

Acute Watershed Infarcts with Global Cerebral Hypoperfusion in Symptomatic CADASIL

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common form of hereditary cerebral angiopathy. We present a case in which a pattern of diffusion signal change compatible with bihemispheric acute watershed infarcts occurred in a symptomatic patient demonstrating global hypoperfusion. To our knowledge, watershed infarcts in the clinical presentation of CADASIL have not been previously described.

CASE REPORT

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A 48 year old female presented to our emergency department with acute short-term memory loss and word finding difficulty. She had a past medical history significant for CADASIL, diagnosed in 2003 by genetic assessment for NOTCH 3 gene mutation. At the time of initial diagnosis, she presented with aphasia, sleep disturbances, and mood disorder. During the interval from her initial diagnosis to the present, she has experienced numerous episodes of short-term memory loss, word finding difficulties, and mood disturbances. Her mother was diagnosed with CADASIL in 2002. She has a brother and three children (22, 20, 15 years of age) who have not been screened for the NOTCH 3 mutation.

On clinical examination, she was normotensive with no motor deficits. Her cranial nerves and sensory function were intact with no extrapyramidal signs. Typical white matter increased T2 signal intensity abnormalities in the bilateral anterior temporal lobes, external capsules and periventricular as well as deep white matter regions was identified by MRI imaging (Fig 1 A,B and C). Multifocal hyperintense signal in a distribution pattern compatible with watershed and superficial perforator territory infarcts was identified on diffusion weighted imaging (DWI) sequences (Figure 2 A, B and C). This was corroborated by ADC mapped sequences

(Fig 3 A, B and C). An MRI perfusion study with gadolinium contrast revealed global white matter bihemispheric hypoperfusion, characterized by decreased cerebral blood flow (CBF), cerebral blood volume (CBV) and increased mean transit time (MTT) (Fig 4A, B and C). The average white matter CBF within the hemispheres bilaterally was 5.9 ml/100ml⁻¹/min⁻¹ [normal range 55.3±27ml/100ml⁻¹/min⁻¹], the CBV 0.1 ml/100ml⁻¹ [normal range 2.69±0.96 ml/100ml⁻¹] and the MTT 11.2 seconds [normal range 3.14±0.61 seconds]. Work up for a cardiac and carotid source of thromboemboli was negative.

DISCUSSION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a non-amyloid type of small vessel arterial disease caused by a mutation of the NOTCH3 gene on chromosome 19q12. The NOTCH3 gene encodes a single pass transmembrane protein that is expressed in vascular smooth muscle and is required for the structural and functional integrity of small arteries by controlling the arterial differentiation and maturation of smooth muscle cells. The missense mutation (more than 150 described) results in a nonfunctional NOTCH3 receptor that

leads to accumulation of the pathognomonic granular osmiophilic material deposits within the cells and subsequent degeneration of smooth muscle fibers. This results in fibrosis and loss of vasomotor reactivity of small vessel walls leading to chronic hypoperfusion, dysfunctional arterial autoregulation and ischemic infarcts [1].

The clinical presentation of CADASIL varies but typically includes migraine with aura (20-40%), subcortical ischemic events (60-85%), mood disorders (20%) apathy (40%), and cognitive impairment (40-80%). The clinical presentation and course of the disease bears a striking resemblance to Binswanger disease (Chronic hypertensive encephalopathy). CADASIL is however familial with no history of hypertension or other vascular risk factors. Multiple sclerosis (MS), Mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS) as well as Familial hemiplegic migraine (FHM) are other clinical diagnoses to consider in the differential. MS is often non familial with symptoms separated in time and space. FHM may be inherited and does not progress to dementia or a pseudo-bulbar palsy and has a younger age of onset. MELAS is a maternally transmitted inherited disorder that is readily diagnosed with abnormal serum pyruvate and lactate levels. (Table 2).

