Case Report

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CADISIL Camouflaging Itself Like Tumefactive Multiple Sclerosis or Brain Tumour on Imaging Studies: Current Evidence and Review of Literature

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ABSTRACT

Purpose: To describe a rare and unusual case of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL in a middle-aged patient camouflaging itself as tumefactive multiple sclerosis.

Case Description: We report a case of a 49-year-old man who presented with migraine like headaches, stroke-like symptoms, memory loss, gait disturbances and blurred vision. Brain imaging revealed findings suggestive of CADASIL. The white matter lesions were so extensive that they closely disguised as tumfactive multiple sclerosis or brain lesions. His gene testing for NOTCH3 was positive, thus confirming the diagnosis. He was given symptomatic therapy and recommended regular follow up to detect any new lesions.

Conclusion: This clinical case highlights the manifestation of very rare neurological disorders with migraine like headaches, stroke, mood disorders, cognitive impairment, dementia and disability. The main pathology is occlusion of small and medium vessels of brain due to accumulation of abnormal osmiophilic material in the intimal media. CADISIL has a very hallmark radiological finding in the MRI (Magnetic Resonance Imaging). With no specific treatments available, most patients are managed with symptomatic therapy. They also require regular follow up with MRI scans to detect new lesions in their brain so that treatment can be tailored accordingly.

Keywords: CADISIL; Multiple Sclerosis; Small Vessel Occlusion; Stroke; Lacunar Infarcts; Migraine; Cognitive Decline

Abbreviations: ED: Emergency Department; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; EGF: Epidermal Growth Factor; GOM: Granular Osmiophilic Material; BBB: Blood Brain Barrier

Introduction

The term CADISIL was proposed by the French researchers to designate the pathophysiology in the year 1993 [1]. CADASIL is one of the rare autosomal dominant disorders of the nervous system presenting with wide variety of focal neurological deficits due to compromised arterial supply of the white matter. The prevalence of this neurological disorder is around 4 cases per 100,000 population [2,3]. The average age of presentation of CADISIL is approximately 45-50 years [4]. Given the progressive disease process and multiple symptomatology, most of the patients with CADISIL have reduced life expectancy with average of death at around 65-70 years [4].

Case Presentation

We report a case of a 49-year-old man who presented to the emergency department (ED) with headache for 3 days duration and no imaging was performed in ED. He later referred to the neurology clinic and upon further evaluation, he revealed having episodes of numbness, fatigue, vertigo, confusion, weakness, dizziness, memory loss, imbalance, blurring vision and difficulty in walk for the past 10-15 years. He was previously told by a neurologist that his brain MRI results were abnormal, but he did not follow up. We ordered an MRI (Magnetic Resonance Imaging) which widespread and significant white matter lesions (Figures 1, 2A & 2B) suggestive of Cerebral Auto-

somal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). The white matter lesions were so extensive that they closely disguised as tumfactive multiple sclerosis or brain lesions. It is diagnosed by genetic testing for NOTCH3 gene, which was positive in this patient. Currently, there are no specific treatments are available for this disorder and he was managed with symptomatic management for his migraine headache, memory loss, and muscle weakness reducing mortality and morbidity.

