Acta neurol. belg., 2006, **106**, 219-221

Intracerebral haemorrhage in CADASIL. A case report

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Abstract

CADASIL is an autosomal dominant inherited arteriopathy caused by a point mutation in the Notch3 gene. Classically, it is characterised by recurrent ischemic strokes, often resulting in mental decline. Intracerebral haemorrhages in CADASIL have rarely been reported. We describe a young male with a genetically proven CADASIL who developed an intracerebral haemorrhage while on anticoagulant therapy.

Key words : Anticoagulant drugs ; CADASIL ; dementia ; intracerebral haemorrhage ; microhaemorrhage.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited autosomal dominant neurological disorder with full penetrance. It is clinically characterized by the occurrence of recurrent transient ischemic attacks and ischemic strokes leading to subcortical lacunar infarcts. Eventually this leads to multi-infarct dementia, with typical frontal lobe involvement, and to invalidating motor and sensory disturbances. CADASIL is also associated with migraine with aura and pseudobulbar palsy (Guidetti *et al.*, 2006).

The genetic cause of the disorder lies in a well described spectrum of point mutations in the Notch3 gene on the short arm of chromosome 19. Notch3 encodes for a transmembrane receptor. The mutation leads to the accumulation of non-atherosclerotic granular osmiophilic material (GOM) in white matter and leptomeningeal arteries (Joutel *et al.*, 1996). On pathologic examination, a marked thickening of the media of small cerebral arteries is noted and also a loss of vascular smooth muscle cells (Lesnik *et al.*, 2001). This eventually leads to the progressive disintegration of the vascular wall (Dichgans *et al.*, 2002). Although the sensitivity is rather low (45%), the presence of GOM in the basal lamina of arteriolar smooth muscle cells in skin, is a 100% specific marker for CADASIL in symptomatic patients and can be used for diagnostic purposes (Guidetti *et al.*, 2006).

Magnetic resonance imaging shows high intensity signal lesions, typically in the temporal lobes, and areas of lacunar degeneration of subcortical white matter and basal ganglia (Guidetti *et al.*, 2006 ; Van Den Boom *et al.*, 2003). Recently the occurrence of microbleeds has been described in about 31 percent of all symptomatic CADASIL patients, while virtually none were found in asymptomatic CADASIL subjects and healthy control patients (Lesnik *et al.*, 2001).

Case report

A 45-year-old male was admitted to our hospital with an episode of acute unresponsiveness. He had collapsed at night after a short period of dysarthria and gait disturbance and was unresponsive upon arrival. Blood pressure was 140/80 mmHg. There was no fever. A spastic right hemiplegia was present besides a formerly known left hemiparesis. Bilateral Babinski signs and a right-sided Hoffman sign were present. Ankle clonus could be evoked on both sides. Anisocoria was noted with a mydriasis of the right eye. Cornea reflex of the right eye was absent, though pupillary reflexes were present.

Medical history included a genetically proven CADASIL syndrome, associated with recurrent migraine attacks and recurrent ischaemic stroke episodes. Genetic testing had revealed a point mutation (R182C) in exon 4 of the Notch3 gene corresponding with an arginin to cysteine substitution. According the patient's general practitioner, there was a well controlled arterial hypertension and hypercholesterolemia. There was no past history of diabetes mellitus or coagulopathy. The patient did not smoke, nor was there any alcohol abuse. The patient's daily drug regimen included verapamil 240 mg, atorvastatin 20 mg and warfarin to prevent recurrent ischemic stroke.

The patient's father and paternal uncle were also diagnosed with CADASIL, due to the same Notch3 gene mutation. Both suffered from severe multi-infarct dementia.

Computed tomography of the brain showed an acute intraparenchymal haemorrhage in the left putamen and capsula interna with surrounding

