SciMedCentral

Annals of Clinical Cytology and Pathology

Mini Review

The Pathogenesis of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL, OMIM #125310)

Bowirrat Abdalla*

Department of Clinical Neuroscience, EMMS Nazareth Hospital, Israel

***Corresponding author**

Bowirrat Abdalla, Department of Clinical Neuroscience, Director of the research Center, EMMS Nazareth Hospital, Nazareth Zip code:16100, Israel, Tel: 972-4635-6133; Email: Prof. Bowirrat@yahoo.com; bowirrat@Gmail.com

Submitted: 28 September 2014

Accepted: 12 October 2014

Published: 15 October 2014

Keywords

- Pathology
- Cerebral arteriopathy
- subcortical infarcts
- CADASIL
- NOTCH

Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL, OMIM #125310) is a rare hereditary systemic vasculopathy and an example of pleiotropism i.e. single gene effects on multiple phenotypic traits. CADASIL is the most common monogenic form of hereditary cerebral microangiopathy disorder manifesting usually in early adulthood which cause a highly stereotyped mutations within the extracellular domain of the NOTCH3 gene. NOTCH3 mutations within the receptor extracellular domain, lead to abnormal extracellular matrix accumulation of granular osmiophilic material (GOM) in the close vicinity of vascular smooth muscle cells (VSMCs) and around small caliber arteries and arterioles, eventually leading to a progressive loss of VSMCs.

In the brain, degeneration of smooth muscle cells in small arteries results in an impaired cerebral blood flow, arteriolar stenosis and lacunar infarcts, mainly in cerebral white matter and deep gray matter. Affected individuals exhibit a variety of symptoms, and clinical presentation of CADASIL varies even among and within families. The disease is characterized by six main symptoms: migraine with aura, subcortical ischemic events, mood disturbances, apathy, cognitive impairment and subcortical dementia.

Usually, at the age of 30–50, patients begin to suffer from recurrent transient ischaemic attacks (TIAs) or ischaemic strokes due to subcortical lacunar infarcts. These will eventually lead to a progressive cognitive decline, psychiatric disorders, and to a subcortical type of vascular dementia. Strokes are typically ischemic, while hemorrhagic events have been only sporadically described. However, cerebral microbleeds have been found in 31-69% of CADASIL patients.

CADASIL phenotype is highly variable and although the full clinical-neuroimaging picture may be suggestive of the disease, three methods are usually needed to confirm the diagnosis of CADASIL: The genetic testing; skin biopsy and MRI. However, a genetic test remains the diagnostic gold standard to confirm the diagnosis and to identify a mutation in the underlying gene NOTCH3 encoding a transmembrane receptor protein, which is caused by at least 200 mutations in the NOTCH3 gene at locus 19p13.1–13.26. NOTCH3 mutations are usually assessed by restriction enzyme analysis of specific mutations or by sequence analysis; pathological test used to identify the GOM deposition around VSMCs examined by electron microscopy (EM) in skin biopsies is extremely helpful and 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 (SLLs) and Cerebral microbleeds are usually seen. No specific treatment is available at present, but only symptomatic treatment is obtainable. In this review we will discuss briefly the pathogenesis of CADASIL and on the mutations of NOTCH3 gene.

INTRODUCTION

CADASIL is essentially a microangiopathy disorder affecting essentially the brain and is the most common monogenic form of hereditary cerebral microangiopathy disorder manifesting usually in early adulthood. To date, more than 200 mutations of *NOTCH* homolog *3* gene, located on chromosome-19p13.1–13.26., have been reported in CADASIL patients [1-3]. Over 95% of the mutations are mapped in EGF-like repeat domain of NOTCH3 [data from HGMD]. Almost all of the mutations are missense and lead to either gain or loss of a Cysteine residue, causing an odd number of Cysteine and further misfolding of the EGF-like repeat domain. This misfolding may change the maturation, targeting, degradation and function of the NOTCH3 receptor, which plays a key role for most phenotypes of CADASIL affected families.

CADASIL is a dominantly inherited neurodegenerative disease and the most common cause of hereditary pure vascular dementia. Penetrance of the disease is probably 100%, but expression varies in age of onset, severity of the clinical symptoms, and progression of the disease. Affected individuals exhibit a variety of symptoms, and clinical presentation of CADASIL

