Rare disease

CADASIL: how to avoid the unavoidable?

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All three siblings (one female/two males) of a family presented successively with cerebrovascular events at the ages of 55, 63 and 65. The first one manifested extensive left subcortical haemorrhage and both the second and third patient, showed left lacunar ischemic stroke. Their mother had died from vascular dementia at the age of 60 after several subcortical ischaemic strokes. Their maternal grandfather had died in his fifties from haemorrhagic stroke. All of them showed extensive white matter involvement. The genetic study revealed a mutation in exon 11 of the Notch3 gene in two family members. They were diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Although CADASIL is a well-established disease, little is known about this disorder. The fact that all three siblings presented with CADASIL successively may appear disheartening, further studies are needed in order to control the clinical course of this devastating and unavoidable disorder.

BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic small-vessel disease caused by an accumulation of an eosinophilic protein in the small vessels of the brain,¹ producing an extensive vascular disease different from arteriosclerotic or amyloid angiopathies.² All siblings of a family, two brothers and one sister, presented successively

with cerebrovascular events at the ages of 55, 63 and 65, respectively. Their mother had died from vascular dementia at the age of 60 after several subcortical ischemic strokes. Their maternal grandfather had died in his fifties from haemorrhagic stroke.

In spite of the knowledge related to CADASIL, there is no specific treatment and it seems that there is no possibility of avoiding the path the disease takes. The authors

Figure 1 (A and B) Patient 1: axial projections of brain CT showed a large left subcortical hematoma at admission. (C and D) Patient 1: axial projections of brain MRI showed a diffuse increased signal on T2-weighted sequences with a large subcortical haematoma without underlying vascular abnormalities.

Figure 2 (A) Patient 2: axial projection of brain MRI showed an acute right centrum semiovale stroke in diffusion sequences. (B) Patient 2: axial projection of brain MRI showed a diffuse leukoencephalopathy on fluid-attenuated inversion recovery (FLAIR) T2 sequences. (C) Patient 3: axial projections of brain MRI showed a right centrum semiovale stroke in diffusion sequences. (D) Patient 3: axial projection of brain MRI showed a diffuse leukoencephalopathy on FLAIR T2 sequences.

wish to highlight the successive affectation of all of three siblings which may appear disheartening, for the patients and for the doctors involved.

CASE PRESENTATION

Patient 1 A 55-year-old male, without cerebrovascular risk factors or other comorbid conditions was admitted to the emergency department in April 1999. He manifested right hemiparesis and global dysphasia. A cranial CT showed a large left subcortical haematoma (figure 1 A,B). Blood tests were normal. Cranial MRI and conventional angiography precluded intracranial vascular disease (including vasculitis) (figure 1 C,D). The patient was referred to physiotherapists in the rehabilitation centre and remained clinically stable for 11 years.

Patient 2 A 65-year-old female with the following cerebrovascular risk factors – a heavy smoker (two packets/day) with high blood pressure and dyslipemia. The patient suffered from migraine headaches (without aura) and these were occasionally treated with the usual analgesics, until the beginning menopause when they disappeared. She was admitted in April 2009 for left hemiparesis (4/5). Cranial CT showed severe leukoencephalopathy and cranial MRI revealed acute right centrum semiovale infarct in diffusion-weighted sequences (figure 2 A,B). Blood tests, cardiac examination and neurovascular studies were normal. The findings in the neuroimaging study and family history provided grounds for a genetic test which identified an Arg 607 > Cys mutation in exon 11 of the Notch3 gene on chromosome 19.

Patient 3 A 63-year-old male, without cerebrovascular risk factors or other comorbid conditions was admitted in August 2010 because of left leg paresis (4/5). Cranial MRI showed severe leukoencephalopathy with right centrum semiovale infarct in diffusion-weighted sequences (figure 2 C,D). Blood tests, cardiac examination and neurovascular studies were normal. Genetic testing revealed an Arg 607 > Cys mutation in exon 11 of the Notch3 gene on chromosome 19.

DISCUSSION

CADASIL is a genetic small-vessel disease.¹ In 1996 Jautel *et al* identified Notch3 as the defective gene in CADASIL.³ A mutation in the Notch3 gene on chromosome 19 produces an accumulation of an eosinophilic protein in the small vessels of the brain, causing an extensive vascular disease, different from arteriosclerotic or amyloid angiopathies.² This lesion is confined to the brain, skin, spleen, liver, kidneys, muscles, carotid arteries or aorta. However, no clinical manifestations occur outside the brain, and so clinical presentation is characterised by five neurological symptoms: migraine with aura, subcortical ischemic strokes, mood disturbances, apathy and cognitive impairment. As the disease advances, these manifestations develop progressing to dementia.² The age of onset of ischaemic events has been described at 49.3 ± 10.7 years and the age of onset of dementia at 58.2 ± 9.1 years, the mean age of death being approximately at 64.5 years.³ It is well known that vascular dementia is the second cause of dementia after Alzheimer's disease, with an occasional

overlapping of both. Due to its characteristics, CADASIL has been defined as a prototype of pure subcortical vascular dementia⁴ and it is considered to be the most common cause of vascular cognitive impairment in adults.²

In the case of CADASIL, cranial MRI reveals white matter involvement. Affection of the anterior temporal pole and external capsule is significant for the diagnosis, but while for the former the specificity is high, for the latter it is low.⁵ Skin biopsy could be useful, since it is a widespread vascular disease.⁶ Some authors suggest that skin biopsy should be performed in cases with a high index of clinical suspicion and negative genetic test results.⁶ Notwithstanding, genetic tests remain the gold standard for the diagnosis of this disease, because of the characterisation of Notch3 on chromosome 19. Although Notch3 has 33 exons, all mutations have been described in exons 2–24.² Almost 90% of these mutations are detected in exons 2–6, with the most frequent mutation in exon 4 followed by exon 3.^{5,7} However, Oberstein *et al* point out that mutations in exon 11 are quite common.⁸ Actually, in the Dutch population, mutation in exon 11 was the second most frequent site following exon 4.⁸

CADASIL was suspected in our patients due to the finding of extensive white matter involvement identified on cranial MRI, although no characteristic pattern distribution was established. The most frequent mutation was not found in the genetic test either. Mutation in exon 11 of Notch3 was found in two family members with a confirmed diagnosis of CADASIL (the first patient declined to take the genetic test). We should, therefore, consider extending the genetic study to include characterisation of exon 11 in routine genetic studies. On the other hand, the age of onset of ischaemic stroke in both patients was later than expected (over 60), even though one of the patients had several cerebrovascular risk factors. Currently, they lead a completely independent daily life.

Learning points

- An eventual relationship between mutation type, age and clinical manifestations should be studied in order to further understand this disease. Although CADASIL is a well-documented disease, little is known about this disorder. The fact that all three siblings presented with CADASIL successively may appear disheartening, further studies are needed in order to control the clinical course of this devastating and unavoidable disorder.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Delgado MG, Coto E, Tuñón A, Sáiz A. CADASIL: how to avoid the unavoidable?. *BMJ Case Reports* 2011;10.1136/bcr.08.2011.4727, Published XXX

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