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Chapter

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Carmine Ungaro and Teresa Sprovieri

Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebrovascular disease whose key features are recurrent transient ischemic attacks (TIA), strokes, migraine with aura, vascular dementia, and diffuse white matter abnormalities detectable through neuroimaging. The disease results from mutations in the NOTCH3 gene, encoding a transmembrane receptor involved in cellular signaling and fate during embryonic development. Genetic testing is the gold standard for diagnosing this condition, but the syndrome can be suspected clinically based on family history and characteristic findings of white matter changes. Nevertheless, different individual symptom types, onset, and disease severity, even among individuals in the same family, have been increasingly recognized. The molecular mechanisms by which NOTCH3 mutations lead to vascular degeneration remain unclear. Most CADASIL-associated mutations result in either a gain or loss of cysteine residue in one of the 34 EGF-like repeats in the extracellular domain of the Notch3 protein, thus sparing the number of cysteine residues. More than 200 different mutations in the NOTCH3 gene have been reported in CADASIL patients, of which 95% are missense point mutations. Although it has been suggested that some mutations may be associated with a milder or more severe phenotype, so far no clear genotype-phenotype correlation has been found. To date, no disease-modifying treatment is available for this condition.

Keywords: arteriopathy, leukoencephalopathy, cerebrovascular disease, NOTCH3 gene, Notch3 protein

1. Introduction

CADASIL (MIM 125310) is the acronym for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, coined in 1993 to define a hereditary small vessel disease of the brain affecting middle-aged adults and leading to disability and dementia [1, 2]. The disease was first described in 1955 by Van Bogaert as "Binswanger's disease with a rapid course in two sisters" [3]. Before 1993, a number of families with an apparently hereditary vascular dementia accompanied by a Binswanger-like arteriopathy were described [3–5], but only in 1991, Tournier-Lasserve et al. [6] described nine patients of a single family, with

recurrent cerebrovascular ischemic events and dementia, variably associated with migraine headaches and epilepsy, suggesting the term "autosomal dominant syndrome with stroke-like episodes and leukoencephalopathy." In 1993, a linkage analysis of two unrelated European families led to the mapping of the defective gene to chromosome 19q12, and the syndrome was renamed CADASIL [1]. Compared with other inherited brain disorders such as Huntington's disease or inherited early-onset Alzheimer's dementia, CADASIL is still relatively unknown in the medical community. This is not so much due to the fact that it is a rare disease but more to the fact that there is only a short history of recognition of the disease [7].

2. Clinical picture

CADASIL is an inherited cerebrovascular disorder, whose main clinical features are migraine with aura, recurrent subcortical ischemic attacks, strokes, vascular dementia, cognitive impairment, psychiatric disturbances, and apathy [8–16]. Due to the rarity of the disease, CADASIL is often overlooked and misdiagnosed; nevertheless, the combined symptomatic and asymptomatic prevalence of CADASIL is estimated at least 10.7 per 100,000 adults [11, 12, 17–20]. Migraine with aura is an early sign, with average onset in the third decade of life, and it is typically reported to occur in 20–40% of patients [9, 21]. Transient ischemic attacks (TIA) or lacunar ischemic strokes are the most common signs, occurring in up to 85% of individuals with a mean onset in the fifth or sixth decade; usually they take the form of clinical lacunar syndromes [21, 22]. The second most frequent clinical manifestation is cognitive impairment, often leading to dementia, which occurs in a very high proportion of patients by the age of 50 years. Mood disturbances are reported in 20% of CADASIL patients, presenting as severe depressive episodes [21]. Moreover, researchers recognize apathy, which is independent from depression, as a major clinical manifestation, affecting about 40% of patients [23]. Patients with CADASIL exhibit, even more rarely, other clinical manifestations such as seizures in 5–10% of cases [22]; intracerebral hemorrhages [24], mostly in hypertensive patients, in 16–25% of cases [25, 26]; and, in a few cases, territorial infarcts [27], deafness [6], and parkinsonism [28]. All symptomatic patients present typical magnetic resonance imaging (MRI) findings, including noticeable signal abnormalities with hyperintense lesions on the T2-weighted images in the subcortical white matter, basal ganglia, and thalamus (a crucial difference from multiple sclerosis, a frequent mimic of CADASIL) [1, 6, 29–33]. Anterior temporal lobe hyperintensities may be more specific than external capsule changes and appear in young presymptomatic subjects [34]. In the vast majority of patients, brain MRI abnormalities precede the onset of symptoms by 10–15 years; thus, brain MRI is crucial for the diagnosis of CADASIL. Although marked population differences in the clinical and radiological manifestation of CADASIL have been recognized, potentially due to differences in underlying genetic mutations [21, 35–37], in the proper clinical evaluation based on symptoms suggestive of CADASIL, confluent anterior temporal pole white matter changes show sensitivity and specificity of 89 and 86%, respectively, based on case series. From a pathological point of view, CADASIL patients have a systemic non-amyloid, non-atherosclerotic angiopathy affecting the walls of small blood vessels [38, 39]. The accumulation of granular osmiophilic material (GOM) within the smooth muscle cell basement membrane and the surrounding extracellular matrix is pathognomonic [40–42]. Because the arteriopathy in CADASIL is systemic, GOM deposits, which contain Notch3 proteins, among other poorly defined components [40, 43, 44], can be detected in arteries of many different organs, including dermal arterioles. In fact, actually GOMs are detected in skin biopsies, but the reported

