CASE REPORT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL): a rare cause of dementia

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SUMMARY

The clinical course of a 60-year-old gentleman with a history of atypical migraine, recurrent encephalopathic episodes and progressive cognitive impairment is presented. He was diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy, a rare genetic disorder of the cerebral blood vessels caused by mutations in the *Notch 3* gene on chromosome 19. The diagnosis was confirmed by MRI, skin biopsy and genetic testing. His cognitive function has progressively deteriorated and he continues to receive supportive care provision. The course and review of the condition are highlighted.

BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an autosomal dominant disorder with high penetrance. It has been known as a rare condition, but the number of reported cases is increasing due to the increasing recognition and diagnosis. The main manifestations of CADASIL are encountered commonly in clinical practice and may be frequently diagnosed as other conditions. They include recurrent ischaemic strokes, migraine, progressive cognitive impairment, psychiatric symptoms and epileptic seizures. It is one of the causes of early-onset dementia. The typical age for a patient to be diagnosed with CADASIL is between 35 and 55 years, although many patients might have migraine for many years prior to diagnosis. In most patients, there may be no clues from the migraine that they are at risk of developing a progressive vascular dementia. A high index of suspicion is required by clinicians to identify and investigate potential patients appropriately.

CASE PRESENTATION

Mr Smith (not his real name) was first admitted to hospital at the age of 50 years with a pyrexial illness associated with confusion, marked left-sided focal neurological signs including weakness, apraxia and neglect, with left homonymous hemianopia. It was felt that he had an encephalitic illness probably of bacterial or viral origin. Haematological, biochemistry and cerebrospinal fluid (CSF) examinations were normal and brain CT scan excluded intracranial or subarachnoid haemorrhage. EEG showed non-specific changes. The working diagnosis was viral encephalitis and he was treated with a course of intravenous acyclovir with some response to treatment. He was

discharged from the hospital about 2 weeks later, with a plan to have an MRI scan of the brain done during his follow-up review at the outpatients clinic. He went on to recover fully from that episode of illness; however, the impairments in his memory and concentration persisted.

The MRI scan showed extensive signal change in the white matter of both cerebral hemispheres, and the findings were felt to be more consistent with a vascular aetiology than encephalitis.

Further enquiry revealed that his memory and concentration problems appeared to have existed prior to his admission but in a milder form. He had a history of migraine over the previous 7 years with episodes associated with visual disturbances followed by right-sided paraesthesia spreading from the face to involve the right side. The episodes lasted about 40 min and were not always accompanied by a headache. There was no history of hypertension or cardiac disease and ECG tracings were normal. There was a positive family history of severe migraine and the patient's father suffered from memory problems prior to his death in his early 60s. The possibility of CADASIL was strongly considered and further investigations were carried out to confirm or exclude the diagnosis. These included an autoantibody screen, thrombophilia screen, echocardiogram and psychometric assessment and finally a skin biopsy which confirmed the diagnosis of CADASIL.

Following his diagnosis, Mr Smith has been under the care and follow-up of various specialists including neurologists, neuropsychologists, psychiatrists, psychologists, speech and language therapists, occupational therapists, a urologist, a general practitioner, ophthalmology input and the community mental health team.

Over the course of the next 10 years, he experienced significant deterioration in his cognitive ability with worsening word-finding difficulty and short-term memory impairment. He had increasing frequency of neurological and encephalopathic episodes characterised by visual disturbance, headache, slurred speech, dysphasia, abnormal head movements, migrating numbness and confusion lasting 3–4 days. These occurred about once weekly and he did not seem to make full recovery after each episode. He was hospitalised on one occasion for episodes that involved generalised stiffness and periods of unresponsiveness lasting up to 1 h and confusion lasting for days to weeks. Brain CT scan at the time showed no evidence of intracranial haemorrhage.

To cite: Toni-Uebari TK. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007285

Neurological assessment revealed marked cognitive impairment in the areas of memory, speed of information processing, expressive language and executive functioning. These difficulties had significant impact on his level of everyday functioning. He became increasingly reliant on his wife for support in carrying out most activities of daily living as he could do very little for himself and needed constant supervision. He went from being an active sportsman to being unsteady on his feet. Communication was difficult as he could not understand most of what was said to him, increasing his frustration.

One of his most distressing symptoms was nocturia, sometimes getting up about 10–15 times during the night. This had a devastating effect on his sleep pattern as well as his wife's, especially as he required her help to get in and out of bed and to navigate to the bathroom. Urology assessment attributed his symptoms to a neurological syndrome with variable and incomplete detrusor contraction rather than bladder or prostrate-related causes. He became progressively incontinent of urine at night and sometimes during the day. He was very restless, pacing about all day and tossing and turning most of the night.

He continued to have encephalopathic episodes, requiring constant observation, as his risk of falling increased. His wife continued to provide care and support over the period but was increasingly becoming exhausted and worn out.

