Bipolar disorder against a background of a rare vascular dementia

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare cause of vascular dementia which is underdiagnosed and whose prevalence is currently undetermined. Here, Drs Bangash and Saad describe a highly uncommon case of manic symptoms in CADASIL and the diagnostic criteria and clinical management for this condition.

CADASIL is a rare hereditary disorder caused by mutations in the NOTCH3 gene on chromosome 19p13.1.1 The progressive degeneration of smooth muscle cells in the blood vessels and consequently the reduction in blood supply to the brain can result in migraines, seizures, mini strokes or transient ischaemic attacks (TIAs) and strokes. Vascular dementia is a prominent feature of the end stage of the illness. Neuropsychiatric manifestations of the illness also include mood disturbances (in 10–20 per cent of patients), which are often associated with various degrees of cognitive impairment.

Neuropsychiatric manifestations can be observed in all stages of the disorder.2 CADASIL occurs worldwide and has been reported in many ethnic groups. The prevalence and disease burden are still undetermined.3 This may reflect underdiagnosis or misdiagnosis due to familial history being seldom recognised, as well as possible sporadic cases. Most of the patients have been found in Caucasian families in Europe. Reports from North America and Asia are rare.4,5 The aim of this case note is to discuss not only this rare case of vascular dementia but also to focus on the features of mania. Manic symptoms appear to be uncommon in CADASIL. Psychiatric disturbances have been mentioned in nearly all studies in patients with CADASIL but few have focussed on this aspect.6

Presentation
Mrs X is a 62-year-old lady who was born and raised in Coventry. Her childhood was a happy one and she had been a good student throughout her school years. Between the ages of 20 and 57 years she worked as a physiotherapist. She was married during her early 20s. From this marriage she had two children who are now in their 30s. The marriage ended in divorce and she has been happily married to her second husband since 2009. She has never smoked cigarettes and her alcohol history is of little significance. There is no family history of psychiatric problems. Her mother died of a stroke at the age of 68 years.

Mrs X had occasional migraines throughout her early adulthood. At the age of 57 years she suffered two TIAs without having any risk factors for vascular events. A year later her husband and children noticed that she was becoming more forgetful. Her speech became repetitive in nature with word-finding difficulty. She began to forget the names of people she knew well. However, the

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<th>Diagnostic criteria for vascular dementia (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition)</th>
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<td>The development of multiple cognitive deficits manifested by both:</td>
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<td>1. Memory impairment (impaired ability to learn new information or to recall previously learned information)</td>
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<td>2. One or more of the following cognitive disturbances:</td>
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<td>• aphasia (language disturbance)</td>
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<td>• apraxia (impairment to carry out motor activities despite intact motor function)</td>
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<td>• agnosia (failure to recognize or identify objects despite intact sensory function)</td>
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<td>• disturbance in executive functioning (ie planning, organizing, sequencing, abstracting)</td>
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<td>The cognitive deficits in criteria 1 and 2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.</td>
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<td>Focal neurological signs and symptoms (such as gait abnormalities) or laboratory evidence indicative of cerebrovascular disease (for example, multiple infarctions involving the cortex and underlying white matter) that are judged to be etiologically related to the disturbance.</td>
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<td>The deficits do not occur exclusively during the course of a delirium.</td>
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memory impairment was considered to be minimal and the family did not seek advice for it.

At the age of 58 years she was admitted to the local psychiatric hospital due to concerns from her family. She had not been previously known to psychiatric services. Her mood was elevated and she described her thoughts as being racing in nature. Her speech was rapid and tangential. She was restless and getting only a couple of hours of sleep at night. Her oral intake had decreased markedly. She said that she knew the head of the Freemasons personally (her family confirmed that this was not the case). She also believed that she had the power to heal others and would frequently talk of being world famous for this. There were frequent periods of irritability during which she would get verbally abusive towards her family who were finding it hard to look after her. Her son had to restrain her from lashing out at her husband on a few occasions. Her symptoms were considered to be due to a manic episode. A CT head was undertaken, to rule out an organic cause of her illness, which showed multiple small white matter infarcts with low temporal lobe density. A subsequent MRI head showed areas of multiple signal change in the subcortical, periventricular and deep white matter, also in the pons, bilateral inferior temporal lobe and posterior fossa, which were most likely to be ischaemic in origin. The findings were suggestive of CADASIL. Her symptoms settled over two weeks with an antipsychotic (olanzapine) used up to a dose of 15mg daily. At that time she refused genetic blood testing for CADASIL.

