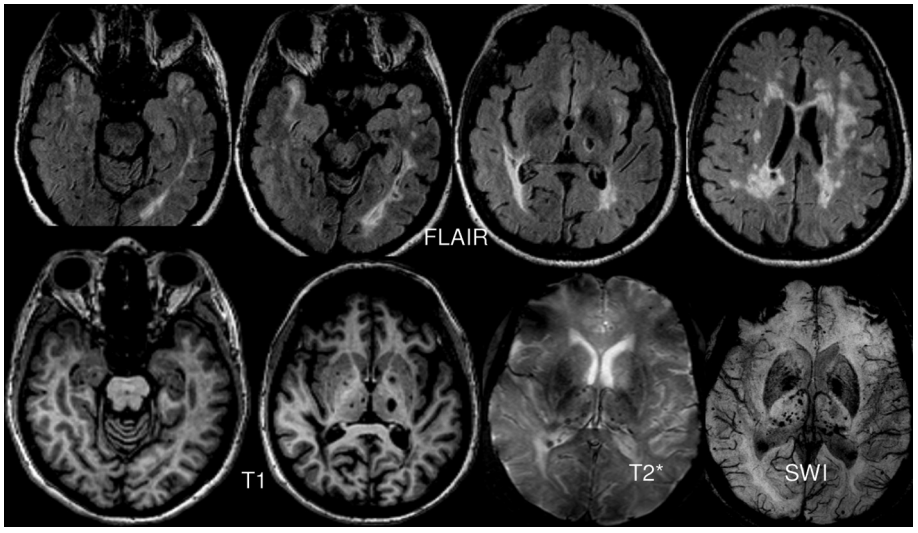

Fig 2. Magnetic resonance imaging in CADASIL in a 62-year old woman with multiple strokes and dementia (courtesy of Dr. Emerson Gasparetto, from the Federal University of Rio de Janeiro). In FLAIR sequences, the characteristic distribution of white matter changes are shown. Note the accumulation of demyelination areas in deep areas, especially periventricular and external capsule (mainly in the left hemisphere). In T1 images, lacunar infarctions of bilateral asymmetric distribution and cortical atrophy, characteristic of advanced stages of disease. Lacunes are seen near the posterior horn of the right lateral ventricle and the left ventricular wall. SWI and T2* image: Scattered punctate deposits of hemosiderin in basal ganglia and cerebral hemispheres, characteristic of old microbleeds. SWI have higher sensitivity for detection of old microbleeds than T2* images.

and basal ganglia; focal hypointensities on T1 (lacunar infarcts) and lesions suggestive of microhemorrhages in SWI or gradient-echo T2* (Fig 2);

3. Positive familial history: autosomal dominant pattern for one or more of the typical clinical features.

CADASIL is sometimes not even considered in differential diagnoisis for several reasons, especially lack of MRI availability and apparently negative family history. Computed tomography (CT) clearly shows the subcortical infarcts - typically lacunar, but also larger lesions[31] - and also shows white matter lesions, especially in more advanced cases. In a study specifically designed to answer the second question, 30% of patients with CADASIL apparently had a documented negative family history[32]. This is mainly related to a restricted search only for early cerebrovascular disease in the family, and neglecting other clinical presentations, such as mood disorders, cognitive impairment and headache.

Definitive diagnosis is confirmed in patients with clinical and radiological features (see below) by the finding of mutations in the Notch 3 gene, located on chromosome 19 - 19p13.1. Mutations that promote orientation errors (missense mutations) are the most common, followed by those that promote simple gene deletions. Pathogenic mutations remove or insert cysteine residues in EGF-repeats in the extracellular domain of Notch 3 receptor (N3ECD)[8,33].

The molecular diagnosis of CADASIL can be, however, tiring and fruitless, especially if it does not follow a rational routine. Most mutations are found in gene exon 4: this site should be investigated first in suspected cases. In a British study prospectively evaluating different diagnostic strategies, 15 different mutations were identified in 48 families, 73% of them in exon 4 (less than 10% each in exons 3, 5 and 6)[9].

