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Research Paper

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

Medical Science

KEYWORDS : CADASIL, Cerebral Autosomal Dominant, Arteriopathy, NOTCH Genes.

Youssef Awni	Senior Physician Specialists in Medicine and Head of Medical Consulting Center, Nazareath Towers, General Medical Services " sheruti briut clalit" Nazareth, Israel
Bisharat Bishara	Senior Physician Specialists in Family Medicine, Director of EMMS Nazareth Hospital, Faculty of Medicine in the Galilee, Bar Ilan University.
Bowirrat Abdalla	Prof. of Clinical Neuroscience and Population Genetics – Director of Research Center, EMMS Nazareth Hospital, Faculty of Medicine in the Galilee, Bar Ilan University

ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL, OMIM #125310) is a rare mid-adult onset monogenic form of hereditary cerebral microangiopathy, caused by mutations in the NOTCH3 gene which lead to abnormal extracellular matrix accumulation of granular osmiophilic material (GOM) in the vicinity of vascular smooth muscle cells (VSMCs) causing degeneration and loss of VSMCs in small arteries and arterioles. Clinically the syndrome is manifested as migraine with aura, recurrent subcortical ischaemic events or strokes, subcortical vascular dementia and mood disorders. Strokes are typically ischemic, while hemorrhagic events have been only sporadically described. Diagnosis of CADASIL is established on the basis of results of genetic testing; skin biopsy and MRI. However, a genetic test is the gold standard to confirm the diagnosis and to identify a mutation in the underlying gene NOTCH3, which is caused by at least 170 mutations in the NOTCH3 gene at locus 19p13.1–13.26. Pathological test used to identify the GOM deposition around VSMCs examined by electron microscopy in skin biopsies is considered a specific diagnostic tool for CADASIL. In addition, imaging abnormalities in CADASIL evolve as the disease progresses: Typical MRI findings are T2 weighted hyperintensities in white matter and the capsula externa, Subcortical lacunar lesions and cerebral microbleeds are seen. Only symptomatic treatment is obtainable for CADASIL. In this review we will discuss briefly the NOTCH subtypes and concentrate on NOTCH3 and its involvement in CADASIL syndrome.

Background

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL, OMIM #125310) is the most common form of hereditary cerebral angiopathy which affects mainly the brain, and is caused by over 170 different mutations in the NOTCH3 gene at chromosome 19,[1-3] (Figure 1) which shows considerable genetic heterogeneity.[4,5]

The condition was first described more than 30 years ago in a Swedish family,[6] although the acronym CADASIL did not emerge until the early 1990s.[7] CADASIL is caused by mutations in NOTCH3 gene encoding a 280 kDa transmembrane receptor and is present in more than 90% of individuals. NOTCH3 is the only gene in which mutations are known to cause CADASIL.[8] The mutations cause progressive vascular smooth muscle cell (VSMC) degeneration, thickening and fibrosis of the vessel walls and accumulation of the Notch3 extracellular domain (N3ECD) on the VSMCs.[9,10]

Linked to mutations in the NOTCH3 gene, CADASIL vasculopathy is considered the most common single gene form of hereditary cerebral angiopathy, caused by highly stereotyped mutations within the extracellular domain of the NOTCH3 receptor [Notch3 (ECD)] that result in an odd number of cysteine residues. The characteristic type of the mutations, which change the total number of cysteine residues within the epidermal growth factor-like repeats (EGFR), suggests that all mutations divide common mechanisms.[11,12]

Clinically, CADASIL, has various and different pathologies, is linked with cerebral infarcts in more than two third of cases, especially multi-lacunar infarcts engaging the subcortical white matter, deep gray matter nuclei, and brain stem, as well as progressive cognitive decline (subcortical dementia with pseudobulbar palsy and urinary incontinence) in half of cases which are the main clinical signs of CADASIL (Figure 2). Additional neurological manifestations include migraine with aura in 22%–64% of patients.[13, 14]

CADASIL is characterized by transient ischemic attacks or strokes observed in approximately 85% of symptomatic patients. A classic lacunar syndrome (small infarcts) occurs in at least two-thirds of affected patients while hemispheric strokes are much less common. It is worthy to note that ischemic strokes typically occur in the absence of traditional cardiovascular risk factors. Absence of hypertension or other known vascular risk factors is essential for the clinical diagnosis.[15-17]

