Brain Stem MRI Signal Abnormalities in CADASIL

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Background—We recently showed that the severity of MRI signal abnormalities increases with age in CADASIL, an arteriopathy due to mutations of *notch 3* gene on chromosome 19. Previous results also suggest that the various hemispheric subcortical areas have a different vulnerability to ischemia in this disease. The distribution of the lesions at the brain stem level has not yet been reported.

Case Descriptions—We reviewed the MRIs of 68 affected patients having signal abnormalities in the hemispheric white matter to assess the distribution and clinical consequences of brain stem signal abnormalities in CADASIL. We found hypersignals on T2-weighted images in the brain stem in 45% of the subjects. The pons was more frequently involved (100%) than the mesencephalon (69%) and the medulla (35%). Hyposignals on T1-weighted images, at the brain stem level, were observed only in two thirds of these subjects. The lack of signal abnormalities reaching the brain stem surface and the absence of cerebellar lesions were noteworthy.

Conclusions—Brain stem signal abnormalities observed in CADASIL are found in regions irrigated only by perforating arteries. These results support parallel observations made for CADASIL-associated signal abnormalities in the cerebral hemispheres and emphasize the importance of the angioarchitecture of the cerebral vasculature to explain why a condition characterized by a systemic vessel wall pathology is manifested only as a brain disease. *(Stroke. 1999;30:457-459.)*

Key Words: brain stem ■ CADASIL ■ cerebral arteries ■ hypersignals ■ magnetic resonance imaging

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a hereditary small-artery disease of the brain secondary to mutations of *notch 3* gene on chromosome 19. It is responsible for recurrent subcortical strokes in midadulthood, and it leads progressively to dementia 10 to 30 years after onset. A major feature of this disease is the presence of increased signal intensities (hypersignals) on T2-weighted images in the hemispheric white matter in all clinically affected subjects and in asymptomatic carriers of the mutated gene. In a series of 75 patients, we previously demonstrated that the severity of hemispheric white matter hypersignals dramatically increases with age in CADASIL. We also showed that whereas hypersignals were constant in the periventricular white matter, they were less common at a distance from these areas, suggesting a variable topographical susceptibility to ischemia among the different regions irrigated by the perforating arteries. The aim of the present study was to investigate the distribution of signal abnormalities within the brain stem.

Subjects and Methods

We studied the frequency, location and clinical significance of brain stem MRI signal abnormalities in 68 CADASIL patients having hemispheric hypersignals on T2 weighted images (28% with hypersignals located in basal ganglia). All of them carried the affected haplotype and belonged to families with at least 1 member having a proven deleterious mutation in *notch 3* gene (error risk of <1/10000 compared with direct screening of mutation in each subject). MRI examinations performed in different neuroradiological centers between 1993 and 1997 included coronal, axial, or sagittal T1-weighted and coronal or axial T2-weighted images of thicknesses varying between 5 and 10 mm. The following parameters were evaluated on MRI: (1) frequency of brain stem lesions according to age; (2) frequency and location of lesions at the 3 brain stem levels; and (3) maximal surface of hypersignals at the midpons (calculated with tracing paper) and correlation with the severity of hemispheric hypersignals calculated according to the Scheltens method (sum of the scores of hypersignals in the deep white matter obtained for the frontal, parietal, temporal, and occipital lobes, each score varying from 0 to 6).

Results

Thirty-one of 68 patients (45%; mean±SD age, 52±12 years) had signal abnormalities in the brain stem. The frequency of these lesions increases with age (25% <30 years, 85% >60 years).

Clinically, 5 subjects (16%) were totally asymptomatic. The others had a previous history of transient ischemic attacks (n=5), completed strokes (n=15), mood disorders (n=5), or migraine with aura (n=6). Eight subjects were...
demented. One third had a pseudobulbar palsy; none presented with a complete cranial nerve palsy.