A case in which the molecular diagnosis was made in a fetus whose father was affected by CADASIL has been published[34]. The possibility of early intra-uterus diagnosis in a progressive disease with high, but incomplete, penetrance raises new ethical questions to the medical profession.

In the study of Markus et al.[9], the diagnostic value of characteristic MRI changes was also evaluated. Moderate to severe white matter changes in the anterior temporal regions exhibited slightly lower sensitivity (89% vs. 93%), but much higher specificity than those in the external capsule (86% vs. 45%).

Skin biopsy is considered useful in diagnosis. Specificity is high, approaching 100%, but sensitivity is low (less than 50%); the involvement is often focal, and thourough assessment of the material is necessary to make the diagnosis[9,35].

Clinical and radiological manifestations

CADASIL may be seen as a pleomorphic disease: the dominant manifestations may vary in different families; and the clinical picture and functional course also differ in individuals of the same family. Important phenotypic differences between families could be attributed in part to the various causal mutations[36]. As in other "pure" dominant diseases, homozygotes do not seem to do worse than heterozygotes, even if they exhibit increased burden of GOM in tissues[37].

The possible role of additional genetic influences, like the presence of specific alleles of the Apolipoprotein E, on disease progression is debated[38]. The white matter lesion load, the amount and specific location of ischemic lesions, the presence and number of microhemorrhages, the degree of cerebral atrophy, and functional (diasquisis) or anatomical changes of critical intra-and interhemispheric connecting pathways are other factors that may influence the nature and severity of clinical manifestations (see section on cognitive changes) .

Cardinal clinical manifestations however include migraine with aura, transient ischemic attacks (TIAs) and

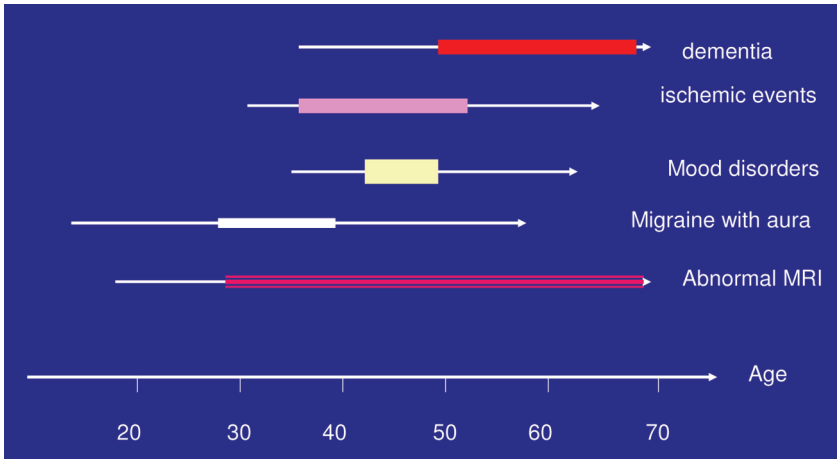

Fig 3. The natural history of CADASIL (redrawn from ref. 92). The main manifestations usually arise at different stages of the disease. Changes in magnetic resonance imaging (MRI) are also presented.

fixed focal neurologic deficits caused by lacunar infarctions, and cognitive decline of subcortical type. In some patients, mood disorders, especially depression, may predominate. In the long run the disease always worsens, but in shorter periods - two years, for example - evolution is much variable: there may be periods of rapid deterioration, clinical stability or even occasionally improvement[39]. Time to death is also highly variable - 10 to 30 years. Death occurs around 65 (men) 70 years (women) on average, from accumulation of morbidities and clinical complications related to infection and immobility[40].

The dominant clinical findings vary according to the disease stage (Fig 3). Neuroradiological abnormalities, which may be present from childhood[41], are often already detected at symptom onset and are almost universally present in symptomatic patients (possible exception in individuals with migraine only) or around 35 years[42,43].

