EJCRIM
European Journal
of Case Reports
in Internal Medicine

A NOVEL MUTATION OF THE NOTCH3 GENE IN A YOUNG PATIENT PRESENTING WITH AN ACUTE STROKE: CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

Inas Ragab[1], Meave Higgins[1], Antonio F. Caballero-Bermejo[2], Karl Boyle[1], Kai Covin[3], Leena Abdelmoti[4]

[1] Beaumont Hospital, Dublin, Ireland
[2] Mater Misericordiae University Hospital, Eccles St, Phibsborough, Dublin, Ireland
[3] Edward Via College of Osteopathic Medicine-Louisiana Campus, Monroe, USA
[4] National Rehab Hospital, Dublin, Ireland

Corresponding author's e-mail: nusaragab@gmail.com

Received: 27/02/2025
Accepted: 09/06/2025
Published: 12/08/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Verbal and written consent for the publication of his case were obtained from patient.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Ragab I, Higgins M, Caballero-Bermejo AF, Boyle K, Covin K. A novel mutation of the NOTCH3 gene in a young patient presenting with an acute stroke: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *EJCRIM* 2025;**12**:doi:10.12890/2025_005297

ABSTRACT

This report provides a detailed analysis of a singular case involving cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in a male patient who suffered a stroke. Our investigation delves into the clinical manifestations, genetic foundations, diagnostic complexities, and prognosis associated with CADASIL. As a notable contributor to stroke occurrence in young patients, CADASIL's impact on morbidity and mortality is influenced by stroke-related complications and cognitive decline. Notably, our report highlights a novel genetic variant (C.3025T>C; p.Cys1009Arg) in the *NOTCH3* gene linked to CADASIL, shedding light on its underlying pathogenesis. Furthermore, our patient exhibited unexpected white matter changes, challenging conventional age-related norms. These findings underscore the essential role of genetic testing and emphasize the potential diversity in CADASIL's clinical presentation. Further exploration is imperative to enhance our understanding of CADASIL and refine diagnostic strategies, thereby facilitating improved patient prognosis and management.

KEYWORDS

Dysarthria, CADSIL, small vessel disease, stroke

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a significant cause of stroke in young patients, with stroke-related complications and cognitive impairment contributing to morbidity and mortality.
- Increasing awareness of CADASIL's clinical presentation and the availability of genetic testing has led to a rise in reported cases.
- CADASIL is caused by mutations in the *NOTCH3* gene, primarily involving missense substitutions and leading to cysteine residue alterations.
- There have been many pathogenic variants reported around the world and some families might exhibit private pathogenic variants.

INTRODUCTION/BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infracts and leukoencephalopathy (CADASIL) is an inherited, monogenic, small vessel disease. It is clinically associated with early, recurrent, subcortical cerebral infarcts; progressive dementia; mood disturbances and migraines. CADASIL is predominantly caused by pathogenic missense variants in exons 2-24 of the *NOTCH3* gene, which usually lead to loss or gain of a cysteine residue in one of the epidermal growth factor-like repeat (EGFr) domains in the extracellular portion of the *NOTCH3* receptor. In this case, we report a new variant; C.3025T>C; p.Cys1009Arg in gene *NOTCH3* in a heterozygous state. Genetic testing for *NOTCH3* mutations allows for a definitive diagnosis and understanding the genetic basis which helps identify at-risk family members early and enables informed reproductive choices.

The estimated prevalence of *NOTCH3* genetic variant is 0.8-5 per 100,000 individuals. Subsequent reports suggested higher prevalence as high as 1 in 300 worldwide, highlighting potential underdiagnosis or variable expression.

Understanding the molecular mechanism of *NOTCH3* mutations provides insight into the pathophysiology of the disease, opening avenues for targeted therapies and potential gene-based treatments in the future.

CASE DESCRIPTION

We report the case of a 43-year-old gentleman who presented with right sided upper limb weakness with sensory disturbance and mild dysarthria, which he noticed when he awoke in the early hours of the morning. His National Institutes of Health Stroke Scale (NIHSS) was 2 at the time of presentation; 1 for a right upper limb drift, 1 for right upper limb ataxia. This progressed to a score of 5 after 24 hours with worsening right sided weakness scoring him a 2 for right arm weakness, a 2 for right lower limb weakness and persistent ataxia in his right upper limb. He also had intermittent dysarthria and a mild right sided facial palsy. Prior to this the patient was a well 43-year-old; he had no significant background medical history and was not taking any regular medications. He was an ex-smoker with a 3 pack-year-history. As regards family history he had an aunt who had a stroke at the age of 50. At the time of his acute presentation, he had a computed tomography (CT) scan brain and CT angiography of the intracranial vessels and carotids/vertebral arteries as well as a CT perfusion scan of the brain which did not show an acute infarct at that time. He was admitted to the acute stroke unit and underwent

