CADASIL Presenting with a Movement Disorder: A Clinical Study of a Chilean Kindred

Marcelo Miranda, MD,[1]* Martin Dichgans, MD,[2] Andrea Slachevsky, MD,[3] Francisco Urbina, MD,[1] Ismael Mena, MD,[1] Pablo Venegas, MD,[1] and Marcelo Galvez, MD[1]

[1]*Department of Neurology, Nuclear Medicine and Dermatology, Clinica Las Condes and Universidad de Chile, Santiago, Chile*
[2]*Department of Neurology Ludwig-Maximilians University, Muenchen, Germany*
[3]*Department of Cognitive Neurology and Dementia, Department of Neurology, Hospital del Salvador, Santiago, Chile*

Abstract: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary vascular disease that usually begins with migraine, followed by repeated strokes and progressive dementia. We describe an unusual clinical presentation of this condition in members of a Chilean family with an established *NOTCH3* mutation. We report early clinical, neuropsychological, transcranial ultrasound, magnetic resonance imaging (MRI), cerebral blood flow, and skin biopsy findings on these patients. Of the patients, 2 presented with facial dystonia, 1 of whom had abnormal single photon emission computed tomography and transcranial ultrasound studies after normal brain MRI scans. Our report emphasizes that CADASIL must be considered in the study of patients with secondary dystonia.

Key words: CADASIL; movement disorders; dystonia; atypical presentation

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is an increasingly recognized clinical entity, characterized by migraines, stroke, and dementia.[1,2] CADASIL is one of a family of hereditary small vessel vasculopathies. It is the result of mutations in the NOTCH 3 gene that codes for a transmembrane protein expressed in vascular smooth muscle cells.[1,2] The variable expression of this mutation has led to widespread underrecognition and misdiagnosis of this syndrome.[1,2] Accordingly, the prevalence of this condition remains uncertain. Herein, we expand this phenotype by describing a kindred presenting with focal dystonia. To the best of our knowledge, only one other case of CADASIL has been reported presenting with a movement disorder, mainly atypical Parkinsonism mimicking progressive supranuclear palsy.[3]

*Correspondence to: Dr. Marcelo Miranda, Antonio Varas 175 Suite 201, Santiago, Chile. E-mail: marcelomiranda@terra.cl

PATIENTS AND METHODS

After obtaining informed consent, we studied a local family whose 2 affected members presented in 1999 with facial dystonia (Fig. 1). Patients were followed up for a period of 5 years. Patients received a complete neurologic examination that included funduscopy, fluorescein retinal angiography, and visual evoked potentials. Cardiac evaluation was made in all patients by a resting electrocardiogram and treadmill test with a thallium perfusion myocardial study. A neuropsychological evaluation was also performed on all patients with tests aimed at assessing global cognitive performance, attention capabilities, verbal learning, executive functions, depression (Geriatric Depression Scale),[4] and anxiety (Zung Anxiety Scale).[5]

Imaging procedures conducted in all clinically affected individuals included transcranial ultrasound, sin-

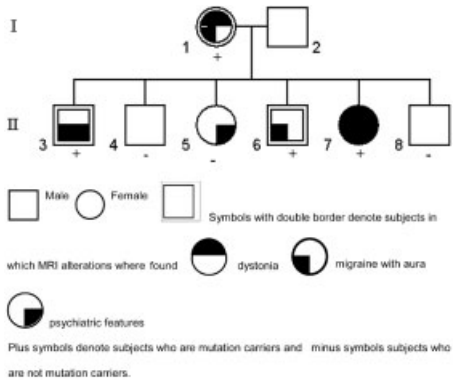

FIG. 1. Pedigree of the affected family.

gle photon emission computed tomography (SPECT) using HMPAO (Ceretec, Amersham), and brain magnetic resonance imaging (MRI) using a 1.5-Tesla Philips Gyroscan. Transmission electron microscopy study (Philips Electronic, Amsterdam, the Netherlands) was performed on a skin biopsy taken from the forearm as described elsewhere.[2] Mutational screening of the *NOTCH 3* was performed in all family members using a previously described methodology.[6] The study was approved by the local ethics committee.