CADASIL may be classified in three clinical/radiological stages[44]:

I: generally between 20 to 40 years of age, with migraine and MRI showing white matter-defined lesions[42].

II: age between 40 and 60, characterized by transient or permanent ischemic insults leading to motor disorders, sensory, sensory and cognitive impairments, with or without psychiatric disorders. MRI shows basal ganglia and confluent white matter lesions;

III: usually after 60 years, with subcortical dementia associated with pseudobulbar signs - dysarthria, dysphagia and emotional lability; and in some cases apathy, mutism and akinesia. Pyramidal signs are almost always marked. MRI shows diffuse leukoencephalopaty and multiple infarcts of basal ganglia.

Some individuals with the mutation may remain asymptomatic for long periods, even with well-defined lesions on MRI[45,46], while others exhibit only one major disease characteristic, such as migraine with aura, TIA or lacunar infarctions, depression or anxiety, or slow evolution of cognitive impairment[42,47]. Diagnosis is usually made around age 45, but greater attention to relatives of affected patients to detect neurological and psychiatric manifestations may lead to an earlier diagnosis. The average age for symptom onset is 37 years[48], and is independent of gender[49,50].

Migraine is common between 20 and 40 years, occurring in about one quarter of patients, but can already be present in the early teens. Ischemic events, occurring in at least 60 to 80% of individuals, arise mainly between 30 to 50 years, accumulating over two or three decades, with increasing functional limitation. Mood disorders, primarily depression, occur in 10 to 20% of subjects, appearing at any age, but mostly around 40 to 50 years, a period in which cognitive disorders, initially subtle, may lead to the slow development of advanced dementia in the sixth and seventh decades.

Migraine

The most characteristic initial symptom is migraine, usually with aura. The International Headache Society considers migraine as an inappropriate diagnosis in the presence of an obvious vascular cause, but there is a trend to keep the name migraine in patients with CADASIL.

Its frequency varies considerably among affected families[49,51]. Among 45 patients in 7 CADASIL families, migraine with aura was present in 22%[49]. Desmond et al found migraine in 42 of 105 individuals (40%). On the other hand, none of the members of an Italian family presented symptoms[52]. There are other families in which migraine and later insidiously progressive cognitive disorders are the sole manifestations of the disease, but the final diagnosis of CADASIL in these cases is still uncertain[53].

The first migraine attacks occur before 20 years of age[44,54] and may precede or be linked to early neuroradiological changes - punctate hyperintensities in deep hemisphere or periventricular white matter - that may also be present in some individuals with primary migraine[30]. Women with CADASIL and migraine with aura tend to have symptom onset earlier than affected men[43].

In the study by Dichgans et al.[50], migraine was present in 30% of men and 44% of women, and 95% of patients affected by migraine headaches presented uo to 38 years of age; also, 14% reported increased frequency or severity of migraine near the first ischemic event. This clinical deterioration could therefore have predictive value.

The relationship between migraine and CADASIL may be justified by the identification of genetic abnormalities in the same chromosome 19 in familial hemiplegic migraine and episodic hereditary cerebellar ataxia. As in primary migraine with aura, visual or sensory symptoms predominate. However, more than 50% of individuals may exhibit atypical, hemiplegic or prolonged auras[43], and even rarer presentations, with meningism, mental confusion, fever and coma[55]. The frequency of attacks varies between affected individuals, from less than one to several attacks a month[56].

In addition to the therapeutic and prophylactic measures in the primary migraine, patients with CADASIL may show benefit with the prophylactic use of acetazolamide[57,58].

