Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: MR Findings

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PURPOSE: To describe the MR appearances of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. **METHODS:** MR examinations were performed on 15 family members (both symptomatic and asymptomatic). The phenotype was defined by the presence of abnormalities on MR scanning in genetically susceptible individuals. **RESULTS:** There were 10 abnormal and 5 normal MR scans. Three subjects with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy had moderate or severe neurologic deficits, 4 had transient focal neurologic symptoms, 2 had migraine, and 1 was asymptomatic (all these had abnormal MR scans). Only 1 subject with migraine had a normal MR. Four other asymptomatic family members had normal scans. Two main abnormalities emerged. First, small, linear, and punctate lesions were identified in the periventricular white matter, brain stem, basal ganglia, and thalamus. Second, large confluent patches of abnormal tissue were present in subcortical regions that often were symmetric and had a tendency to occur in the temporal lobes. **CONCLUSIONS:** The diffuse myelin loss and small infarcts that cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are well demonstrated with MR. Presymptomatic abnormalities can be seen on MR.

Index terms: Arteries, diseases; Brain, diseases; Brain, magnetic resonance; Familial conditions

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Several families with a condition characterized by recurrent strokes, with stepwise progression of neurologic deficits and, ultimately, dementia and severe motor disability, have been described in the literature (1–7). An autosomal dominant mode of inheritance has been demonstrated and recently the genetic defect causing the disease has been located in chromosome 19q12 (8). The actual gene responsible has not yet been identified, but several markers are known to span the region that contains it on chromosome 19. *Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (*CADASIL*) is the unwieldy name that the syndrome has been given. Brief descriptions of the neuroimaging abnormalities associated with CADASIL have been published (5, 6). The purpose of this study was to evaluate in detail the characteristic magnetic resonance (MR) findings in a family with this rare disorder and, in addition, to study their asymptomatic first-degree relatives.

Subjects and Methods

Fifteen members of an Irish family affected with CADASIL agreed to undergo examination. Noncontrast scans were obtained using either a 0.5-T GE or a 1.5-T Siemens scanner. Three scans were performed on the latter, courtesy of Dr David Miller, National Hospital, Queen Square, London, England. Sagittal T1-weighted images (440/14/2 [repetition time/echo time/excitations]), axial T2-weighted (2500–2900/100/1–2), and proton-density (2500–2900/20–40/1–2) sections were used. Section thickness was 5 mm and a 256 × 256 (sagittal) or 160 × 256 (axial) matrix was used. The phenotype of CADASIL was defined as the presence of characteristic MR findings in a genetically at-risk family member. Linkage analysis was performed on blood drawn from all patients to determine genetic susceptibility, using six markers spanning the CADASIL locus, as described in detail elsewhere (9). The ethics committee of St Vincent's

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Clinical and MR features of 15 subjects with CADASIL

Patient	Age, y (onset)	Clinical Features	MR Leukoencephalopathy	MR Infarcts
1	60 (37)	Spastic quadriparesis, pseudobulbar palsy, incontinence, and dementia	Symmetric, widespread lesions in temporal lobes and deep white matter of cerebral hemispheres Focal low signal areas within these lesions	Multiple, involving brain stem, left thalamus, basal ganglia, and left dentate nucleus
2	36 (32)	Transient focal neurologic symptoms lasting hours	None	Basal ganglia and subcortical white matter of frontal, parietal, and occipital lobes
3	31 (21)	Transient leg weakness 10 years ago	None	Periventricular white matter, right thalamus, and bilateral external capsule
4	36 (35)	Common migraine	Early confluent change in both temporal lobes and adjacent to anterior horns of lateral ventricles	Right side of pons, basal ganglia, centrum semiovale, and left thalamus
5	39 (4)	Hemiplegic migraine	Both temporal, occipital, and frontal lobes, and corona radiata	Both thalami, basal ganglia, pons, and external capsules
6	27 (24)	Single transient episode of dysphasia	Anterior portions of temporal lobes bilaterally; left frontal lobe	Left thalamus, basal ganglia, and bilateral deep white matter
7	37	None	None	None
8	29	None	None	None
9	36	Migraine	None	None
10	35 (27)	Three transient episodes of sensory/motor loss	Bilateral centrum semiovale and temporal lobes	Bilateral deep white matter, with sparing of basal ganglia
11	33	None	None	None
12	35	None	Small areas adjacent to occipital horns	Bilateral subcortical and deep white matter
13	63 (28)	Lower limb spasticity	Large areas in both temporal and occipital lobes	Pons, basal ganglia, thalami, and external capsule
14	24	None	None	None
15	61 (47)	Spastic quadriparesis, pseudobulbar palsy	Bilateral temporal lobes and corona radiata	Bilateral subcortical and periventricular deep white matter

Hospital sanctioned the study. It was decided not to examine patients under the age of 20 years.

