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Case Report

Novel Neuroimaging "Encephalitic-Like Brain MRI Phenotype" in a Patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Rodica Elena Petrea[1]*, Dharan Mudugal[2], Angel Mironov[3] and Sanjay P Singh[4]

[1]Research Scientist at Boston University School of Medicine and Framingham Heart Study, Boston and Assistant Professor of Neurology, Department of Neurology at Creighton University School of Medicine and Catholic Health Initiative, Omaha, NE, USA

[2]Assistant Professor of Neurology, Department of Neurology, Creighton University School of Medicine and Catholic Health Initiative, Omaha, NE, USA

[3]Professor of Neuroradiology, Department of Neurology and Neuroradiology at Creighton University School of Medicine and Catholic Health Initiative, Omaha, NE, USA

[4]Professor of Neurology, Department of Neurology, Creighton University School of Medicine and Catholic Health Initiative, Omaha, NE, USA

***Corresponding Author:** Rodica Elena Petrea, Boston University School of Medicine, Framingham Heart Study, Boston and Creighton University School of Medicine, Catholic Health Initiative, Omaha, NE, USA.

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most prevalent (2-5/100.000) and known monogenic cerebral small vessel disease. CADASIL incidence is less well known due to the infrequency and diagnostic challenge of the disease. CADASIL is the result of mutations in NOTCH 3 on the chromosome 19. The pathology of CADASIL is typical of a small cerebral arteries arteriopathy and the result of granular osmiophilic material deposition in close relation to the vascular smooth muscle cells and sometimes in capillaries. CADASIL brain magnetic resonance imaging (MRI) phenotypes are several with some pathognomonic features, such as extensive white matter hyperintensities in the anterior poles of the temporal lobes and external capsule along with T1 hypointensities in subcortical white matter suggestive of lacunar strokes.

We report a case of newly diagnosed CADASIL and chronic scleroderma disease. The CADASIL genotype is a positive notch3 c.3062A>G; p. Tyr1021Cys heterozygous missense mutation. The novelty of this case is a different neuroimaging pattern of CADASIL, an "encephalitic-like brain MRI phenotype", not previously reported and characterized by the presence of bilateral confluent medial temporal lobe hyperintensities, predominantly on FLAIR and T2 weighted brain MRI images. This new pattern is seen in addition to the extensive white matter disease in the anterior poles of the temporal lobes, periventricular, subcortical and external capsule. The clinical phenotype of this CADASIL case manifests primarily with complicated migraines, with and without visual aura, sensory symptoms, and occasional mild, transient, memory difficulties and family history of dementia.

Keywords: CADASIL; Migraine Headaches; Visual Aura; Brain MRI; Temporal Lobe Hyperintensities; Encephalitis; Dementia; Notch 3

Abbreviations

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MRI: Magnetic Resonance Imaging; HI: Hyperintensities; MMSE: Mini Mental Status Examination; Ig G: Immunoglobulin G; CSVD: Cerebral Small Vessel Disease; SPECT: Single Photon Emission Computed Tomography; DTI: Diffusion Tensor Imaging; FA: Fractional Anisotropy; MD: Mean Diffusivity; CSF: Cerebrospinal Fluid; CGRP: Calcitonin gene-related peptide.

Introduction

CADASIL brain MRI phenotypes [2,3,5-8,11] are defined by characteristic HI in T2 and FLAIR weighted images, pathognomonic in the anterior segments of the temporal lobes (high sensitivity and specificity) and in external capsule (high sensitivity but low specificity). The frequency of the HI signals in the brain is highest in the white matter disease, mostly periventricular and subcortical, followed by superficial white matter, basal ganglia and brainstem; pons lesions more frequent than midbrain and medulla. Anterior temporal lobes are less often affected in Asian patients comparing to European patients. The concomitant hyposignals in T1 weighted images in subcortical white matter and brainstem, suggestive of lacunar strokes, are also quite pathognomonic. Cortical thinning is another characteristic of patients with CADASIL in multiple brain areas. More recent case reports added the possible finding of cerebral microbleeds to the radiological pattern of CADASIL.

Literature search to date did not report FLAIR or T2 HI in medial temporal lobes on brain MRI in patients with CADASIL.