Lacunar infarcts and other cerebrovascular injuries

In individuals with CADASIL ischemic strokes usually occur in the absence of classical vascular risk factors. Cerebrovascular disease is usually characterized by the appearance of relatively pure neurological symptoms (related to the small size of most subcortical infarcts), often transient, starting from 30 or 40 years. About two thirds of symptomatic patients present transient or fixed isch-

emic insults. The average age of their initial occurrence is 42 years, with extremes of 20 to 65 years[48-50]. The postpartum period may be of high risk, but this is still poorly studied[59]. Transient vascular events may initially be confused with migraine with atypical or prolonged aura. The onset and severity of ischemic events may vary greatly within a family. The progressive accumulation of ischemic lesions probably contributes to the emergence of cognitive manifestations, particularly executive dysfunction, slowly progressing to dementia.

Most lesions have a diameter smaller than 15 mm and are typically rounded or oval lacunar infarctions (Fig 2). Larger infarctions and atypical - elongated, complex lesions are not, however, rare - 17% of injuries according to one series[60]. These larger lesions could be due to the involvement of small arteries of larger dimensions, the confluence of smaller lesions, or secondary tissue degeneration. Although the disease affects predominantly smaller arteries and long penetrating arterioles up to 100-120 μm, stenosis of intracranial major arteries is occasionally detected[61].

Classical lacunar syndromes such as isolated unilateral motor or sensory deficits and ataxic hemiparesis-dysarthria are typical[49]. Other presentations such as aphasia, hemianopia and other cortical disorders are observed less frequently. Vascular events usually occur in the early stages of the disease and as they accumulate, are associated with other clinical manifestations such as mood disorders and cognitive deficits[51]. In later stages, varied neurological sequelae, inability to walk, urinary incontinence, and pseudobulbar manifestations are almost universally present in demented patients.

Small asymptomatic ischemic lesions are not uncommon, occurring in 10% of patients evaluated prospectively[62,63]. Multiple infarcts can also occur concurrently[64].

Cerebral hemorrhage is traditionally considered rare, constituting the subject of literature reports[65,66]. This vision has been, however, challenged, with case series referring up to 25% of patients with CADASIL with symptomatic hemorrhage[67]. Asymptomatic microbleeds (predominantly in the thalamus, basal ganglia and brainstem) are even more common, and seem to increase in incidence with advancing age of the patients[67-69] (Fig 2). Predisposing factors for cerebral bleeding are poorly understood but may include, in addition to microhemorrhages, the extent of white matter changes and ischemic lesion burden, the use of antiplatelet agents, disturbances in glucose metabolism and hypertension[68,70].

Epilepsy

Although little discussed, seizures have significant relevance: 5 to 10% of patients with CADASIL develop epilepsy. The mean age of onset is 50 years[50]. It usually appears after the onset of ischemic strokes or cognitive problems. Clinical worsening after the occurrence of seizures was reported in six of 10 patients who had grand mal seizures[50]. Most cases are well controlled with commonly used anticonvulsants. Some patients, however, develop *status epilepticus*, including non-convulsive[71]. This can even be the explanation (alternative to atypical migraine crisis) to some of the reported cases of acute encephalopathy and rapid onset coma[55,72,73], although other explanations have also been proposed[74].

Psychiatric disorders

At least 20 to 40% of patients with CADASIL exhibit psychiatric disorders. In a report of 454 patients, 106 (24%) had mood disorders[75]. Depression is the most common manifestation - at least half of the cases. The incidence varies widely in different families, and the severity can also vary in members of one family, with some episodes being especially difficult to treat[39]. Manic and depressive episodes may alternate in a few cases[76]. Ischemic lesions in specific locations - such as basal ganglia and frontal white matter - may facilitate the emergence of mood disorders[77,78].

Mood changes and other psychiatric manifestations - adjustment disorders and anxiety, psychotic events and rarely schizophrenia[79], usually appear after diagnosis, from 40 years on, in patients with previous ischemic episodes or cognitive disorders[l]. Exceptions may lead to diagnostic errors[80,81].