With further deterioration in his cognitive function, agitation, restlessness, anxiety, sleep disturbances and increasing care needs, he was admitted to the elderly psychiatry ward for further assessment and care, as well as to provide some respite for his wife. He was admitted for 9 months in total. During this period, his cognitive function continued to deteriorate as a result of the progressive nature of CADASIL. He continued to pace about constantly in the ward despite being unsteady on his feet, increasing his risk of falls. Hip protectors and protective hats were used to mitigate the impact from falls. Sleep remained a problem despite night sedation and there was a little or no improvement in urinary symptoms even with treatment trials.

Following a comprehensive assessment of his care needs, Mr Smith was discharged home with a support package consisting of additional carer input of 12 h at night for six nights per week and for 4–6 h during the day for 5 days per week.

Mr Smith's wife remains his main carer. He has no siblings, no children and no extended family. He was a very able man but stopped work shortly after being diagnosed with CADASIL due to deteriorating cognitive ability.

INVESTIGATIONS

EEG on his initial presentation showed slowing over the right hemisphere but no specific changes of encephalitis. CT of the brain and CSF examination were normal.

Sagittal T1 MRI sequence revealed extensive signal alteration affecting the deep and subcortical white matter of both cerebral hemispheres, with involvement of the basal nuclei. The cortex did not appear to be involved. There was faint signal alteration affecting the central pons with a discreet lacuna on the right. The pattern and distribution of the lesions were more suggestive of a vascular than demyelinating aetiology, but the latter could not be excluded. CADASIL and mitochondrial disease were suggested as options.

Autoantibodies screen, thrombophilia screen and echocardiogram showed no significant abnormality.

Skin biopsy showed amorphous irregular or roughly circular osmiophilic patches related to the smooth muscle cells of arterioles, in some cases associated with collagen fibres. Several

vessels were severely affected with large areas of osmiophilic material within the vessel wall. The findings were consistent with CADASIL.

Genetic studies revealed a mutation in the *Notch 3* gene, exon 18 (G2935T), finally confirming a diagnosis of CADASIL.

Psychometric assessment showed evidence of significant neuropsychological dysfunction limited to non-verbal memory tests and tests of executive function. Premorbid IQ was estimated as 117, prorated verbal IQ using Wechsler Adult Intelligence Scale—Revised (WAIS-R) test was 115 while performance IQ was 89.

His homocysteine level was within normal range.

DIFFERENTIAL DIAGNOSIS

Encephalitis and ischaemic cerebrovascular disease were initial considerations prior to the results of investigations. The MRI findings, though not suggestive of a demyelinating aetiology, did not completely exclude multiple sclerosis. With Binswanger disease, there are similar neuroimaging and pathological findings to CADASIL, but there is hypertension and other vascular risk factors which may not always be encountered with CADASIL. Multi-infarct dementia was a possibility, but there was minimal cognitive impairment at initial presentation. The results of his investigations were most useful in determining the definitive diagnosis.

TREATMENT

There is no effective treatment for CADASIL. He developed hypertension and was treated with Ramipril and Simvastatin to minimise his cardiovascular risk factors. Acetazolamide was introduced for migraine prophylaxis, but this was discontinued after about 2 years due to no perceived benefit.

He had trials of Promazine, Temazepam and Diazepam, respectively, to manage nocturnal agitation and restlessness, but these were discontinued due to poor effect and associated risks. He was subsequently treated with Mirtazapine for coexisting depression and nocturnal agitation, and this seemed to improve his mental state but worsened the nocturia. To manage his urinary symptoms, he had trials of Solifenacin, Oxybutynin, Imipramine, Desmopressin and Tolterodine at different periods with little or no effect. Other treatments included Xalacom eye drops for glaucoma and prophylactic treatment with aspirin to possibly slow down the disease process and help prevent strokes.

OUTCOME AND FOLLOW-UP

At the time of the writing of this report, about 11 years into his diagnosis, Mr Smith has deteriorated further. He is relatively immobile and currently uses a wheelchair. His risk of falls remains very high as he constantly makes attempts to stand up. He is very resistive to personal care and exhibits challenging behaviour including extreme agitation, biting, spitting and shouting, pushing and pinching, lashing out with his arm, requiring the assistance of at least two people to provide personal care. He poses risk of physical harm to his wife and carers while they try to provide personal care for him. He has increased bite reflex which interferes with his ability to drink fluids, increasing the risk of dehydration and constipation. He is unable to resist biting inappropriate objects within his reach, including clothes, and therefore requires constant supervision. He has lost weight and is doubly incontinent. His conversation is limited to monosyllables. His current medications include Mirtazapine, Aspirin, Simvastatin and a laxative. His care package is being reviewed.

DISCUSSION

CADASIL is the most common single-gene disorder of cerebral blood vessels and is caused by mutations in the *Notch 3* gene on chromosome 19. It should be suspected in individuals with an early onset of a vascular dementia with a history of migraine and few vascular risk factors. The number of reported cases has been increasing gradually due to wider recognition and diagnostic facilities.

