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Case Report
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R544C *NOTCH3* Mutation in a *CADASIL* Patient with Parkinsonism: A Case Report

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Abstract

Background: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (*CADASIL*) is an autosomal dominant hereditary disease of cerebral small vessels. It is the most frequent heritable disease that causes stroke and vascular dementia. In China, a significant number of patients exhibit the c.1630C>T (p.Arg544Cys) mutation, displaying hallmark symptoms such as migraine with aura, Transient Ischemic Attacks (TIA), ischemic stroke, intracranial hemorrhage, cognitive impairment, and psychiatric disturbance. However, Parkinsonism as an early symptom is scarcely documented among *CADASIL* patients.

Case Report: We describe a 65-year-old male diagnosed with parkinsonism who was subsequently identified as having *CADASIL* with a c.1630C>T (p. Arg544Cys) mutation located in exon 11 of the *NOTCH3* gene. His primary symptoms included progressive gait instability and rigidity. Head MRI revealed white matter hyperintensities in the bilateral periventricular and semiovale regions. FDOPA-PET scans indicated normal bilateral striatal FDOPA uptake.

Conclusion: Parkinsonism might be a novel onset symptom in *CADASIL* patients with the c.1630C>T (p.Arg544Cys) mutation. Clinicians need to investigate thoroughly when encountering parkinsonism to possibly detect *CADASIL*.

Keywords: *CADASIL*; Parkinsonism; *NOTCH3* gene

Introduction

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a progressive hereditary cerebral small vessel disease caused by mutations in the *NOTCH3* gene. These mutations are distributed across the extracellular domain of the *NOTCH3* receptor, comprising 34 Epidermal Growth Factor-Like Repeats (EGFRs), leading to the gain or loss of a cysteine residue within one of these EGFRs. White Matter Hyperintensities (WMH) on head Magnetic Resonance Imaging (MRI) are typical, primarily affecting the frontal and parietal lobes, bilateral temporal pole, corpus callosum, and external capsule. *CADASIL* is characterized pathologically by the deposition of Granular Osmiophilic Material (GOM) on the surface of vascular smooth muscle cells. Clinical manifestations include cognitive impairment, dementia, migraine, recurrent strokes [1].

The c.1630C>T (p.Arg544Cys) mutation is frequently detected in Taiwan and Korea and is associated with unique traits such as a later onset of stroke, higher cognitive impairment or dementia rates, a lower incidence of headaches and migraines with aura, and frequent involvement of the Anterior Temporal Pole (ATL) in WMH [2-5].

However, existing reports and studies related to *CADASIL* with the R544C mutation rarely mention Parkinsonism as a phenotype. This case report presents a *CADASIL* patient carrying the c.1630C>T (p.R544Cys) mutation with a distinct onset of Parkinsonism.

Case Presentation

A 65-year-old man with progressively worsening gait issues was admitted to the hospital. One year before admission, the patient began experiencing slow movements, leg freezing while walking, and a shuffling gait. Notably, the patient had no tremors, headaches, vertigo, or memory issues. Treatment with Levodopa initiated at a local hospital did not improve gait instability, leading to referral to our hospital for further evaluation.

Upon admission, the patient displayed bradykinesia, postural instability, a stooped posture, and

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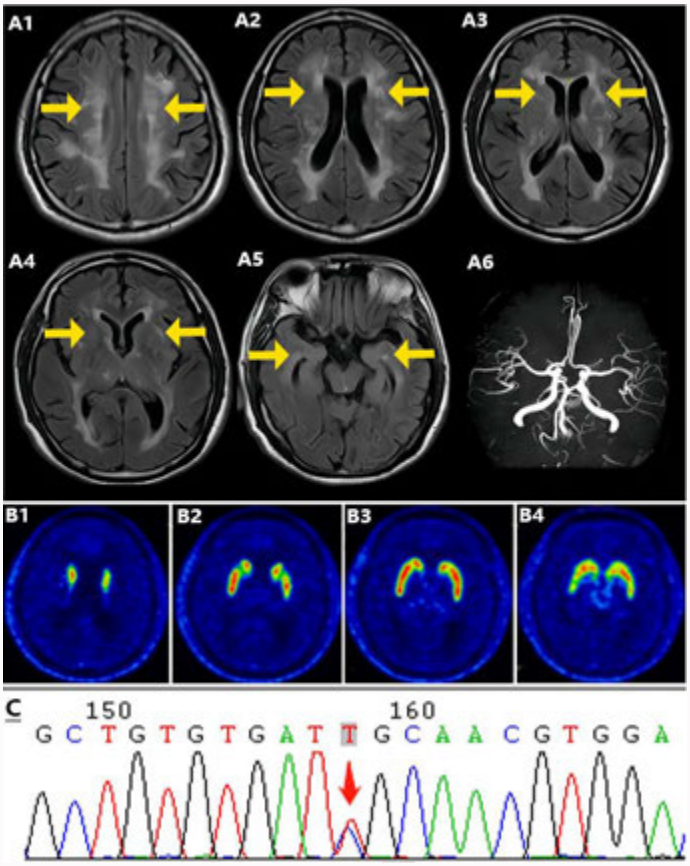

Figure 1: A1-A3) FLAIR and T2-weighted brain MRI, PET-MR, and Sanger sequencing. radiation crown and periventricular white matter hyperintensity. A4) white matter hyperintensity of the external capsule. A5) Bilateral temporal poles show normal signal. A6) No abnormalities in the intracranial vessels. B1-B4) PET-MR shows FDOPA uptake in the bilateral striatum was normal. C) Sanger sequencing confirmed the mutation.

an almost expressionless face. Cognitive impairment and Parkinson's disease were excluded through evaluations using cognitive impairment and Parkinson's disease scales (Table 1). The patient had a history of smoking for 30 years in the past, while hypertension, diabetes, hyperlipidemia, alcohol consumption, and stroke risk factors were denied. Unfortunately, access to the patient's family history was limited due to deceased parents and family members unwillingness to undergo necessary examinations.