Cognitive decline and dementia

Cognitive impairment and dementia are the second most common manifestation of CADASIL, after cerebrovascular injury[82]. The emergence of neuropsychological changes may however occur late, even in patients with well-established manifestations of the disease. In a study done in Colombia, young individuals with typical mutation maintained their normal cognitive performance (when compared to non-carrier members of the same family) over 4 years[83]. In another Italian study, asymptomatic mutation carriers with or without visible white matter lesions on MRI showed no decline in cognitive performance over 2 years of follow-up[82].

Not infrequently, on the other hand, subtle and insidiously worsening cognitive symptoms may appear years before TIA and cerebral infarctions. Symptomatic (for vascular lesions) individuals without cognitive complaints already show changes in tests of executive function[84]. In addition, about 10% of individuals with CADASIL show relatively pure cognitive dysfunction[85].

Dementia develops in at least one third of patients. The incidence increases with advancing age, reaching 60% of symptomatic individuals aged 60 years or more[50]. De-

mentia is an ominous prognostic finding, present in about 80% of patients at the time of death[49].

In young people, manifestations of executive dysfunction (almost 100% between 35 and 50 years of age) and attentional deficits (69%) are among the earliest cognitive changes[86]. Working memory is also hampered[87]. Insight may be impaired, leading the patient to deny any specific complaint. Worried family members not infrequently bring patients to assessment, with the vague impression of innatention, behavioural changes or indifference. The initial signs denote essentially underlying dysfunction of frontal-subcortical circuits[86,88]. In this initial stage, verbal episodic memory and visuospatial functions - which tend to predominate in standard screening tests commonly performed in clinical practice - are usually preserved, which can lead to the false impression of depression and normal cognitition. A characteristic pattern of mnestic problems mainly affecting free recall, may be present in 70% of patients (see below).

Neuropsychological tests sensitive to unveil these changes in the early stages of "subcortical" cognitive impairment include: Digit span (forward and reverse order); Trail making B; Stroop Test; Digit-symbols Correlation; Wiskonsin Cards Test; Rey-Osterreith Figure Memory Test.

The digit-span in direct order essentially tests the ability to hold increasing amounts of information (sequences of increasing numbers) for a very short period, and is essentially a test of working memory. In reverse order (backward repetition of number sequences), the test evaluates, moreover, the ability to process information quickly while it is retained in memory, typically an executive function.

Many of the other tests mentioned here are measured against the clock, *ie*, speed-dependent tests[89]. Patients with CADASIL exhibit markedly slow performance in this type of test. These tests also assess the ability of the individual to switch concepts and work with sequential tasks, create strategies and planning, and to both monitor and solve problems in their own performance. Errors in planning and monitoring of responses are also frequent in this context. Patients with CADASIL may also display impaired performance on tests of verbal fluency and ideational praxis in relatively early stages of the disease[88,90].

The error profile on memory tests is characteristic and represents preservation of the mesiotemporal cortex circuits responsible for the processes of encoding information (usually damaged in Alzheimer's disease and related conditions). In trials evaluating various aspects of memory, such as the Grober and Buschke test (16 words of different semantic categories)[91] and other similar tests, patients with CADASIL have relative preservation of the stages of encoding information and recognition of the saved information but in contrast exhibit marked disturbance on free recall - early and late - of this information (often with intrusions), although its performance improve partially with the presentation of hints and tips[86,92].

This same pattern of mnestic change may still be present in advanced disease stages in up to two thirds of patients[86]. In many cases, however, as age advances and the burden of white matter lesions and subcortical infarcts increases, a general decline in cognitive function tends to manifest with progressive involvement of new cognitive domains, such as instrumental activities, reasoning, language, and visuospatial functions[86,87,93]. This general decline indicates increasing cortical dysfunction combined with the initial subcortical aggression, and is associated with the development of more or less diffuse brain atrophy and extensive spread of white matter aggression. There can be rapid deterioration on occasions, possibly (but not exclusively) related to new ischemic events, but progression is usually insidious, often with long periods of apparent stability (and even some improvement)[39], in a pattern similar to neurodegenerative disorders.