varies even among and within families. The main symptoms are an early recurrent ischemic strokes (84%), subcortical vascular dementia (80%), migraine with atypical aura (35%), and psychiatric disturbances (20%). The pathological hallmarks of CADASIL are profound demyelination and axonal damage, as well as arteriopathy involving distinctive degeneration of the arterial smooth muscle cells in the brain and peripheral organs [4]. Gradual destruction of vascular smooth muscle cells (VSMCs) leads to progressive wall thickening, fibrosis, and luminal narrowing in small and medium-sized penetrating arteries. The reduced cerebral blood flow finally causes lacunar infarcts, mainly in the basal ganglia and fronto-temporal white matter, which leads to cognitive impairments and dementia. Additionally, other hallmarks of the disease are the widespread vasculopathy, and the pathognomonic accumulation within the tunica media of arterial walls of granular osmiophilic material (GOM) [5] which is distinct from arteriosclerotic and amyloid angiopathy generally affecting leptomeningeal. Skin biopsy typically shows ultrastructural alterations of skin vessels similar to those of brain arteries [6-8] Imaging abnormalities in CADASIL develop as the disease progresses [9].

Magnetic Resonance Imaging (MRI) hyperintensities signals in subcortical white matter and basal ganglia, are consistently visualized from age 21 years onward [10]. In patients aged 20-30 years with a pathogenic mutation, typical white matter hyper intensities first appear in the anterior temporal lobes, but the rest of the white matter, except for periventricular caps, appear unaffected [10]. Affected patients' white matter hyper intensities are symmetrically distributed and located in the periventricular and deep white matter.

Within the white matter, the frontal lobe is the site with the highest lesion load, followed by the temporal and parietal lobes [11] and Subcortical lacunar lesions (SLLs). Linearly arranged groups of rounded, circumscribed lesions at the junction of the grey and white matter with signal intensity identical to that of cerebrospinal fluid and SLLs are found in approximately two-thirds of affected patients and may be a specific marker for CADASIL [12] Cerebral micro bleeds are located predominantly in the thalamus and are best visualized with T2 - weighted gradient echo imaging [13].

NOTCH3 gene mutation causes CADASIL Pathology

Mutations in NOTCH3 have been identified as the underlying cause of CADASIL. NOTCH3 gene is located in the short arm of chromosome 19q13.1–13.26 [14] and it is a large (~41.3 kilobase) gene containing 33 exons. The gene is 2321 amino acids glycosylated transmembrane receptor [14]. The identification of a pathogenic NOTCH3 mutation is an indisputable evidence for CADASIL, until today, it is known over 200 different NOTCH3 gene defects [1-3,15].

Pathogenic mutations in CADASIL patients identified to date are predominantly missense mutations within the NOTCH3 extracellular domain, which either add or delete Cysteine residues resulting in an odd number of Cysteines [16]. This is believed to promote abnormal Cysteine-Cysteine interactions leading to conformational changes, pathological homo/heterodimerization or multimerization [17-19]. Indeed, in CADASIL, NOTCH3 extracellular domain accumulates in the cytoplasmic membrane of VSMCs [17,18-21] This gene encodes the third discovered human homologue of the Drosophilia melanogaster type I membrane protein notch. Four different Notch receptors (Notch 1—4) and five Notch ligands (Deltalike-1,-3,-4, Jagged-1,-2) have been identified in mammals. Notch signaling has an essential role in different developmental events during the embryonic development as well as in adult tissues. In mammals, Notch3 signaling influences cell-destiny decisions by regulating gene expression, cell differentiation, proliferation, and apoptosis and is periodically expressed in many different tissues in several phases of the embryonic development.

In addition, the regulation of neurogenesis, myogenesis, angiogenesis, haematopoiesis and epithelial–mesenchymal transition are all crucially influenced by Notch signaling. In the adult human, the *NOTCH3* gene is expressed almost exclusively in the VSMCs [22]. And plays a crucial roles in postnatal differentiation, maturation and phenotypic behavior of VSMCs, regulation of VSMCs growth and apoptosis, response to vascular injury, and regulation of actins cytoskeleton in response to mechanical stretching of the vessel wall by intraluminal pressure [23-25].

CONCLUSION

The Notch signaling pathway indicates a very complicated cell interaction mechanism, playing an essential part in metazoan development, which ultimately determines cell destinies in regards of differentiation, proliferation and apoptosis. CADASIL is a rare autosomal dominant disease that is essentially a micro-angiopathy affecting mainly the brain and is caused by mutations in NOTCH3 gene located in the short arm of chromosome 19. Most 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 found in over 90% of cases [26-28] Geographic variations have been described, showing variability in the distribution of the disease worldwide, for example, mutations in exon 3 of the NOTCH3 gene represent the second most common mutation site in the French, British and German populations, whereas mutations in exon 11 are more frequently seen in the Dutch [26-28].

