

## CEREBRAL AUTOSOMAL-DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY – CADASIL

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Clin Biomed Res. 2016;36(4):252-253

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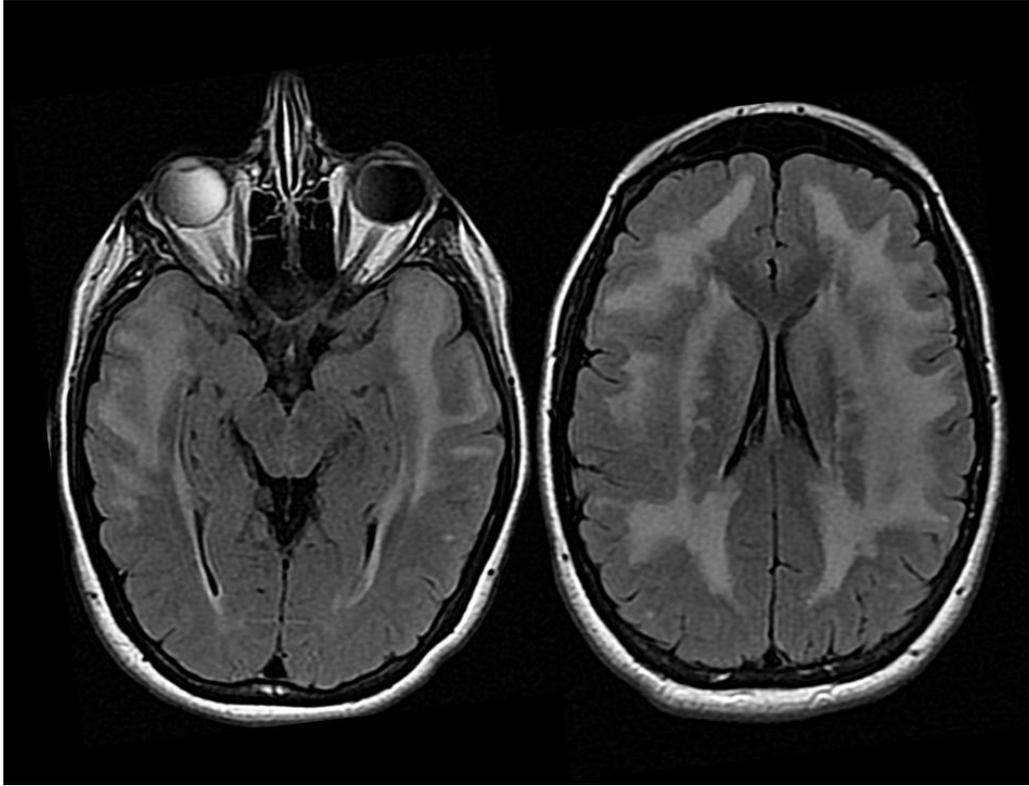
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A 41 year-old female patient came to our outpatient clinic complaining of long-time episodes of headache. The pain was intense, migrainous, without aura, and with variable periodicity. During her life she was seen by some physicians without an appropriate diagnosis and used different therapeutic modalities without satisfactory results. She had no other health problems. Her family history was unremarkable, except for history of stroke and migraine in some of her relatives. An MRI showed abundant T2-weighted hyperintensities in subcortical white matter, with involvement of the temporal lobe (figure 1). A DNA test for *NOTCH3* gene in the patient, but not in the family, revealed a mutation fully compatible with CADASIL disease.

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Online Mendelian Inheritance in Man (OMIM #125310), is a rare form of familial cerebrovascular disorder. It is caused by mutation of the *NOTCH3* gene, located on the short arm of chromosome 19 (19p13.2-p13.1), and is the most common form of hereditary stroke disorder<sup>1-5</sup>. CADASIL is characterized by migrainous headaches, with or without aura, and relapsing strokes. About 10% of patients might develop seizures. Strokes are characterized by transient ischemic attacks or lacunar strokes and these are the most consistent clinical findings. With progression of disease, patients may also develop different forms of neuropsychiatric symptoms. In advanced cases, patients might evolve to a vascular dementia of subcortical type. The disease affects relatively young adults of both sexes. Family history suggests an autosomal dominant pattern<sup>1-5</sup>. More than 95% of patients present mutations in the *NOTCH3* gene, which encodes a single pass transmembrane protein belonging to an evolutionarily conserved NOTCH receptor family<sup>1,4</sup>. After ligand binding, the intracellular domain translocates to the nucleus and activates transcription factors. The Notch signaling pathway plays a central role in the development and maturation of organs. The protein product Notch3 is critical for vascular smooth muscle cell differentiation and vascular development<sup>1,3,4</sup>. In adults, Notch3 expression is limited to vascular muscle cells. Mutations in the *NOTCH3* gene result in abnormal protein that deposits and accumulates in the cytoplasmic membrane of vascular muscle cells and pericytes. This results in granular osmiophilic deposits, characteristic of disease. The deposits are toxic and impair blood flow, leading patients to develop vascular symptoms<sup>1,3,4</sup>. MRI is the best neuroimaging modality to investigate CADASIL<sup>1,2,5</sup> (see figure 1). The diagnosis of CADASIL should be considered when MRI characteristics are associated with typical clinical findings. Differential diagnosis of CADASIL includes multiple sclerosis, primary angiitis of the nervous system, sporadic small vessel disease including Binswanger's disease, cerebral autosomal recessive arteriopathy with subcortical



**Figure 1:** Magnetic resonance imaging fluid-attenuated inversion recovery (MRI-FLAIR) axial scans. Brain MRI-FLAIR axial scans showing lacunar infarcts and less-well demarcated hyperintensities characteristically located in the subcortical white matter (large white lesions). These white matter hyperintensities can be observed in anterior temporal lobe and occur in about 90% of patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

infarcts and leukoencephalopathy (CARASIL), and some other forms of leukodystrophy<sup>1-5</sup>. There is no specific treatment for CADASIL. Antiplatelet agents such as aspirin might help to prevent new strokes. Other symptoms, like headache, seizures, or other neuropsychiatric manifestations, should be appropriately treated<sup>1,2,5</sup>.

### Acknowledgements

This study was fully supported by the Brazilian Government research grant agencies CNPq, FAPERGS, and FIPE/HCPA.

Bianchin MM is further supported by CNPq (#307084/2014-0). We declare no conflict of interest.

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Received: July 19, 2016  
Accepted: Dec 13, 2016