Results

The disorder affecting this family showed conclusive linkage to the CADASIL locus on chromosome 19. This was established by obtaining highly significant lodscores for two of the markers, with positive lodscores for the other four, in all family members. The genetic results are more fully described elsewhere (9). The Table outlines the clinical and imaging characteristics of all 15 subjects; there were, by MR criteria, 10 individuals with CADASIL and 5 unaffected family members. Nine patients had definite clinical features of CADASIL, and all of these had abnormal MR findings. One asymptomatic family member had an abnormal MR finding and by definition, therefore, CADASIL.

A spectrum of abnormality was observed. Patient 1 (the index case) was chairbound and totally dependent on nursing care. MR showed very severe disease throughout the brain, with virtually no normal white matter (Fig 1). This contrasts with patient 6, for example, who had suffered only a single transient neurologic episode and was normal clinically at the time of examination. She was obviously at a significantly earlier stage of disease development, and this correlated well with the much more subtle MR abnormalities (Fig 2). In general, there was a reasonable correlation between clinical severity and the degree of abnormality on imaging, although patient 5 was a notable exception. She had severe MR changes (Fig 3),

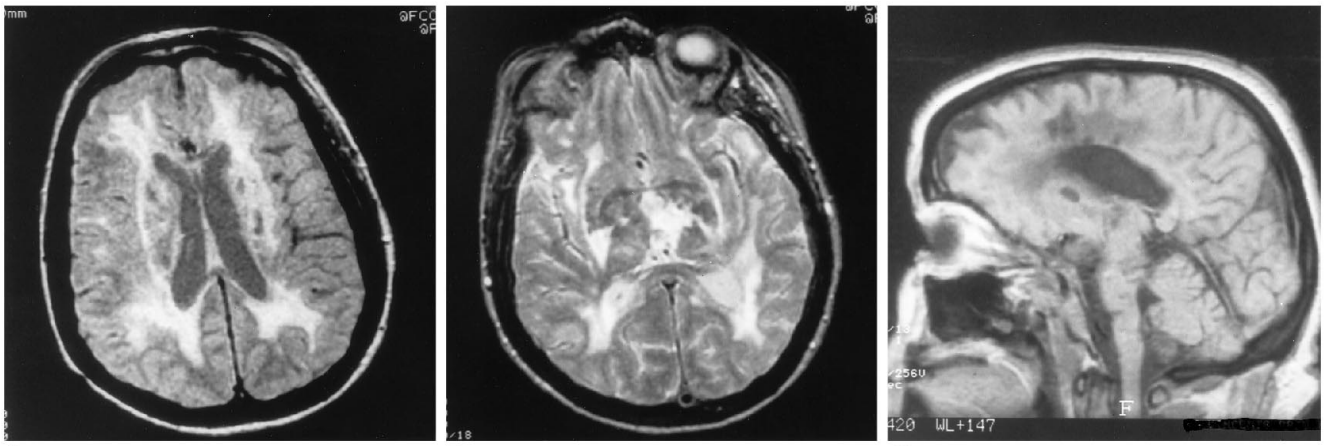

Fig 1. Images from the index patient, who was 60 years old at the time of scanning. Transient neurologic deficits had begun 27 years before. Permanent strokes over the last 9 years had led to dementia, pseudobulbar palsy, and spastic quadriparesis.

A, Axial image (2500/40/2) shows almost complete replacement of the white matter by abnormal high signal. Both the internal and external capsules are involved. Focal low-signal areas (representing cystic degeneration) are present within these larger abnormalities. There is notable cortical sparing.

B, Axial image (2500/100/2) with confluent regions of high signal in the anterior part of the temporal lobe and the periventricular white matter of the occipital lobe. In addition, a smaller focal lesion is present in the left thalamus. This small lesion also was hyperintense with proton-density weighting, consistent with an infarct.

C, Sagittal image (440/14/2), 5 mm to the right of the midline, shows several focal low-signal lesions in the corpus callosum, pericallosal region, and thalamus, with the same signal as cerebrospinal fluid. With T1 weighting, a more widespread intermediate- to low-signal lesion is seen in the white matter superior to the corpus callosum.

and although she had suffered from frequent disabling attacks of hemiplegic migraine as a child, she had only one or two bouts a year as she grew older. One patient (patient 9) with a history of migraine had a normal scan. Of the five patients who were clinically asymptomatic, one (patient 12) had an abnormal scan and, thus, a positive phenotype.

Large confluent areas of high-signal change on T2- and proton density–weighted images were seen throughout the white matter, although a definite predilection for the anterior part of the temporal lobes and the periventricular portion of the occipital lobes was observed. The abnormal areas were reasonably well defined and extended from the periventricular white matter to the subcortical white matter in the most severe cases. These lesions were of low signal on T1-weighted images.

