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Case Reports

Novel NOTCH3 mutation c.1564 T > A (p.Cys522Ser) presenting with early-onset Parkinsonism and white matter lesions

Nicola Rifino [a,1,*], Silvia Baratta [b,1], Esteban Zacarias [a], Isabella Canavero [a], Benedetta Storti [a], Mario Stanziano [c], Emanuela Maderna [d], Gianluca Marucci [d], Franco Taroni [b], Anna Bersano [a]

[a] Cerebrovascular Unit Fondazione IRCCS Istituto Neurologico Carlo Besta Milan Italy
[b] Unit of Medical Genetics and Neurogenetics Fondazione IRCCS Istituto Neurologico Carlo Besta Milan Italy
[c] Neuroradiology Unit Fondazione IRCCS Istituto Neurologico Carlo Besta Milan Italy
[d] Neuropathology Unit Fondazione IRCCS Istituto Neurologico Carlo Besta Milan Italy

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ABSTRACT

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a hereditary small vessel disease caused by mutations in the NOTCH3 gene, characterized by recurrent strokes, cognitive decline, and psychiatric symptoms. This report presents a novel NOTCH3 c.1564 T > A (p.Cys522Ser) mutation associated with early-onset parkinsonism and significant white matter lesions. We describe a patient who presented with early-onset parkinsonism, characterized by bradykinesia and rigidity, alongside extensive white matter lesions observed through neuroimaging. Genetic testing revealed a novel c.1564 T > A (p.Cys522Ser) mutation in the NOTCH3 gene, contributing to the clinical diagnosis of CADASIL. This case underscores the phenotypic variability of CADASIL and the potential for atypical presentations, including parkinsonism. Early identification of genetic mutations can facilitate appropriate management and counseling for affected individuals and their families. Further research is warranted to explore the mechanisms underlying the association between NOTCH3 mutations and parkinsonism. Our findings contribute to the understanding of CADASIL, suggesting that clinicians should consider CADASIL in differential diagnoses of early-onset parkinsonism, especially in patients with concurrent white matter lesions.

1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare hereditary small vessel disease characterized by migraine, recurrent strokes, and early-onset dementia. It is caused by a dominant mutation in the NOTCH3 gene (chr19p13.1), which encodes a transmembrane receptor predominantly expressed in vascular smooth muscle cells. This receptor plays a vital role in signal transduction and cell differentiation [1]. The gene's extracellular domain consists of 34 tandem repeats of epidermal growth factor-like domains (EGFR), with most disease-causing variants occurring in exons 2–23. These missense mutations typically alter the number of cysteine residues in the receptor [1]. Recent studies have attempted to establish genotype-phenotype correlations, suggesting that variants in EGFR domains 1-6, 8, 11, and 26 are associated with a more severe disease course, earlier stroke onset, larger volumes of white matter hyperintensities (WMHs), and shorter survival [2].

The clinical course of CADASIL is highly variable, and its overall prevalence remains uncertain. Symptoms can range from early-onset migraine to strokes, cognitive decline, and less commonly, parkinsonism [3]. Parkinsonian features, although reported, are usually considered late manifestations of the disease. Genetic testing, identifying pathogenic variants in NOTCH3, is crucial for diagnosis, especially in cases where clinical presentation is atypical. Electron microscopy of a skin biopsy can also detect granular osmiophilic material (GOM) deposits in vascular smooth muscle cells, aiding the diagnosis, particularly in patients with variants of unknown significance [4].

In this report, we describe the case of a patient with a novel heterozygous missense mutation (c.1564 T > A; p.Cys522Ser) in EGFR domain 13, who presented with early-onset parkinsonism, an unusual feature of CADASIL.

* Corresponding author at: Via Celoria 11, 20134 Milan, Italy.
E-mail address: nicola.rifino@istituto-besta.it (N. Rifino).
[1] Silvia Baratta and Nicola Rifino contributed equally to this work.

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2. Case description

The index patient, a male, had a history of hypertension but no other cerebrovascular risk factors. From the age of 55, he experienced progressive balance disturbances and frequent falls. He also reported a long history of severe bitemporal and periorbital headaches without aura, which had begun in adolescence and occurred 1–3 times per week, with spontaneous resolution. Notably, there were no previous episodes of stroke, transient ischemic attacks, cognitive impairment, or psychiatric symptoms.

The patient's family history was significant for cerebrovascular disease. His mother and her sister had experienced ischemic strokes around the age of 60, and his mother developed mild cognitive impairment before dying from a heart attack at 72. However, no detailed clinical information was available for either relative, as they had not sought medical care.

