



Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case report

CADASIL mimicking multiple sclerosis: The importance of clinical and MRI red flags

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ARTICLE INFO

Article history:

Received 13 June 2016

Accepted 28 September 2016

Available online xxxx

Keywords:

CADASIL

MS

Multiple sclerosis

Mimic

Red flag

ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease, manifesting as recurrent ischaemic events, migraine with aura, behavioural disturbance and cognitive decline. We report two patients with CADASIL masquerading as multiple sclerosis (MS). A 23 year old female presented with a visual scotoma and was discovered to have a corresponding retinal cotton wool spot. MRI brain revealed diffuse T2 hyperintensities suggestive of demyelination. A 56 year old male presented with transient sequential paraesthesia, initially of the perineum followed by the right leg. He also reported memory and mood impairment with a history of migraine with aura. MRI of the brain showed diffuse bilateral white matter lesions with sparing of the anterior temporal poles. Both patients satisfied the modified McDonald diagnostic criteria and were initially thought to have MS. However, they did not satisfy the caveat of “no better explanation” and on subsequent testing NOTCH 3 mutations were identified in both patients [1]. These cases highlight the importance of careful clinical assessment and neuroimaging findings in identifying clinical and paraclinical ‘red-flags’ for a diagnosis other than MS.

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1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an angiopathy that is caused by mutations in the NOTCH3 gene on chromosome 19 [3]. Similarities between clinical and radiological findings of multiple sclerosis (MS) and CADASIL often lead to misdiagnosis and diagnostic delay.

Here we report two cases of patients with CADASIL, who were initially suspected to have multiple sclerosis.

1. A 23 year old Caucasian female, was referred to our service after presenting with visual disturbance. She described a monocular right inferior scotoma affecting her right eye only. This fluctuated over the course of one week before resolving completely. She had seen an ophthalmologist who discovered a small cotton-wool spot in the right fundus beyond the superior temporal arcade (Fig. 1). Repeat fundal examination some weeks later was normal and there were no other neurological findings. It is unclear whether the cotton wool spot was related to her visual symptoms, however it was certainly unusual and her ophthalmologist arranged further testing. Thrombophilia and vasculitis screening

was normal. She underwent an MRI of her brain which showed numerous foci of white matter hyperintensities within the deep and subcortical white matter in the frontal, parietal and temporal lobes involving both the periventricular and pericallosal white matter regions. There was no restricted diffusion seen to suggest acute infarcts. She reported a past history of migraine without aura, but was otherwise well.

The index patient’s mother had been diagnosed with multiple sclerosis 12 years prior, though had an unusually benign pattern of disease. Her initial presentation was of a transient right sided paralysis of the face, arm and leg lasting only a few hours, but leaving her with persistent allodynia and numbness of the right foot. This was associated with an intense headache and pain behind the right eye. An MRI of the brain at the time revealed multiple T2 hyperintense foci in the white matter of bilateral cerebral hemispheres, most marked at the callosal – septal interface and peritrigonal white matter. She was diagnosed with MS and commenced on Interferon beta 1a treatment, on which she remained well. After a number of years of treatment she decided to stop the drug and has stayed off it since. At a ten year interval her imaging had not changed greatly and she did not have any progress in her symptoms. Her only complaints were that of an intermittent spinothalamic disturbance from the mid-calf into the right foot. On examination, pin prick and temperature had altered quality on the right leg from

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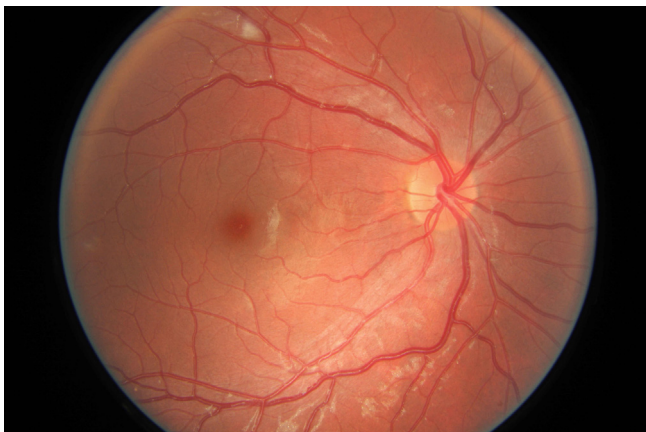


Fig. 1. Retinal photograph showing a small cotton wool spot beyond the right superior temporal arcade.

the mid-calf downwards in a sock distribution. She also had symmetrically augmented reflexes in the lower limbs. Overall, after at least a 10 year history of 'multiple sclerosis', she had very few deficits.

The index patient underwent genetic testing for CADASIL and was found to have a NOTCH3 gene mutation in exon 3. She was referred onto a neuro-genetics clinic for counselling. On subsequent testing, her mother was also found to have this mutation.

2. A 56 year old man who presented with a history of numbness involving and between the penis and anus lasting a week. Some months later, he noticed tingling and discomfort in the right toe and pain in the right calf. Subsequently he developed paraesthesia over the entire upper lip and both hands. In addition to his sensory symptoms, he also described symptoms of low mood and significant anxiety. He reported episodes of forgetfulness and incidences where he had performed poorly at work, which was unusual for him and contributing to his anxiety.