A characteristic MRI imaging feature to CADASIL is the presence of T2 hyperintensity white matter lesions in the anterior temporal poles and external capsules [1]. Associated white matter hyperintense T2 signal is commonly seen in the periventricular and deep white matter. Additional typical features include focal or subcortical white matter increased T2 signal changes in the superior frontal lobes. These lesions are associated with true restricted diffusion in the acute phase with no associated enhancement after gadolinium administration [2, 3]. In Binswanger disease, focal increased white matter T2 signal change is identified in the deep grey matter structures, corona radiata and centrum semiovale with identification of true restricted diffusion in the acute phase. Ovoid configuration white matter T2 signal abnormality distributed in a periventricular distribution pattern is typical for MS, with active lesions demonstrating enhancement with or without increased true diffusion signal. In MELAS, multifocal cortical and subcortical T2 signal abnormalities are identified. In the acute phase, swollen gyri are identified on T1 weighted sequences. In the subacute phase cortical lamina necrosis with cortical T1 hyperintensity is noted. This is replaced by cortical atrophy in the chronic phase. Multifocal subcortical and periventricular abnormal white matter T2 signal change is present in FHM with no associated diffusion signal change or enhancement. (Table 2).

Symptoms of CADASIL appear between 30 and 50 years of age and the diagnosis maybe confirmed before the first stroke on the basis of characteristic white matter T2 hyperintensities identified by brain MRI imaging and by the presence of pathognomonic granular osmiophilic material in arterial walls from skin biopsies [1]. Most patients develop cognitive decline before the age of 60 and demonstrate a progressive course leading to severe disability and premature death. Therefore, in a relatively young person with ischemic symptoms and a typical pattern of white matter signal

abnormality distribution by MRI imaging, a diagnosis of CADASIL should be considered. MRI findings in CADASIL can be seen prior to the onset of symptoms by 10 to 15 years and lesion volume correlates with the level of disability. MRI findings of increased microbleeds, lacunar infarcts and ventricular volume over time have been associated with progressive cognitive decline in executive function [4]. Increased water diffusion is present within and external to white matter lesions. Quantification of this in time may be an important in monitoring for clinical deterioration [5].

Only one other clinical CADASIL case report that mimics our findings of bilateral hemispheric acute infarcts has been published [2]. The authors of that paper suggested an embolic source for which none was found. Multifocal acute infarcts in a distribution pattern parallel to the lateral ventricles are typical of watershed infarcts. Watershed infarcts are a well-recognized phenomenon confirmed by autopsy studies and global hypotension as an etiology has been confirmed in animal models [6]. Microcirculatory watershed hypoperfusion as an etiologic factor in CADASIL has been suggested in conjunction with vessel wall hypotonia and hypo-permeability. These pathophysiologic phenomenon occur consequent to the destruction of vascular wall muscle cells and its subsequent failure to secrete vascular permeability factors, rather than luminal stenosis, as has identified in skin biopsies of CADASIL patients [7]. Mouse model studies have supported the theory that cerebrovascular dysfunction and microcirculation failure are key contributors to hypoperfusion and precede white matter damage [8]. It has been shown that patients with CADASIL have lower ambient systemic blood pressure profiles [9]. Multifocal ischemic events may then occur as a result of the concomitant intracranial small vessel hypoperfusion and prolonged phases of systemic hypotension. [3]. Lacunar type infarcts are the predominant ischemic event in CADASIL [10]. MRI imaging in our case showed global hypoperfusion with bihemispheric acute watershed infarcts not previously described.

Quantification and characterization of tissue microcirculation by CBF, CBV and MTT acquired through dynamic bolus chase MR imaging can be performed using deconvolution of the arterial input function and tissue signal change after intravenous gadolinium contrast injection. Decreased CBF and CBV in white matter lesions as well globally within the centrum semiovale in patients with CADASIL, relative to normal patients has been demonstrated [11]. Baseline global CBF in normal subjects in this study was $55.3 \pm 27 \text{ ml}/100 \text{ ml}^{-1}/\text{min}^{-1}$, global CBV $2.69 \pm 0.96 \text{ ml}/100 \text{ ml}^{-1}$ and global MTT baseline 3.14 ± 0.61 seconds. The global white matter CBF was reduced to $17.3 \pm 11.5 \text{ ml}/100 \text{ ml}^{-1}$ and the CBV to $0.8 \pm 0.39 \text{ ml}/100 \text{ ml}^{-1}$ in patients with CADASIL. There was also a 42% reduction in mean CBF and 50% reduction in CBV relative to normal subjects in typical white matter lesions. Interestingly, perfusion parameters in affected and non-affected white matter regions were identified with normal MTT [11]. Sonographic and other CT perfusion studies have in contradistinction demonstrated an overall increase in cerebral perfusion times. A cerebral perfusion time by sonography was measured at 4.4 ± 1.9 seconds in patients with CADASIL and 1.3 ± 0.5 in normal subjects [12].

