

Unusual clinical features and early brain MRI lesions in a family with cerebral autosomal dominant arteriopathy

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Article abstract—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a recently described inherited disorder. The pathologic gene maps on chromosome 19. The clinical spectrum of the disease consists of recurrent strokes, migraine, transient ischemic attacks, mood changes, and dementia. We report a genetically assessed CADASIL family with atypical clinical presentations of epileptic seizures. In two asymptomatic family members there were early brain abnormalities on MRI. Our report expands the clinical spectrum of CADASIL and suggests that it is possibly an undiagnosed disorder.

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The acronym CADASIL^{1,2} (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) designates a recently described adult-onset inherited disease.^{1,3–11} The neuropathologic hallmark consists of thickening of the tunica media of the small cerebral arteries caused by deposition of granular electron-dense material and leading to subcortical ischemic lesions.^{5,8,11–13} Brain MR images show bilateral confluent ischemic areas in the cerebral white matter.^{1,2,5–11} The pathologic gene has been mapped on chromosome 19.^{2,14} The clinical picture, characterized by transient ischemic attacks, migraine, neuropsychiatric changes, strokes, and dementia is similar to that of ischemic cerebrovascular disorders.¹⁵ Apart from dominant transmission, CADASIL should be suspected when there is a lack of vascular risk factors and confirmed by molecular genetic analysis.

Here we describe a previously unreported Italian family with CADASIL in which affected members did not have the typical clinical manifestations of the disease. Seizures and leukoencephalopathy were the most salient features, and at least one of the patients had clinical stroke.

Patients and methods. *Family study (figure 1).* II/4, 76 years. At age 47 this woman developed grand mal seizures. Until the age of 65, the frequency was one every 1 to 2 months. At age 65, she was treated with phenobarbital and phenytoin, and the seizures reduced in frequency. At age 76, she had a sudden right hemiparesis with aphasia. The patient had no memory impairment or dementia. T₂-

weighted images of brain MRI showed many bilateral confluent areas of altered signal in the white matter of the centrum semiovale and corona radiata (figure 2).

III/3, 56 years. This patient was healthy until age 49, when she developed absence-type seizures with a frequency of 5 to 7 per week. The seizures are characterized by detachment from the environment, a duration of 10 or 20 seconds, and motor automatisms (fumbling of the limbs or fingers). She is currently being treated with 400 mg/day carbamazepine. Neurologic and mental status examination are normal. She has occasional episodes of forgetfulness that do not limit her daily activities. T₂-weighted brain MR images showed bilateral and partially confluent areas of altered signal in the white matter of the centrum semiovale (figure 3). Similar focal lesions were evident in the pons.

III/6, 40 years. This man appears healthy, with normal neurologic examination. Brain MRI showed small sporadic bilateral ischemic lesions in the cerebral white matter (figure 4).

III/8, 38 years. This woman complains of occasional episodes of memory impairment that do not affect her daily activities. Neurologic and mental status examinations are normal. T₂-weighted brain MR images showed many bilateral areas of altered signal with diameters of about 5 mm in the cerebral white matter (figure 5).

Laboratory tests. Routine blood chemistry, apoproteins A and B, leukocyte lysosomal enzymes, partial thromboplastin time, platelet function, anti-phospholipid antibodies, immunologic and enzyme assays for protein C and S activity, plasminogen and protein C activators, heparin cofactor II and antithrombin III function were negative or normal in the four family members, with the exception of