The age of onset of CADASIL varies greatly, which also depends on the criterion used for the onset of the disease. At the age of 30–50, patients begin to suffer from recurrent transient ischaemic attacks (TIAs) or ischaemic strokes due to subcortical lacunar infarcts usually beginning after the age of 50. The age at the first ever stroke varies from approximately 25 to 70 years with a reported peak around 40-50 years of age and with great variation even within the same family,[18-20] and even between monozygotic twins.[21]

These cerebrovascular events will eventually lead to early cognitive impairment/dementia that progresses into frank dementia of subcortical type associated with pseudobulbar palsy and urinary incontinence later in life. Executive and organizing cognitive functions are impaired first, memory is affected late.[22] Cerebral microbleeds have been found in 31-69% of CADASIL patients.[23,24] Physiologically, cerebral blood volume and cerebral glucose utilization are significantly reduced.[25] Furthermore, cerebral vasoreactivity and fragility are impaired, consistent with the observed degeneration of vascular smooth muscle cells in small arteries and arterioles.[26]

Recurrent migraine attacks with aura (often atypical or isolated, seen in 30%-40% of individuals) sometimes accompanied with confusion, fever, meningitis or coma.

Progressive white matter degeneration are other features of the disease, in addition, affected individuals exhibit a variety of symptoms, including seizures, bipolar disorder, personality changes, mood disturbance, apathy, and premature death, commonly within 20-25 years after symptoms have occurred.[27-31]

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The pathologic hallmark of CADASIL is electron-dense granules osmiophilic material (GOM), which contains extracellular domains of Notch3, in the media of arterioles that can often be identified by electron microscopic (EM) evaluation of skin biopsies. NOTCH3 mutations within the receptor extracellular domain leads to abnormal extracellular matrix accumulation of GOM and NOTCH3 extracellular domain around small caliber arteries and arterioles and eventual progressive loss of vascular smooth muscle cells.9 CADASIL shows true dominancy and the vast majority of CADASIL mutations (95%) are missense mutations removing or inserting cysteine residues within 1–34 epidermal growth factor-like repeats in the NOTCH3 protein. Small inframe deletions are observed and splice-site mutations in the NOTCH3 gene encoding a transmembrane receptor are also seen, which invariably cause inframe deletions resulting in loss of cysteine residues.[32-36]

Indeed, six pathogenic deletions, one combined deletion and insertion (or two adjacent nucleotide substitutions), two duplications, and two splice-site mutations have been described. In addition to these common types of cysteine affecting CADASIL mutations, seven mutations not altering the number of cysteines have been reported. One of these mutations is a deletion which removes the amino acids between two cysteines, and the remainder is missense mutations leading to one amino acid substitution.[37, 38, 8, 32, 34]

Whether these substitutions are truly pathogenic mutations or merely variants is yet unclear. So far, only three reports of patients homozygous for pathogenic NOTCH3 mutations have been published.[39-41]

In addition, two confirmed de novo mutations in CADASIL patients have been reported.[42, 43] Thus, either a cysteine residue is deleted or altered to another amino acid residue or, conversely, mutations of noncysteine residues lead to introduction of novel cysteine residues.[34] This results in an uneven number of cysteine residues in the given domain, most likely modifying the tertiary structure of the protein.[32] At least three mechanisms mediate the pathogenic effects of NOTCH[3] mutation in CADASIL, i.e., loss of receptor function, gain of function, and neomorphic (eg, toxic) processes.

Mutations of NOTCH[3] characteristically lead to an epidermal growth factor-like repeat domain (six repeats in the normal domain) and an odd number of cysteine residues (either five or seven) through gain or loss of a residue.[8] Some researchers claim that no mutations leading to three cysteine residues or not involving a cysteine residue have ever been reported.[33, 44] However, it is not yet known whether these mutations primarily affect receptor trafficking, maturation, and/or signaling.[45]

The History of CADASIL

Historically, on the basis of thorough scrutiny of the literature, the first CADASIL family is now believed to have been reported in 1955 by Van Bogaert,[46, 47] who described two sisters with rapidly progressive subcortical encephalopathy of Binswanger's type.[48]

In 1977, Sourander and Walinder reported a Swedish family with a CADASIL mutation and multi-infarct dementia of autosomal-dominant inheritance, presenting with pyramidal, bulbar, and cerebellar symptoms, a relapsing course, and gradually evolving severe dementia.[6] In 2007, Low et al verified that the hereditary multi-infarct dementia in the Swedish family reported by Sourander and Walinder was erroneously attributed to CADASIL, and that the patients did not show the characteristic features of CADASIL on pathological examination.[49]

In Finland, the first family with CADASIL was identified and published as hereditary multi-infarct dementia in 1987.[50]