The true prevalence of CADASIL is unknown, but worldwide, about 400 affected families have been reported.¹ The UK prevalence is estimated to be 1 : 100 000, but a recent Scottish study has suggested a prevalence of 2 : 100 000 in the region.^{2–3} There is no gender difference in incidence. Patients typically become symptomatic in adulthood between 30 and 50 years of age.

The underlying pathology is progressive degeneration of the smooth muscle cells in blood vessels. Mutations in the *Notch 3* gene cause abnormal accumulation of Notch 3 at the cytoplasmic membrane of vascular smooth-muscle cells in the cerebral and extracerebral vessels. These are seen as granular osmiophilic deposits on electron microscopy. As the pattern of inheritance is autosomal dominant with high penetrance, children of affected parents have a 50% chance of inheriting the disorder. The condition manifests usually after the individual has had a family, highlighting the importance of identifying affected individuals and genetic counselling for affected family members. New mutations are rare.

The most common initial clinical feature of CADASIL is migraine, usually preceded by aura, affecting about 90% of patients by the age of 40 years.⁴ Ischaemic stroke is the commonest clinical manifestation of the condition with most symptomatic individuals developing transient ischaemic attacks or stroke(s). The classical lacunar infarcts could occur even in the absence of traditional cardiovascular risk factors, though there is emerging evidence regarding the role of vascular risk factors in the disease process. Features of lacunar syndrome include dysarthria, motor or sensory strokes and ataxic hemiparesis, with some patients showing insidious or stepwise evolution up to several days. Seventy per cent of patients have recurrent strokes and some patients develop pseudobulbar palsy and vascular parkinsonism from recurrent subcortical infarctions.^{4–5} Recurrent silent strokes, with or without clinical strokes, often lead to cognitive decline and overt subcortical dementia.

Cognitive deficit occurs in about 60% of CADASIL patients with attention and behavioural problems, progressive memory loss and dementia.⁴ Two-thirds of patients develop dementia by 65 years of age. Mood disorders are the commonest psychiatric manifestations. Rarely epileptic seizures occur. MRI is able to detect signs of the disease years prior to clinical manifestation of the disease.

The clinical course of CADASIL is highly variable. Migraine with aura usually starts during the third decade in 30–40% of patients.⁴ This is followed by ischaemic events between the ages of 30 and 60 years, progressing to dementia and death. Migraines usually appear about 10 years earlier than the ischaemic stroke. Recurrent silent strokes, with or without clinical strokes, often lead to stepwise cognitive decline and overt subcortical dementia.^{5–6} Many patients become immobilised at an early age, posing a significant burden on both patients and caregivers. This burden is increased by cognitive deficits and other manifestations, such as dysphagia and incontinence, which are both frequent and a source of further complications. The median age at death has been reported as 64.6 years for men and 70.7 years for women.⁷ Male sex is a risk factor for early immobilisation and death in

CADASIL. Pneumonia was the most frequent cause of death followed by sudden unexpected death and asphyxia.⁷

The definitive test is genetic testing through identification of the mutated gene from a blood sample. This yields a mutation detection rate of more than 95%. Arteriopathy is quite extensive and evidence of the mutation can be found in small- and medium-sized arteries following skin biopsy. MRI can show the progression of white matter changes even decades before the onset of symptoms. These changes consist of MRIs hyperintensities on T2-weighted images concentrated around the basal ganglia, periventricular white matter and the pons. However, the MRI features are not specific to CADASIL and thus cannot alone confirm diagnosis of the condition.⁸

There is no specific treatment available for CADASIL at present. The primary approach to treatment includes genetic counselling, supportive care, medications for treating depression, migraine and the secondary prevention of ischaemic stroke. Although Acetazolamide has been shown in some studies to be effective management for migraine in some patients in CADASIL, it seemed to have little or no effect on Mr Smith and so was discontinued.^{4–9–11} There is merit in controlling vascular risk factors such as hypertension and hypercholesterolaemia as well as therapy for primary or secondary prevention of ischaemic stroke. Antiplatelet agents such as aspirin have been used prophylactically to slow down disease and possibly prevent strokes, but the effects are uncertain. Anticoagulants are not recommended due to risk of haemorrhagic stroke. Donepezil has been shown to improve executive functioning in CADASIL, but the clinical relevance of this is unclear.¹²

In conclusion, there is need for more awareness and recognition by clinicians of this rare, underdiagnosed genetic condition—CADASIL.

Learning points

- ▶ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), though rare, is relatively under-recognised and underdiagnosed.
- ▶ Consider CADASIL as a possible cause in patients with migraine, ischaemic episodes or early-onset dementia.
- ▶ MRI is able to detect signs of CADASIL many years before the onset of clinical symptoms.
- ▶ Identification of affected patients would enable family members to seek genetic counselling.
- ▶ A comprehensive care package is needed to support the CADASIL patients and family during the period of cognitive decline.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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