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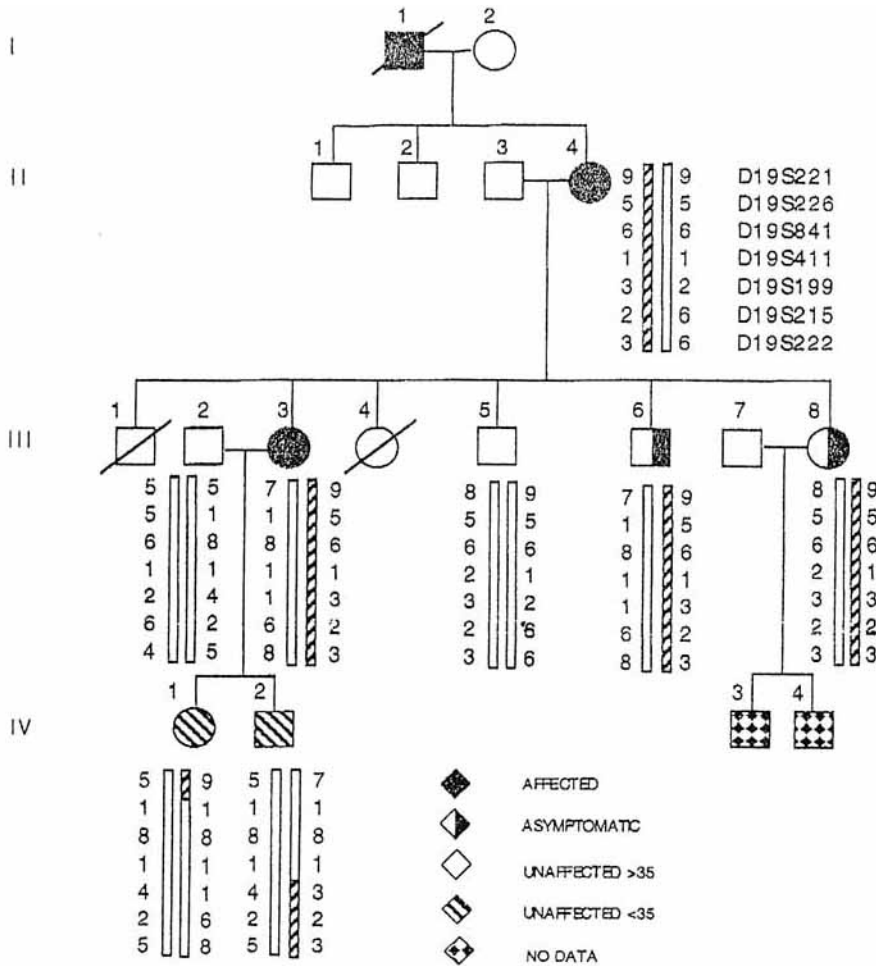


Figure 1. Pedigree and segregation of haplotypes. Open bars represent the low-risk haplotype. Cross-hatched bars represent the high-risk haplotype. The generations are indicated by Roman numerals. Filled symbols represent subjects with abnormal MRI and neurologic symptoms. Half-filled symbols represent asymptomatic subjects with abnormal MRI. Empty symbols represent unaffected subjects older than age 35 without neurologic symptoms. Hatched symbols indicate unaffected subjects younger than age 35 without neurologic symptoms and with normal MRI results.

elevated serum levels of cholesterol (347 mg%) in patient II/4. ECGs and echocardiograms were normal. None of the four patients had hypertension. Doppler ultrasonography of the carotid vessels (normal in patients III/3 and III/6) showed bilateral calcified plaque at the origin of the internal carotid arteries in patient II/4. EEG was normal in patients III/3 and III/6; patient II/4 showed diffuse theta activity.

Other family members. Subject I/1 died at age 78 years of unknown causes. He suffered from frequent grand mal-type epileptic seizures from the age of about 50 years. Subjects III/4, IV/1, and IV/2 were apparently healthy; neurologic examinations were normal. Brain MRI was normal in subjects IV/1 and IV/2 and was not performed in subject III/4. Subjects III/1 and III/4 died in the perinatal period of unknown causes. Doppler ultrasonography of the carotid vessels and EEG were normal in subject III/5. Subjects II/1 (aged 84 years), II/2 (81 years), IV/3 (10 years), and IV/4 (7 years) were reported to be healthy, but were not available for examination.

Molecular genetic analysis. Microsatellite analysis. A linkage study was performed in order to see whether CADASIL was linked to chromosome 19 in this family. Seven polymorphic microsatellite markers from the Génethon linkage map¹⁶ (D19S221, D19S226, D19S841, D19S411, D19S199, D19S215, D19S222) within the previously mapped region on chromosome 19 were analyzed.² The analyzed region spans a 14-cM interval between D19S221 and D19S222. In particular, markers D19S226,

841, 411, and 199 span a 2-cM interval on 19p13.1, where gene location was recently refined.¹⁴

Genomic DNA was extracted from peripheral blood lymphocytes by standard techniques.¹⁷ Microsatellite genomic sequences were amplified by polymerase chain reaction and analyzed by 6% polyacrylamide gel electrophoresis as previously described.¹¹ Microsatellite analysis was performed in the following subjects, including two with CADASIL and two asymptomatic carriers: II/4, III/2, III/3, III/5, III/6, III/8, IV/1, IV/2.

Linkage analysis. Linkage analysis was performed using the Linkage package, version 5.1.¹⁸ Lod scores were calculated for each marker for various recombination fractions. Marker allele frequencies and number of alleles of the Genome Data Bank were used. Disease status was based on brain MRI results as described by Tournier-Lasserre et al.² Asymptomatic subjects IV/1 and IV/2, under the age of 35 years, with normal brain MRIs, were regarded as being of unknown status. Subjects III/6 and III/8 with abnormal brain MRIs were considered to be asymptomatic carriers. Haplotypes were inferred by minimizing the number of crossovers.