The other type of abnormality consisted of 0.5- to 2-cm linear or punctate lesions with a tendency to occur in the periventricular deep

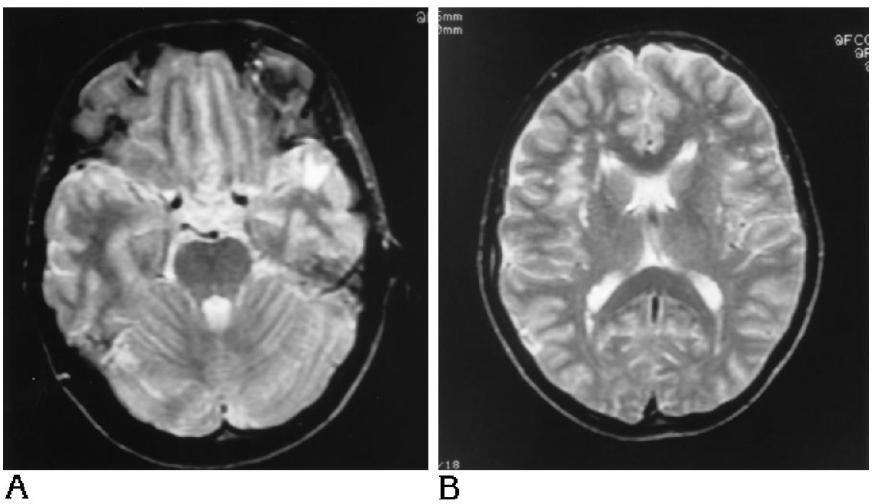

Fig 2. A 27-year-old patient who had a single transient episode of dysphasia 3 years before.

A, Axial image (2500/100/2) shows a small area of confluent high-signal change in the subcortical white matter of the left temporal lobe.

B, Axial image (2500/100/2) at a higher level in the same patient demonstrates multiple small linear and punctate lesions in the periventricular regions and in both external capsules. These also were hyperintense with proton-density weighting. Early confluent white matter change is present lateral to the anterior horn of the right lateral ventricle.

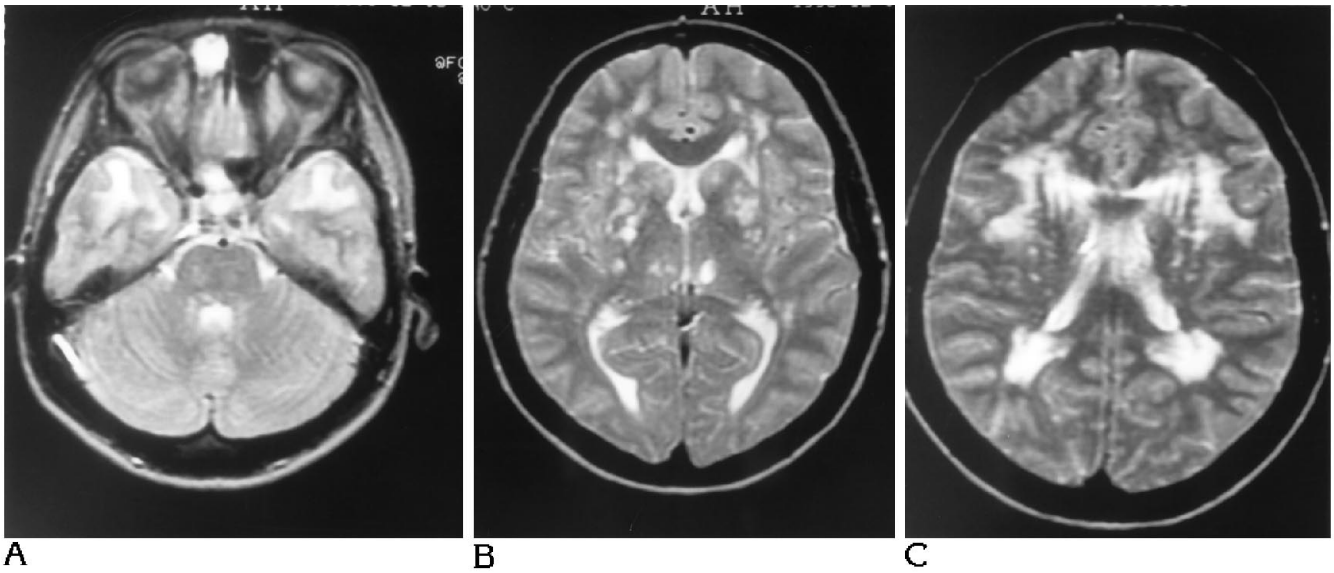

Fig 3. A 39-year-old woman, now clinically healthy, who had frequent childhood attacks of hemiplegic migraine since 4 years of age.