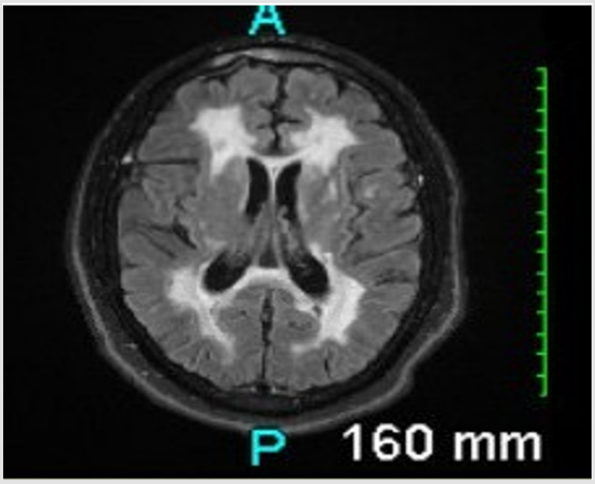

Figure 1: MRI brain with and without contrast: Extensive confluent white matter changes diffusely in both cerebral hemispheres including the temporal, frontal, and parietal lobes as described. There are no areas of abnormal enhancement following contrast administration. There are scattered foci of microhemorrhage in the thalami, frontal, and temporal lobes. White matter changes are more extensive than typically seen in a patient this age or associated with atherosclerotic vascular disease, hypertension, diabetes, etc. Appearance is not typical for MS.

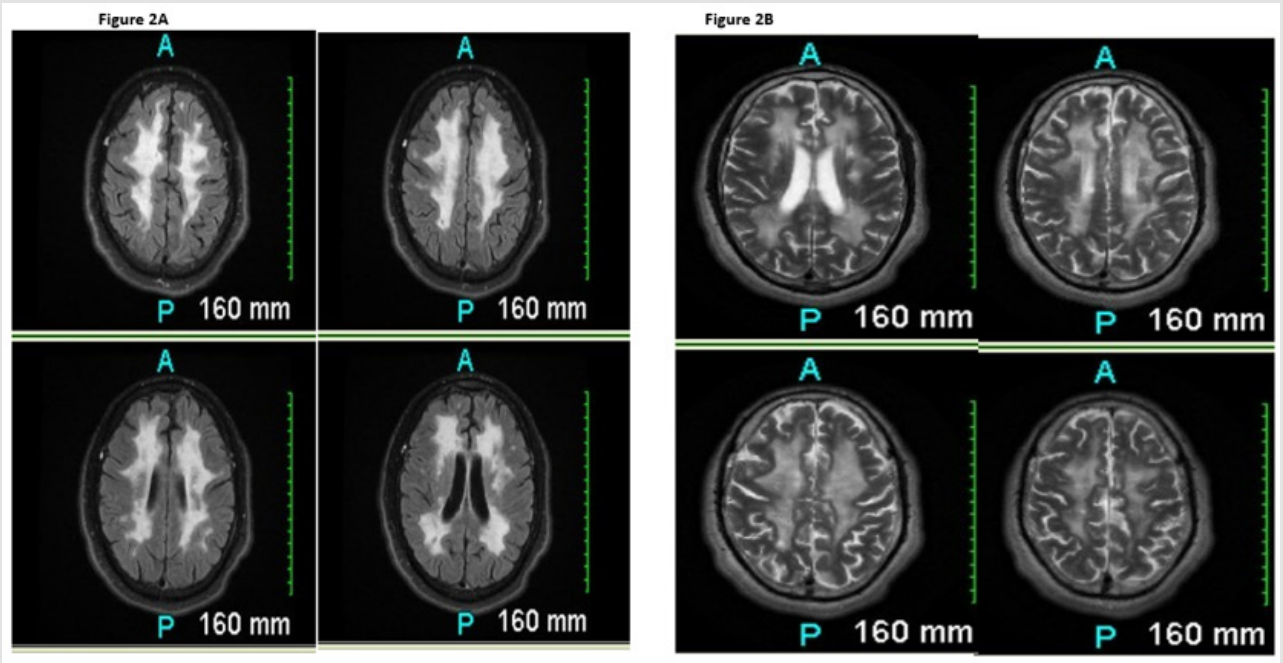

Figure 2: MRI brain with and without contrast: Acute small lacunar type infarct involving the subcortical left parietal white matter above. detailed abovExtensive multifocal confluent areas of abvenormal signal involving the supratentorial white matter as detailed above otherwise minimally changed from previous exam. Hypercoagulable states including CADASIL May BE considered given this distribution.