Gait problems (90%), urinary incontinence (80 to 90%) and pseudobulbar symptoms and signs (50%) are extremely frequent. In advanced stages, patients are unable to walk[40] and frequently apathetic/abulic, but rarely exhibit typical 'cortical' changes such as aphasia, apraxia and agnosia[86]. The dissociated pattern of memory loss (with relative preservation of recognition and some improvement with clues and hints) often remains.

Systematic analysis of several groups of diagnostic criteria for vascular dementia indicated that the NINDS-AIREN criteria exhibit 90% sensitivity for correct classification of CADASIL patients with dementia[94]. The missed cases are mainly those in which there are no focal neurological signs. Concomitant use of neuroradiological information virtually eliminates doubt in these cases: all dementia patients show MRI abnormalities.

Many authors tried to define the main determinants of onset and progression of cognitive impairment. The most consistently found predictor is age[39,95,96]. The severity of MRI structural changes, extensively evaluated in volumetric, regional blood volume and anisotropy (diffusion tensor imaging) studies is also correlated to cognitive changes. Specifically, variables such as the specific location of white matter lesions (*eg* the cingulate pathway and frontal regions), the number and total volume of ischemic lesions, the degree of diffuse cortical atrophy or the presence of atrophy in specific areas such as hippocampus and thalamus, correlate (with marked variations between studies) to the evolution of cognitive impairment and progression of secondary functional limitations[95-100]. The extension of white matter lesions *per se* and the presence and extent of microhemorrhages exhibit lower correlation with cognitive disorders.

Other manifestations of the disease

Unusual presentations appearing in the international literature will be only briefly mentioned.

Regarding the central nervous system, there are several reports of clinical epileptic syndromes and complex and acute encephalopathies, including the rapid development of coma (see the epilepsy section for references). Parkinsonism and other extrapyramidal manifestations such as dystonias are occasionally reported[101-103], as well as disconnection syndromes from involvement of the corpus callosum[104,105]. Also isolated cases of thrombophilia, primary vasculitis and vascular malformations and cerebral aneurysms associated with CADASIL have been reported[106-108].

Visual impairment from retinal migraine has been described[109]. Possible involvement of the optic nerve and retina, including arteriolar narrowing and possible microinfarctions or bleeding, is much discussed in the literature. Although pathological, electrophysiological and vascular reactivity changes are frequent and relatively well studied, clinically relevant impairment seems rare[110-116]. Injury of other cranial nerves, especially the eighth cranial nerve is eventually described, and may be related to ischemia in the pontine nuclei[117-119] .

Abnormal electromyographic findings are probably common. Polyneuropathy and myopathy (related to mitochondrial dysfunction or vascular insufficiency) are occasionally reported[120-122]. Myelopathy, even related to coexisting tumor, has also been described[123].

Vascular involvement in other areas, such as the coronary arteries, has also been reported. Prospective studies suggest, however, that this type of event must be rare[11,124]. Alopecia (a common feature in CARASIL) or prominent lesions of the skin or other organs and systems also appear to be rare[125-127]. Venous insufficiency was a frequent manifestation in one oriental family[128].

Treatment of CADASIL

Present treatment of CADASIL is basically empirical, mainly because only a few patients are usually included in different therapeutic studies. Thus, the management of acute complications of stroke, migraine (except for the use of acetazolamide), epilepsy, and psychiatric disorders follows trends in other patient groups. Occasional reports suggest that traditional approaches to medical and surgical problems may also be appropriate in patients with CADASIL[129,130]. Also, attempts to rehabilitate patients with dementia or more subtle cognitive changes are based on the presumprion that the natural process of motor cortical reorganization that occurs in CADASIL as axonal injury increases[131] may be influenced, without any confirmatory evidence.