A, Axial image (2500/100/2). The anterior portions of both temporal lobes show confluent symmetric white matter abnormality.

B, Axial image (2500/100/2) at the level of the thalami in the same patient. Punctate lesions are seen in the thalami and lentiform nucleus bilaterally. Early change of the more confluent type has occurred adjacent to the frontal horns of the lateral ventricles.

C, Axial image (2500/100/2) demonstrates abnormal white matter signal beside the frontal and occipital horns of the lateral ventricles, as well as multiple tiny, sharply defined lesions in the deep white matter.

white matter, subcortical white matter, external capsule, basal ganglia, thalamus, and pons. These more sharply defined areas were of higher signal on T2-weighted images than the larger lesions. On the proton density–weighted images, some of these lesions were abnormally hyperintense, suggesting infarction. Others, particularly in the more severely affected patients, had the same signal as cerebrospinal fluid, indicating lacunar degeneration. With T1 weighting, they were of lower signal than the confluent areas of abnormality, again having in some instances the same signal as fluid.

Discussion

CADASIL affects patients in midlife, with recurrent neurologic episodes that are initially transient motor and sensory disturbances. It is clear from our family members that the initial symptom may be migrainous—common, classical, or hemiplegic. Late in the course of the condition, the neurologic deficits become permanent, and patients develop a stepwise deterioration that leads to spastic quadriparesis, pseudobulbar palsy, incontinence, and dementia. Death generally occurs in the seventh decade because of complications of these problems. The mode of transmission appears to be autosomal dominant in this and other families with CADASIL. The disease locus has been assigned to chromosome 19q12 in two unrelated French families by Tournier-Lasserve (8). These genetic findings have been confirmed in our family.

The MR findings are striking. Broad, confluent areas of white matter are replaced by tissue with abnormal high signal on T2 and proton-density weighting. Symmetric involvement of the temporal and occipital lobes and of the centrum semiovale were found. Previous studies have described a diffuse involvement of the white matter, without noting a propensity for these regions (5, 6). One autopsy study of a patient suffering from CADASIL has been described in the literature (10). On examination with special stains for myelin, there was pallor of the white matter with some sparing of the U fibers, especially in the frontal lobes. MR had shown a diffuse white matter abnormality. It seems reasonable to assume that diffuse myelin loss forms the substrate for the confluent patches of abnormal white matter signal in our series.

The other type of abnormality we observed was a smaller, more sharply defined, linear or punctate lesion. The MR appearances were consistent with small infarcts, some of which had become lacunar, and, indeed, multiple old cys-

tic infarcts were found in the brain of the patient who had an autopsy (10). We observed these lesions at many sites. Characteristically, they involved the white matter either in immediate periventricular or subcortical regions. Unlike the other main finding, no propensity for the white matter of any particular lobe was demonstrated for these lesions. They also were found with regularity in the basal ganglia, brain stem, thalamus, and external capsule. Mas et al also noted multiple lesions in the basal ganglia, thalamus, brain stem, and cerebral white matter (6). However, they also reported many patients with cerebellar lesions, whereas only 1 of our 10 affected subjects had such an abnormality. Of note, both this and other studies have demonstrated a tendency for involvement of the external capsule (5, 6).

In general, there was a reasonable correlation between the severity of the clinical syndrome and the degree of brain involvement on MR grounds. However, one of our patients (patient 5) seemed to be an exception, as described previously in "Results." It could be argued that the frequent, severe attacks of hemiplegic migraine that occurred throughout her childhood were the presenting symptoms of CADASIL.

Several other conditions are characterized by recurrent strokes and leukoencephalopathy. Binswanger disease causes both focal and more-widespread signal changes in the white matter on MR (11). However, it presents later, is associated with hypertension, and does not have a familial pattern of occurrence. Various other rare familial conditions are associated with recurrent strokes, such as hereditary dyslipoproteinemias, thrombotic disorders, homocystinuria, and Fabry disease. These all have characteristic clinical features that allow them to be distinguished.

It is naturally difficult to spot a familial link in conditions that occur relatively late in life, especially when they are characterized by common problems such as stroke. A genetic association easily could be overlooked or ignored by the patient or physician. We believe that a knowledge of this condition may lead to the discovery of many more affected families. Although it is often difficult to differentiate between white matter disorders with MR scanning (especially as the patient gets older), the abnormalities we have described, when allied to the appropriate clinical setting, should enable diagnosis. The small number of families described in the literature is no doubt an underestimation of the prevalence of this disease. MR is valuable not only in the diagnosis of those patients who are clearly affected clinically, but also (as shown in patient 12) in identification of patients at an asymptomatic stage.

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