Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL): a familial cause of depression and headache

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Abstract

A 31 year-old man with a history of a depressive episode presented with acute severe 'thunderclap' headache. Magnetic resonance imaging (MRI) revealed abnormalities typical of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), which was subsequently confirmed by genetic analysis. The psychiatric features of this genetic cause of depression and headache are discussed.

Key words: CADASIL; Depression; Headache; Notch 3 mutation; Chromosome 19.

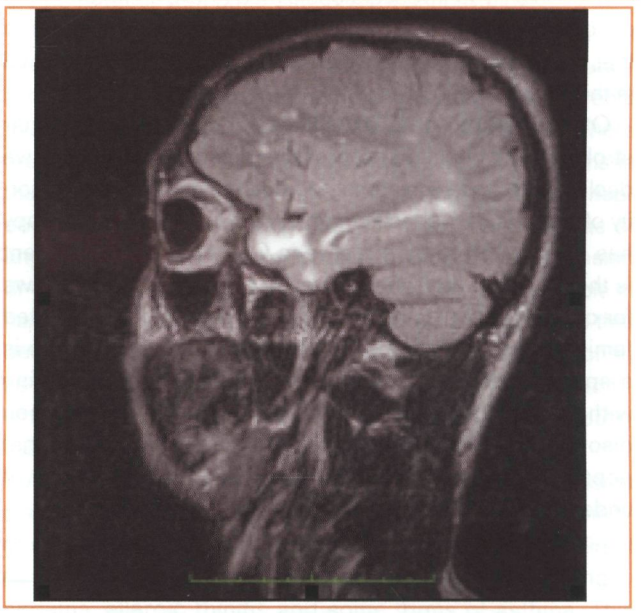
Case report

A 31 year-old man awoke from sleep with severe occipital throbbing headache and presented to the emergency department. Physical examination revealed brisk deep tendon reflexes and a mildly ataxic gait. Emergency computed tomographic (CT) imaging of the brain was performed in order to exclude subarachnoid haemorrhage; this revealed bilateral areas of low attenuation in the deep white matter. No blood was seen. Vital signs and routine laboratory indices were normal. The patient declined lumbar puncture, and the headache resolved within 24 hours. There was no prior history of headache.

Originally from the UK, the patient had left school at the age of 15 without qualifications and emigrated to Ireland where he worked as a kitchen assistant. Several years prior to presentation there was a depressive episode which was treated by a general practitioner initially with dothiepin and subsequently with paroxetine. He admitted to using amphetamine at that time but denied other illicit drug use. There were no subsequent depressive episodes and the patient had discontinued prescribed psychotropic medication, while continuing to self-medicate with St John's Wort. There was no retrospective evidence of DSM-IV manic symptoms at any time. He had never been evaluated by a psychiatrist or treated with mood stabilizing medication.

The patient's father had sustained a stroke at the age of 60 and his mother was a migraineur. He had three siblings who were apparently well. No further details in relation to family history were available. In view of the CT findings, magnetic resonance imaging (MRI) was performed and demonstrated confluent areas of abnormal signal in the anterior temporal poles known as O'Sullivan's sign (*see Figure 1*).[1] Given that this appearance is highly specific for cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a skin biopsy was performed to look for pathognomonic granular osmiophilic material (GOM) in the dermal vasculature on electron microscopy with negative results. Genetic testing subsequently proved that the patient was heterozygous for the pathogenic mutation c.268C>T in exon 3 of the notch 3 gene on chromosome 19, confirming the diagnosis of CADASIL (Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium). NOTCH 3 encodes a transmembrane receptor primarily expressed in arterial smooth muscle cells. Pathogenic mutations lead to an odd number of cysteine residues within the NOTCH 3 extracellular domain. Studies suggest a novel pathogenic role for the mutant NOTCH 3 protein rather than compromised NOTCH 3 function as the primary determinant of CADASIL.[2]

Figure 1: O'Sullivan's sign: Sagittal T2-weighted image showing high signal in the anterior temporal lobe



Discussion

CADASIL is an autosomal dominantly-inherited vasculopathy with high penetrance and varying expressivity, causing small deep infarcts in the brain. Prevalence is at least 1.98 per 100,000 adults, an estimate based on genetically proven

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cases.[3] Mood disorders are said to occur in 24% of cases, with the vast majority of these patients suffering from major depression.[4] CADASIL presents with mood disturbance in up to 9% of cases,[5] usually depression,[6] but sometimes also bipolar disorder.[7] The cause of the mood disturbance is not clear. MRI studies in unipolar patients have failed to demonstrate an increased volume of abnormal white matter signal,[8] and linkage analysis has failed to support notch 3 as a candidate gene for bipolar disorder.[9] Headache occurs in 40% of CADASIL patients and usually takes the form of migraine with aura.[5] This case is unique in that acute severe "thunderclap" headache has not previously been described in CADASIL and led initially to investigations aimed at excluding the presence of subarachnoid haemorrhage. However, it is possible that the headache and the genetic disorder are coincidental in this case.

Other features of CADASIL include recurrent lacunar strokes which result in progressive disability, and cognitive decline with supervening sub-cortical dementia in the majority of patients.[5] No specific form of disease-modifying therapy has been found to be effective in CADASIL, and treatment is therefore symptomatic. However, correct diagnosis allows for crucial genetic counselling to be put in place for affected families. Among patients with recurrent headache there is a specific association between depression and migraine with aura.[10] Therefore, the probability that these common disorders co-exist is much greater than the probability that depression and migraine with aura are manifestations of underlying CADASIL.

However, this case illustrates that MRI may be an appropriate investigation in selected patients with depressive episodes if there is a strong personal or family history of migraine with aura, stroke, or cognitive impairment.[11] When abnormal signal is seen in the regions of the anterior temporal poles or external capsule-insula, skin biopsy may be considered. Skin biopsy is a rapid and highly specific method of diagnosis[12] but suffers from low sensitivity; a negative skin biopsy in the context of a high index of suspicion should thus prompt genetic testing for this disorder.

Declaration of Interest: None.

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Case report

Risperidone induced periorbital oedema

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Abstract

Antipsychotic medications are associated with adverse cutaneous reactions (ACRs) in approximately 2-3% of patients.[1] We present three cases of possible risperidone induced periorbital oedema in the absence of any other systemic or local cause responsible for the oedema. The development of periorbital oedema after the initiation of risperidone therapy, and disappearance after the discontinuation of this drug, suggests a possible causal relationship between periorbital oedema and risperidone. To our knowledge, there are very few reports of risperidone therapy and development of periorbital oedema. Risperidone is a valid and effective choice amongst antipsychotic medications, but these cases call for caution regarding ACRs at the time of prescribing.

Key words: Risperidone; Schizophrenia; Periorbital oedema.

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Case studies

Case 1

A 30 year old female admitted to our hospital for the management of undifferentiated schizophrenia of seven years duration, characterised by delusion of persecution, thought