Prolonged MTT was identified in our patient. There are technical limitations in determining perfusion parameters of the cortex and assessment controversy remains with some studies showing a global decrease and some just in the cortical regions of the occipital lobe [3,11]. The exact relationship between CBF and CBV in CADASIL is unknown. Importantly, correlation between white matter signal abnormality CBV and clinical symptoms may allow for using this singular parameter for monitoring treatment protocols and or asses individual progression [3].

Basal perfusion and hemodynamic reserve are diminished in regions of white matter signal change and these correspond to clinical severity [3]. More severe reduction in CBF and CBV are identified in white matter lesions of demented CADASIL patients [11]. Diminished global white matter CBV reflects diffuse small artery disease with maximal vasodilatation and not infarction, despite having commensurate decreased CBF. Acetazolamide has been shown to increase CBF and CBV in the cortex and white matter as well as more significantly within white matter lesions of affected patients and treatment with this drug has demonstrated clinical benefit [11,14].

Dysfunctional cerebrovascular autoregulation is a significant factor in the pathogenesis of CADASIL and has been demonstrated as the precursor to ischemic insults in animal models. [15]. To our knowledge, imaging findings compatible with bihemispheric acute watershed infarcts in the context of global hypoperfusion in a patient with acute symptomatic CADASIL has not been described. Prospective observational study of watershed infarcts in a significant number of CADASIL patients is required and the findings may have important implications in the diagnosis and management of this condition.

TEACHING POINT

The most characteristic MRI imaging feature to CADASIL is the presence of T2 hyperintensity white matter lesions in the anterior temporal poles and external capsules. These white matter signal abnormalities have diminished CBV that correlate with clinical outcomes. Microcirculatory hypoperfusion related watershed infarction in the context of global hypoperfusion may be a causative factor in symptomatic CADASIL.