Past history includes migraine with aura since age 11. Episodes comprise of teichopsia followed by bilateral occipital headaches becoming bitemporal with photophobia, nausea and vomiting lasting 12 h. These previously occurred at a monthly frequency, progressing to almost weekly, when the possibility of a diagnosis of multiple sclerosis was raised. Detailed neurological examination was unremarkable, though the patient was noted to be extremely anxious during the assessment.

MRI of his brain revealed juxtacortical and deep white matter lesions but no involvement of the corpus callosum or posterior fossa (Figs. 2 and 3). MRI of his spine did not reveal any lesions and his CSF was bland and negative for oligoclonal bands. Testing for the CADASIL revealed a mutation in the NOTCH 3 gene.

2. Discussion

CADASIL presents in young adults with recurrent ischaemic events. Clinically, similar to MS, these patients can have episodes of acute focal neurologic deficit with partial or complete recovery. Other clinical features that are commonly seen in CADASIL include migraine with aura, mood disturbance, behavioural alterations and progressive cognitive impairment [3]. Though retinal abnormalities are seen commonly in patients with CADASIL, they tend to be clinically silent and are rarely the presenting feature [2]. The most common findings include cotton wool spots and retinal nerve fibre layer defects. These abnormalities are not associated with conventional vascular risk factors, and may be considered peripheral markers of this disorder.

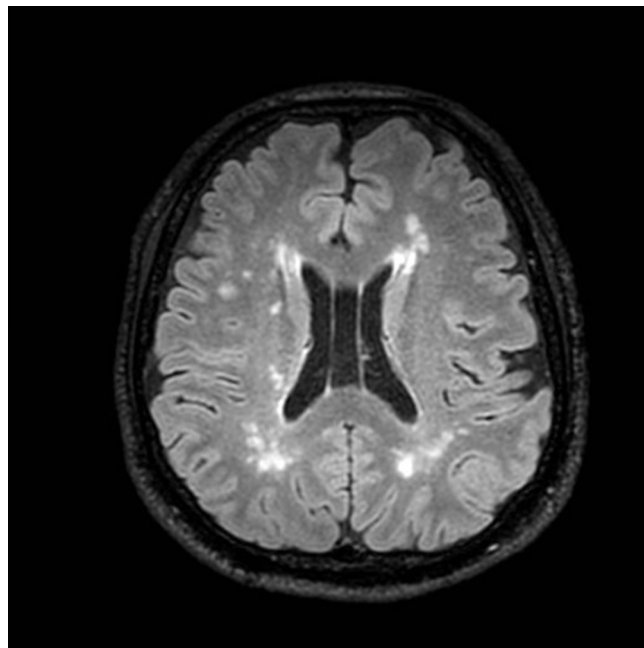


Fig. 2. Periventricular and subcortical white matter lesions in both cerebral hemispheres. There is relative sparing of the juxtacortical, brain stem and anterior temporal lobe regions. There is an incidental finding of cavum septum pellucidum.



Fig. 3. Periventricular and subcortical white matter lesions in both cerebral hemispheres. There is relative sparing of the juxtacortical, brain stem and anterior temporal lobe regions.

Most patients with CADASIL will have an autosomal dominantly inherited mutation in NOTCH3, and therefore an affected parent, however de novo mutations can occur and therefore the diagnosis should still be considered in the absence of a positive family history, as with our second case [5]. Unmatched oligoclonal bands are found frequently in patients with MS, whereas most patients with CADASIL will have normal CSF studies [3].

MRI findings in CADASIL are classically those of T2 hyperintense lesions of the anterior temporal pole, U-fibres of the vertex, external capsules and insular regions [5]. The basal ganglia and thalamus are often affected, a crucial difference from multiple sclerosis. Multiple bilateral microhaemorrhages may also be seen [3,5]. Our second patient's MRI did not show typical features suggestive of CADASIL, and though there were diffuse white matter lesions, the anterior temporal poles were spared. Nevertheless, clinical red flags prompted genetic testing for CADASIL.

A diagnosis of MS requires evidence of disease dissemination in time and space [4]. Though there aren't any definitive exclusion criteria, the McDonald criteria do highlight the importance of excluding other conditions. The role of MRI has become particularly prominent, and clinicians may rely too much on non-specific T2 abnormalities as the principle support for an MS diagnosis. This can lead to inappropriate treatment and potentially missed opportunities for other helpful interventions. Clinicians must show vigilance for clinical and paraclinical red flags to prompt consideration for diagnoses other than MS before committing a patient to long term immunosuppressive therapy, as emphasized by the two cases above.

Even though there is no specific disease modifying treatment available for CADASIL, the diagnosis is important to make, as it has significant implications for the patient, their offspring and

any other family members. For young patients of child bearing age, family planning should be discussed and the options of pre-implantation and prenatal diagnosis outlined by a geneticist. Asymptomatic children should not be tested, while adults at risk should receive genetic counselling prior to consideration of predictive genetic testing [6].

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