After the gene test became available, 15 new families comprising approximately 100 patients or presymptomatic carriers of the gene defect have been identified in Finland. Fourteen of the 15 families identified in Finland carry the same C475T transition mutation of the NOTCH3 gene, which leads to substitution of the 133 arginine by cysteine (R133C).[51, 29, 50]

Information concerning the exact global incidence and prevalence of CADASIL is limited. In the west of Scotland, the prevalence of confirmed CADASIL cases in 2004 was 1.98/100,000 and the estimated prevalence based on pedigree information was 4.15/100,000.[50] In Finland, a similar prevalence has been estimated.[52, 53]

In 1993, Tournier-Lasserve et al operated linkage analysis to two extended distinct French families with CADASIL, and connected the disease to chromosome 19q12.14 a more recent study by Tikka et al investigated different pathogenic mutations in 34 patients in France, and demonstrated three novel point mutations (p.Cys67Ser, p.Cys251Tyr, and p.Tyr1069Cys) and a novel duplication (p.Glu434-Leu436dup). In this cohort, the congruence between NOTCH3 mutations and deposition of granular osmiophilic material around vascular smooth muscle cells, which is the gold standard for confirmation of a diagnosis of CADASIL, was 100%.[1] In 2002, Markus et al performed a large genetic study of 48 British families and showed that most mutations of CADASIL were located in exon 4, followed by exons 3, 5, 6, 8, 18, and 22.[54]

Another study from a Dutch DNA diagnostic laboratory (44 Dutch and 22 foreign families) also found the mutation rate of CADASIL was highest in exon 4, followed by exon 3, 5, 6, 11, and 19.[55]

Thus, it is suggested that exons 3–6 should be screened first, and then exons 11 and 18–23. In fact, worldwide variations have been described, showing exon 3 to be the second most common mutation site in French, British, and German individuals,[34, 54, 56-57] while exon 11 frequently harbors mutations in affected Dutch individuals.[56]

Epidemiologically, the precise frequency and mortality rate of CADASIL worldwide is still unknown. The mean age of death has been reported to be 61 years after a mean disease duration of approximately 23 years.[19] Men tend to die earlier than women,[3] but mortality appears to be equally distributed between the genders, and the onset of clinical symptoms usually occurs in the fourth decade of life, with a mean age at presentation of 46.1 years.[58, 19]

Fewer than half of patients older than 60 years can walk without assistance and nearly 80% of patients are completely dependent immediately before death.[3]

However, the number of reported cases of CADASIL is gradually increasing as the clinical picture becomes more widely recognized and genetic testing becomes available. CADASIL occurs worldwide and has been reported in many ethnic groups. So far, most of the CADASIL patients have been found in Caucasian families, including France, Germany, the UK, Finland, Sweden, Italy, and the Netherlands.[14, 19, 51, 53, 56, 59-63]

Reports from North America are relatively sparse, despite the high level of academic activity in this region. In 2007, Bohlega et al.[64] studied three families from Arab countries (Saudi Arabia, Kuwait, and Yemen) containing 19 individuals affected by CADASIL. All NOTCH3 exons were screened for mutations, which showed the presence of formerly described mutations in c.406C . T (p.Arg110 . Cys) in two families from the middle east (Saudi Arabia and Kuwait), and a c.475C . T (p.Arg133. Cys) mutation

in the family from Yemen. The investigators concluded that CADASIL does occur in Arabs, with a clinical phenotype and genotype similar to that in other ethnic groups.

Overview of NOTCH Genes Subtypes (Figure 3)

In mammals, four Notch receptors (Notch 1–4) and five Notch ligands (Delta-like-1, -3, -4, Jagged-1, -2) have been described. An increasing body of evidence suggests that ligand-induced Notch signalling plays a pivotal role, both in various developmental contexts during embryonic development and also in adult tissues.[65-68]

The origin of the term 'Notch' stems from the observations of great genetics scientist Thomas Hunt Morgan,[69] who in 1917 published 'The Theory of the Gene' his paper described a mutant female drosophila fly with serrations at the ends of the wings, which he named 'Notch'. Another fly with a mutant wing shape he called 'Delta'. Decades later, it was observed that the mutant homologues of the fly genes that defects the exoskeleton also causes malformations of the endoskeleton in human.[69]

Currently, we comprehend the Notch pathway, of which Notch and Delta are parts, as a multifaceted intercellular signalling cascade system that is vital to natural development, one that has been preserved across animal species where the body plan contains tissues differentiated into muscles and nerves, that is, metazoans.

