

NEUROLOGICAL RARITIES

S. Saif M. Razvi and Keith W. Muir

Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Road Glasgow G51 4TF, United Kingdom; E-mail: k.muir@clinmed.gla.ac.uk

Practical Neurology, 2004, 4, 50–55

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited, autosomal dominant condition with high penetrance and varying expression. It is an important cause of protracted disability in young adults, with recurrent strokes, psychiatric dysfunction, and dementia. Although some families were identified in the 1950s, the syndrome was characterized and named only in 1993. The prevalence remains unknown, but numbers are increasing in parallel with wider medical recognition.

GENETICS, PATHOLOGY AND PATHOPHYSIOLOGY

CADASIL is caused by mutations in the Notch3 gene (chromosome 19p13) (Joutel *et al.* 1996), which encodes a large single-pass transmembrane receptor. The receptor's extracellular domain contains 34 epidermal growth factor-like tandem repeats (EGF repeats). This receptor is part of a highly conserved signalling pathway that is essential for normal maturation of blood vessels in both fetal and adult brain, and is maximally expressed in small to medium penetrating

arteries in early postnatal development (Fryxell *et al.* 2001; Prakash *et al.* 2002).

Most mutations are found on exons 3–6 of the 33 exons of the gene. Nearly all are missense mutations resulting in expression of an odd number of cysteine residues in an EGF repeat.

CADASIL is characterized pathologically by a systemic, non-amyloid, non-atherosclerotic angiopathy affecting not only small penetrating and lepto-meningeal arteries of the brain, but also vessels in muscle, skin, nerves, heart, and other viscera. There is vascular smooth muscle cell degeneration along with adventitial fibrosis, and eosinophilic periodic-acid-Schiff positive deposits in the tunica media. Electron microscopy reveals characteristic rounded granular osmiophilic material in the basal lamina adjacent to the vascular smooth muscle cells (Okeda, Arima, & Kawai 2002). In addition to structural change, endothelium is functionally impaired.

How CADASIL mutations give rise to these vascular changes is not understood. Recently developed transgenic mouse models replicate many of the pathological features of CADASIL, and may increase understanding of pathophysiology (Ruchoux *et al.* 2003).

Subcortical infarcts and cognitive dysfunction (CADASIL)

CLINICAL FEATURES

Symptoms usually develop in the third to fifth decade, but sometimes as late as the sixth decade. The four characteristic manifestations are:

- strokes;
- migraine with aura;
- mood disturbances;
- cognitive disturbances.

Timing and mode of onset vary considerably among individuals (both within and between pedigrees): differences in age at onset of up to 19 years are described in the same family (Dichgans *et al.* 1998). No relationship has yet been found between phenotype, including age at onset, and individual mutations. Symptoms can occur in isolation, but usually develop cumulatively until death at a mean age of 60 years, after a mean duration from symptom onset of 23 years. Survival until much older age is recognized.

Stroke (85% of patients)

Lacunar strokes typically first occur in the fourth to fifth decade. Recovery is usual initially, but recurrent strokes lead eventually to pseudo-

bulbar palsy, subcortical dementia, impaired mobility (including vascular parkinsonism) and urinary incontinence in most cases. Repeat diffusion weighted MRI studies suggest a low annual recurrence rate.

Migraine (40% of patients)

The migrainous headaches of CADASIL are characterized by aura, which can be atypical, disabling and prolonged. Hemiparesis, hemisensory disturbance and dysphasia (either alone or in combination) are common migraine accompaniments, and it may be difficult to distinguish migrainous events from stroke. Headaches may diminish after a clinically overt stroke.

Mood disturbances (40% of patients)

Recognized mood disturbances include depression, agitation, aggression, mania and emotional lability. Paranoia is frequent and schizophrenia-like symptoms can develop. Depression may be secondary to physical and mental disability, but may also be the first manifestation of CADASIL, even where the

individual has no apparent knowledge of an inherited illness being present in their family. In clinically unaffected but mutation-positive individuals who are aware of long-term implications, fear of the future is common. Mutation-negative pedigree members often suffer guilt and may also need counselling. Family discord is common.