Ignorance is almost complete in some areas. The use of thrombolytics in patients with CADASIL and ischemic brain has not so far been reported. Theoretically, it should be associated with an increased risk of bleeding, especially in patients with many microbleeds in brain MRI. The same increased risk could be present in aspirin users in the prevention of further lacunar infarctions: there are no reports of cerebral hemorrhage associated with the use of antiplatelet agents, and little is known about platelet function in individuals with CADASIL, in which the pathological attack concentrates on the middle layer of arteries. A clinical trial should probably monitor over 600 patients in order to demonstrate a relative reduction of 40% in the number of new infarcts over 2 years in patients with CADASIL[39].

In the future, neurobiological markers of early injury will probably be used in studies trying to influence the onset and progression of clinical changes; this should help reducing the number of patients needed in therapeutic studies. The search for these markers in MR studies involving analysis of the patterns of appearance and progression of atrophy and accumulation of white matter lesions and other typical structural changes is under way, as well as analyses of diffusion histograms and metabolic relations as assessed by spectroscopy[89,132-135].

The main marker of disease progression is, unfortunately, increasing age, which can be seen as a non modifiable risk factor. Additional genetic factors have been studied as determinants of clinical variability, but up to now did not lead to new therapeutic strategies. The main modifiable vascular risk factors are usually absent in patients with CADASIL.

Strict control of blood pressure (BP) is usually considered mandatory in patients at high risk of developing vascular complications. A study of ambulatory blood pressure monitoring in Japanese patients with CADASIL and controls matched for age and gender showed that the former group tend to exhibit impaired reduction of average blood pressure at night[136]. The authors suggested that this could have pathogenic implication in the development of cerebral ischemic complications. The development of microbleeds (but not of ischemic lesions or the volume of white matter changes) in CADASIL seems to be correlated with a history of hypertension and the levels of systolic blood pressure (and glicated hemoglobin)[70] .

These arguments in favor of reducing BP routinely in CADASIL, however, should be confronted with evidence that these patients have problems in autoregulation of cerebral blood flow (CBF) (see section on pathogenesis). In a study submitting 12 individuals with CADASIL to 24-hour BP monitoring, these individuals exhibited lower average levels of systolic, diastolic and mean (day and night) BP (and less decline in BP levels at night) that an age matched control group[137]. In addition, there was a corre-

lation between low levels of mean daytime BP (MBP) and Mini-Mental State Examination (MMSE) scores (but not with the estimated volume of white matter lesions). As BP instability is now considered a risk factor for the worsening or development of white matter changes in sporadic subcortical vascular dementia, reduction of already low average BP levels could contribute to reduction of regional CBF also in individuals with CADASIL, with potential deterioration of cognitive disorders due to further reduction of flow and further damage in areas, mainly of the white matter, in such patients. Hence, until proved otherwise, great care should be taken to avoid excessive or repeated reductions in BP in CADASIL patients.

The induction of endothelial production of nitric oxide by HMG CoA reductase inhibitors (statins) and its potential therapeutic benefit in individuals with CADASIL has been evaluated in a small study with transcranial Doppler in 24 patients using atorvastatin (40 and then 80 mg/day)[138]. The mean flow velocity and vasoreactivity after induction of hypercapnia and after intravenous infusion of l-arginine (the natural substrate of endothelial synthetase of nitric acid) measured before and along 8 weeks of atorvastatin use remained unchanged with the drug use.

Prophylactic manipulation of serum homocysteine - with by its pro-inflammatory and atherogenic effects - has also been proposed. This strategy has not yet been formally tested in clinical trials, but research at the Mayo Clinic showed that patients with CADASIL and cerebrovascular events have higher baseline and post-stimulation (6 hours after oral methionine, 100 mg/kg) homocysteine levels than control subjects also with cerebral ischemia[139].

While attempts to modify the natural course of CADASIL - or to prevent its onset in future studies using preclinical markers as outcomes - are still in very early stages, another strategy has been studied in patients already with significant cognitive deficit. This is the use of centrally acting cholinesterase inhibitors, similar to what occurs in degenerative diseases like Alzheimer's disease and certain groups of sporadic subcortical vascular dementia[140].

