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CADASIL Presenting with Parkinsonism, Intracerebral Hemorrhage, and Atypical White Matter Lesions: A Case Report

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Abstract: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a hereditary cerebrovascular disorder characterized by common clinical manifestations such as frequent migraine episodes, recurrent transient ischemic attacks or strokes, gradual cognitive decline, and emotional disturbances. The typical Magnetic Resonance Imaging (MRI) characteristics for CADASIL include symmetrical white matter hyperintensities (WMHs) in the anterior temporal poles, external capsules, frontal cortex, and surrounding the lateral ventricle, along with multiple lacunar infarcts and cerebral microbleedings (CMBs), and occasionally with intracerebral hemorrhage (ICH). The presence of WMHs in the anterior temporal poles demonstrates high sensitivity and specificity in diagnosing CADASIL. In this report, we present a case featuring clinical manifestations of progressive cognitive impairment, apathy, and parkinsonism, accompanied by ICH. However, the reported case lacked the typical WMHs in the anterior temporal poles, which is generally observed in CADASIL patients. Ultimately, a missense mutation c.1630C>T (p.R544C) in the Notch3 gene was identified through next-generation sequencing, confirming a CADASIL diagnosis. This case implies that the p.R544C mutation may pose a significant risk factor for ICH, and individuals carrying this mutation are more susceptible to developing parkinsonism. Therefore, CADASIL should be considered as a potential diagnosis for patients exhibiting clinical symptoms of recurrent strokes, progressive cognitive dysfunction, mood disturbances, and parkinsonism, even if their imaging findings display atypical white matter lesions (WMLs).

Keywords: CADASIL, Notch3, Intracerebral Hemorrhage, Parkinsonism, White Matter Lesions

1. Introduction

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a monogenic cerebral small vessel disease, caused by mutations in the Notch3 gene, which encodes a transmembrane receptor situated on the short arm of chromosome 19 [1, 2]. Recurrent ischemic stroke, concomitant migraine, cognitive impairments, as well as mental and emotional disorders are the primary clinical manifestations of CADASIL. Although parkinsonism is not traditionally regarded as a characteristic of CADASIL, recent studies have demonstrated its relatively common occurrence, particularly in the late stages of the disease [3]. Characteristically, CADASIL presents symmetrical white matter lesions (WMLs) or white matter hyperintensities (WMHs) in the anterior temporal poles, external capsules, and frontal cortex, as well as around the lateral ventricles, along with multiple lacunar infarcts and cerebral microbleedings (CMBs), and occasionally intracerebral hemorrhage (ICH) [4, 5]. The long T2-weighted signal of Magnetic Resonance Imaging (MRI) in the bilateral anterior temporal lobes, referred to as the "O'Sullivan sign", maintains high sensitivity and specificity for the diagnosis of CADASIL and is often utilized for differentiating CADASIL from other cerebral small vessel diseases. Although ischemic

stroke and attacks represent the most common clinical manifestations of CADASIL and WMHs in the anterior temporal poles are typical imaging findings, both clinical features and MRI manifestations may vary among patients harboring different Notch3 mutations. Consequently, a conclusive diagnosis of CADASIL requires to be confirmed through genetic sequencing or skin biopsy. Here, we report the case of a male patient presenting with parkinsonism and ICH, but without WMHs or WMLs in the anterior temporal poles, who ultimately was diagnosed as CADASIL with a Notch3 c.1630C>T (p.R544C) mutation, as identified via next-generation sequencing.

2. Case Description

2.1. Disease History

A 64-year-old male was admitted to the hospital due to progressive cognitive decline, apathy, and walking difficulties that had been occurring for two years and had worsened over the past 15 days. The patient had experienced right and left frontal lobe hematomas from falls that occurred two years and 15 days ago, respectively. Additionally, the patient had a history of hypertension and was regularly taking anti-hypertensive medications.

2.2. Physical Examination

Upon admission, the patient's blood pressure was 112/80 mmHg. He exhibited clear consciousness, apathy, cognitive decline, dysarthria, and flattened right nasolabial fold. The muscle strength in both upper limbs was scored as grade 5, and that in both lower limbs was scored as grade 4. Muscle tension was significantly elevated in all four limbs. Babinski signs were negative for both sides, and no other neurological abnormalities were observed.