Cognitive decline (50% and increasing with age)

Cognitive changes and difficulties with short-term memory develop frequently in the fifth to sixth decade and can be the predominant feature of the illness. Approximately two-thirds of patients are demented by age 65. Frontal lobe dysfunction, executive dysfunction and impairment of declarative memory with relatively well-preserved language are common. Organization and planning are impaired before overt dementia.

Other features

Seizures develop in less than 10% of patients and their nature and pathophysiology are poorly understood. Retinal vascular changes such as arterial sheathing and narrowing may be found

in up to a third of patients but are still poorly characterized.

Family history

CADASIL is often misdiagnosed, and a number of different neurological diagnoses are often present in a pedigree (Box 1 and Fig. 1). *De novo* mutations are recognized and so the absence of any family history should not necessarily deter genetic testing in an individual with typical symptoms or imaging.

INVESTIGATIONS

Neuroimaging

Magnetic resonance imaging (MRI) of the brain is thought to be abnormal in all mutation carriers by age 35. T2-weighted imaging typically shows confluent, symmetrical white matter high signal (leukoaraiosis), with more discrete regions of lacunar infarction. Changes may be better seen on fluid attenuated inversion recovery (FLAIR) sequences, where CSF signal is suppressed. Changes typically involve the pons and the anterior temporal lobes – the latter appears to be a sensitive indicator of CADASIL as compared with ischaemic leukoaraiosis secondary to

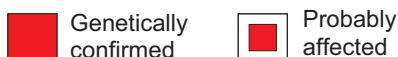
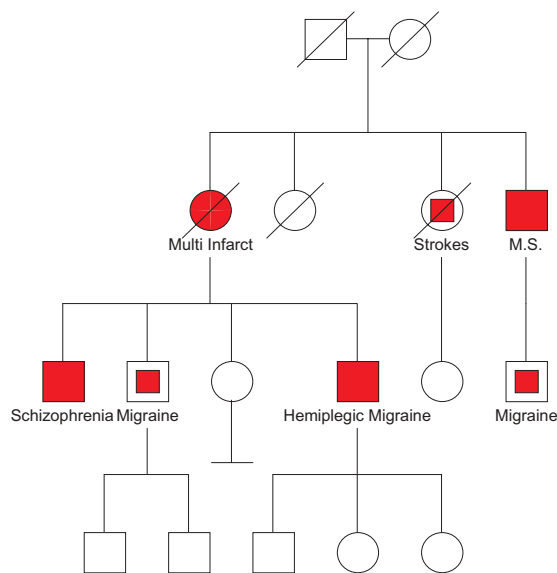


Figure 1 A typical pedigree with their initial diagnoses.

BOX 1: WHEN TO SUSPECT CADASIL

In a patient with:

- recurrent subcortical and lacunar strokes (especially in absence of vascular risk factors);
- migraine with aura;
- cognitive decline and dementia;
- psychological disturbances;
- neuroimaging consistent with bilateral white matter ischaemia.

In families with:

- strokes (including 'multi-infarct state');
- dementia (vascular or Alzheimer's) (senile or presenile);
- multiple sclerosis;
- atypical Parkinson's disease;
- migraine (including hemiplegic migraine);
- depression, mania or schizophrenia;
- CNS vasculitis;
- other leukodystrophies

Remember – different pedigree members, different symptoms, different signs and different (mis-)diagnoses.

BOX 2: DIAGNOSIS OF CADASIL

- Family history.
- Genetic screening – initial screening of mutations on exons 3, 4, 5 and 6 detects approximately 90% of mutations. If negative, screening must be extended to remaining exons.
- Skin or muscle biopsy – granular osmiophilic material on electron microscopy (sensitivity approx. 40%, high specificity).
- Monoclonal antibodies to Notch 3 – tissue specimens can be stained with the antibody. The sensitivity and specificity of this technique still need to be determined.
- Neuroimaging – MRI is abnormal by age 35 in all affected individuals. T2- (including FLAIR) and T1-weighted MRI – diffuse white matter ischaemia with high signal intensities and lacunar infarcts in centrum semiovale, thalamus, basal ganglia and pons. Involvement of anterior temporal poles is an important diagnostic indicator. Gradient echo images – multiple microhaemorrhages.
- CSF – mildly raised protein in a third, normal cell count. Beware – oligoclonal bands reported occasionally.

other causes. The presence of hyper-intensities in the external capsule-insula region is another useful marker (O'Sullivan *et al.* 2001).