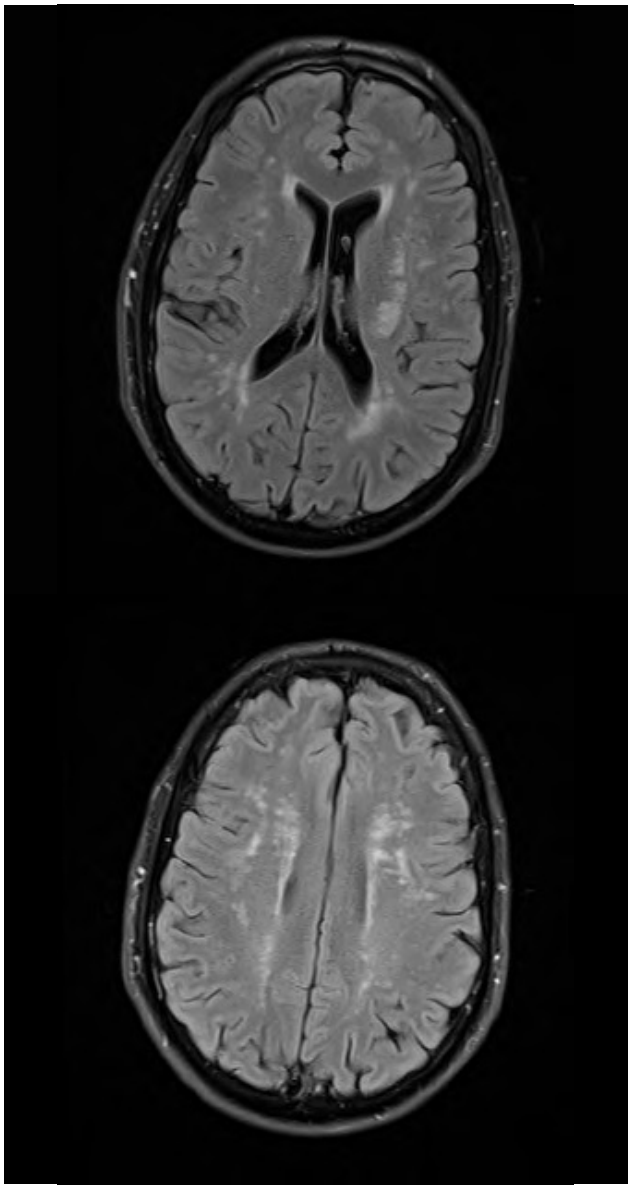


Figure 1. Extensive small vessel disease which is unexpected considering the patient's age.

rehabilitation with the multidisciplinary team. He was started on a high dose statin; atorvastatin 80 mg OD and loaded with dual antiplatelet therapy and then started on regular aspirin and clopidogrel for a duration of 6 weeks and then was switched to clopidogrel only following this. We performed magnetic resonance imaging (MRI) of the brain which showed an acute infarct in the left lentiform nucleus extending to the corona radiata. He also, surprisingly, was found to have extensive white matter changes suggesting small vessel disease which would be unexpected for his age group *(Fig. 1)*. His stroke workup included a transoesophageal echocardiogram and a Holter monitor. Blood tests included a vasculitis screen, connective tissue disease screen, alpha galactosidase and beta hexosaminidase checking for Fabry's disease and anti-phospholipid screen- beta-2 glycoprotein, anti-cardiolipin antibodies and lupus anticoagulant. We preformed syphilis serology, human immunodeficiency virus and viral hepatitis screening. Despite thorough investigation no obvious cause was found for his stroke. He also had a HbA1c and fasting lipid profile to investigate and manage his cardiovascular risk factors. Given his age and the disproportionate microvascular white matter changes seen on the MRI brain, we requested genetic testing which found that he had a genetic variant C.3025T>C; p.Cys1009Arg in gene *NOTCH3* in a heterozygous state which is found in patients with CADASIL. Overall, the patient had a good outcome. He underwent inpatient rehabilitation for 3 weeks and was discharged home under the care of the Stroke Early Supported Discharge community multidisciplinary team where he underwent rehabilitation for 11 further weeks.

DISCUSSION

CADASIL should be suspected in young adults, with a strong family history. CADASIL tends to occur the sequential development of who present migraines with aura around 30years of age, transient ischemic attack (TIA) and early recurrent strokes and mood disorder (40-60 years), dementia (50 and 60 years). Early onset of symptoms does not necessarily predict rapid progression.

The clinical progression in CADASIL varies even within affected families. The onset typically occurs in adulthood however there are case reports of children and adolescent and earliest onset of symptomatic CADASIL reported in a 3-year-old boy, and some patients can be asymptomatic until their 70s.

Genetic counselling and testing are recommended and should be offered to first degree relatives but due to psychological and ethical concerns it has no benefit in asymptomatic children. Extended family members in high-risk families could be considered.