Case Histories

Proband (I:1).

The proband is a 70-year-old woman with no known risk factors for stroke who presented with a 3-year history of a mild oromandibular dystonia. There was no history of exposure to neuroleptics, use of other potential D2 blocker receptor drugs, or dental trauma or migraine. Her facial dystonia started gradually and remained stable during the following 3 years, during which she insidiously developed cognitive decline. The most remarkable finding on neurological examination was the presence at rest of a mild dystonia in the oromandibular region with lateral deviation of the jaw (see Video, Segment 1). Her gait was unstable, and she had mild generalized bradykinesia. As dystonia severity was mild, no specific treatment was given. Neuropsychological evaluation revealed cognitive slowness, a reduced global cognitive capacity, impaired free recall in tests of episodic memory, dysexecutive syndrome, and constructional apraxia.

MRI of the brain showed extensive white matter changes in the periventricular areas, the anterior part of both temporal lobes and the external capsule. There was also a lesion partially involving the left caudate nucleus (Fig. 2). SPECT showed marked reduction of cerebral blood flow in the temporal lobes, cingulate gyrus, and left caudate nucleus (Fig. 3).

Transcranial ultrasound showed a mean velocity of 13 cm/sec in the right middle cerebral artery and 12 cm/sec at left middle cerebral artery (normal reference value: 62 cm/sec $\pm$ 12). Cardiac examination was normal. Ophthalmologic tests, including funduscopy, retinal angiography, and visually evoked potentials were all normal. Because of the characteristic pattern of MRI lesions, a diagnosis of CADASIL was suspected and a skin biopsy was performed. Ultrastructural examination of small blood vessels showed characteristic osmiophilic deposits in close apposition to the endothelial cell membrane (Fig.

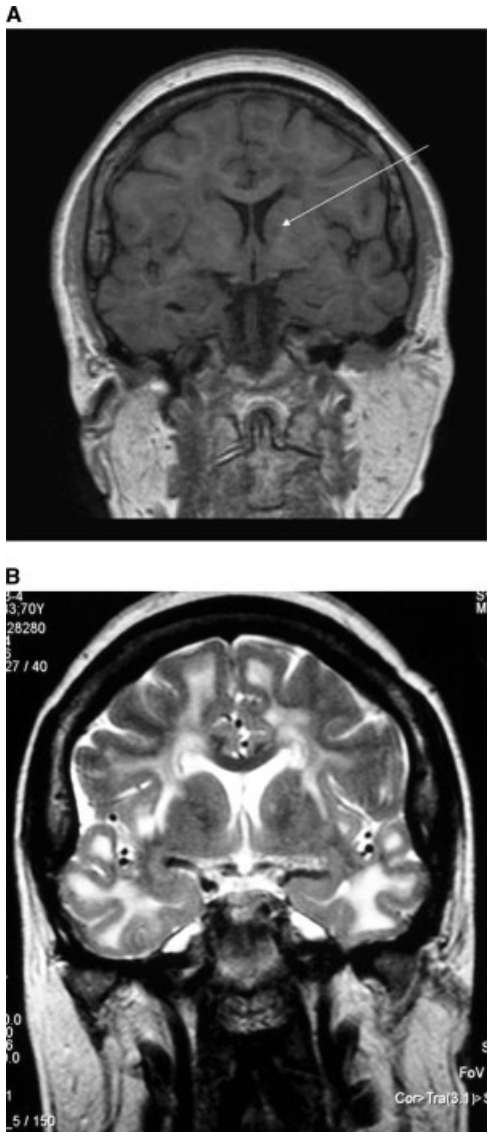

FIG. 2. Coronal T1 magnetic resonance imaging (MRI) scan of the brain showing an infarct involving the left caudate nucleus in the proband (arrow), and coronal T2 MRI scan showing extensive white matter lesions involving periventricular areas, the anterior part of both temporal lobes, and the external capsule.