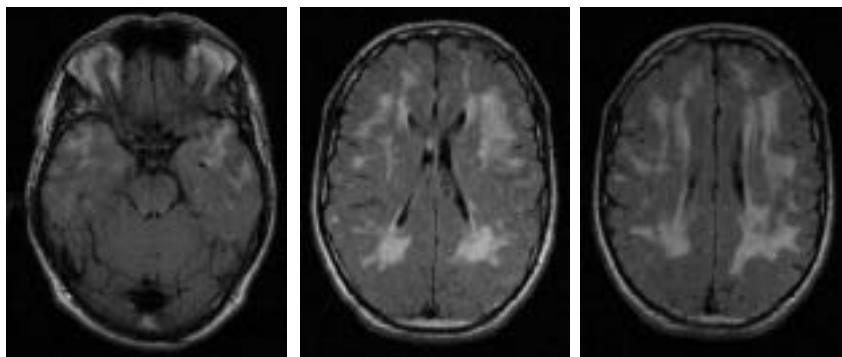
Up to about two-thirds have multifocal microhaemorrhages on gradient-echo MRI, which may correlate with an increased propensity to intracerebral haemorrhage (Lesnik Oberstein *et al.* 2001; Dichgans *et al.* 2002). Changes in normal appearing white matter on diffusion tensor imaging may correlate best with clinical disability.

MRI changes are often striking in asymptomatic individuals, and the abnormalities on standard imaging sequences correlate poorly with clinical state (Fig. 2).

Genetic analysis

Because the Notch 3 gene is large, and mutations scattered, genetic testing involves an initial screen of the common sites (exon 4) followed by an arbitrary number of additional exons based on the local prevalence of different mutations. The commonly involved exons probably differ in different populations, and no ideal strategy has yet been determined. Screening of the entire

Patient A



Patient B

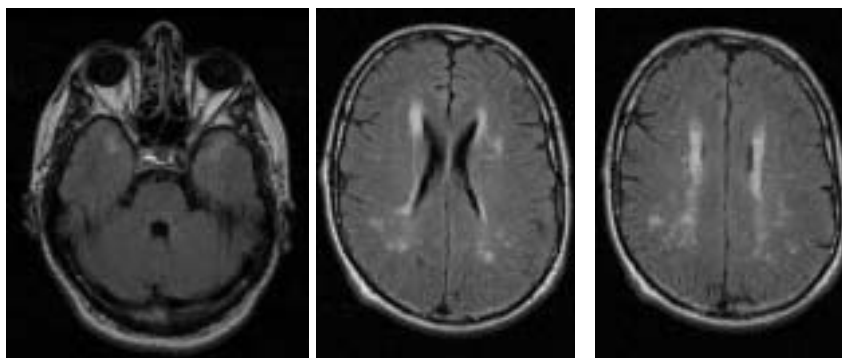


Figure 2 Patient A: Typical appearances of CADASIL on MRI (FLAIR). Note the extensive white matter change with involvement of the anterior temporal poles. Patient B: sibling of Patient A. In contrast, appearances are subtle despite considerable symptoms.

BOX 3: MANAGEMENT

- Counselling and support
- Migraine prophylaxis
- Antidepressants
- Selective serotonin reuptake inhibitors – for emotional lability
- Physiotherapy
- Artificial feeding and nursing care
- Aspirin (not evidence based)
- Avoid anticoagulation and antiplatelet poly therapy

Having a mutation predicts, as far as we know, the inevitable development of disabling and progressive symptoms that impair both physical and mental faculties, with prolonged disability and dependence being usual.

gene is time-consuming and expensive, and current methods cannot rule out a causative mutation. A screen of exon 4 alone may be negative in up to 45% of CADASIL cases. If initial screening is negative, then haplotype analysis of chromosome 19 from different affected individuals within the pedigree can be helpful.

Skin biopsy

Detection of granular osmiophilic material on electron microscopy is pathognomonic of CADASIL, but sensitivity is only 30–40%. Monoclonal antibodies to Notch 3 may improve diagnosis, but provide only qualitative differences rather than straight 'positive' or 'negative' results and sensitivity and specificity need to be determined.