sensitivity is variable [45, 46]. CADASIL is inherited dominantly, with over 500 families detected worldwide and de novo cases observed sporadically [47].

3. Genetics

NOTCH3 gene mutations are causative of the disease. This gene, consisting of 33 exons spanning roughly 7 kb and located on chromosome 19p13 [48], encodes a single-pass transmembrane heterodimer receptor Notch3 of 2321 amino acids involved in cellular signaling and fate during embryonic development [49, 50]. Notch3 protein comprising an N-terminal extracellular domain (NECD) involved in ligand binding, a transmembrane domain (NTMD), and an intracellular domain (NICD), which contains seven ankyrin repeats is required for downstream signal transduction (**Figure 1**) [51, 52]. More specifically, the NECD is non-covalently associated with the membrane-tethered intracellular domain, and it is composed of 34 epidermal growth factor (EGF)-like repeats, followed by 3 Notch/lin12 repeats [53]. Each EGF-like repeat encompasses six cysteine residues, forming three pairs of disulfide bonds [54, 55]. The receptor is synthesized as single precursor protein which is cleaved during transport to the cell surface (S1 cleavage), where it is expressed as heterodimer. Upon binding of its ligand (a protein of the delta/jagged family) [56] at EGF repeats 10–11, Notch3 receptor undergoes two other proteolytic cleavages: at first, N3 is cleaved (S2 cleavage) in its extracellular domain by a TNF-α-converting enzyme (TACE), subsequently in its transmembrane domain (S3 cleavage) in a presenilin-dependent manner. These proteolytic events, mutually dependent, generate the NICD fragment, which released from the NTMD enters the nucleus for activating the transcription of its target genes [53, 57–59]. Although the mutations are highly stereotyped, atypical phenotypes have been recognized, and the disease is probably underdiagnosed in most of the stroke population. Most CADASIL-associated mutations result in a gain or loss of cysteine residue in one of the 34 EGF-like repeats in the extracellular domain of the Notch3 protein, thus sparing the number of cysteine residues within the domain [60–62]. The alteration of the 3-D structure of the Notch3 protein, which is due to an aberrant dimerization of Notch3 through an abnormal disulfide bridging with another Notch3 molecule or with another protein, may play a central role in the pathogenesis of CADASIL [63–65]. A founder effect has been documented for the Finnish population but