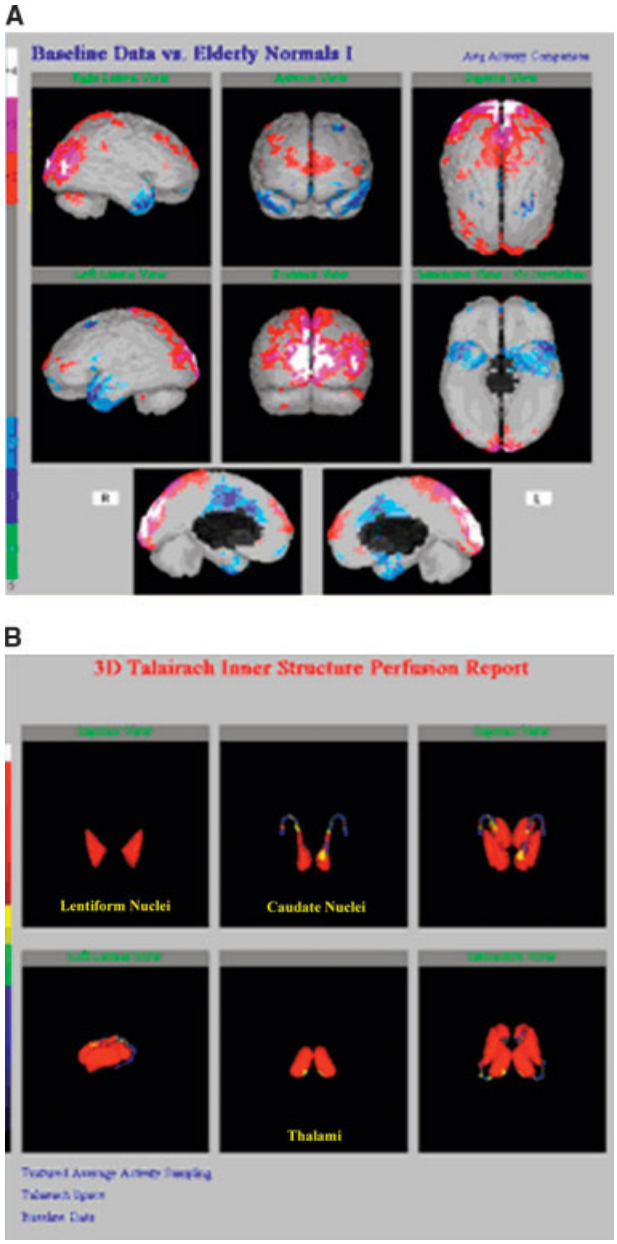

FIG. 3. A: Single photon emission computed tomography (SPECT) findings in proband showing a pattern of hypoperfusion involving temporal lobes and cyngulate gyrus and a decreased focal perfusion in posterior aspect of both thalami. **B:** Similar patterns of hypoperfusion are observed in the head of left caudate nucleus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

4A). Mutational screening of the *NOTCH 3* gene revealed a previously reported mutation (R141C; Fig. 4B).

Case 2 (II:7).

The proband's daughter was a 43-year-old woman who suffered from migraine with aura since 20 years of age. At 38 years of age, she began to experience involuntary closure of her eyes leading to serious disability. There were no reports of sensory tricks to relieve dystonia, and the blepharospasm was clearly precipitated by sunlight. Examination revealed an evident contraction of the orbicularis oculi musculature (see Video, Segment 2). Botulinum toxin injection into the eyelids led to partial improvement in the spasm without relief in a persistent sensation of pressure in her eyelids. Concurrently, she developed a severe depression that did not response to adequate doses of conventional antidepressants. The blepharospasm gradually resolved over of the next 5 years, but the migraine with aura did not. Neuropsychiatric evaluation only revealed a mild dysexecutive syndrome and a severe depressive syndrome.