Case Report

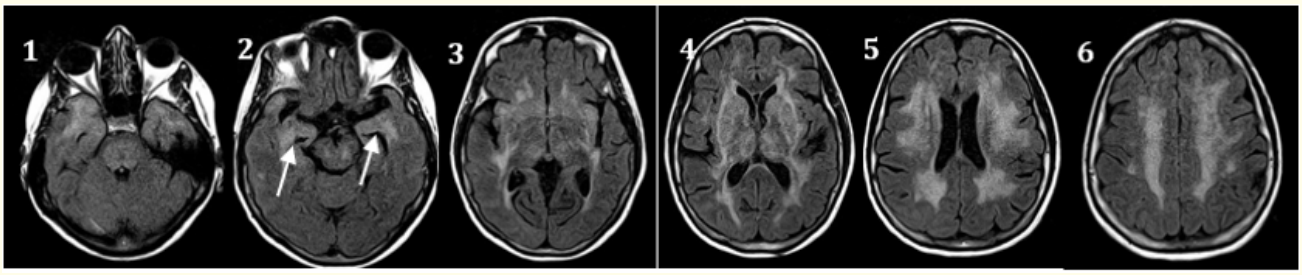
A 58-year-old African-American female with past medical history significant for chronic scleroderma arrived one day at our emergency department of Creighton University Hospital with an intractable headache. The headache was a migraine with visual aura and left-sided sensory symptoms. This was ongoing for approximately 1 week with minimal relief from usual analgesics. Since early adulthood, she had been experiencing either complicated or non-complicated migraine headaches for various periods – sometimes weeks, other times months at a time. She had two prior brain MRI's but had no neurological care. She was on no chronic migraine preventive medications. She had never been diagnosed with a stroke or transient ischemic attack and was not taking antiplatelets or anticoagulants. She was not on chronic immunotherapy for scleroderma either.

Patient had no personal history of dementia but mild, rare confusion or memory problems. There was no particular history of cardiac disease, encephalitis, meningitis or other central nervous system infections. Patient was HIV and RPR negative and had no exposure to Lyme disease.

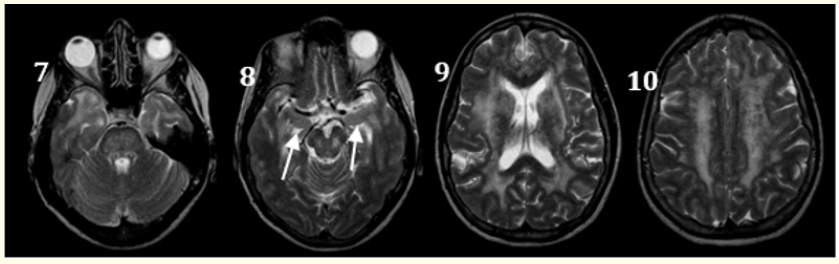
Family History was pertinent for dementia in one parent and HIV-related dementia in one brother, both deceased.

On physical examination our patient was underweight, pleasant, cooperative and with normal alertness. MMSE ~ 26 at the time of hospitalization. She had normal language, chronic mild dysphonia and mild intermittent dysphagia. There were no focal deficits but intermittent Babinski sign bilaterally, frontal release signs, findings of mild peripheral neuropathy and claw hand deformities in both hands, likely sequela from scleroderma for some years. Gait was normal. She showed difficulties only with tandem gait. Romberg sign was absent.

Brain MRI disclosed impressive, extensive, confluent T2/FLAIR white matter disease, including the bilateral medial and anterior temporal lobes HI.



Figures 1-6: Axial FLAIR weighted brain MRI at age 58 (during hospitalization).

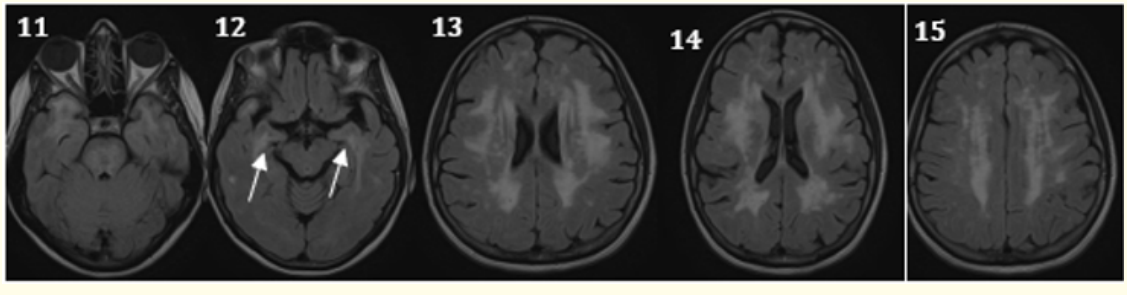


Figures 7-10: Axial T2 weighted brain MRI at age 58.