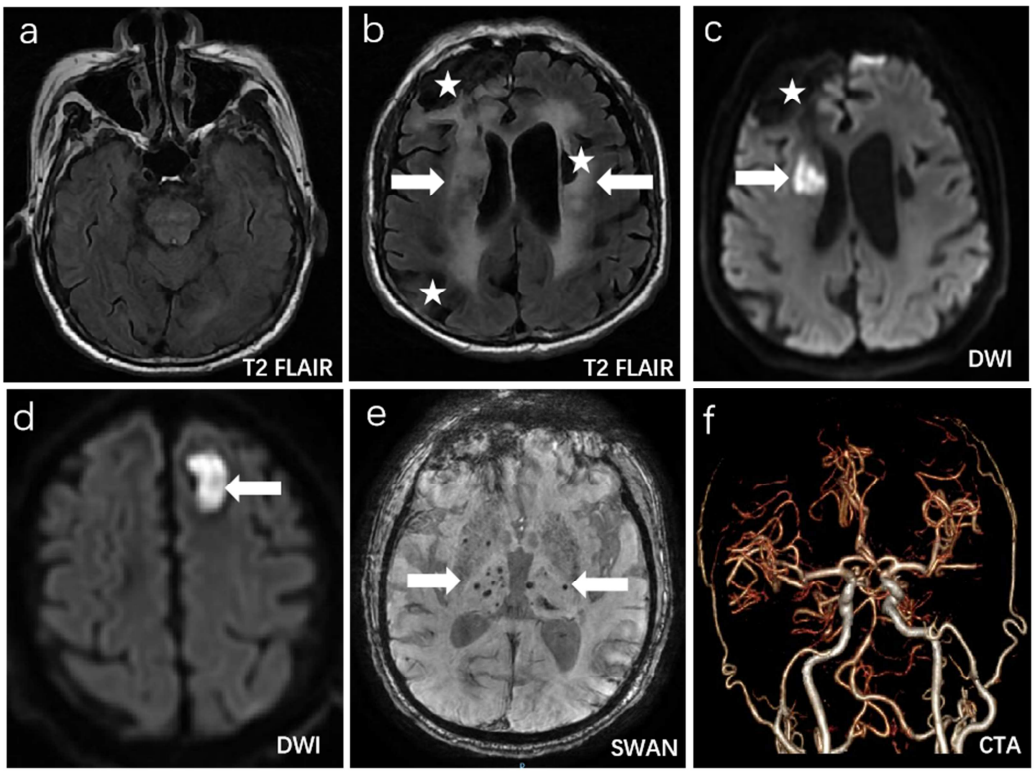

Figure 1. *Representative neuroimaging of the CADASIL patient.*

a. T2-weighted Fluid-Attenuated Inversion Recovery (T2 FLAIR) showed absence of white matter hyperintensities (WMHs) in the anterior temporal poles; b. T2 FLAIR showed WMHs surrounding the lateral ventricles (arrows), and multiple foci of encephalomalacia in the right frontal lobe and bilateral basal ganglia-coronal areas with surrounding gliosis (stars); c. Diffusion-weighted imaging (DWI) showed acute cerebral infarction in the right basal ganglia-radial corona (arrow), and encephalomalacia in the right frontal lobe (star); d. It showed subacute intracerebral hemorrhage (ICH) and surrounding edema in the left frontal lobe (star); e. Susceptibility-weighted angiography (SWAN) showed cerebral microbleedings (CMBs) in bilateral basal ganglia and thalamus (arrows); f. The computed tomography angiography (CTA) showed cerebral arteriosclerosis and mild stenosis in the proximal part of the basilar artery.

2.3. Additional Examinations

Blood cell count, blood sugar, blood lipid, biochemical, urine, and stool test results were all almost within normal ranges. Head MRI with diffusion-weighted imaging (DWI) and susceptibility-weighted angiography (SWAN) sequences showed WMLs around lateral ventricles and multiple areas of encephalomalacia in the right frontal lobe and bilateral basal ganglia-radial corona with surrounding gliosis (Figure 1a-b), acute ischemic cerebral infarction in the right basal ganglia-radial corona and mild cerebral atrophy (Figure 1c), subacute ICH and surrounding edema in the left frontal lobe (Figure 1d). Bilateral low signals were observed in the basal

ganglia and thalamus in the SWAN sequence, considered as CMBs (Figure 1e). A head CT scan and computed tomography angiography (CTA) revealed encephalomalacia in the right frontal lobe and bilateral lateral basal ganglia-radial crown area. The CTA indicated cerebral arteriosclerosis and mild stenosis in the basilar artery (Figure 1f). The patient's Mini-Mental State Examination (MMSE) score was 18, indicative of moderate cognitive decline.

2.4. Genetic Analysis

Given the presence of multiple intracranial foci of unexplained ICH, CMBs, WMLs, and ischemic infarction observed in the MRI, small vessel diseases were suspected. Consequently, genetic analysis for cerebral small vessel diseases was conducted, revealing a Notch3 c.1630C>T (p.R544C) mutation through next-generation sequencing (Figure 2d).

