White matter lesions mimic multiple sclerosis in a minimally symptomatic CADASIL

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CASE REPORT

Abstract

Introduction: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a heritable small-vessel disease of the brain characterized by subcortical ischaemic events, cognitive impairment and leukoencephalopathy. The clinical presentation of the disease varies substantially between and within families and might be modulated by gender and common vascular risk factors.

Case Report: We present the clinical case of a 57-year-old patient initially misdiagnosed with multiple sclerosis. The case illustrates how important it is to re-evaluate family history and imaging features in clinically non-progressive patients and demonstrates the substantial diversity of CADASIL within family members. In this setting, the approach of minimally symptomatic patients with white matter changes can present some diagnostic challenges.

Discussion: This case illustrates the diagnostic challenge of minimally symptomatic CADASIL. The need to reassess the diagnosis in such patients is of uttermost importance, since it has implications for disease management and genetic counseling.

Keywords: CADASIL, Multiple sclerosis, White matter lesions.
Introduction

CADASIL is a form of hereditary small vessel brain disease caused by mutations in the NOTCH3 gene [1]. A study from northeast England provided an estimate of the minimum prevalence of the disease of 1 in 25–50,000 and a risk of developing CADASIL of more than 1 in 13,500 individuals in the general population [2]. The clinical presentation of CADASIL varies substantially between and within families and it appears to be no clear genotype-phenotype correlation [3]. Characteristic features include migraine with aura, subcortical ischaemic events, mood disturbances, apathy and dementia. It is characterized by a wide variability in time from symptom onset to death and typically results in reduced survival. Some studies provide evidence that the clinical presentation of the disease might be different depending on gender and the presence of traditional vascular risk factors [4]. Migraine with aura appears to be more prevalent in women before the usual age of menopause, and stroke more frequent in men before the fifth decade of life. This difference could explain a higher degree of executive dysfunction and disability in men at a later stage of the disease [5]. Besides this possible hormone modulation, traditional vascular risk factors might further influence the disease and increase disease severity.

One of the hallmarks of CADASIL is the presence of striking white matter MRI abnormalities [6]. A recent study suggests that genetic modifiers not related to the NOTCH3 gene might modulate the white matter burden in patients with CADASIL, expanding the range of factors that may be responsible for the clinical and imaging heterogeneity of the disease [7].

So, CADASIL is a condition with a wide spectrum of clinical presentations and MRI changes can mimic other diseases with white matter abnormalities. The approach of minimally symptomatic patients with white matter changes can present some diagnostic challenges.

Case Report

A 57-year-old, right-handed, woman was observed at our center for the assessment of cognitive decline and cerebral white matter lesions. She had been previously diagnosed with multiple sclerosis. The main complaint was a slight difficulty making rapid decisions in relation to her usual performance. In spite of this, she kept her usual professional activity running a business. She had migraine without aura since adolescence and, in the last few years, she was on sertraline for depressive symptoms. Mild dyslipidemia was also reported. The patient did not remember having episodes with visual changes, loss of strength, abnormal sensitivity or ataxia in the past; no story of stroke-like episodes. Her 60-year-old only one brother was diagnosed with a psychiatry disorder a few years earlier and he was bedridden for the last year. Her father and a paternal uncle died in their 70s with dementia.

The patient had recently been subjected to neuropsychological assessment on the basis of her diagnosis. Multiple Sclerosis Functional Composite and the Rao's Brief Repeatable Battery of Neuropsychological Tests showed mild impairment in attention/concentration, information processing speed and semantic verbal fluency. The neurological examination was otherwise unremarkable.

She underwent a brief blood and cerebral spinal fluid screening. Thyroid status and autoimmune profile was normal. Cerebral spinal fluid was unremarkable, including testing for the presence of oligoclonal bands.

Two past brain MRIs were available for reassessment. At the age of 53, her brain scan showed a periventricular lacunar infarct and symmetrical and confluent areas of increased signal on T2-weight and fluid attenuated inversion recovery (FLAIR) sequences, involving the centrum semiovale and periventricular deep white matter, internal and external capsules and the pons. Importantly, the temporal poles showed no significant signal changes. T2*-weighted gradient-echo images were unavailable (Figure 1–3). Spinal cord imaging was unremarkable. We also had access to another MRI scan performed four years earlier, which showed no significant changes of the lesions or gadolinium enhancement (Figure 4).

Despite the patient not presenting criteria for dementia diagnosis or a history of stroke-like episodes, based on her brain MRI and family history of dementia, we decided...
to perform genetic testing to CADASIL. NOTCH3 gene revealed a mutation in codon 4, resulting in the replacement of a cysteine residue with a serine (p.C168S). Skin biopsy showed the presence of granular osmiophilic material near the basement membrane of the smooth muscle cells of an artery.

Further investigation with cervical and transcra\nal ecoDoppler, electrocardiogram and echocardiogram showed normal results.

The patient was subsequently subjected to a screening for other vascular risk factors and initiated acetylsalicylic acid and treatment with statin for control of dyslipidemia.