REFERENCES

- Chabriat H, Joutel A, Dichgans M, Tournier-Lasserre E, Boussier MG. CADASIL. *Lancet Neurol* 2009;8:643-53. PMID:19539236.
- Saito S, Ozaki A, Takahashi M, Ito H, Mastsumoto S, Tomimoto H. Clustering of multifocal cerebral infarctions in CADASIL: a case report. *J Neurol*. 2011 Feb;258(2):325-7. PMID:20803343.
- Bruening R, Dichgans M, Berchtenbreiter C, Yousry T, Seelos KC, Wu RH et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: decrease in regional cerebral blood volume in hyperintense subcortical lesions inversely correlates with disability and cognitive performance. *AJNR Am J Neuroradiol*. 2001 Aug;22(7):1268-7. PMID:11498413.
- Liem MK, Lesnik Oberstein SA, Haan J, van der Neut IL, Ferrari MD, van Buchem MA, et al. MRI correlates of cognitive decline in CADASIL: a 7-year follow-up study. *Neurology*. 2009 Jan 13;72(2):143-8. PMID:19139365.
- Molko N, Pappata S, Mangin JF, Poupon F, LeBihan D, Boussier MG, et al. Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: a study with whole brain histogram analysis. *Stroke*. 2002 Dec;33(12):2902-8. PMID:12468789.
- Derdeyn CP, Khosla A, Videen TO, Fritsch SM, Carpenter DL, Grubb RL, et al. Severe hemodynamic impairment and border zone--region infarction. *Radiology*. 2001 Jul;220(1):195-201. PMID: 11425997.
- Ruchoux MM, Brulin P, Brillault J, Dehouck MP, Cecchelli R, Bataillard M, et al. Lessons from CADASIL. *Ann N Y Acad Sci*. 2002 Nov;977:224-31. PMID :12480754.
- Joutel A, Monet-Lepretre M, Gosele C, Baron-Menguy C, Hammes A, Schmidt S, et al. Cerebrovascular dysfunction and microcirculation rarefaction precede white matter lesions in a mouse genetic model of cerebral ischemic small vessel disease. *J Clin Invest* 2010;120:433-445. PMID:20071773.
- Rufa A, Dotti MT, Franchi M, Stromillo ML, Cevenini G, Bianchi S, et al. Systemic Blood Pressure Profile in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy. *Stroke* 2005; 36:2554-2558. PMID:16282544.
- Ferrer I. Cognitive impairment of vascular origin: neuropathology of cognitive impairment of vascular origin. *J Neurol Sci*. 2010 Dec 15;299(1-2):139-49. Epub 2010 Sep 16. PMID:20846674.
- Chabriat H, Pappata S, Ostergaard L, Clark CA, Pachot-Clouard M, Vahedi K, et al. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. *Stroke*. 2000 Aug;31(8):1904-12. PMID: 10926955.
- Liebetrau M, Herzog J, Kloss CU, Hamann GF, Dichgans M., et al. Prolonged cerebral transit time in CADASIL: a transcranial ultrasound study. *Stroke*. 2002 Feb;33(2):509-12. PMID: 1823661.
- Huang L, Yang Q, Zhang L, Chen X, Huang Q, Wang H, et al. Acetazolamide improves cerebral hemodynamics in CADASIL. *J Neurol Sci*. 2010 May 15;292(1-2):77-80. PMID: 20227091.

14. Lacombe P, Oligo C, Domenga V, Tournier-Lasserre E, Joutel A, et al. Impaired cerebral vasoreactivity in transgenic mouse model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy arteriopathy. *Stroke*. 2005 May;36(5):1053-8. PMID: 15817893

