Early diagnosis in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): the role of MRI

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Accepted for publication: November 26, 2004

Summary

The aim of our work was to evaluate the early presence of white matter changes on magnetic resonance imaging (MRI) in young asymptomatic children of patients with full-blown cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in whom DNA analysis revealed a Notch3 Cys146Tyr missense mutation on chromosome 19.

Brain MRI was performed in all subjects using axial and coronal spin-echo proton density and T2-weighted images, axial fluid-attenuated inversion recovery (FLAIR) and sagittal and axial T1-weighted images.

In asymptomatic subjects with Notch3 gene mutation, MRI showed small T2 hyperintense foci in periventricular and subcortical white matter.

Routine use of MRI in the initial phases of a CADASIL diagnostic work up and the subsequent recognition of early abnormal findings in asymptomatic subjects may lead to prompt diagnosis of the disease in these patients. Moreover, these findings suggest that genetic screening is warranted in the presence of a suspect clinical history with specific MRI abnormalities.

KEY WORDS: CADASIL, magnetic resonance imaging, Notch3, stroke.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal vasculopathy caused by point mutations in the Notch3 gene, located on chromosome 19 (1). This disease is characterised by migraine with aura, recurrent transient ischaemic attacks or stroke, psychiatric disease and subcortical dementia. Vascular risk factors such as hypertension are absent. The finding of a specific mutation in the Notch3 gene by DNA analysis in affected subjects confirms a presumed diagnosis of CADASIL (2).

The pathological hallmark of CADASIL is a non-atherosclerotic, amyloid-negative angiopathy which primarily affects the leptomeningeal and long perforating arteries of the brain. Ultrastructural examination reveals granular osmiophilic deposits within the vascular basal membrane, which are considered diagnostic because they have not been observed in other vascular encephalopathies (3). A number of macroscopic studies have described subcortical lacunar infarcts and diffuse myelin pallor, mainly in periventricular areas (4-7). The vasculopathy leads to destruction of the smooth muscle cells and a fibrous thickening of the arterial wall (5). Magnetic resonance imaging (MRI) in symptomatic CADASIL patients typically reveals diffuse white matter areas with high signal intensity and lacunar infarcts in the centrum semiovale, thalamus, basal ganglia and pons (8-10).

We used MRI to study both the asymptomatic and symptomatic members of a single family with a neuropathologically and genetically confirmed diagnosis of CADASIL to determine the reliability and specificity of the information yielded by MRI.

Materials and methods

Six asymptomatic subjects (IV-1, IV-2, IV-3, IV-5, IV-6, IV-7) gave their informed consent to be enrolled in this study; IV-4 did not. Three subjects (IV-3; IV-6; IV-7) were positive for the Notch3 gene with Cys146Tyr mutation. Extensive laboratory investigations failed to demonstrate any known risk factors for vascular disease. The neuropsychological and neurological examinations were normal.

Three symptomatic subjects (III-2; III-4, III-5, parents of asymptomatic subjects) with the same Notch3 gene mutation were also included in this study. Subject III-2 had a history of recurrent migraine-like episodes, occasionally accompanied by right-sided hemiparesis and motor aphasia which resolved in a few days. Neuropsychological examinations revealed the development of progressive cognitive impairment. Subject III-4 had recurrent migraine-like episodes associated with sensory-motor aphasia and mental confusion. Neuropsychological examinations detected moderate memory loss and attention deficit. Subject III-5 had occasional episodes of migraine-like attacks with spatial and temporal disori-
entation; no deficits were observed on the neuropsychological examinations. Informed consent was also received from these patients.

Molecular analyses were performed on all three children and on their parents, as previously described (11). Brain MRI was performed in all the subjects using a 1.5 T machine (Philips Intera Master, Andover, MA). The protocol included axial and coronal spin-echo proton density and T2-weighted images (TR/TE 2295/20,90), axial fluid-attenuated inversion recovery (FLAIR) images (TR/TE/TI, 6000/100/2000), sagittal and axial T1-weighted images (TR/TE, 582/15).

All the images were reviewed by a neuroradiologist blinded to the clinical details. Lesions involving the U fibres, cerebral white matter, internal and external capsules, corpus callosum, basal ganglia, brainstem and cerebellum were counted and scored from 0 to 3 (0: no lesion; 1: one or two lesions; 2: more than two focal lesions; 3: multiple lesions with confluence) and overall involvement was graded as normal, minimal, moderate or severe (12).

Results

The MRI details of the lesions in each part of the brain are summarised in Table I. The three symptomatic subjects displayed severe white matter abnormalities on MRI characterised by confluent, bilateral, symmetrical areas of hyperintensity in the periventricular and subcortical white matter (Fig. 1).

In the asymptomatic CADASIL subjects, MRI revealed small T2 hyperintense foci in the periventricular white matter in one case (IV-3), and small T2 hyperintense foci in the periventricular white matter combined with small bilateral T2 hyperintense areas in the subcortical white matter in two cases (IV-6, IV-7) (Fig. 2). MRI results were normal in the asymptomatic subject without Notch3 gene mutation.