A year later she was readmitted due to concerns from her family. She had not been taking any medication, including antipsychotics, around that time. The reason for this was not known. Another antipsychotic (aripiprazole) was given, which helped to resolve the symptoms. On discharge she was referred to the Young Onset Dementia Service (YODS) due to her memory having worsened. By this time she was unable to use electronic equipment at home and was losing her way home on leaving the house. She was also unable to manage the finances. Her Mini-Mental State Examination (MMSE) score was 24/30 and the Addenbrooke's Cognitive Examination-Revised (ACE-R) score was 68/100: the attention and orientation score was 16/18; the memory score was 13/26; the fluency score was 5/14; the language score was 24/26, and the visuospatial score was 11/16. She agreed to undergo the genetic blood test for CADASIL and tested positive for the NOTCH3 gene mutation. She stayed under the care of YODS and continued to use aripiprazole at a dose of 5mg daily.

The following year she suffered a stroke following which clopidogrel (an antiplatelet drug) was started. The stroke affected her mobility such that she had to start walking with a frame. Despite her antipsychotic medication compliance she suffered another manic episode six months later, which led to another hospital admission. A mood stabiliser, valproic acid, was started. The discharge dose was 750mg daily. She has not suffered from another manic episode since that time. Her children have declined genetic testing for the time being.

Discussion
The history of describing CADASIL began in 1955. Because the genetic test was not available until the 2000s many cases were misdiagnosed with multiple sclerosis, Alzheimer’s disease or other neurodegenerative disorders.7 There is a wide variation of the onset of the illness being 20–70 years of age. The clinical presentation is also variable. A stroke or migraine can be the initial feature, migraines being commoner in younger people.8 Cognitive function worsens slowly over time, there is variability in the onset and severity of cognitive impairment.

Mood disorders in CADASIL
Psychiatric episodes (the most frequent being mood disorders) occur most frequently after the occurrence of ischaemic events during the fifth or sixth decade.2 Chabriat et al. estimated that about 5 per cent of CADASIL patients suffer from mania.9 A study carried out by Valenti et al. was considered to be the first to approach the topic of mood disorders in CADASIL with a systemic and structured assessment. The mood disorder module of the Structured Clinical interview for the DSM-IV (SCID) and the Young Mania Rating Scale (YMRS) were among some of the instruments used to assess patients. The data revealed a considerable frequency of bipolar disorders. If confirmed in larger series the data suggest that greater attention should be paid to the psychiatric aspects in CADASIL; treating them might improve the quality of life.6

CADASIL occurring with manic features has been described in two case reports by Kumar et al.10 and Park et al.1 Case reports on other aspects of mood disorders include Gamakaranage et al.11 describing a patient with personality changes (mood swings and aggressive behaviour) but with no manic features and Leyhe et al.12 discussing...
two cases with submanic (including mood instability and irritability) and depressive features.

**Investigations**

Genetic screening for the NOTCH3 gene mutation is the gold standard for diagnosis and allows confirmation of the diagnosis with excellent sensitivity and specificity. However, neuroimaging should be carried out in any case of severe psychiatric symptoms of late onset. In younger patients a family history of stroke, dementia or migraine with aura should prompt a brain MRI. MRI can show the progression of white matter changes even decades before onset of symptoms.

**Treatment**

At present, there is no treatment of proven efficacy for CADASIL. Because it is a vascular disorder responsible for ischaemic events, treatment of vascular risk factors and antiplatelet agents are often prescribed for secondary prevention. The diagnosis can have major psychological consequences for the family thus genetic counselling and testing should be carried out only by experienced physicians and counsellors. A positive family history is important but not essential as de novo mutations are possible. Rehabilitation procedures, nursing care and physiotherapy are crucial, particularly when a new ischaemic event occurs. The diagnosis should be considered in middle-aged patients with symmetrical and periventricular white matter lesions on MRI who have a history of migraines, ischaemic events, dementia or mood disturbances.

Early studies suggested coexistent cardiovascular risk factors were rare, however, the findings of the Microvascular Leukoencephalopathy study (MILES) conducted by Ciolli et al. suggest that hypertension may contribute to functional disability in CADASIL and that patients could take advantage of strict control of vascular risk factors.

Increased deep white matter densities (which resemble the radiological findings seen in CADASIL) have been consistently observed in patients with geriatric bipolar disorder. A study carried out by Yuan et al. suggests that valproic acid may exert cytotoxic effects on vascular smooth muscle cells and may be a novel therapeutic agent for the treatment of CADASIL. Valproic acid might decrease the liability of patients with late-life mood disorders to develop deep white matter lesions.

**Declaration of interests**

No conflicts of interest declared.

**References**