While the patient did not exhibit constipation, urinary incontinence, or sexual dysfunction, sonography confirmed minor dysfunctional voiding with approximately 64 ml of residual urine in the bladder. The active standing test showed normal blood pressure responses within three minutes of standing up. Neuroimaging with head MRI displayed characteristic WMH in the bilateral periventricular and semiovale center (Figure 1A). 3,4-Dihydroxy-6-[18F]-Fluoro-L-Phenylalanine (FDOPA) Positron Emission Tomography (PET) demonstrated normal bilateral striatal FDOPA uptake (Figure 1B). Based on clinical presentation, neuroimaging, and auxiliary examination findings, *CADASIL* was suspected. Genetic testing subsequently revealed a missense mutation c.1630C>T (p.R544Cys) in exon 11 of the *Notch3* gene (Figure 1C).

Discussion

The patient, at 65, initially showed Parkinsonism without the typical *CADASIL* symptoms. FDOPA-PET ruled out Parkinson's disease, and head MRI indicated white matter hyperintensities. The

Table 1: Quantitative scoring scale.

Scale	Score	Scale	Score
Hoehn-Yahr stage	II	MMSE	26
UPDRS I	2	MOCA	27
UPDRS II	4	FAB	14
UPDRS III	21	CDT	4
UPDRS IV	3	AD8	1
PDSS	135	CDR	0
HAMD	14		
HAMA	4		

UPDRS: Unified Parkinson's Disease Rating Scale; PDSS: Parkinson's Disease Sleep Scale; MMSE: Mini-Mental Status Examination; HAMD: Hamilton Depression Scale; HAMA: Hamilton; Anxiety Scale; MOCA: Montreal Cognitive Assessment; FAB: Frontal Assessment Battery; CDT: Clock-Drawing Test; AD8: Alzheimer's Disease-8; CDR: Clinical Dementia Rating

confirmed *NOTCH3* mutation presented Parkinsonism as the initial symptom.

One point of interest concerns the clinical features of the patients appearing with Parkinsonism as the initial manifestation. The other interesting finding is that our case absence of some characteristic signs of *CADASIL*, precisely stroke, migraine and cognitive impairment. A previous literature of Italian *CADASIL* patients carrying the R1006C mutation indicated that Parkinsonism is not regarded as a representative symptom [6]. The phenotype mentioned in the miscellaneous periodical of *CADASIL* presenting with parkinsonism

Table 2: Clinical manifestation of previously reported CADASIL patients carrying the c.1630C>T (p.R544Cys).

References	Age, y	Gender%	Protein alteration	Parkinsonism	Generalized seizures	Stroke/TIA	Cognitive impairment	Headache
Yu-Wen Cheng (n=41/1734)	58.5 ± 10.0	M/63.4	p.Arg544Cys	N	N	Y	N	N
Jung-Kook Song (n=58)	59.4 ± 10.0	M/51.7	p.Arg544Cys	N	N	N	Y	N
Jay Chol Choi (n=53)	59.0 ± 12.0	M/54.7	p.Arg544Cys	N	N	41.50%	1.90%	45.30%
Jay Chol Choi (n=65/72)	62.7 ± 11.1	M/57.8	p.Arg544Cys	N	N	42.50%	N	N
Liuhua Pan	54	Female	p.Arg544Cys	N	Y	Y	N	N
Our case	65	Male	p.Arg544Cys	Y	N	N	N	N

F: Female; M; Male; TIA: Transient Ischemic Attacks; Y: Yes; N: No; NA: No Information Available

are distributed throughout the various mutation sites [7,8]. What calls for special attention concerns that there are few clinical case reports or the other researchers referred Parkinsonism as the primary clinical performances of *CADASIL* with R544C mutation [9-13]. We conclude previous studies in Table 2. Weihang Guo documented a p.R544C patient with left limb tremors, though neuroimaging indicated bilateral putamen hypometabolism, differing from our case [14]. These findings not only offered related opinions which characteristics of the R544C mutation, for example, the frequent older age of onset, cognitive dysfunction, stroke and less relevant migraine, but also mentioned the medical imageology presentation that fewer temporal pole lesions.

Previous studies showed that *CADASIL* gene mutation loci are associated with different clinical phenotypes [15-17]. Some studies indicated an association between specific *NOTCH3* mutations and clinical presentation, highlighting the magnitude that dissimilar mutational spectrum is responsible for the phenotype variations among the diverse crowd [2-4,18,19]. Moreover, even in the same family, the manifested clinically and severity of *CADASIL* may be different [20]. The evidence does imply that apart from heredity, the other factors, such as traditional vascular risk factors, environmental differences, treatment compliance and diversified individual daily lifestyle habits also play a key role in the clinical course of *CADASIL* [21].

Conclusion

The presence of Parkinsonism as a novel onset pattern in *CADASIL* patients with c.1630C>T (p.Arg544Cys) variants has been observed. Clinicians should conduct thorough investigations to determine the underlying etiology when presented with individuals exhibiting Parkinsonism, considering the possibility of *CADASIL* diagnosis.

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