Brain MRI of the patient revealed confluent subcortical WMHs, prominently involving the anterior temporal lobes and external capsule (Fig. 1A-C). Based on this clinical and neuroradiological profile, genetic testing for NOTCH3 was performed, which identified a heterozygous missense mutation (c.1564 T > A) that resulted in a cysteine-to-serine substitution at residue 522 in the EGFR domain 13.

The mutation was confirmed by Sanger sequencing, and, notably, it had not been previously reported in the literature in association with CADASIL. Predictive tools such as PolyPhen-2 suggested the likely pathogenicity of the p.Cys522Ser substitution. To further support the diagnosis, a skin biopsy was performed, and electron microscopy revealed numerous GOM deposits between the plasmalemma and the basal lamina of vascular smooth muscle cells (Fig. 1G). The patient provided informed consent.

Genetic testing was also performed on the patient's 33-year-old eldest son, after genetic counseling and signing a proper informed consent, as he expressed a strong interest in undergoing genetic testing, particularly to better understand his risk and explore options for starting a family, revealing that he carries the same NOTCH3 mutation. His medical history included migraines, but he reported no other neurological symptoms. Neurological examination was normal, and brain MRI showed only a few hyperintense lesions in the left anterior capsule (Fig. 1D-F). He did not report any cognitive impairment, psychiatric disturbances, or extrapyramidal features.

Over the subsequent year, the index patient's balance problems worsened, and he developed dysphonia and dysphagia. Neurological examination revealed hypophonia, hypomimia, and vertical gaze limitation, more pronounced in downward gaze, accompanied by saccadic pursuit movements. The patient exhibited mild rigidity in the neck and limbs, more evident on the left side, along with global bradykinesia, predominantly on the left. A camptocormic posture was observed, and the pull-test was positive. Signs of cortical release were present, including a glabellar reflex and bilateral palmomental reflex. Muscle strength and deep tendon reflexes were normal, with no evidence of apraxia or resting tremor. No findings consistent with cerebellar or bulbar syndromes were observed. Despite undergoing speech therapy, these symptoms persisted, and his gait disturbance deteriorated.

Although his cognitive function remained intact as demonstrated by thorough neuropsychological evaluation and testing, which included a normal Montreal Cognitive Assesment (MoCA) score, 123I-FP-CIT SPECT imaging revealed bilateral dopaminergic deficits. However, the patient did not respond to levodopa, which suggested dysfunction in the non-dopaminergic thalamocortical pathway, rather than classical Parkinson's disease. Given the constellation of symptoms, a diagnosis of progressive supranuclear palsy (PSP) was considered. A repeat MRI two years later showed further progression of the vascular lesions.

3. Discussion

This case presents a novel NOTCH3 mutation (c.1564 T > A; p. Cys522Ser) on EGFR domain 13 in a family with CADASIL. The NOTCH3 mutation identified in our patient, p.Cys522Ser, has previously been reported as arising from a different nucleotide substitution (c.1565G > C) [5]. While both mutations alter the same amino acid residue, potentially affecting its function, clinical manifestations differ. The c.1565G > C mutation was associated with cognitive impairment and headache [5], whereas our patient presented with early-onset parkinsonism without cerebrovascular events. This comparison underscores the phenotypic variability even among mutations affecting the same residue.

Our index patient displayed early-onset parkinsonism, which is unusual for CADASIL, as cerebrovascular events like stroke usually