MRI of the brain showed no evidence of white matter lesions or infarcts. However, SPECT of the brain showed a marked reduction in cerebral blood flow in the temporal lobes, cingulated, and frontal lobes (Fig. 5). On transcranial ultrasound, the mean flow velocities in the middle cerebral arteries were 52.8 cm/sec in the right and 34 cm/sec in the left cerebral middle artery. Cardiac and ophthalmologic assessments were normal.

Skin biopsy findings confirmed the presence of the characteristic deposits as seen on CADASIL. Mutational

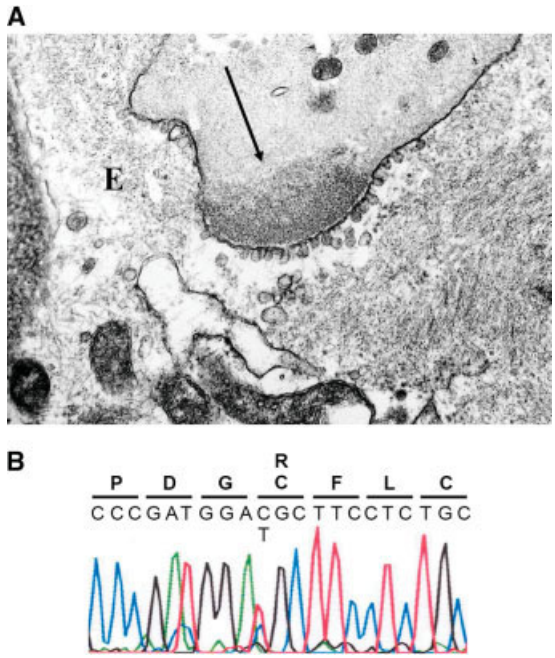

FIG. 4. A: Skin biopsy of the proband. Ultrastructural examination of small blood vessels showed characteristic osmiophilic deposits (arrow) in close apposition to the endothelial cell membrane (E). **B:** Sequencing electropherogram of Notch3 exon 4 from the index patient. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

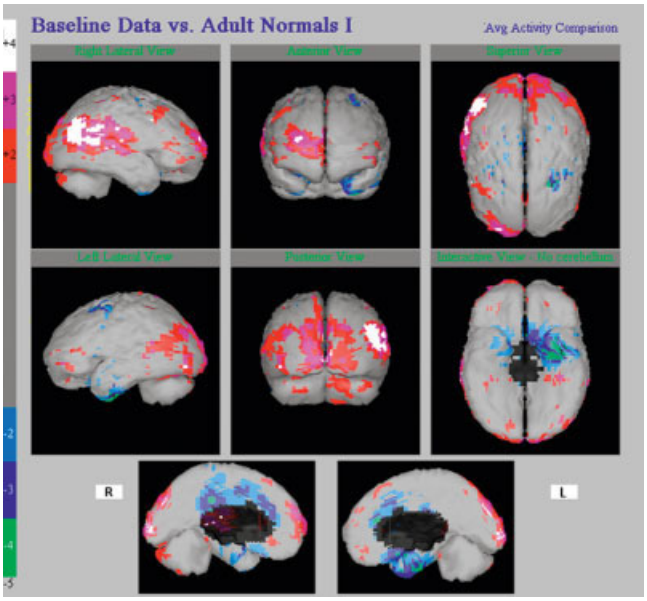

FIG. 5. Single photon emission computed tomography findings in Case 2 with blepharospasm, showing a similar pattern of hypoperfusion involving temporal lobes and cyngulate gyrus as found in her mother; no abnormalities could be detected in basal ganglia (not shown). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

analysis of the *NOTCH 3* gene revealed a R141C mutation.

Other Members of the Family.