A comprehensive systematic neuropsychological re-assessment over 3 years showed normal memory, language, attention and information processing speed. Verbal fluency and executive functions emerged as the most affected cognitive domains, yet not interfering with the activities of daily living.

Discussion

The clinical presentation of CADASIL has no clear genotype-phenotype correlation and varies substantially between and within families. Most mutations are missense mutations that lead to an odd number of cysteine residues within a given epidermal growth factor repeat of the encoded transmembrane receptor [2]. Our patient has a novel mutation that we have no knowledge of being previously described.

Core features include migraine with aura, subcortical ischaemic events, mood disturbances, apathy and dementia, but there is a wide variability in time from symptom onset to death. The most frequent initial symptoms may become evident in young or middle adulthood with migraine or an ischemic event. Up to 10% of patients have progressive cognitive decline without other symptoms, but in most patients cognitive impairment is associated with recurrent strokes with motor disability, gait disturbances and pseudobulbar palsy [2-4]. Some studies suggest that disease severity might be different regarding gender and the presence of traditional vascular risk factors [5, 6].

Besides this possible hormone modulation, traditional vascular risk factors might further influence the disease and increase disease severity. It has been reported that hypertension increases the risk of stroke in CADASIL patients and that smoking is associated with an earlier onset of stroke, suggesting that these risk factors should be treated aggressively [8]. According to these data, the family of our patient also displays a significant variability of possible cases with CADASIL. The patient has no other vascular risk factors other than dyslipidemia, and this may partly explain the relatively benign evolution of her clinical condition.

The main MRI features of CADASIL are leukoencephalopathy, lacunar infarcts, subcortical lacunar lesions (SLL) and microbleeds [9]. All individuals carrying the mutation have MRI changes after the age of 35 years and almost all patients present with MRI abnormalities before symptom onset [2]. The earliest and most characteristic findings are areas of increased signal on T2-weight imaging or FLAIR involving the periventricular and deep white matter. Later in life, these lesions become confluent and are mostly sym-
metrical. The thalamus, the basal ganglia and the brainstem, especially thepons, can also be affected. The most suggestive feature of CADASIL is the involvement of the external capsules and the temporal poles. These regions tend to be much more affected in comparison to sporadic leukoaraiosis and should raise suspicion of the diagnosis [9, 10]. Some have reported that the external capsule involvement appears to be age-related as opposed to the temporal pole hyperintensities that seem to be an early marker of the disease [11-13]. Small deep infarcts identified on T1-weight imaging follow the same distribution, developing preferentially at the edges of the expanding white matter lesions and later becoming surrounded by them [7, 11]. A recent study suggests that genetic modifiers not related to the NOTCH3 gene might modulate the white matter burden in patients with CADASIL, expanding the range of factors that may be responsible for the clinical and imaging heterogeneity of the disease [3].

SLL are preferentially located in the cortico-subcortical junction of the temporal and frontal lobes. Histologically, these lesions are similar to dilated Virchow-Robin spaces and exhibit the same MRI signal features. SLL increase with age, may occur before the lacunar infarcts, and appear to be highly specific of CADASIL [11-13].

In multiple sclerosis, periventricular lesions often display an ovoid shape and radial orientation away from the ventricles, giving rise to the classic Dawson’s fingers appearance on sagittal imaging. Juxtaocular lesions and infratentorial lesions typically seen along the floor of the fourth ventricle or at the surface of the pons, are not commonly seen in microvascular disease. In the latter, infratentorial lesions typically have a central pontine location [13].

Cerebral microbleeds are small focal areas of signal loss on T2*-weighted gradient-echo images caused by the deposition of chronic blood products in tissues. Approximately 35–69% of patients with CADASIL have these alterations scattered throughout the brain without a clear predilection for specific locations, suggesting a distinct pathological process. Microbleeds are associated with age, blood pressure, hemoglobin A1c concentration, lacunar infarcts, leukoencephalopathy and a poor functional outcome [15].

In our case temporal pole involvement was not present and we have not identified subcortical lacunar lesions neither cerebral microbleeds (Figures 1–4).

CADASIL is a progressive and debilitating disease affecting young and middle-aged adults that leads to a dramatic terminal stage within a mean of 25 years after disease onset, characterized by dementia, motor impairment, gait disturbances and pseudobulbar palsy. There are few cases reported, however, that differ from this pattern with a very rapid or very slow clinical progression. The life expectancy is about 65 years in men and 71 years in women [2]. We present the clinical case of a 57-year-old patient with a minimally clinical symptomatic CADASIL and with a pattern of white matter changes not completely typical for CADASIL. This case initially misdiagnosed as multiple sclerosis demonstrates the clinical and imagiological diversity of CADASIL.

Since CADASIL is the most frequent hereditary vasculopathy, it is important to have high level of suspicion, even in the absence of typical clinical events, like stroke, and classic imaging features.

Abbreviations
CADASIL: Cerebral autosomal-dominant arteriopathy with subcortical infarcts; FLAIR: Fluid-attenuated inversion recovery; MRI: Magnetic resonance imaging; SLL: Subcortical lacunar lesions

Competing interests
The authors declare no conflict of interest.

References