FIGURES

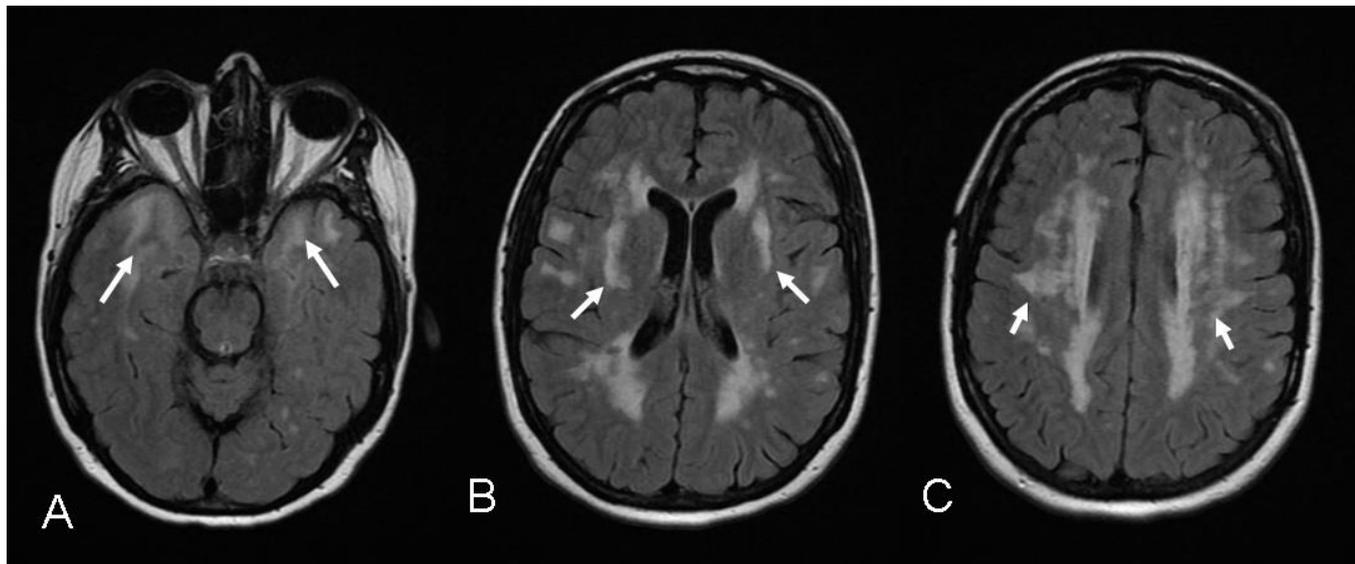


Figure 1: 48 year old female with acute symptomatic Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Select axial FLAIR sequences demonstrating confluent near symmetric bihemispheric subcortical increased white matter T2 hyperintense signal in the temporal lobes (arrows in A), extreme capsules (arrows in B) and the subcortical white matter (arrows in C), typical for CADASIL (1.5 Tesla magnet, TR 8.000, TE 127.30, NEX 1.5, Flip 160.15, slice thickness 5mm)

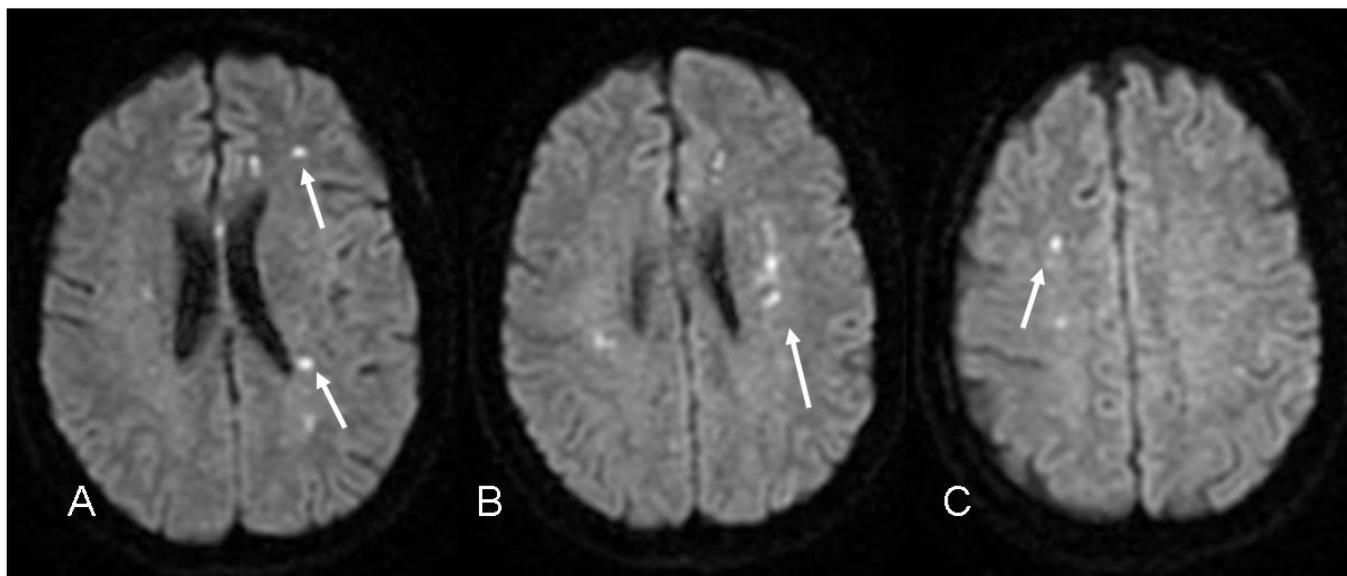


Figure 2: 48 year old female with acute symptomatic Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Select axial diffusion sequences demonstrating bihemispheric multiple foci of increased signal, distributed in a typical peri-ventricular pattern compatible with acute watershed infarcts (arrows). The anterior arrow in "A" additionally identifies acute punctate infarction in the superficial perforator territory. (1.5 Tesla magnet, TR 8,600, TE 74.50, NEX 1.0, Flip 90, slice thickness 5mm)