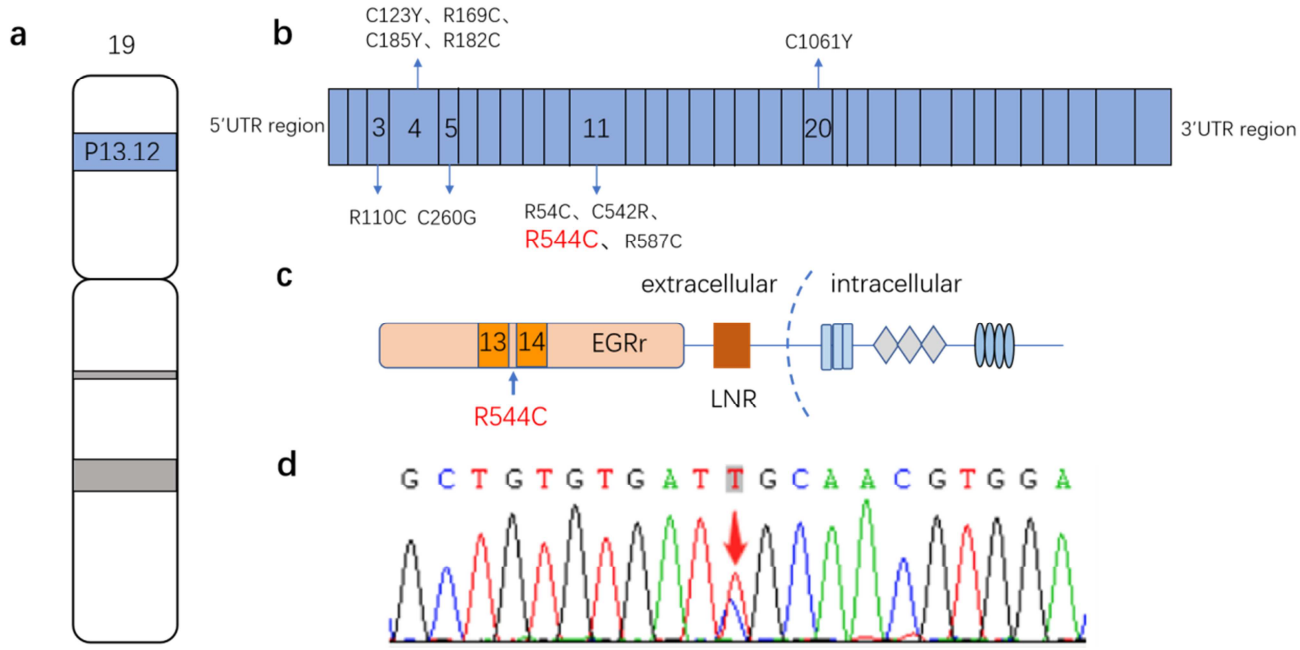

Figure 2. *Schematic of Notch3 mutations in CADASIL.*

a. Notch3 gene is located on chromosome 19 p13.12; b. Location distribution of popular Notch3 mutations in CADASIL; c. Schematic diagram of the p.R544C mutation located between the 13th and 14th EGFr domains of Notch3; d. Genetic analysis revealed the heterozygous c.1630C>T (p.R544C) mutation in the exon 11 of Notch3 gene.

2.5. Discharge Diagnosis

The patient was diagnosed with 1) CADASIL, 2) Basilar artery stenosis, 3) Cerebral hemorrhage in the bilateral frontal lobes, 4) Cognitive decline, and 5) Grade 3 hypertension (very high risk).

2.6. Treatment and Follow-Up

Following a two-week treatment consisting of amlodipine, statins, levodopa, and baclofen etc, the patient was discharged. In a telephone follow-up one month after discharge, the patient's family reported that he was able to walk independently, albeit with a wide-based gait and small steps.

3. Discussion

In this reported case, the patient developed ICH shortly after experiencing two falls, along with presenting symptoms of parkinsonism, both of which are uncommon in CADASIL. Furthermore, MRI revealed that WMHs were predominantly situated around the lateral ventricles, rather than within the anterior temporal lobes (Figure 1a). Despite the atypical clinical features and imaging results, a diagnosis of CADASIL was still considered due to the co-occurrence of ICH, ischemic infarcts, and CMBs in the brain. As anticipated, the genetic analysis identified a Notch3 c.1630C>T (p.R544C) mutation, confirming the CADASIL diagnosis.