The Notch genes encode considerable cell surface transmembrane receptors whose role is to arbitrate fundamental cellular functions through direct cell–cell contact. The initiation of membrane-bound Notch by specific ligands results in proteolytic cleavage, by g-secretase activity, of the Notch intracellular domain (NICD) from the plasma membrane, and this protein directly translocates to the nucleus to play a role in the transcriptional regulation of target genes, where it converts downstream targets from transcriptional repressors to transcriptional activators.

In this mode the pathway influences cell destiny and lineage commitment through differentiation, proliferation and apoptosis in the procedures of neurogenesis, myogenesis, angiogenesis, haematopoiesis and epithelial–mesenchymal transition. A cornerstone role of the pathway is in the developmental integrity of somitogenesis. Somites are paired blocks of tissue that form sequentially from the presomitic mesoderm (PSM) either side of the notochord in a rostrocaudal direction. Finally they differentiate into vertebrae, ribs, muscles, tendons and ligaments.

Germline mutations in Notch pathway genes give rise to a array of syndromes which, presently, can be clustered into: (1) The spondylocostal dysostosis (SCD); (2) Alagille syndrome (ALGS), NOTCH1-related congenital heart disease (CHD) and CADASIL; (3) Hajdu–Cheney syndrome (HJCYS), a multisystem disorder dominated by skeletal anomalies and (4) Alzheimer disease type 3. In this review we will discuss briefly the NOTCH subtypes and will concentrate on NOTCH3 in specific, taking in consideration its involvement in CADASIL syndrome.[70]

NOTCH1–associated with Congenital Heart Disease (CHD)

Garg et al. [71] first observed the involvement of the Notch1 receptor gene with CHD by studying two families with heterozygous mutations whose main feature was bicuspid aortic valve (BAV) and calcification.

Mutations in Notch1 in CHD in human are considered to be a susceptibility factor, rather than playing an essential role in terms of Mendelian disease. Urbanek et al.[72] have observed in a study conducted on cardiac stem cells (CSCs) in newborn mice, a presence of Nkx2.5 (a protein important to cardiac development, and mutations in the gene are associated with human CHD), coupled with the Notch1 intracellular domain in one multipotent cell line CSCs.[72] Furthermore, NOTCH1 has been associated with gastric cancer and was observed in both premalignant and malignant tissues.[73] Moreover, Notch1 may play a vital role in both encouraging metaplastic transition of gastric epithelial cells and in the preservation of proliferating intestinalised epithelial cells.[73]

NOTCH2 - Multisystem Disorder (Skeletal Effects)

Mutations in Notch2 pathway genes are associated with two multisystem disorders, namely ALGS (Alagille syndrome) and HJCYS (Hajdu–Cheney syndrome). Roughly 1% of ALGS is caused by mutated NOTCH2, which is also the only known gene linked to HJCYS.[74]

The finding of NOTCH2 mutations was a breakthrough for exome sequencing in two different studies conducted by Simpson and Isidor. [75,76] All reported mutations occur in exon 34, which is the last exon of NOTCH2, and all are predicted to lead to shortening of the protein product.[75,76]

NOTCH3 – CADASIL

NOTCH3 (N3) is a member of the Notch receptor family, which regulates cell destiny during embryonic development77 and is chiefly present in vascular smooth muscle cells (VSMC) in adulthood.[8, 78] The human NOTCH3 gene consists of 33 exons extending roughly [7] kb, was mapped to chromosome 19q13.1–13.26, and encodes a transmembrane protein comprising 2321 amino acids.[79]

NOTCH3 is a membrane-spanning protein with a large extracellular domain (N3ECD) containing 34 epidermal growth factor-like (EGF-like) repeats and a smaller intracellular domain with six ankyrin repeats. Each EGF-like domain contains six conserved cysteine residues, [18] which are vital for the correct folding of the EGF-like repeats and possibly for the function of the receptor.[80] An increasing body of evidence suggests that ligand-induced Notch signalling plays a pivotal role, both in various developmental contexts during embryonic development and also in adult tissues.[80] However, the specific role of Notch3 signalling in different developmental paradigms remains unclear and its function is not crucial for embryonic development but is needed after birth. NOTCH3 directs postnatal arterial maturation and helps to maintain arterial integrity. It is involved in regulation of vascular tone and in the wound healing of a vascular injury. In addition, NOTCH3 promotes cell survival by inducing expression of anti-apoptotic proteins.