CADASIL is the most common cause of hereditary stroke, hereditary pure vascular dementia and disabling systemic condition in adulthood, characterized by migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The clinical presentation of CADASIL is heterogeneous, and may be confused with multiple sclerosis, Alzheimer dementia, and Binswanger disease, that's why an accurate differential diagnosis is needed. The specific clinical signs and symptoms, along with genetic testing and brain MRI findings, are essential in determining the diagnosis of CADASIL. When the differential diagnosis includes CADASIL, various other tests are available for diagnosis such as: Immunohistochemistry assay of a skin biopsy sample, detection of granular osmiophilic material (GOM) in the same skin biopsy sample by electron microscopy. Genetic testing, by direct sequencing of selected exons or of exons 2-24 of the NOTCH3 gene is also important for the diagnosis.

ACKNOWLEDGMENTS

We thank Miss Aia Bowirrat for her contribution in revising and editing the manuscript.

REFERENCES

1. Shahien R, Bianchi S, Bowirrat A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in an Israeli family. Neuropsychiatric disease and treatment 2011; 7: 383–390.
2. Joutel A. Pathogenesis of CADASIL: transgenic and knock-out mice to probe function and dysfunction of the mutated gene, Notch3, in the cerebrovasculature. Bioessays. 2011; 33: 73-80.
3. Ge W, Kuang H, Wei B, Bo L, Xu Z, Xu X. A novel cysteine-sparing NOTCH3 mutation in a Chinese family with CADASIL. PLoS One. 2014; 9: e104533.
4. Adib-Samii P, Brice G, Martin RJ, Markus HS. Clinical spectrum of CADASIL and the effect of cardiovascular risk factors on phenotype: study in 200 consecutively recruited individuals. Stroke. 2010; 41: 630-634.
5. Goebel HH, Meyermann R, Rosin R, Schlote W. Characteristic morphologic manifestation of CADASIL, cerebral autosomal- dominant arteriopathy with subcortical infarcts and leukoencephalopathy, in skeletal muscle and skin. Muscle Nerve. 1997; 20: 625–627.
6. LaPoint SF, Patel U, Rubio A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Adv Anat Pathol. 2000; 7: 307-321.
7. Malandrini A, Gaudiano C, Gambelli S, Berti G, Serni G, Bianchi S. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. Neurology. 2007; 68: 1430-1432.
8. Gutiérrez-Molina M, Caminero Rodríguez A, Martínez García C, Arpa Gutiérrez J, Morales Bastos C, Amer G. Small arterial granular degeneration in familial Binswanger's syndrome. Acta Neuropathol. 1994; 87: 98-105.
9. 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: 1978-1980.
10. Oberstein SA. Diagnostic strategies in CADASIL. Neurology. 2003; 60: 2020.
11. 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: 628-634.
12. van Den Boom R, Lesnik Oberstein SA, van Duinen SG, Bornebroek M, Ferrari MD, Haan J, et al. Subcortical lacunar lesions: an MR imaging finding in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Radiology. 2002; 224: 791-796.
13. Dichgans M, Holtmannspötter 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.
14. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature. 1996; 383: 707-710.
15. Tikka S, Mykkänen K, Ruchoux MM, Bergholm R, Junna M, Pöyhönen M. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. Brain. 2009; 132: 933-939.
16. Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. Arch Neurol. 2005; 62: 1091-1094.
17. Dichgans M, Ludwig H, Müller-Höcker 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: 280-285.
18. Donahue CP, Kosik KS. Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL. Genomics. 2004; 83: 59-65.
19. Opherk C1, Duering M, Peters N, Karpinska A, Rosner S, Schneider E. CADASIL mutations enhance spontaneous multimerization of NOTCH3. Hum Mol Genet. 2009; 18: 2761-2767.
20. 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: 280–285.
21. Donahue CP, Kosik KS. Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL. Genomics. 2004; 83: 59-65.
22. Joutel A, Andreux F, Gaulis S, Domenga V, Cecillon M, Battail N. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. J Clin Invest. 2000; 105: 597-605.
23. Domenga V, Fardoux P, Lacombe P, Monet M, Maciazek J, Krebs LT. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. Genes Dev. 2004; 18: 2730-2735.
24. Wang T, Baron M, Trump D. An overview of Notch3 functions in vascular smooth muscle cells. Prog Biophys Mol Biol. 2008; 96: 499-509.
25. Turnpenny PD. Syndromes and Diseases Associated with the Notch Signalling Pathway. In: eLS. John Wiley & Sons, Ltd. 2014.
26. Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH. Diagnostic strategies in CADASIL. Neurology. 2002; 59: 1134-1138.
27. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssière C. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. Lancet. 1997; 350: 1511-1515.
28. Razvi SS, Davidson R, Bone I, Muir KW. Diagnostic strategies in CADASIL. Neurology. 2003; 60: 2019-2020.

Cite this article

Abdalla B (2014) The Pathogenesis of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL, OMIM #125310). Ann Clin Cytol Pathol 1(1): 1002.