Up to now, over 200 Notch3 mutations related to CADASIL development have been recognized, with the majority occurring in exons 2-23, and exons 4 and 11 being the most frequent. Most mutations are found within the 34 epidermal growth factor-like repeat (EGFr) domain of Notch3, with variants including missense, splice site mutations, and small in-frame deletions (Figure 2a-b) [4, 6-8]. The p.R544C mutation, as observed in this case, is located between the 13th and 14th EGFr domains of Notch3 (Figure 2c) and is primarily reported in Asian populations, particularly those from Southern China, Taiwan, and Korea [9]. Although anterior temporal lobe WMHs are characteristic manifestations in CADASIL patients, they are not universally present. Choi *et al*. discovered that while the p.R544C mutation accounted for 75% of CADASIL patients in a clinical study on the Jeju Island of Korea, only 20% showed WMHs involvement in

anterior temporal pole [10]. Additionally, Liao *et al*. found that among 112 Chinese CADASIL patients in Taiwan, 44.8% displayed moderate to severe WMHs in the anterior temporal pole, while only 28.4% of those with the p.R544C mutation showed such involvement [9]. These findings suggest that WMHs induced by the p.R544C mutation are less likely to accumulate in the anterior temporal poles, which could explain the atypical imaging results in this case.

In this reported case, the patient was susceptible to ICH, as two incidents occurred in the frontal lobes shortly after each fall. Hypertension and CMBs have been identified as primary risk factors for ICH development in CADASIL patients, and CMBs are present in almost all CADASIL patients who develop ICH [11-18]. Notably, Notch3 mutations have also been associated with ICH, with the p.R544C mutation being significantly linked to an increased ICH risk [14]. Chen *et al*. reported that up to 40% of patients carrying the p.R544C mutation developed ICH during follow-up in a multi-center study in the Taiwan region [19]. The ICH in our case was located in the frontal lobes, differing from the typical site of hypertensive brain hemorrhage, which is often observed in the basal ganglia. This suggests that ICH occurrence in this reported case might be related to the p.R544C mutation. Moreover, the patient exhibited clinical features of parkinsonism, which are not commonly observed in CADASIL. However, a recent study found that parkinsonism represents a new pattern of CADASIL onset in patients carrying the p.R544C mutation [20]. Thus, the unique clinical manifestations of increased susceptibility to ICH and parkinsonism in this case are likely attributable to the p.R544C mutation.

4. Conclusion

In conclusion, the Notch3 c.1630C>T (p.R544C) mutation may be highly associated with development of ICH and parkinsonism in CADASIL. The p.R544C mutation may potentially be a significant risk factor for ICH, and CADASIL patient with which is predisposed to the development of parkinsonism. The diagnosis of CADASIL should be considered when patients exhibit clinical manifestations, including recurrent stroke, progressive cognitive impairment, mood disturbances, and parkinsonism, even if imaging findings of WMLs display atypical characteristics.

Conflict of Interest

The authors no conflict of interest.

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References

[1] Baudrimont M., Dubas F., Joutel A., Tournier-Lasserve E., and Bousser M. G., Autosomal Dominant Leukoencephalopathy and Subcortical Ischemic Stroke. A Clinicopathological Study. Stroke, 1993. 24 (1): p. 122-5.

[2] Markus H. S., Diagnostic Challenges in CADASIL. Arquivos de Neuro-psiquiatria, 2023. 81 (5): p. 415-416.

[3] Ragno M., Berbellini A., Cacchiò G., Manca A., Marzio F. D., Pianese L., Rosa A. D., Silvestri S., Scarcella M., and Michele G. D., Parkinsonism Is a Late, Not Rare, Feature of CADASIL. Stroke, 2013. 44 (4): p. 1147-1149.

[4] Peters N., Opherk C., Bergmann T., Castro M., Herzog J., and Dichgans M., Spectrum of Mutations in Biopsy-Proven CADASIL: Implications for Diagnostic Strategies. Archives of Neurology, 2005. 62 (7): p. 1091-1094.

[5] Stojanov D., Vojinovic S., Aracki-Trenkic A., Tasic A., Benedeto-Stojanov D., Ljubisavljevic S., and Vujnovic S., Imaging Characteristics of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL). Bosnian Journal of Basic Medical Sciences, 2015. 15 (1): p. 1-8.

[6] Joutel A., Vahedi K., Corpechot C., Troesch A., Chabriat H., Vayssiere C., Cruaud C., Maciazek J., Weissenbach J., Bousser M. G., Bach J. F., and Tournier-Lasserve E., Strong Clustering and Stereotyped Nature of Notch3 Mutations in CADASIL Patients. Lancet, 1997. 350 (9090): p. 1511-5.