In 2003, Mesulam et al. studied the brain of a 36 year-old patient and showed that cortical cholinergic deficit exclusively attributable to small subcortical infarcts was present even in the absence of pathology suggestive of Alzheimer-type dementia[141].

In vitro study of the brains of patients with CADASIL detected a large reduction of both the activity of acetylcholine transferase in frontal and temporal neocortex and its distribution, as assessed by immunocytochemistry, of this enzyme and of the Neurotropin p75 receptor in Meynert's *nucleus basalis*[142]. In a different approach, Italian researchers evaluated cortical cholinergic innervation through an electrophysiological technique - observation of a phenomenon called short latency afferent inhibition (SAI). This phenomenon is observed in the analysis of evoked motor potentials when transcranial magnetic stimulation is induced with some delay from the time needed to an afferent input to reach the somatosensory cortex, and is a function of cortical cholinergic activity in that region[143] In this study of 10 patients with CADASIL and 10 age-matched controls, the amount of SAI was significantly lower in individuals with CADASIL, again indicating the presence of a cholinergic deficit.

Together, therefore, several research lines point to the presence of a cholinergic deficit in patients with CADASIL, justifying the planning of a clinical trial specifically evaluating the use of a centrally acting anticholinesterase - donepezil. CADASIL seems particularly suitable for therapeutic studies in vascular dementia, due to homogeneity of the underlying pathology, although the disease actually have greatly variable its clinical presentation and progression varies greatly.

This multicentric study, involving researchers in 10 countries, was published in 2008[144]. It evaluated 168 patients, using evolutive changes in a cognitive subscore adapted for vascular dementia - the Vascular-Alzheimer's Disease Assessment Scale-cognitive subscale (V-ADAS-cog) - as the primary endpoint and evaluating a number of secondary outcomes. In summary, the study failed to demonstrate beneficial effects of the use of donepezil - 10 mg/day - on the V-ADAS-cog scale (p=0.956) or MMSE after 18 weeks of use. Ten of 84 patients discontinued the drug because of side effects. The use of donepezil was associated with improved performance in some tests that assess executive functions - such as trail making A and B (TMT-A and TMT-B) and EXIT-25 (a structured interview[145]). However, the actual clinical implications of these effects detected are unknown, and treatment did not influence positively the ability to perform activities of daily living or a number of other secondary outcomes.

A series of critics regarding the study methodology appeared following its publication[146]. One relates to the use of the V-ADAS Cog as an evaluation tool. This instrument supplements ADAS-cog (maximum score - 70 points) with a maze test and a number cancellation test for better assessment of attention and executive function (10 additional points)[147] but possibly has, as the original instrument, low sensitivity to detect evolutive changes in patients who traditionally do not show major problems in orientation, memory and understanding.

Also, significant imbalances were found between the treated and placebo with regard to distribution by gender - less men in the treated group that also had a greater frequency of depression and antidepressant use (both of which can influence cognitive performance) and a better initial TMT-B performance. Furthermore, the study may in fact have not evaluated the population that would most

likely benefit from the use of cholinesterase inhibitors, since only a minority of included subjects met criteria for dementia - for example, more than two thirds scored normally (27 or more points) in the MMSE. It should be remembered that clinical trials using cholinesterase inhibitors or memantine in patients with dementia of vascular origin only included patients fulfilling strict clinical criteria for dementia[140].

CONCLUSION

Despite recent developments in understanding CADASIL, the disease is still little known, especially in its most intimate pathogenetic mechanisms and hence the primary determinants of clinical course, which is quite variable in different families and even in individuals of the same family.

In the near future the development and critical evaluation of protocols for pharmacological intervention and cognitive rehabilitation should be priorized. These treatment protocols need to better address the cognitive characteristics of the disease and include measures of functional impact of interventions.

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