Discussion

Reports suggest that CADISIL is very frequently misdiagnosed as MS in spite of few case reports revealing their frequent co-existence [5,6]. In this regard, CADISIL is known to induce ischemic lesions that tend to closely mimic Balo concentric sclerosis lesions [5]. Alternatively, Balo concentric sclerosis and CADISIL can included in the same disease spectrum caused by NOTCH3 mutations. In our case, patient's father is falsely diagnosed as Multiple Sclerosis instead of CADISIL. Widespread white matter lesions along with positive NOTCH3 gene and family history raised the suspicion of CADISIL in our patient. Furthermore, the MRI brain lesions in our patient were very extensive and they disguised as tumfactive multiple sclerosis which are cerebral demyelination foci > 2 cm scattered all over the brain tissues [7]. The underlying abnormality is mutation of the NOTCH3 which is mainly involved with development of the media of arteries [8,9]. Missence mutations were found in the cysteine residues in the 2-24 exons of the NOTCH3 gene that encode epidermal growth factor (EGF) present in the extrcellular domain [10]. Physiologically, there are 6 cysteine residues and three di-sulphide bonds in the normal NOTCH3 gene [11]. Missence mutations alters the cysteine residues and di-sulphide bonds, thus bringing to light structural abnormalities in the gene [11].

Given this gene mutation, there is impaired synthesis of intimal media of the microvasculature [8]. As a result, small and medium sized arteries get thickened due to accumulating NOTCH3 ectodomain along with presence of intimal hyperplasia and hyalinization of the vessels. Sometimes, patients will have all the clinical symptoms and signs of CADISIL with negative NOTCH3 mutation [12]. Out of the all the cysteine altering NOTCH3 gene variants, variants in EGFR 1-6 were associated with earlier stroke onset as compared to EGFR 7-34 [13]. Important tell-tale sign on histopathology is the stockpiling of granular osmiophilic material (GOM) within the smooth muscles of the microvasculature [4]. On the account is this, smooth muscle in the tunica media, undergoes degeneration, wall thickening and a loss of vascular integrity. This incites progressive damage of small and medium-sized arteries in the brain, thence leading to reduced blood flow to the deep brain structures. These aforementioned pathological changes form the underlying basis for hypoperfusion, white matter changes, lacunar infarcts and hemorrhages seen in CADISIL. Furthermore, there is heaping up of GOM in the perivascular routes, pericytes, astrocytes and endothelial cells, thence provoking blood brain barrier (BBB) disruption [4,14,15]. This BBB dysfunction leads to migration of neurotoxic factors and potentiates neuronal mutilation and ischemia seen in CADISIL [15].

Furthermore, collagenosis of veins in the white matter might also contribute to the pathogenesis of CADISIL, thus emphasizing the importance of venous circulation in maintain the white matter integrity [16]. There is frequent association of autoimmunity and infections with CADISIL, raising the possibility of infection mediated autoimmune component in the pathogenesis of white matter lesions [17-21]. Most common clinical features of CADISIL include migraine like headache, recurrent ischemic episodes (Trasient ischemic attack and stroke), gait disturbances, urinary incontinence, pseudobulbar palsy, psychiatric disorders (Bipolar disorder, Depression, schizophrenia and panic disorder) and cognitive decline (Dementia, disturbances in language, memory, verbal and reasoning abilities) [4,22-24]. Studies suggest that, executive function is compromised with lapses in memory and concentration in 90% of the patients [24]. Language (verbal fluency and naming ability) and memory (learning, immediate recall and free recall) abnormalities were frequently noted in CADISIL patients [25]. It has been speculated that the probable causes for cognitive dysfunction in CADISIL patient might be messed up cortico-subcortical connections, lacunar infarcts and ventriculomegaly [24,26,27]. Accordingly, stroke and lacunar infarcts in MRI might be regarded as independent predictors for onset of vascular cognitive impairment in CADISIL [28]. A previous case report revealed the presence of chorioretinopathy in a CADISIL patient secondary to abnormal GOM deposits in the vascular smooth muscles of the choroidal retinal capillaries [29].