Cerebrospinal Fluid

CSF protein may be mildly raised in a third of patients, with a normal cell count. Oligoclonal bands are reported occasionally and may lead to a misdiagnosis of multiple sclerosis.

MANAGEMENT

Counselling and support are a major part of CADASIL management, for affected individuals and their families. There are parallels with Huntington's disease, in that most individuals become symptomatic only after they have had children. Having a mutation predicts, as far as we know, the inevitable development of disabling and progressive symptoms that impair both physical and mental faculties, with prolonged disability and dependence being usual. Within this context, ongoing knowledgeable clinical support is vital.

No treatments have been tested specifically in CADASIL, and medical management is extrapolated from stroke studies. Pragmatically, most patients are prescribed aspirin, while multi-agent antiplatelet therapy and anticoagulation are avoided in the light of the microhaemorrhages on MRI.

Statins are commonly prescribed on account of their supposed effect on endothelial dysfunction. Some antihypertensive agents may have a similar influence, but blood pressure is seldom raised significantly in CADASIL patients, and lowering it may not be beneficial.

Symptomatic treatment for migraine, depression, paranoia, and emotional lability is often tried, but is of uncertain value. In the long term, physical rehabilitation, management of urinary incontinence and artificial feeding are often needed.

BOX 4: PITFALLS AND DIAGNOSTIC PROBLEMS

- Migraine in a member of a CADASIL family is not synonymous with CADASIL: common migraine can occur in the absence of mutation. Family histories are often not of stroke and dementia: be suspicious if there is a history of parkinsonism, multiple sclerosis, Alzheimer's disease or psychiatric illness in different individuals within a pedigree.
- De novo mutations do occur.
- Negative mutation screening and skin biopsy results do not rule out CADASIL.
- Imaging findings may be very mild and indistinguishable from those in other neurological diseases (e.g. multiple sclerosis).
- CADASIL may cause prolonged visual evoked responses.
- Disease manifestations and age of onset in one family member do not reliably predict those in any other family member.

SUMMARY

CADASIL is an increasingly recognized syndrome characterized by white matter disease with recurrent subcortical infarcts, progressing to disability and dependence at a young age. The large number of causative mutations and limited sensitivity of skin biopsy make diagnosis difficult. Medical management is currently extrapolated from stroke studies. It may be wise to avoid excessive antiplatelet therapy and anticoagulation.

ACKNOWLEDGEMENTS

We wish to acknowledge the support of Chest, Heart and Stroke, Scotland.

REFERENCES

- Dichgans M, Holtmannspotter M, Herzog J, Peters N, Bergmann M & Youssry TA (2002) Cerebral microbleeds in CADASIL: a gradient-echo magnetic resonance imaging and autopsy study. *Stroke*, **33**, 67–71.
- Dichgans M, Mayer M, Uttner I *et al.* (1998) The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol*, **44**, 731–9.
- Fryxell KJ, Soderlund M & Jordan TV (2001) An animal model for the molecular genetics of CADASIL. (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). *Stroke*, **32**, 6–11.
- Joutel A, Corpechot C, Ducros A *et al.* (1996) Notch 3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*, **383**, 707–10.
- Lesnik Oberstein SABR, van Buchem MA, van Houwelingen HC *et al.* (2001) Cerebral microbleeds in CADASIL. *Neurology*, **57**, 1066–70.
- O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF & Markus HS (2001) MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology*, **56**, 628–34.
- Okeda R, Arima K & Kawai M (2002) Arterial changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in relation to pathogenesis of diffuse myelin loss of cerebral white matter: examination of cerebral medullary arteries by reconstruction of serial sections of an autopsy case. *Stroke*, **33**, 2565–9.
- Prakash N, Hansson E, Betsholtz C, Mitsiadis T & Lendahl U (2002) Mouse Notch 3 expression in the pre- and postnatal brain: relationship to the stroke and dementia syndrome CADASIL. *Exp Cell Res*, **278**, 31–44.
- Ruchoux MM, Domenga V, Brulin P *et al.* (2003) Transgenic mice expressing mutant Notch3 develop vascular alterations characteristic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Am J Pathol*, **162**, 329–42.