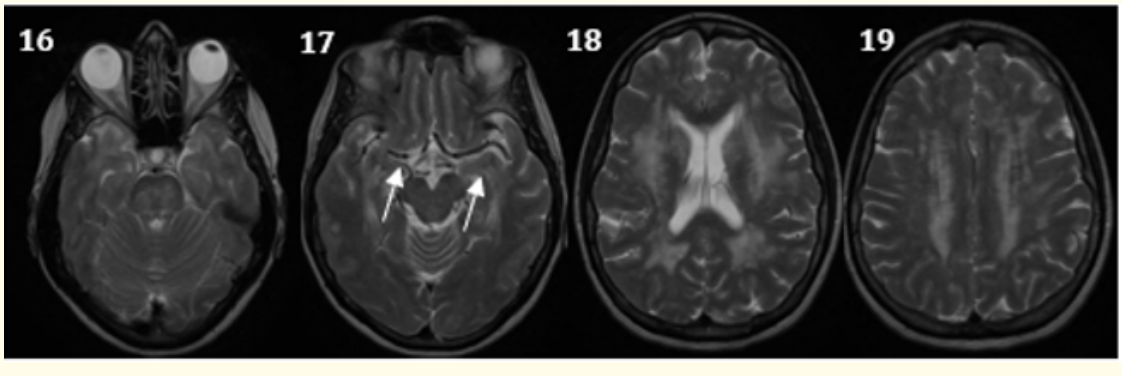
A comparison of the above brain MRI (performed during this reported patient's hospitalization at age 58) was done with prior patient's brain MRIs performed at age 53 and age 54. The assessment revealed both, progression of the white matter disease over years and the unusual extensive and confluent pattern of HI in the medial temporal lobes suggestive of "encephalitic-like brain MRI phenotype", predominantly on FLAIR and less prominent inT2 weighted brain MRI. MRA head and neck was performed and was normal.

Abnormal brain MRI at age 53 showed extensive white matter disease including HI in the anterior temporal lobe, some in the medial temporal lobe predominantly in FLAIR weighted brain MRI (Figure 1-5) and less prominent in T2 weighted brain MRI (Figure 6-9).

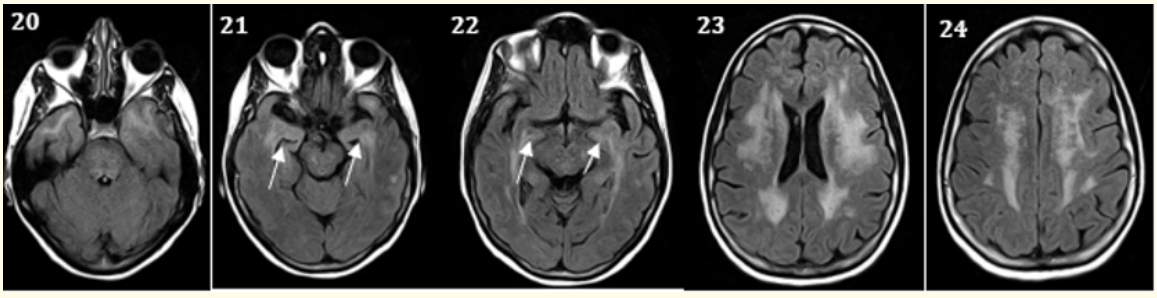
Abnormal brain MRI at age 54, showed somewhat more extensive white matter disease, including anterior and medial temporal lobe HI, predominantly in FLAIR weighted brain MRI images.



Figures 11-15: Axial FLAIR weighted brain MRI at age 53.



Figures 16-19: Axial T2 brain weighted MRI at age 53.



Figures 20-24: Axial FLAIR brain MRI at age 54.

Genetic testing confirmed our suspicion of CADASIL diagnosis. This was positive for notch 3 c.3062A>G; p. Tyr1021Cys heterozygous missense mutation, pathogenic and autosomal dominant. A panel for vanishing demyelinating disorders was negative. Lumbar puncture was negative for multiple sclerosis, acute meningitis, encephalitis or active vasculitis but mild nonspecific hyperactive IgG in cerebrospinal fluid (CSF).

Patient was started empirically on baby aspirin and migraine prophylaxis treatment while vascular risk factors were addressed. MMSE was 28 at 2 month follow-up.