Rarely, CADASIL can present with progressive bulbar palsy secondary to bilateral subcortical infarctions [30]. Rarely, CADISIL can present as acute encephalopathy following surgery due to cerebral hypoperfusion secondary to combination of risk factors including dehydration, blood loss, anemia and cerebral vasoconstriction [31]. In a pooled analysis of 105 cases to analyze the natural clinical course of CADISIL, it was revealed that the disease becomes evident in the early middle age with migraine attacks or ischemic stroke and gradually progresses to present itself as recurrent subcortical stroke and dementia, ultimately leading to progressive decline and reduced life span [32]. Patients presenting with these clinical syndromes should raise the suspicion of CADISIL and imaging studies with MRI is the next step as there are typical radiological features associated with this clinical disorder. Early radiological signs identified in CADISIL include white matter hyperintensities on T2 weighted images widely scattered around the brain. These hyperintensities were more likely to be symmetrical and localized to periventricular regions and centrum seminovale [8]. Most important characteristic of CADISIL is the involvement of anterior poles of temporal lobes [8].

In later stages of disease process, subcortical, lacunar infarcts, dilated perivascular spaces, microhemorrhages and brain atrophy. The most important confirmatory test for diagnosis include by genetic testing for Notch-3 which is present in almost most of the cases due to missense mutations [33] Typical electron-microscopic findings consist of non-amyloid granular osmiophilic materials (GOMs) within the media of the skin arteries [4]. Skin biopsy to identify the vascular lesions which demonstrate the accumulation of GOM in the intimal media of small vessels is only used to confirm the diagnosis when there is an inconclusive finding on genetic testing [8]. Immunostaining is based on the use of NOTCH3 protein-targeted monoclonal antibodies to detect the accumulation of NOTCH3 protein in the vessel wall is

also occasionally used [4]. There are no specific therapies currently available for CADISIL. Patients with CADISIL are currently managed with symptomatic treatment of common clinical manifestations including stroke, hypertension, seizures, migraine, hypercholestraemia, cognitive dysfunction and psychiatric manifestations [22, 34-40]. Although experimental, some clinical research studies demonstrated modest clinical benefit with NOTCH3 exon skipping strategy, immunotherapy targeting NOTCH2 protein and stem-cell factors/ granulocyte colony-stimulating factor [4].

Conclusion

CADISIL is a very rare and complex neurological disorder that presents with assortment of symptoms ranging from migraine, cognitive dysfunction, stroke, psychiatric manifestations. Thorough clinical history including family history and high degree of clinical suspicion is deemed necessary for prompt diagnosis. It can be regarding as one of clinical conundrum as it can closely impersonate tumefactive multiple sclerosis or brain tumors. It is not uncommon for both these disorders to coexist due to their common gene mutations. Infection and autoimmunity are postulated to the trigger factors for onset of pathogenesis in CADISIL. MRI imaging with hallmark signs along with genetic testing is required for confirmation of diagnosis. In case genetic testing results were inconclusive, then skin biopsy and histopathological diagnosis of GOM in the intimal media of small and medium arteries is required for diagnosis. Once diagnosed efforts should be directed towards symptomatic management as there are no specific therapies available to mitigate this disorder. Clinical research studies are looking into the gene and immunotherapies for alleviating this disorder, although none of them have shown fruitful efficacy. We recommend future research studies looking into the predisposing and pathogenesis of CADISIL so that potent therapies can be crafted in the foreseeable future.

Declarations

- **Ethical Approval and Consent to participate:** Not Applicable
- **Consent for publication:** Consent taken
- **Availability of data and materials:** Not Applicable
- **Competing interests:** Not Applicable
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Authors' Contributions

Conceptualization, S.H.K; Methodology, S.H.K; Software, N.G.; Validation, N.A; Formal Analysis, N.A.; Investigation, S.H.K; Resources, N.A.; Data Curation, N.A.; Writing– Original Draft Preparation, S.H.K; Writing– Review & Editing, S.H.K.; Visualization, S.H.K.; Supervision, K.M; Project Administration, K.M.

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