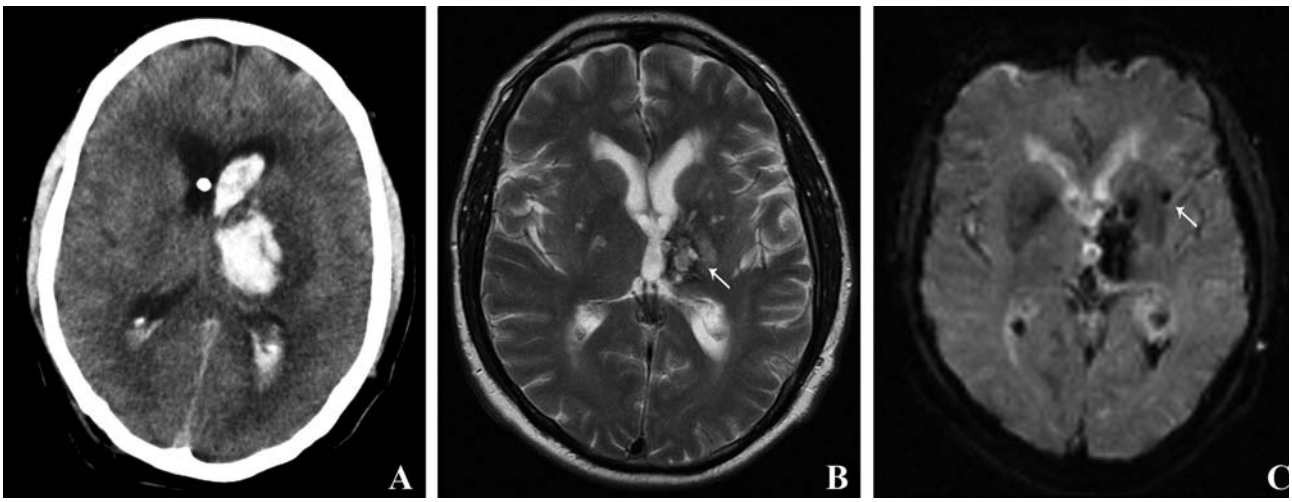

FIG. 1. — A : Computed tomography of the brain shortly after the first bleeding shows an acute haemorrhage in the left putamen and capsula interna with surrounding edema ; B : Follow-up MRI one year after the first bleeding. T2 weighted image shows the sequellae of the intracerebral haemorrhage ; C : Hypointense lesion compatible with a microhaemorrhage (arrow) as seen on perfusion weighted imaging.

edema. There was also breakthrough in the ventricular system for which a ventricular drain was inserted. There was no evidence for head trauma, aneurysms, hemangioma, arteriovenous malformations or neoplasia (Fig. 1).

Respiratory failure required urgent intubation of the trachea. The patient recovered gradually and partially over the following weeks with improved gait and autonomy. Follow-up routine MRI one year after, showed the sequellae of the haemorrhage and extensive white matter degeneration both in periventricular and lenticulostriatal areas. On perfusion weighted images there was evidence for at least six microbleeds (Fig. 1). Magnetic resonance angiography was not done. At the time of imaging, the patient was under aspirin and clopidogrel antiaggregant therapy. In the following years the patient developed a progressive multi-infarct dementia with a frontal personality disorder due to recurrent minor ischemic stroke episodes.

Discussion

CADASIL is characterised by recurrent transient ischemic attacks and ischemic strokes leading to multi-infarct dementia. Intracerebral haemorrhages have only rarely been reported. Maclean *et al.* reported a right frontal lobar haemorrhage in a patient with CADASIL in the absence of cerebrovascular risk factors. Ragoschke-Schumm *et al.* described a hypertensive left cerebellar haemorrhage in a genetically non confirmed CADASIL patient. Large patient series reported by Chabriat *et al.* and Dichgans *et al.* showed no cases of intracerebral haemorrhages. We report a male patient with a genetically proven CADASIL who developed an intracerebral haemorrhage while on anticoagulant therapy.

Blood pressure was well controlled making a hypertensive bleeding unlikely. In this case the combination of warfarin therapy with an underlying arteriopathy seems to have evoked the bleeding. Since CADASIL is characterised by granular depositions in vascular smooth muscle, these changes contribute to a progressive disintegration of the vascular wall. The affected smooth muscle cells degenerate and eventually disappear making the small arteries more bleed-prone (Dichgans *et al.*, 2002). Cerebral angiography should be avoided, since CADASIL patients are at higher risk for complications (69%) than expected (0,5-5,6%). Furthermore, angiography does not contribute to the diagnosis of CADASIL. Neurological complications due to the use of contrast agents include dysphasia, cortical blindness, confusion, headache, seizures, vomiting and vertigo and can lead to cerebral infarction. (Dichgans *et al.*, 1997)

Asymptomatic cerebral microbleeds are described in nearly all symptomatic CADASIL patients (Choi *et al.*, 2006). Van den Boom *et al.* found a mean of nine microbleeds per patient. The finding of numerous microhaemorrhages on MRI reflects the state of disease progression. Microbleeds mostly occur in areas with large numbers of lacunes and correlate with age (Lesnik *et al.*, 2001). The role of high blood pressure in the development of microhaemorrhages is unclear (Viswanathan *et al.*, 2006). Since microbleeds are a marker of increased risk for intracerebral haemorrhage (Fazekas *et al.*, 1999), a well-thought use of antiplatelet or anticoagulative drugs is advised. Previous authors already warned for the risk of bleeding by giving oral anticoagulants to CADASIL patients (Dichgans *et al.*, 2002 ; Fazekas *et al.*, 1999). Lesnik *et al.* found that antiplatelet drug therapy does not correlate with the

presence of microbleeds nor with an increased risk for cerebral bleeding in CADASIL. The risk of ischaemia versus haemorrhage should carefully be weighed when treating CADASIL patients. MRI screening for microhaemorrhages might be helpful in this risk stratification (Lesnik *et al.*, 2001).

The present case illustrates the importance of a well considered choice of antiaggregant or anticoagulative therapy in CADASIL patients. Although recurrent infarcts under secondary preventive antiaggregant therapy tend to lead clinicians to start oral anticoagulants, this practice is probably deleterious, especially in those subjects with asymptomatic microbleeds on gradient-echo T2* MR imaging.

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