CADASIL presents with abnormal T2 weighted imaging or fluid-attenuated inversion recovery (FLAIR) hyperintensity on MRI brain, a similar appearance to that which is seen in chronic microvascular disease. These lesions are usually symmetrical and are predominantly found in the periventricular regions and deep white matter, involving the anterior temporal poles, external capsule and paramedian superior frontal subcortical white matter. In CADASIL, the volume of the MRI lesion typically clinically correlates with the level of disability observed.

Other features of lacunar or subcortical infarcts can also be seen with CADASIL, these manifest as foci of restricted diffusion on diffusion-weighted imaging (DWI) / apparent diffusion coefficient (ADC) sequences. Micro-bleeds are also seen on the gradient-echo sequences which are less specific but more prevalent in patients with CADASIL[1]. In our patient, we suspected CADASIL given the age and MRI findings. We requested genetic testing which subsequently detected the variant C.3025T>C; p.Cys1009Arg in gene *NOTCH3* in a heterozygous state. In accordance with the pathomechanism of CADASIL, the missense variant leads to the replacement of a cysteine residue by arginine in one of the EGF-like repeat domains and is predicted to be deleterious by in silico tools. This variant has not been described yet in the scientific literature. The variant p.Cys1009Phe, affecting the same amino acid position has been associated with CADASIL in one patient in a Japanese cohort study; however, no segregation analysis was performed in this study[2]. In some cases, skin biopsy can be performed, which shows accumulation of granular eosinophilic material around smooth muscle in CADASIL. It is usually reserved as a second line diagnostic test for more difficult to diagnose cases, in patients where we have a high suspicion for the diagnosis of CADASIL but have negative genetic testing.

CADASIL was first described in a Swedish family in the late 19th century and was given its designated acronym in the early 1990s. It is caused by mutations in the *NOTCH3* gene, which map to the short arm of chromosome 19. In most cases, typical mutations are related to missense substitutions of a single base, leading to loss or gain of a cysteine residue within one of the EGFRs' external capsules and the temporal pole of the *NOTCH3* gene.

NOTCH3 is a large gene containing 33 exons and formerly most of the pathogenic mutations in CADASIL were thought to be located in exons 2-24, coding for 34 EGFr domains. With advancements in genetic studies, a wider spectrum of *NOTCH3* variant-associated disease has been reported in the past few years. In 2020, a mutation on exon 29 of the *NOTCH3* gene was reported in a Chinese family[3].

Two separate studies were conducted in Asia to identify the genotype-phenotype correlations of the different mutations. In Japan, case analysis proved that mutations in EGFr 1-6, excluding the cysteine-sparing mutation p.Arg75Pro, correlated significantly with a younger age at the onset of stroke/TIA compared to those in EGFr 7-34[2].

In Korea, a study showed a different EGFr distribution in Korean patients in comparison with European patients, and this was also associated with a later onset of stroke[4]. To this day there is no cure or disease modifying treatment for CADASIL. The management is the same as that of a stroke from small vessel disease, i.e., acute stroke management, admission to the acute stroke unit with rehabilitation

involving the multidisciplinary team. There is no role for reperfusion therapy in CADASIL.

Secondary prevention by optimisation of any modifiable risk factors; hypertension, good glycaemic control, lipid management with statins, antiplatelet therapy and lifestyle modifications including dietary changes, and smoking cessation can slow progression and improve quality of life. In addition to this, management involves treating symptoms relating to the disease (e.g. migraine and mood disturbance).

CONCLUSION

CADSIL, unfortunately, remains one of the most disabling small vessel diseases of the young. Case reports of new presentations and their specific genetic mutations will contribute to our understanding of the genetic map of the disease and the correlation between genotype and phenotype. This will help us to understand and recognise the manifestations of the disease, aiding us in our early recognition of this condition aiming for early diagnosis, screening tools and assisting us in the search for treatment options for the disease.

REFERENCES

1. Cramer J, White ML. Cerebral Autosomal Dominant Arteriopathy. [Updated 2021 Aug 11]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470293/
2. Mukai M, Mizuta I, Watanabe-Hosomi A, Koizumi T, Matsuura J, Hamano A, et al. Genotype-phenotype correlations and effect of mutation location in Japanese CADASIL patients. *J Hum Genet* 2020;**65**:637-646. doi: 10.1038/s10038-020-0751-9
3. Wang W, Ren Z, Shi Y, Zhang J. A Novel Mutation Outside of the EGFr Encoding Exons of NOTCH3 Gene in a Chinese with CADASIL. *J Stroke Cerebrovasc Dis* 2020;**29**:105410. doi: 10.1016/j.jstrokecerebrovasdis.2020.105410
4. Min JY, Park SJ, Kang EJ, Hwang SY, Han SH. Mutation spectrum and genotype-phenotype correlations in 157 Korean CADASIL patients: a multicenter study. *Neurogenetics* 2022;**23**:45-58. doi: 10.1007/s10048-021-00674-1