Discussion

CADASIL is the most known monogenic CSVD as a result of mutations in NOTCH 3 on the chromosome 19 [1-6].

The typical clinical syndrome [1,3-6] of CADASIL is defined differently at each age. CADASIL can affect patients in their 30's by the presence of migraine with aura. In mid to late adulthood, between 40 and60 years of age, the most frequent clinical manifestations of CADASIL are transient ischemic attacks and recurrent subcortical ischemic strokes with significant mood disturbances, predominantly depression. Two decades later patients can develop encephalopathy and cognitive disorder, as severe as vascular dementia, with pseudobulbar palsy, urinary incontinence and eventually death. Retinal abnormalities [12] like cotton wool spots, retinal nerve fiber layer defects have been reported in CADASIL patients. Some case reports added less typical symptoms, including atypical, infrequent, spinal cord involvement and CADASIL coma [13].

Genetics. There is large phenotype variability [1,2,5,6]. This might be due to the > 200 different homo or heterozygous NOTCH 3 gene mutations reported already in exons 2-24 out of 33, with loss or gain of cysteine, which lead to a NOTCH3 receptor with unpaired cysteines in the epidermal growth factor-like (EGF-like) repeats in the vascular wall with neomorphic effects and impairment of the structural and functional stability. There are very few reported mutations, mainly in Asian patients, that spare the cysteine.

Pathology: The pathological hallmark of CADASIL is the granular osmiophilic material deposition in close relation to the cerebral small vessels vascular smooth muscle cells, retinal vessels, spleen, liver, kidneys, muscle, aorta and skin [5,6].

Neuroimaging: Single Photon Emission Computed Tomography (SPECT) and Diffusion Tensor Imaging (DTI) studies in CADASIL patients [9,10] can bring additional information beyond the already described characteristic of brain MRI phenotypes.

SPECT studies in CADASIL patients with migraines, strokes and vascular dementia can reveal cerebral blood flow reduction which matches MRI brain signal abnormalities.

DTI studies in patients with CADASIL reveal decreased FA (fractional anisotropy) and increased MD (mean diffusivity) values in extensive symmetric areas compared to healthy controls.

CSF biomarkers [14] in CADSIL, as a cause of pure vascular dementia, are consistent with Aβ 42 levels significantly lower but t-tau and p-tau protein levels normal.

There is no defined treatment for CADASIL. Treatment for migraine headaches and vascular dementia is symptomatic. Antiplatelet therapy for stroke prevention can be used but hasn't been proved to have definite clinical benefit in the prevention of stroke.

Genetic counseling should be offered to patients with CADASIL and even before the genetic testing for CADASIL.

Genetic testing is the gold standard for CADASIL diagnosis in most of the patients today. In rare, undefined mutations, a skin biopsy can also be obtained.

A correlation between progression of white matter disease, activity of Ig G, other CSF markers and co-morbidities in patients with CADASIL is unknown or still scarcely studied.

Very few literature reports to date include patients with associated systemic diseases, autoimmunity and CADASIL, mimicking multiple sclerosis. In those patients immunotherapy was used, with some effect on inflammatory-like presentation of CADASIL [15,16].

A mouse model with NOTCH 3 receptor agonist antibody was used to support that patients with CSVD can benefit from NOTCH 3 signaling normalization, to prevent mural cell loss, plasma protein aggregation and NOTCH 3 extracellular domain [17].

We emphasize and concur with the need to further study the association of CADASIL with other systemic disorders and other CSF bio and immunomarkers in order to identify co-occurrence of inflammatory triggers and potential risk factors for progression and aggravation of disease. In such cases, we envision that immune therapy, monoclonal antibodies, the new anti-calcitonin gene-related peptide (CGRP), the Acetazolamide (already tried for migraine prophylaxis and hemodynamic studies in CADASIL) and other membrane stabilizer drugs will be likely a target of some future clinical trials. There is evidence that altered blood-brain barrier is associated with increased accumulation of white matter disease on brain MRI [18].

Targeting the vascular smooth muscle cells and pericytes could perhaps have impact on the progression of white matter disease and clinical symptoms in CADASIL.

Conclusions

Bilateral medial temporal lobe T2/FLAIR hyperintensities (HI) in this patient with newly diagnosed CADASIL and scleroderma represents a novel neuroimaging encephalitic type brain MRI phenotype in CADASIL patients. We highlight the benefit for CADASIL testing in patients with even partial clinical features of the disease in association with extensive white matter disease on brain MRI.

Acknowledgements

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Conflict of Interest

None.

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