Results. Figure 1 shows the haplotyping of the family. Crossovers were observed in subjects IV/1 and IV/2; in particular, the affected chromosome inherited from the mother was recombinant proximal to D19S221 and distal to D19S199, respectively. These two individuals (IV/1, aged 32 years, and IV/2, aged 28 years) were asymptomatic,

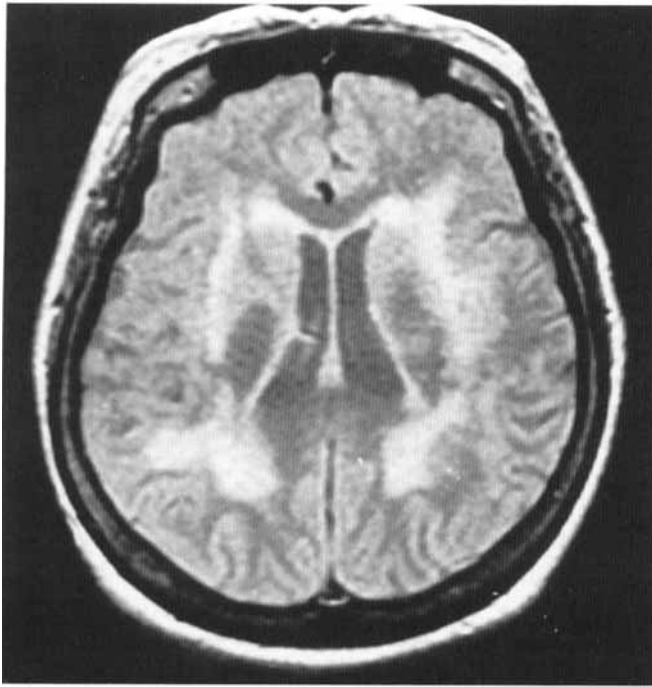


Figure 2. (Patient II/4) Brain MRI showing bilateral confluent areas of altered signal in the white matter of the centrum semiovale.

with a normal MRI; thus, according to Tournier-Lasserre et al.,² who mapped the gene within D19S226 and D19S199, they should not develop the disease. This point is supported by Chabriat et al.,¹⁵ who reported positive neuroimaging signs between ages 30 and 40 years.

The pairwise linkage analysis gave positive but not sig-

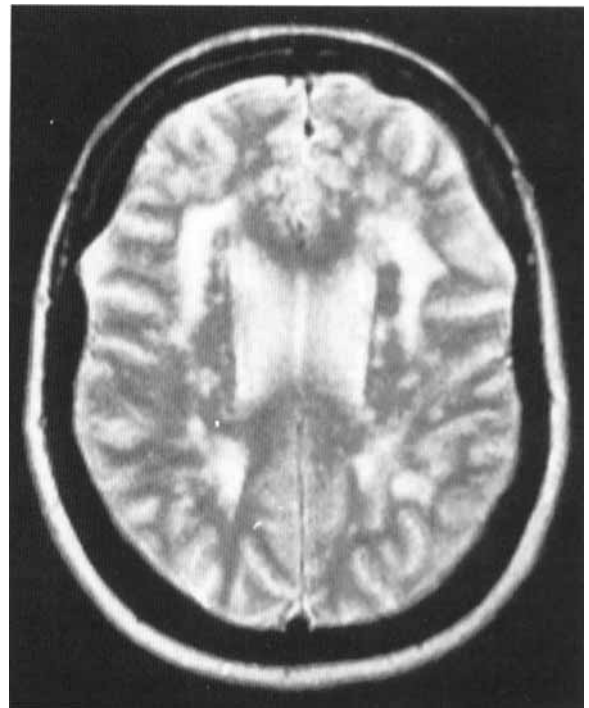


Figure 3. (Patient III/3) T₂-weighted brain MRI showing focal and partially confluent bilateral areas of hyperdensity in the cerebral white matter.

nificant lod score values with markers D19S199 and D19S222 (0.6 at O = 0) (table). The low values (Z = 0.0 at O = 0) with markers D19S221, D19S226, D19S841, and D19S411 can be explained by the low informativity of this family.