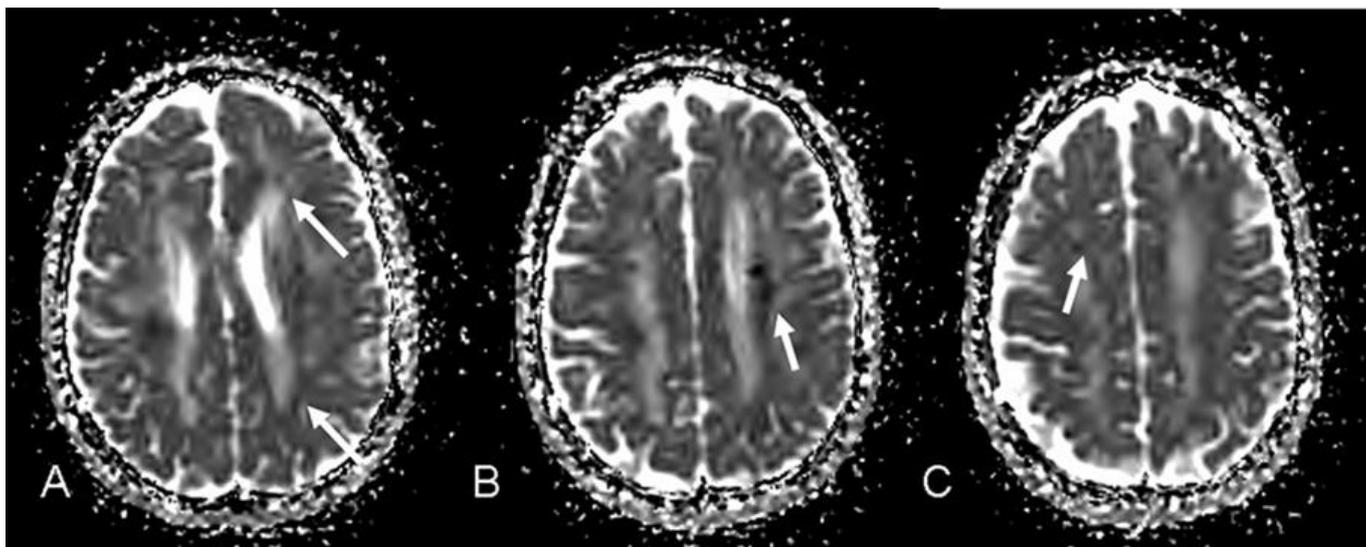


Figure 3: 48 year old female with acute symptomatic Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Select axial ADC mapped sequences demonstrating multiple foci of true restricted diffusion decreased signal distributed in a typical peri-ventricular pattern compatible with acute watershed infarcts (arrows), corresponding to the abnormalities identified by diffusion weighted imaging. The anterior arrow in "A" additionally identifies acute punctate signal loss related to punctuate infarction in the superficial perforator territory. (1.5 Tesla magnet, TR 8,600, TE 74.50, NEX 1.0, Flip 90, slice thickness 5mm)