Within this sample, the frequency of T2 hypersignals was 100% in the pons, 69% in the mesencephalon, and 35% in the medulla. No signal abnormality was observed in cerebellum. Decreased signal intensities on T1-weighted images (hypointensities) in brain stem were found in 64% of the patients with brain stem T2 hypersignals (Figure 1). They were found in pons (63%) and mesencephalon (33%) but not in medulla.

At the pons level (n = 38), T2 hypersignals were found along the entire rostral-caudal extent of the pons, but only in the core of the structure, never reaching the surface (Figure 1). The lesions were most evident in the mid and inferior axial segments (n = 26 and n = 23, respectively) compared with the rostral portion (n = 11). They were symmetrical in 40% of cases (n = 11), overlapped the medial line in 27% of cases, and were located within the vascular territory of the anteromedial (n = 24), anterolateral (n = 15), or lateral (n = 11) group of arteries arising from the basilar artery.10 In contrast with signal abnormalities found in other territories, those observed in the lateral territory were never isolated. At the midpons level, the total area of hypersignals on T2-weighted images varied from 7 to 351 mm² (median, 60 mm²) and was not correlated with the mean score of severity calculated for the hemispheric white matter hypersignals according to the Schetens’ method. The Rankin Scale score was 1.8 ± 1.5 when this mid-pontine surface was <60 mm² and 2.2 ± 2 when it was >60 mm².

At the mesencephalon level (n = 20), hypersignals were mainly found in the vicinity of substantia nigra within the territories of anteromedial and anterolateral group of arteries arising from the arteries from the interpeduncular fossa or choroidal arteries.10

At the medullar level, hypersignals were observed at distance from the surface, sometimes overlapping different territories of the arteries arising from anterior spinal and vertebral arteries.

**Discussion**

Our results11 confirm that brain stem signal abnormalities are frequently observed in CADASIL patients. As reported for hemispheric white matter hypersignals,6 their frequency increases with age and greatly varies among the different arterial territories. The clinical manifestations observed in our series are difficult to ascribe to these signal abnormalities because of the constant presence of multiple other lesions at higher levels of the brain. However, it is noteworthy that brain stem signal abnormalities can remain totally silent in some patients, as previously reported12,13 in pontine rarefaction secondary to other arterial diseases, although the brain stem hypersignals are mainly observed at the most severe clinical stages of CADASIL.6

These signal abnormalities predominate at the rostrocaudal center of the pons; they are less frequent in the mesencephalon and rare in the medulla, in accordance with few pathological data.14 They spare the basal surface and the cerebellum. This distribution is in accordance with that reported for “pontine ischemic rarefaction” or for lacunar infarcts secondary to arteriosclerosis of pontine perforating arteries which are “terminal arteries.”13 It differs from that of infarcts extending to the brain stem surface, mostly caused by atherosclerosis or cardioembolism.15 The variable frequency of the signal abnormalities at the 3 levels of brain stem might be related to the differing lengths of perforating arteries irrigating these areas, as observed in different hemispheric regions.6

Because CADASIL is a systemic arterial disease but has a purely cerebral clinical presentation,16–18 our data suggest that the underlying pathophysiological process depends mainly on some specific characteristics of the brain angioarchitecture and patterns of circulation. Some severe hemody-
namic disturbances might result from the destruction of arterial smooth muscle cells, a pathological hallmark of CADASIL.\(^\text{16,17,19}\)

The role of these cells appears crucial in the maintenance of perfusion pressure and cerebral blood flow autoregulation in areas irrigated by perforating arteries.\(^\text{20}\)

Indeed, regions first involved in this disease are the most vulnerable, i.e., periventricular and deep white matter, which are irrigated by the longest vessels.

Our results also provide some additional information on the distribution of lesions in CADASIL and support an underlying hemodynamic ischemic pathogenesis. Furthermore, in a context of familial disorder leading to white matter MR hypersignals, some negative features might point to CADASIL: the lack of signal abnormalities reaching the surface of the brain stem, the lack of hyposignals within the medulla, and the absence of cerebellar signal abnormalities.

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