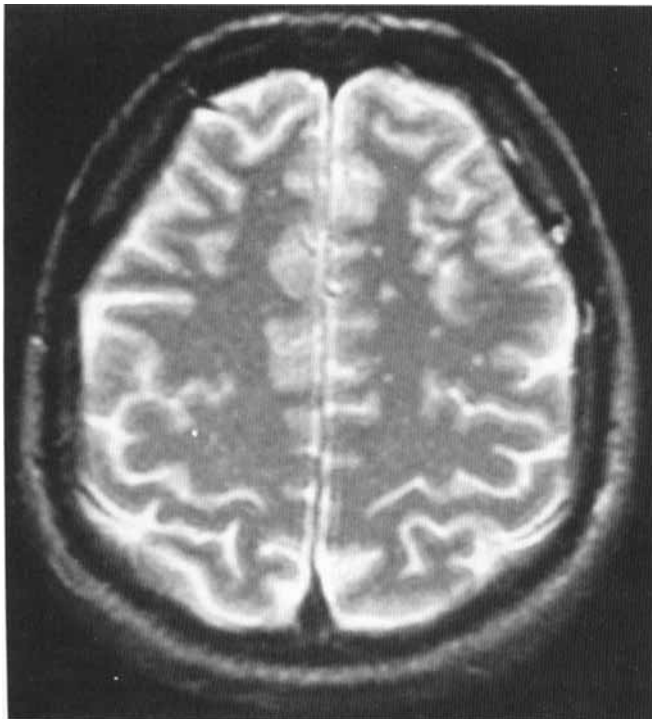


Figure 4. (Patient III/6) T₂-weighted brain MRI showing small focal areas of hyperdensity in the white matter of the cerebral hemispheres.

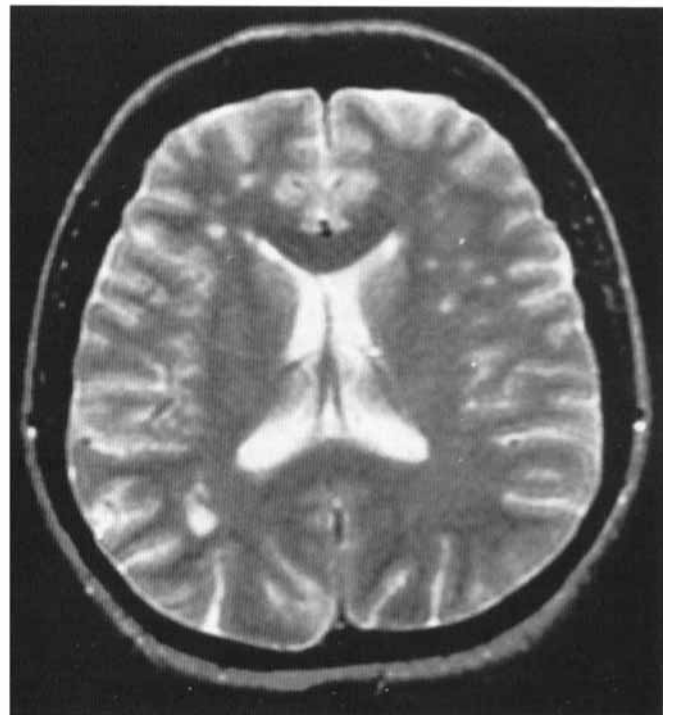


Figure 5. (Patient III/8) T₂-weighted brain MRI showing bilateral focal areas of hyperdensity in the cerebral white matter.

Table Two-point lod scores between CADASIL and chromosome 19 markers

Locus	Recombination fractions (θ)						
	0.00	0.001	0.05	0.10	0.20	0.30	0.40
D19S199	0.60	0.59	0.54	0.47	0.32	0.17	0.05
D19S215	-0.24	-0.23	-0.18	-0.14	-0.07	-0.03	-0.01
D19S222	0.60	0.59	0.54	0.47	0.32	0.17	0.05

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Discussion. In the present family, two-point linkage analysis confirmed association of the disease with anomalies of chromosome 19. Our report expands the clinical spectrum and understanding of CADASIL. Seizures occurred in three members belonging to three generations and were the main, often the only, clinical presentation. Apart from the hemiparesis in patient II/4 at age 76 years, none of the usual cardinal manifestations was present in the affected members. The small cortical microinfarcts could have been responsible for seizures in our patients. Excluding seizures caused by dysmetabolic encephalopathies, the genetic epileptic syndromes are limited to a few special forms, such as benign familiar convulsions or juvenile myoclonic epilepsy.¹⁹ Genetic epilepsies usually have infantile onset, a typical familial EEG pattern, and clinical homogeneity in a single family. The present patients did not meet these diagnostic criteria; the EEG abnormalities in patient II/4 were nonspecific.

Chabriat et al.¹⁵ recommended that the MRI finding of small focal ischemic areas in the cerebral white matter of young or adult subjects, in the absence of any known risk factors for vascular disease, should prompt investigation of family members for CADASIL. On the basis of the present report, the association of familial epilepsy and brain MRI abnormalities should also suggest CADASIL. Because two asymptomatic family members had slight white matter abnormalities, brain MRI is confirmed as the best diagnostic tool, prior to molecular genetic analysis. Our family suggests that CADASIL is possibly an underestimated disorder.

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