A third patient (II:6), was a 45-year-old restaurant employee who initially received the diagnosis of multiple sclerosis. The diagnosis was questioned after his 2 relatives were correctly diagnosed. He presented at age 44 years with a sudden episode of transient left arm paresis and gait ataxia lasting 2 days. The symptoms followed a significant change in mood with overt depression that responded well to sertraline 50 mg/day. There was no history of migraine. Diagnostic funduscopy, retinal angiography and visually evoked potentials were all normal.

Neurological examination revealed left-sided hyperreflexia with no paresis. Neuropsychiatric evaluation revealed impairment in visuoconstructive abilities, a mild dysexecutive syndrome, and a marked depression with anxiety. MRI of the brain showed extensive white matter lesions in the periventricular regions, brainstem lacunar infarcts, and marked white matter lesions involving the temporal lobes and cingulate gyrus.

SPECT showed the typical pattern of flow reduction described above. Transcranial ultrasonography revealed a mean flow velocity in the middle cerebral artery of 33 cm/sec in the right and 31 cm/sec in the left middle cerebral artery. Skin biopsy revealed the typical deposits associated with CADASIL. Mutational analysis of the *NOTCH 3* gene revealed a R141C mutation. The other three 3 members of the family suffered from migraine and depression, but none of them presented with abnormal movements.

DISCUSSION

Our report describes an atypical clinical presentation of CADASIL in 2 members of an extended family. It consists of a movement disorder, which should be added to other recently reported unusual presentations of this disorder.[7,8] Dystonia has not been reported previously in this condition, and Parkinsonism has been described in a single case report recently.[3] Sporadic causes of stroke can induce delayed onset dystonia due to lesions involving components of the cortico-thalamic-basal ganglia circuits, with most lesions involving the striatum or thalamus.[9] In this report, we postulate that patients insidiously developed dystonia due to chronic subcortical ischemia. The late onset, the neuroimaging findings, the pathology, and genetic testing make idiopathic dystonia highly unlikely. Accordingly, we postulate that dystonia in the proband (Patient I.1) can be explained by an infarction partially involving the left caudate nucleus. In her daughter (Patient II.7), we interpret the blepharospasm as a clinical sign of temporary basal ganglia ischemia. However, we acknowledge that this hypothesis does not adequately account for the gradual disappearance of the dystonia after 5 years. It is noteworthy that in this patient with a normal brain MRI there were early changes evident detected on cerebral SPECT in areas typically involved in this condition. Thus, far there appears to be a weak correlation between brain imaging and the clinical manifestations of this entity. For instance, in a recent report, SPECT changes preceded the development of infarcts.[10] In different reports, early brain white matter abnormalities were detected in the MRI of asymptomatic carriers of NOTCH 3 mutations.[11] and symptomatic patients with *NOTCH 3* mutation and positive skin biopsies have been reported to have normal brain MRI scans.[12.] In this series, Patient II.7 had reduced cerebral blood flow by transcranial Doppler and a normal brain MRI scan. The asymmetric reduction in blood flow in this patient (more severe in the left cerebral middle artery compared to the right) was consistent with the lateralization of her symptoms. It is noteworthy that transcranial ultrasound evaluation of the four clinically affected members of this family clearly demonstrated a progressive reduction in cerebral blood flow velocities in keeping with their age and the severity of neurologic involvement.

The four members of this family presented important psychiatric disturbances, even the patient (Case 2) whose MRI was normal. The psychiatric disturbances of this patient may be explained by the pattern of reduction in cerebral blood flow observed in SPECT images involving the anterior parts of temporal lobes, cyngulate gyrus, and frontal regions.[13,14]

Furthermore, the dysexecutive syndrome evidenced by these patients is consistent with the periventricular white matter lesions in their MRI scans. In Case 2, psychiatric disturbances and cognitive dysfunction, mainly executive dysfunction, could be explained by the hypoperfusion observed in the SPECT scan even in the absence of structural MRI lesions. This finding supports the notion that, in this condition, there is a progressive decline in cerebral blood supply and that early clinical symptomatology can be explained by chronic ischemia that precedes the infarcts.[15,16]

It is noteworthy that none of our patients had visual involvement that had been reported as an early finding in CADASIL.[17] Similarly, we did not detect cardiac involvement as has been reported recently in 25% of a series of 41 patients with CADASIL where, in all cases, the cardiac involvement predated any major neurologic involvement.[18] In contrast, all our patients had normal electrocardiograms and myocardial perfusion tests.