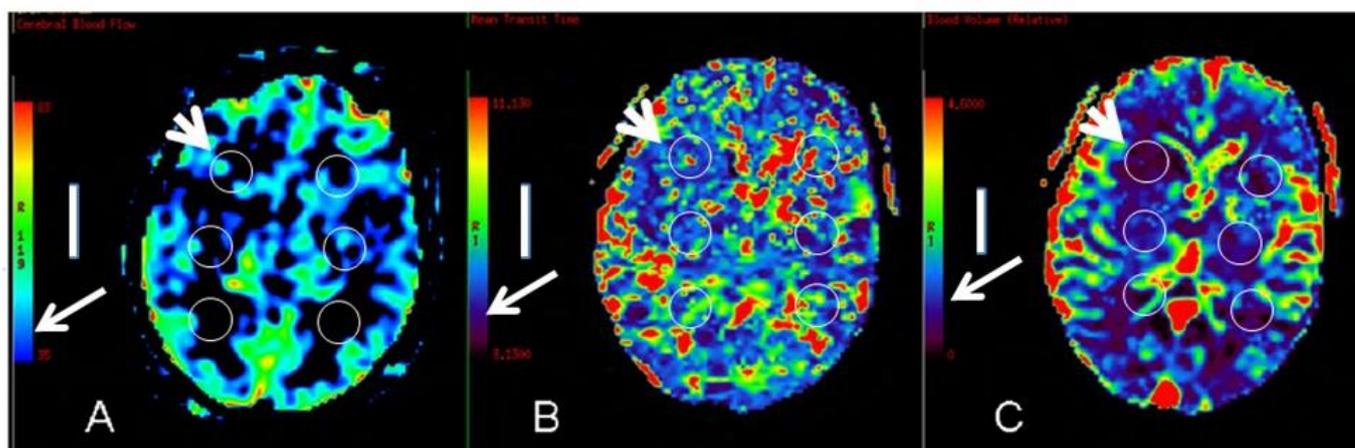


Figure 4: 48 year old female with acute symptomatic Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Qualitative assessment of perfusion MRI imaging demonstrates bihemispheric decreased cerebral blood flow (A) increased mean transit time (B) and decreased cerebral blood volume (C), as shown by long white arrows along the expected range. Normal range delineated by white bar. (1.5 Tesla magnet, Echo Planar Imaging, TR 2000, TE 13.20, NEX1, Flip 60, Slice thickness 5 mm, Dynamic imaging performed before, during and after a single 0.2mmol/kg dose Multihance (Gadobenate dimeglumine, Bracco Diagnostics, Princeton, NJ) power injection at a rate of 4 cc/s. The arterial input function to calculate perfusion parameters determined from the middle cerebral artery. Calculation of relative CBF, CBV and MTT from multiple regions of interest placed within the cerebral hemispheres bilaterally as shown by short white arrows).

Etiology	Autosomal dominant disorder caused by mutation in Notch3 on chromosome 19. NOTCH3 is a large gene of 33 coding exons. Most of the mutations in CADASIL occur in exon 3 or 4. The mutation can rarely arise de novo.
Incidence	The prevalence of CADASIL is unknown. Since 1993, several hundred families with CADASIL have been identified. Most of the affected families have been identified in Western Europe, Japan and North America.
Gender ratio	None
Age predilection	Symptoms appear between 30 and 50 years of age. Mean onset at 45.1 years.
Risk factors	None
Treatment	Antiplatelet and anticoagulant medications as with lacunar type infarcts. These may be contraindicated in patients with intra-cerebral hemorrhage. No evidence that any form of treatment changes the natural history of CADASIL. Management of blood pressure and glucose levels could influence the course of CADASIL. Cholinesterase inhibitors presently controversial with some evidence of improved executive function.
Prognosis	The clinical course is characterized by a stepwise deterioration in sensory/motor function, development of a pseudobulbar palsy, and progressive dementia. Most patients with CADASIL die within 10 to 20 years of clinical onset.
Imaging	<p>COMPUTERIZED TOMOGRAPHY Multifocal subcortical bihemispheric hypodense regions.</p> <p>MRI</p> <ul style="list-style-type: none"> • Multiple subcortical lacunar infarcts and a diffuse non-specific white matter changes. White matter hyperintensity on T2-weighted MRI images in temporal lobe poles is highly specific. Involvement of the external capsule has a highly sensitivity but is not as specific. • Non enhancing large coalescent intermediate T1 or small discrete hypointense T1 subcortical white matter lesions. • Subcortical lesions may appear bright on diffusion weighted imaging in acute phase. Increased water diffusion is present within and external to white matter lesions • Time-related changes in diffusion tensor imaging correlates with clinical worsening and may become an important prognosticating tool. • Global decreased CBF and CBV in normal and abnormal white matter regions with preserved MTT. Pronounced decrease in CBV within white matter lesions with increase after acetazolamide challenge. <p>ULTRASOUND Transcranial Doppler show decrease middle cerebral artery mean flow and decreased CO2 reactivity. Global decrease in cerebral perfusion time.</p> <p>ANGIOGRAPHY Angiographic studies in CADASIL are typically normal. High complication rate of cerebral angiography and is contraindicated.</p> <p>SCINTIGRAPHY 18-F FDG PET demonstrates severe decrease in cortical and subcortical glucose metabolism.</p>