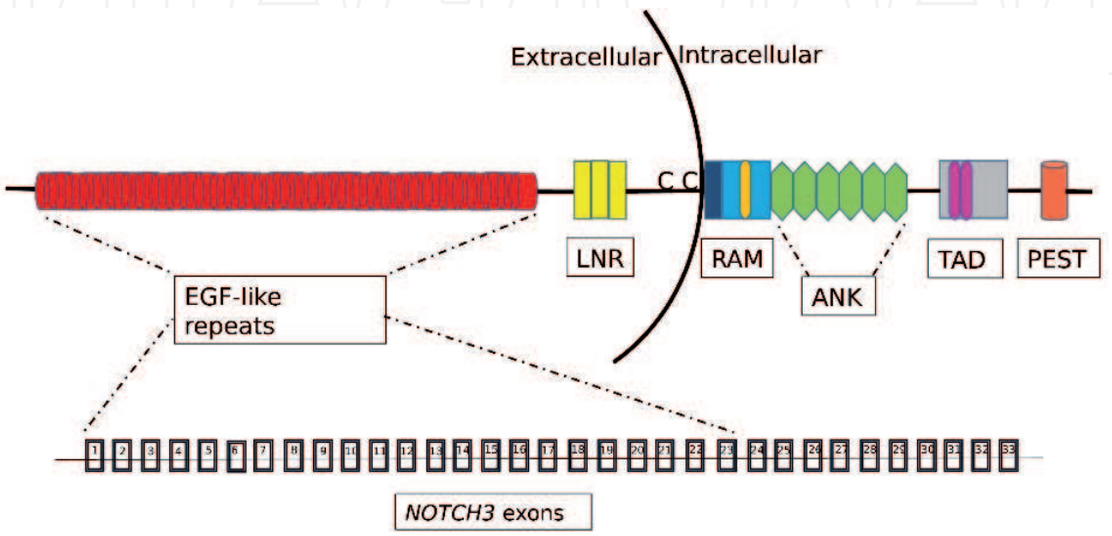

Figure 1.
Schematic structure of Notch3 protein: Notch3 domains are differently colored.

not for other countries [66]. To date, more than 200 different mutations in the NOTCH3 gene have been reported in CADASIL patients, of which 95% are heterozygous missense point mutations [67]. The remaining consist of small deletions, duplications, in frame [68–71] and frame shift mutations, splice site mutations [36], and a small deletion not directly involving a cysteine residue [72]. Moreover, a three-nucleotide insertion has been described as the first pathogenic insertion [73]. Recent studies have found that mutations that do not affect the number of cysteines (unlike the typical mutations) seem to be associated with clinical CADASIL syndrome. However, the pathogenic role of these mutations is uncertain. Although it has been suggested that some mutations may be associated with a milder or more severe phenotype, so far no clear genotype-phenotype correlation has been found [7]. Moreover, only a few cases in the literature reported homozygous mutations of NOTCH3 [74–78]. Many polymorphisms have also been identified in the NOTCH3 coding sequence [67], some of them leading to amino acid substitutions [79]. However, it is unknown whether these polymorphisms affect Notch signaling or whether they are involved in cerebrovascular disease.

4. Diagnosis

The pathology should be suspected in all cases with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia, consistent with an autosomal dominant inheritance. However, because affected family members may have been misdiagnosed [80] and de novo cases have been described [69, 81], the lack of an apparent family history of CADASIL does not preclude the diagnosis. Several groups of clinicians [13, 14, 82] proposed suitable diagnostic strategies to be used in the clinical setting for the selection of patients to be subjected to NOTCH3 gene analysis. In fact, in order to establish a correct diagnosis, clinical signs, neuroimaging findings, and family history need to be evaluated. Molecular screening is the gold standard for the diagnosis and is based on the identification in a proband of a pathogenic variation in the NOTCH3 coding sequence [36, 83]. With a suggestive diagnosis of CADASIL, a single-gene testing or a multigene panel could be applied; if NOTCH3 screening is unavailable or gives a negative result in a patient with convincing clinical and MRI findings highly suggestive of CADASIL, a skin biopsy analysis using both Notch3 immunostaining and electron microscopy should be recommended to confirm or reject the diagnosis [21, 84]. If CADASIL phenotype overlaps with other inherited cerebrovascular diseases, a comprehensive genomic testing, such as exome sequencing, should be recommended in evaluating different genes involved.

5. Therapeutic approach and outlooks

CADASIL is one of the most monogenic causes of stroke. No disease-modifying treatment is available. Being a genetic disease, two possible gene therapeutic approaches have been highlighted [85, 86], but, to date, only a symptomatic therapy focused on mitigating symptoms and management of the patient's vascular risk factor can be applied [87, 88], beginning as immediate action to promote healthy individual behaviors, i.e., to refrain from smoking. Anyway, it is important that patients be referred to multidisciplinary and specialized centers, not only providing genetic counseling but also integrating the clinical and neuroimaging follow-up with neuropsychiatric, psychologic, and physical rehabilitation consultations.

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Conflict of interest

The authors declare no conflict of interest.

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