Neither the symptomatic nor the asymptomatic subjects showed any evidence of cerebellar, brainstem, basal ganglia or corpus callosum U-fibre involvement.

Discussion

Neuroimaging has played an important role in the study of CADASIL ever since this disease was first hypothesised to be hereditary (13,14). The subcortical infarcts and leukoencephalopathies that characterise CADASIL can be identified in vivo only by means of MRI. In symptomatic CADASIL, MRI can be used to detect specific abnormalities in the subcortical white matter, as well as in other brain regions, including the subcortical grey matter (8,15,16).

Neuroimaging, always crucial in the diagnosis of

![Figure 1 - Symptomatic CADASIL subjects. Axial fluid-attenuated inversion recovery (6000/100/2000) MRI shows confluent, bilateral, symmetrical areas of hyperintensity in the subcortical white matter in case III-2 (a), III-4 (b) and III-5 (c).](image)

![Figure 2 - Asymptomatic CADASIL subjects. Axial fluid-attenuated inversion recovery (6000/100/2000) MRI shows bilateral hyperintense foci in the periventricular white matter in case IV-3 (a); small bilateral hyperintense areas are also evident in the subcortical white matter in case IV-6 (b) and in case IV-7 (c).](image)

### Table I - Detailed MRI scoring of lesions.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Notch3 mutation</th>
<th>U fibres</th>
<th>White matter</th>
<th>Capsules</th>
<th>Corpus callosum</th>
<th>Basal ganglia</th>
<th>Brainstem</th>
<th>Cerebellum</th>
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<tr>
<td></td>
<td></td>
<td>Subcortical</td>
<td>Deep</td>
<td>Periventricular</td>
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<td>External</td>
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0=no lesions; 1=one or two focal lesions; 2=more than two focal lesions; 3=multiple lesions with confluence.
CADASIL, could, in the light of recent findings, be regarded as indispensable even when this disease is merely suspected (17,18). Differentiation of CADASIL from other white matter diseases, such as ischaemic small vessel diseases, may be difficult in clinical practice, especially in the early phases of disease. Recent studies have shown that T2-weighted and FLAIR MRI (19), which are characterised by high resolution and sensitivity, best detect minimal abnormalities in CADASIL. In symptomatic CADASIL subjects, T2-weighted and FLAIR MRI hyperintensities in the cerebral white matter, located in the anterior temporal lobes, periventricular changes and external capsules, are known to be the characteristic findings in this pathology; given that periventricular hyperintensities are present in 96% of patients, their absence is an exclusion criteria for diagnosis of CADASIL (8).

In our study, T2-weighted and FLAIR MRI disclosed early signal intensity changes in the subcortical and periventricular white matter in asymptomatic CADASIL subjects. Although differentiation of CADASIL lesions from other causes of white matter abnormalities is still a problem (15), the clinical and genetic context encourages us to suppose that the MRI lesions observed in our patients represent small and/or punctate lacunes of ischaemic nature. However, more recently a similar type of lacunar lesion caused by a distension of the perivascular space of perforating arteries at the level of the junctions of grey and white matter and by spongiosis in the surrounding parenchyma has been reported in CADASIL patients (20).

These findings may, in agreement with Couthard et al. (21), represent an early sign in young subjects that, over time, is likely to involve progressively more white matter. Our results suggest that the early appearance of cerebral lesions in young subjects may be the main prognostic indicator of progressive lesion development in CADASIL. This finding supports data from a previous electrophysiological study performed on asymptomatic CADASIL subjects, which showed early vascular retinal impairment associated with MRI abnormalities, particularly in young asymptomatic subjects (22). Our data, as might be assumed comparing the MRI abnormalities observed in the asymptomatic and symptomatic subjects, could indicate that silent lesions gradually become clinically apparent as the number of lesions grows and the compensatory mechanisms are no longer able to cope, which is what is reported to occur in the retinal layers. Since penetrance of the disease is complete (23), but expression varies as regards age at onset, severity of clinical symptoms, and progression, we believe that the possibility of identifying MRI abnormalities in asymptomatic subjects will, by allowing a chronoclinical chrono-radiological staging of the disease, increase knowledge of its natural course. Although the main purpose of genetic counselling is detection of a notch3 gene mutation, MRI could be useful in those CADASIL cases in whom no mutation can be found; early detection of cerebral lesions on MRI could play a crucial role within the framework of counselling, giving patients the possibility of making family and life planning choices.

In conclusion, MRI should be considered a fundamental investigation for the early diagnosis of CADASIL in asymptomatic “at risk” subjects, as well as in subjects with a family history of migraine-like attacks not associated with other risk factors. CADASIL should be suspected when MRI shows subcortical white matter abnormalities, particularly if retinal impairment is detected. Genetic analyses may then be performed to confirm the diagnosis unequivocally.

References