Table 1: Summary table for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

	Chronic hypertensive encephalopathy (Binswanger disease)	Multiple sclerosis	Mitochondrial encephalomyopathy with Lactic acidosis and Stroke like Episodes (MELAS)	Familial hemiplegic migraine
CLINICAL	<ul style="list-style-type: none"> Associated with hypertension or other vascular risk factors Non familial 	<ul style="list-style-type: none"> Separation of symptoms in time and space Often non familial 	<ul style="list-style-type: none"> Abnormal lactate and pyruvate serum levels Abnormal muscle biopsy and genetic profile Maternally transmitted inherited disorder 	<ul style="list-style-type: none"> Typical onset before age of 40. No pseudobulbar palsy and progressive dementia May be inherited
MRI	<ul style="list-style-type: none"> Multifocal deep grey matter structure, corona radiata and centrum semiovale T2 hyperintensity Multifocal hypointense lesions on GRE sequences Discrete foci of restricted diffusion signal in acute phase 	<ul style="list-style-type: none"> Multiple perpendicular calloseptal T2 hyperintensity Ovoid configuration white matter T2 hyperintensity in a peri-ventricular distribution T1 hypointensity in chronic lesions +/- Increased diffusion signal in acute lesions 	<ul style="list-style-type: none"> Multifocal cortical and subcortical T2 hyperintensity <p><i>Acute phase:</i></p> <ul style="list-style-type: none"> swollen gyri <p><i>Subacute phase:</i> cortical T1 hyperintensity from laminar necrosis</p> <p><i>Chronic phase:</i></p> <ul style="list-style-type: none"> cortical atrophy with sparing of hippocampi Increased diffusion signal in acute lesions 	<ul style="list-style-type: none"> Multifocal subcortical and periventricular T2 hyperintensity No abnormal T1 or diffusion signal
Gd +	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Transient during acute phase 	<ul style="list-style-type: none"> Gyriform enhancement acute phase 	<ul style="list-style-type: none"> None
CT	<ul style="list-style-type: none"> Multifocal hypodense regions No enhancement 	<ul style="list-style-type: none"> Iso/hypodense lesions with variable enhancement 	<ul style="list-style-type: none"> Acute phase swollen cortex. Chronic phase atrophy 	<ul style="list-style-type: none"> Normal
US	<ul style="list-style-type: none"> Transcranial doppler: increased middle cerebral artery resistance in hypertensive patients 	<ul style="list-style-type: none"> Non contributory 	<ul style="list-style-type: none"> Non contributory 	<ul style="list-style-type: none"> Non contributory
SCINTI-GRAPHY	<ul style="list-style-type: none"> PET: hyper-metabolism in cingulate and superior frontal gyri 	<ul style="list-style-type: none"> Non contributory 	<ul style="list-style-type: none"> 99mTc-HMPAO SPECT: increased tracer accumulation 	<ul style="list-style-type: none"> Non contributory

Table 2: Differential diagnoses table for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

ABBREVIATIONS

CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBF = Cerebral blood flow
CBV = Cerebral blood volume
CT = Computerized tomography
FHM = Familial hemiplegic migraine
FLAIR = Fluid attenuation inversion recovery
Gd+ = Gadolinium enhancement
GRE = Gradient recall echo sequences
MRI = Magnetic resonance imaging
MTT = Mean transit time
MELAS = Mitochondrial encephalo-myopathy with lactic acidosis and stroke like episodes
MS = Multiple sclerosis
PET = Positron emission tomography
US = Ultrasound

KEYWORDS

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CADASIL; Watershed infarcts; Global cerebral hypoperfusion; MRI

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