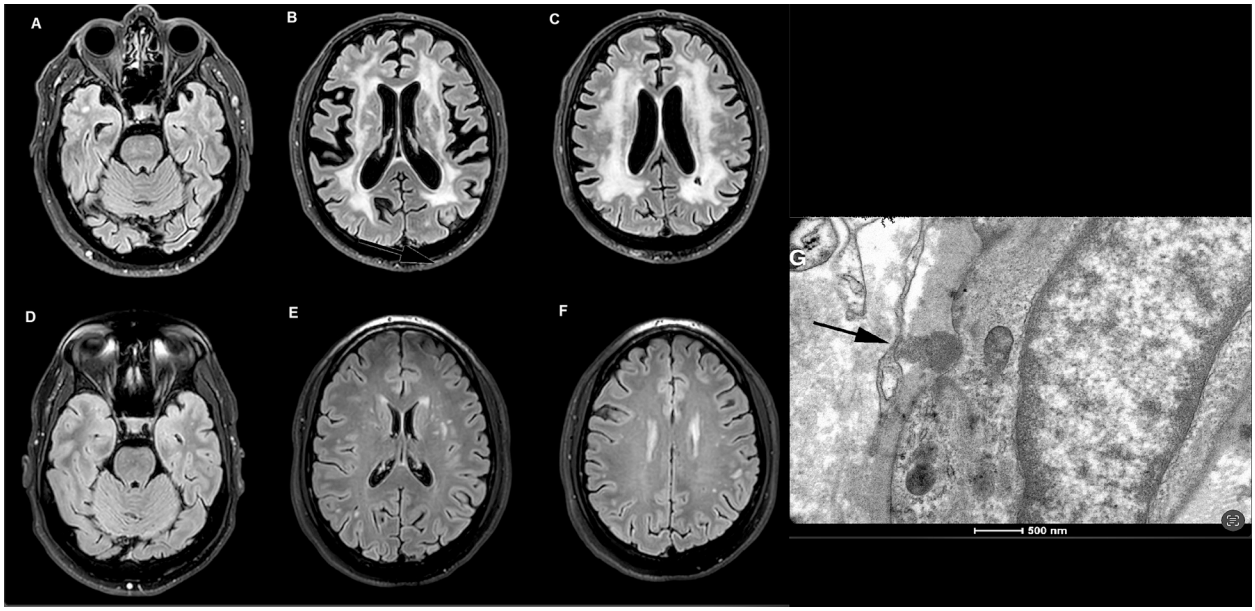

Fig. 1. Widespread confluent white matter hyperintensities are evident on T2-weighted images in the index patient (A-B-C); the brain MRI of his son revealed some hyperintense lesions of the white matter, most prominent in the left anterior capsule (D-E-F). Trasmission electron microscopy: GOM deposits (see arrow), variable in size and shape, infolded in smooth muscle cell plasmalemma (x53000) (G).

dominate the clinical presentation. The absence of strokes in this patient, combined with the progressive parkinsonian features, highlights the clinical variability of CADASIL and the complexity of its phenotypic spectrum.

Genetic analysis confirmed the novel NOTCH3 mutation, and PolyPhen-2 predicted it to be pathogenic. This finding was further supported by the identification of GOM deposits on skin biopsy and the same mutation in the patient's son. CADASIL is often described as a genetically heterogeneous disease with incomplete penetrance, which contributes to its wide spectrum of clinical manifestations [1].

Although parkinsonism is a rarely reported feature in CADASIL, and generally a late manifestation, this patient developed early-onset vascular parkinsonism, which worsened rapidly. A similar clinical presentation of CADASIL mimicking PSP was previously reported by Van Gerpen et al. [6], highlighting the potential for CADASIL to manifest as atypical parkinsonian syndromes and underscoring the diagnostic challenges posed by this condition.

In our case, the clinical picture, the lack of response to dopaminergic treatment and MRI findings fit the diagnosis of a vascular parkinsonism. The extensive leukoencephalopathy seen in this case may have damaged brain regions typically associated with parkinsonism, such as the substantia nigra, the putamen, the caudate, and the basal ganglia thalamocortical circuit. However, parkinsonism does not occur in all CADASIL patients, suggesting that additional, yet unidentified, predisposing factors may influence its development [7].

In conclusion, although further studies are needed to investigate whether parkinsonism is associated with some specific variants of the *NOTCH3* gene, as well as with p.Cys522Ser, our report contributes to broadening the clinical and genetic spectrum of CADASIL, supporting clinicians in considering CADASIL in the differential diagnosis of vascular parkinsonism.

4. Author declaration

I, Nicola Rifino, confirm that I have made substantial contributions to the conception, design, drafting, and revision of the article. I have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part are appropriately investigated and resolved.

Silvia Baratta contributed as the first author. Esteban Zacarias, Isabella Canavero, Benedetta Storti, Mario Stanziano, Emanuela Maderna, and Gianluca Marucci contributed to the critical review of the manuscript, as well as the collection of clinical, neuroradiological, and neuropathological data. Franco Taroni and Anna Bersano supervised the project and were instrumental in conceiving and overseeing the writing of the case report.

CRediT authorship contribution statement

Nicola Rifino: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Silvia Baratta:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Esteban Zacarias:** Writing – review & editing, Investigation. **Isabella Canavero:** Writing – review & editing, Investigation. **Benedetta Storti:** Writing – review & editing, Investigation. **Mario Stanziano:** Writing – review & editing, Investigation. **Emanuela Maderna:** Writing – review & editing, Investigation. **Gianluca Marucci:** Writing – review & editing, Investigation. **Franco Taroni:** Writing – review & editing, Supervision, Investigation. **Anna Bersano:** Writing – review & editing, Supervision, Investigation.

Declaration of competing interest

The authors declare that the article was written without any external funding or financial support. The authors have no financial relationships or competing interests to disclose that could influence the content or interpretation of the work.

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