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LETTER TO THE EDITORS

A family with atypical CADASIL

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Dear Sirs,

Patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) typically manifest migraine with aura, subcortical ischemic events, mood disturbances, apathy and cognitive impairment [1–3]. We report three of four siblings with atypical CADASIL manifestations, namely progressive ataxia and spastic paraparesis.

Patient 1 (female b. 1953) complained of tension type headache, reduced concentration and memory, and fatigue after a moderate whiplash injury in 1998. Neurological examination at that time was normal, but Wechsler memory scale test showed reduced visuospatial memory. CSF and evoked potentials were normal, but MRI showed hyperintense white matter lesions. When re-examined in 2009 (Fig. 1a, b) her cognitive complaints were unchanged and neurological examination remained normal. MRI showed minor progression of the white matter disease.

Patient 2 (male b. 1940) was diagnosed as having possible multiple sclerosis in 1993 because of spastic paraparesis and internuclear ophthalmoplegia. CSF and evoked potentials at that time were normal, but MRI showed hyperintense signals in white matter (examination no longer available). Re-examination in 2001 and 2009 still showed a spastic paraparesis, but also the presence of a truncal ataxia. MRI in 2009 showed hyperintense white matter lesions (Fig. 1c, d).

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Patient 3 (male b.1943) complained of slowly progressive unsteadiness from 1998. Neurological examination in 2001 and 2008 showed bilateral dysdiadochokinesis, truncal ataxia and mild spasticity in the lower limbs with hypereflexia. MRI in 2008 showed hyperintense white matter signals and subcortical infarcts in both hemispheres and basal ganglia (Fig. 1e, f).

Patient 4 (male b. 1937) complained of unsteadiness from 2008. Neurological examination in 2009 showed pathological ocular smooth pursuit and bilateral dysdiadochokinesis. MRI in 2009 showed similar hyperintense white matter lesions as seen in the other siblings (Fig. 1e, f).

Molecular genetic testing showed that all four siblings had the *NOTCH3* gene mutation *c*.3065G>T that changes a cysteine to phenylalanine at position 1022.

Three of our patients had features of slowly progressive cerebellar disease combined in two with pyramidal tract signs. No MRI lesions or atrophy involving the cerebellum were seen in our patients, but subcortical lacunar infarcts were present in patient 3. Patient 2, who was initially diagnosed with possible multiple sclerosis, had a transient diplopia and the finding of an internuclear ophthalmoplegia, was probably caused by a brain stem infarction.

Ischemic episodes or transient ischemic attacks occur in 60–85% of the patients with CADASIL, and most of these are subcortical ischemic events [1–3]. Our patients had slowly progressive cognitive, cerebellar and/or pyramidal signs most likely due to the cerebral arteriopathy *NOTCH3* mutations, which affects vascular smooth muscle cells [4]. The main mechanism of the progressive symptoms in our patients is probably chronic hypoperfusion due to the arteriopathy which is characterised by a failure of arteries to dilate properly [4].

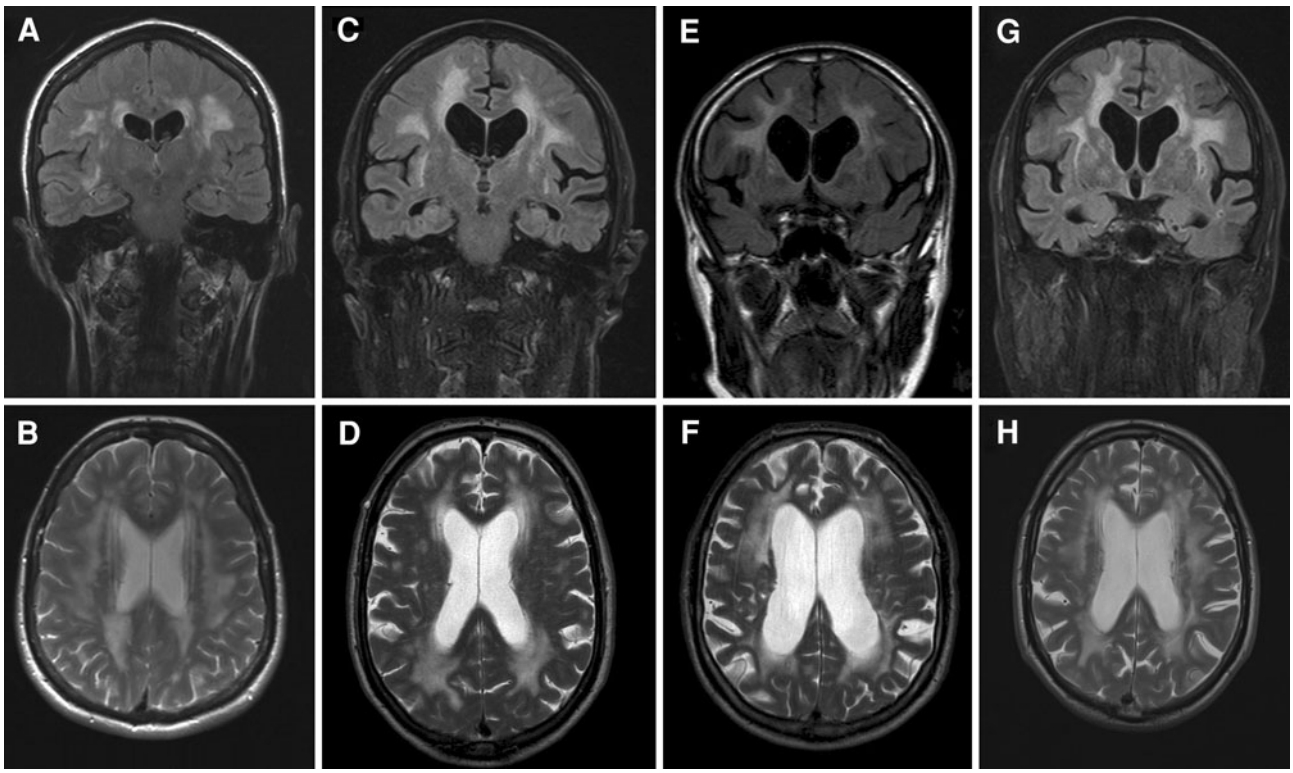

Fig. 1 All four patients had characteristic MRI findings of CADASIL. Coronar (FLAIR) and axial (T2) MRIs of patients 1 (**a**, **b**), 2 (**c**, **d**), 3 (**e**, **f**) and 4 (**g**, **h**) show hyperintense signals of white matter. Figure **e** and **f** also shows subcortical lacunar infarcts

We have no information on the siblings' children and only little information concerning their parents who are both dead. The father was apparently healthy, but the mother had progressive visual impairment said to be due to retinitis pigmentosa. Of her six siblings, one also had progressive blindness and two had cerebrovascular attacks. We have no MRI or biological material available for genetic testing from any of these individuals. Retinal abnormalities with axonal loss have been described in CADASIL while no visual symptoms were present in these patients [5, 6]. It therefore remains possible that the mother of our patients was a carrier of the *NOTCH3* mutation.

We present a family with CADASIL in which cerebellar disease including ataxia was a major feature in three of four siblings and two of these also had pyramidal tract signs. Only one of the siblings presented with a feature typical for CADASIL, namely cognitive impairment. This family confirms the intrafamilial variation in CADASIL and demonstrates that ataxia and spastic paraparesis can be presenting features.

Conflict of interest None.

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