Our report demonstrates a new presentation of CADASIL, adding to the pleomorphic clinical presentation of this condition and, thus, making the clinical diagnosis of this entity increasingly difficult. Our findings suggest that CADASIL should be considered in the differential diagnosis of secondary dystonia.

Acknowledgments: We thank Dr. Jorge L. Juncos for reviewing the manuscript and Dr. Sergio Gonzalez for providing the photomicrograph.

LEGENDS TO THE VIDEO

Segment 1. This segment shows the proband affected with facial dystonic movements with intermittent lateral deviation of the jaw.

Segment 2. This segment demonstrates the proband's daughter affected with blepharospasm.

REFERENCES

1. Tournier-Lasserve E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infracts and leukoencephalopathy maps to chromosome 19q12. Nat Genet 1993;3:256–259.
2. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL; clinical findings in 102 cases. Ann Neurol 1998;44: 731–732.
3. Van Gerpen J, Ahskog J, Petty G. Progressive supranuclear palsy: phenotype secondary to CADASIL. Parkinsonism Relat Disord 2003;9:367–369.
4. Yesavage JA. 1988. Geriatric depression scale. Psychopharmacol Bull 1988;24:709–711.
5. Zung WW. A rating instrument for anxiety disorders. Psychosomatics 1971;12:371–379.
6. Dichgans M, Herzog J, Gasser T. NOTCH3 mutation involving three cysteine residues in a family with typical CADASIL. Neurology 2001;57:1714–1717.
7. Engelter S, Rueeg S, Kirsch EC, et al. Cadasil mimicking primary angiitis of the central nervous system. Arch Neurol 2002;59:1480–1483.
8. Le Ber I, Carluer L, Derache N, Lalevée C, Ledoze F, Defer GL. Unusual presentation of CADASIL with reversible coma and confusion. Neurology 2002;59:1115–1116.
9. Jankovic J. Blepharospasm with basal ganglia lesions. Arch Neurol 1986;43:866–868.
10. Bruening R, Dichgans M, Berchtenbreiter C, 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;22:1268–1274.
11. Fattapposta F, Restuccia R, Pirro C, et al. Early diagnosis in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): the role of MRI. Funct Neurol 2004;19:239–242.
12. Ebke M, Dichgans M, Bergmann M, et al. Cadasil: skin biopsy allows diagnosis in early stages. Acta Neurol Sand 1997;95:351–357.
13. Cummings JL, Mega MS. Neuropsychiatry and behavioral neuroscience. Oxford: Oxford University Press; 2003.
14. Leinberg HS. Frontal lobe dysfunction in secondary depression. J Neuropsychiatry Clin Neurosci 1994;6:428–442.
15. Liebetrau M, Herzog J, Kloss C, Hermann G, Dichgans M. Prolonged cerebral transit time in CADASIL: a transcranial ultrasound study. Stroke 2002;33:509–512.
16. van den Boom R, Lesnik O, Spilt A, et al. Cerebral hemodynamics and white matter hyperintensities in CADASIL. J Cereb Blood Flow Metab 2003;23:599–604.
17. Parisi V, Pierelli F, Fattaposta F, et al. Early visual function impairment in CADASIL. Neurology 2003;60:2008–2010.
18. Lesnik Oberstein SA, Jukema JW, Van Duinen SG, et al. Myocardial infarction in cerebral autosomal dominant arteriopathy with subcortical infracts and leucoencephalopathy. Medicine (Baltimore) 2003;82:251–256.