[7] Rutten J. W., Haan J., Terwindt G. M., van Duinen S. G., Boon E. M., and Lesnik Oberstein S. A., Interpretation of Notch3 Mutations in the Diagnosis of CADASIL. Expert Review of Molecular Diagnostics, 2014. 14 (5): p. 593-603.

[8] Wang W., Ren Z., Shi Y., and Zhang J., A Novel Mutation Outside of the Egfr Encoding Exons of Notch3 Gene in a Chinese with CADASIL. Journal of Stroke and Cerebrovascular Diseases, 2020. 29 (12): p. 105410.

[9] Liao Y.-C., Hsiao C.-T., Fuh J.-L., Chern C.-M., Lee W.-J., Guo Y.-C., Wang S.-J., Lee I. H., Liu Y.-T., Wang Y.-F., Chang F.-C., Chang M.-H., Soong B.-W., and Lee Y.-C., Characterization of CADASIL among the Han Chinese in Taiwan: Distinct Genotypic and Phenotypic Profiles. PloS One, 2015. 10 (8): p. e0136501.

[10] Choi J. C., Kang S. Y., Kang J. H., and Park J. K., Intracerebral Hemorrhages in CADASIL. Neurology, 2006. 67 (11): p. 2042-4.

[11] Greenberg S. M., Cerebral Microbleeds and Prediction of Intracranial Haemorrhage. The Lancet. Neurology, 2021. 20 (4): p. 252-254.

[12] Lai Q.-L., Zhang Y.-X., Wang J.-J., Mo Y.-J., Zhuang L.-Y., Cheng L., Weng S.-T., Qiao S., and Liu L., Occurrence of Intracranial Hemorrhage and Associated Risk Factors in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: A Systematic Review and Meta-Analysis. Journal of Clinical Neurology (Seoul, Korea), 2022. 18 (5): p. 499-506.

[13] Lee J. S., Ko K., Oh J.-H., Park J. H., Lee H. K., Floriolli D., Paganini-Hill A., and Fisher M., Cerebral Microbleeds, Hypertension, and Intracerebral Hemorrhage in Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. Frontiers In Neurology, 2017. 8: p. 203.

[14] Lee Y.-C., Liu C.-S., Chang M.-H., Lin K.-P., Fuh J.-L., Lu Y.-C., Liu Y.-F., and Soong B.-W., Population-Specific Spectrum of Notch3 Mutations, Mri Features and Founder Effect of CADASIL in Chinese. Journal of Neurology, 2009. 256 (2): p. 249-255.

[15] Liao Y.-C., Hu Y.-C., Chung C.-P., Wang Y.-F., Guo Y.-C., Tsai Y.-S., and Lee Y.-C., Intracerebral Hemorrhage in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: Prevalence, Clinical and Neuroimaging Features and Risk Factors. Stroke, 2021. 52 (3): p. 985-993.

[16] Nannucci S., Rinnoci V., Pracucci G., MacKinnon A. D., Pescini F., Adib-Samii P., Bianchi S., Dotti M. T., Federico A., Inzitari D., Markus H. S., and Pantoni L., Location, Number and Factors Associated with Cerebral Microbleeds in an Italian-British Cohort of CADASIL Patients. PloS One, 2018. 13 (1): p. e0190878.

[17] Palazzo P., Le Guyader G., and Neau J. P., Intracerebral Hemorrhage in CADASIL. Revue Neurologique, 2021. 177 (4): p. 422-430.

[18] Zhang C., Li W., Li S., Niu S., Wang X., Tang H., Yu X., Chen B., Shi Y., Chen Q., Guo L., Pan Y., Wang Y., and Zhang Z., CADASIL: Two New Cases with Intracerebral Hemorrhage. Annals of Clinical and Translational Neurology, 2017. 4 (4): p. 266-271.

[19] Chen C.-H., Tang S.-C., Cheng Y.-W., Tsai H.-H., Chi N.-F., Sung P.-S., Yeh H.-L., Lien L.-M., Lin H.-J., Lee M.-J., Hu C.-J., Chiou H.-Y., and Jeng J.-S., Detrimental Effects of Intracerebral Haemorrhage on Patients with CADASIL Harbouring Notch3 R544C Mutation. Journal of Neurology, Neurosurgery, and Psychiatry, 2019. 90 (7): p. 841-843.

[20] Wang X., Ke M., Fan P., Ding Y., and Zhang Y., Parkinsonism Is a New Pattern Onset of CADASIL Patients Carrying with R544C Mutation: A Case Report. Research Square, 2023: p. PPR634008.