The majority of mutations in the NOTCH3 gene in patients with CADASIL are located in exon 4, followed by exons 3, 5, 6 and 11, and mutations are present in 50% of cases. All CADASIL-causing mutations identified so far are located in the EGF-like domains of NOTCH3 and the majority of the mutations cause gain or loss of one cysteine residue in one of these repeats leading to an odd number of cysteine residues, which in turn leads to misfolding of N3ECD. This misfolding most likely alters the maturation, targetting, degradation and/or function of the NOTCH3 receptor.[80, 82, 83]

NOTCH4 - Metastatic Melanoma

Notch4 may play a crucial role in the equilibrium of cell growth and regulation of the aggressive phenotype and functions of Nodal which has been demonstrated in the study of Hardy et al.,[84] as a regulator of aggressive tumor cells in metastatic Melanoma, for studies have showed a very close correlation between Notch4 and Nodal expression in multiple aggressive cell lines.[84]

Conclusions

Germline mutations in Notch pathway genes give rise to a array of syndromes which, presently, can be clustered into: (1) The

spondylocostal dysostosis (SCD); (2) Alagille syndrome (ALGS), NOTCH1-related congenital heart disease (CHD) and CADASIL; (3) Hajdu–Cheney syndrome (HJCYS), a multisystem disorder dominated by skeletal anomalies and (4) Alzheimer disease type 3. In this review we will discuss briefly the NOTCH subtypes and will concentrate on NOTCH3 in specific, taking in consideration its involvement in CADASIL syndrome.[70]

development and is chiefly present in vascular smooth muscle cells (VSMC) in adulthood. Mutations in NOTCH3 create the malfunctioning gene causing CADASIL pathology.

CADASIL is the most common form of hereditary subcortical vascular dementia. The main clinical features are migraine with aura (often atypical or isolated), strokes, cognitive decline, dementia, and psychiatric symptoms. Smooth muscle cells in the small arteries throughout the body degenerate and vessel walls become fibrotic. In the brain, this results in circulatory disturbances and lacunar infarcts, mainly in the cerebral white matter and deep gray matter.

Conflict of interest.
The authors declare no conflict of interest.

Authors' contributions
YA- Participated in writing the study, collected data from the literature and reviewed the manuscript final version.

BB – Participated in the study design, conclusion writing and collection of data, performed part of the figures.

BA – Conceived the study, and participated in its design and coordination and wrote almost all manuscript (introduction & discussion) and helped to draft the manuscript.

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Figure 1: The exonic structure of the human NOTCH3 gene and the domains of the NOTCH3 receptor protein.

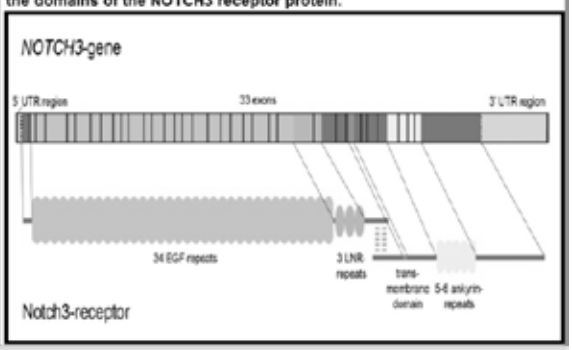
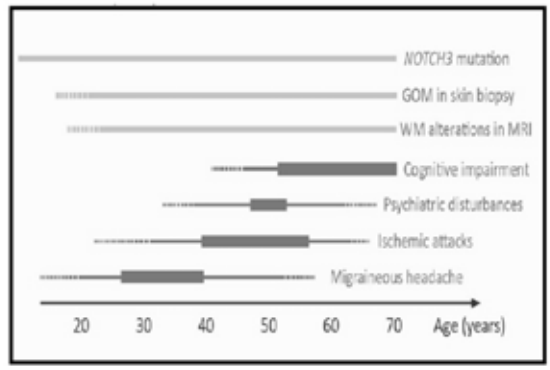
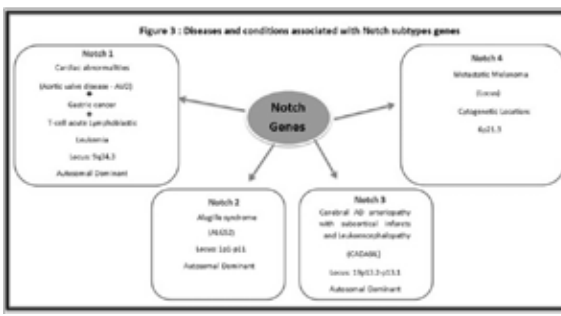


Figure 2: The symptom manifestation and findings in CADASIL during the disease course. WM; White Matter, MRI; Magnetic Resonance Imaging, GOM; Granular Osmiophilic Material.





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