

Case Report

CADASIL presenting as schizophreniform organic psychosis

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ABSTRACT

Objective: To describe an Asian patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) presenting with schizophreniform organic psychosis.**Methods:** Case report.**Results:** We report a case of CADASIL in an Asian female presenting with frank psychotic symptoms. After resolution of her psychosis, she showed persistent distractibility, which indicated signs of cognitive impairment.**Conclusion:** Although neuropsychiatric symptoms are commonly present in this disorder, psychotic symptoms are rare and should be recognized. There is a need for timely diagnosis and management of this disorder.

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1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare autosomal-dominant systemic nonamyloid, nonatherosclerotic arteriopathy with prevalence of approximately 2–4 per 100,000 [1] but likely to be underestimated due to frequent misdiagnosis and poor awareness by physicians. It is generally characterized by symptoms of migraine with aura, subcortical ischemic events, mood disturbances, cognitive impairment and apathy; although clinical presentations vary substantially with age, gender [2] and disease duration [3]. Despite its commonly manifested neuropsychiatric symptoms, it has gathered little attention in psychiatry [4]. We describe a case of schizophreniform psychosis in CADASIL, which is important for enhancing awareness in the timely detection and management of this multifaceted syndrome.

2. Case report

In May 2014, a 45-year-old Chinese lady was admitted to our medical psychiatric unit for investigation of mood disturbances and behavioral changes that occurred over 5 months. Her mood was labile with episodes of inappropriate laughing and crying. Her speech was irrelevant with loosening of associations. She reported auditory hallucinations of multiple voices talking to her and visual hallucinations of deceased people. She also expressed grandiose delusions of being able

to travel through heaven but no other symptoms suggestive of mania. She was not depressed, and there were no obvious memory impairment, neurological deficits or history of migraine. She had no prior medical or mental health problems. One of her brothers experienced “mild stroke” at 71 years old. Her parents passed away in their 80s, and there was no further family history of stroke, dementia, psychiatric illness or migraines.

Her physical and, specifically, neurological examination was normal. Mini-mental state examination (MMSE) could not be done as she was disorientated with loosening of association. Laboratory results were normal for full blood count, electrolytes, thyroid function, antidouble stranded DNA antibodies and antibodies to nuclear antigens. Thrombophilia screen was negative. Magnetic resonance imaging (MRI) revealed multiple old lacunar infarcts throughout the brain including basal ganglia, pons, subcortical white matter and periventricular white matter T2 hyperintensities (Fig. 1). Electron microscopy of her skin biopsy showed granular osmiophilic material (GOM) deposited focally around blood vessels (Fig. 2). Genetic testing was however not done due to cost issues faced by the patient. The unique combination of characteristic distribution of hyperintensities in the external capsule and subcortical white matter and distinguishing morphological changes of blood vessels on histopathology helped to arrive at a probable diagnosis of CADASIL [5]. Due to her psychotic symptoms and disorganized thoughts, she was diagnosed to have schizophreniform organic psychosis, which was an unusual first presentation in CADASIL. Her psychotic symptoms resolved with risperidone 4 mg and sodium valproate 800 mg, and she was discharged 1 month later. Nevertheless, she continued to have relapses of psychotic symptoms, leading to another hospitalization within the next 2 months. She was subsequently stabilized with additional intramuscular fluanxol

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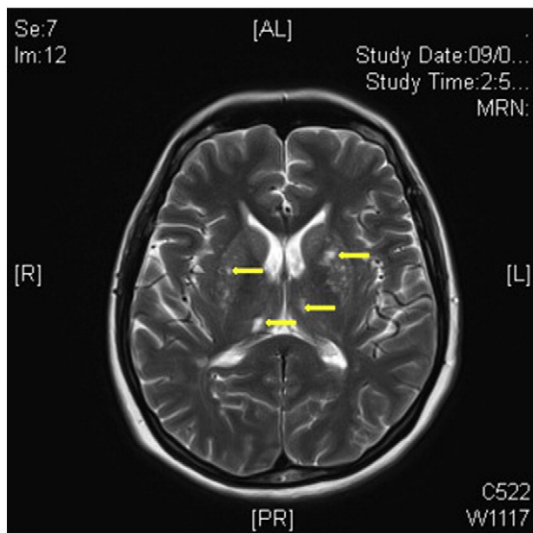


Fig. 1. T2-weighted MRI of the brain showing hyperintensities in the thalamus and putamen.

depot injection 20 mg every month. Repeat MMSE was attempted when her psychotic symptoms abated, but she was distractible and unable to complete the assessment. She subsequently declined further memory testing. According to her family, since her second hospital discharge, she was inattentive but able to function independently at home.

3. Discussion

CADASIL is caused by mutations in the *NOTCH3* gene located on chromosome 19p13.1 encoding for transmembrane receptor NOTCH3, which is important for development and homeostasis of the cardiovascular system [6]. Diagnosis is established by (a) characteristic MRI scan findings of increased signal on T2 or fluid-attenuated inversion recovery sequences in periventricular white matter, basal ganglia, thalamus, anterior part of temporal lobe, internal and external capsules and pons; (b) genetic testing of *NOTCH3* mutations; and (c) presence of GOM on electron microscopic study of skin biopsy in cases of negative finding for *NOTCH3* mutations.

The rarity of CADASIL, wide variation in clinical presentation and lack of distinctive clinical examination findings make diagnosis difficult. This is particularly so in places where cardiovascular disease and multiple sclerosis are highly prevalent. Psychiatric manifestations are

the initial presentation in 15% of cases, and 30% of patients have psychiatric symptoms, of which mood and stress-related disorders and subcortical dementia are more frequent [7]. Nonaffective psychotic illness is extremely rare, and in current literature, only one case of schizophrenia associated with CADASIL was described [8]. Our patient's presentation was unique as she presented initially with disorganized psychotic symptoms, which could easily be misdiagnosed as late-onset schizophrenia. Cognitive deficit needs to be particularly screened for, as it is the second most frequent clinical manifestation of CADASIL, of which executive dysfunction and poor concentration are most predominant [9] and tend to worsen with lesion load on MRI [10], though memory is comparatively preserved. Our patient's extent of cognitive impairment could not be accurately assessed due to her inability to perform MMSE, possibly affected by frank psychotic symptoms. Furthermore, the inception of cognitive impairment is often mild and insidious, making it difficult to establish the onset. Her distractibility post psychosis likely heralded cognitive impairment, and she would benefit from formal neuropsychological assessment longitudinally to monitor disease progression.

Our patient's presentation showed distinct characteristics unique in Asian studies of CADASIL [11]. She did not have migraine, commonly encountered in more than one third of Caucasian patients but less reported in Asians. She also did not have a dominantly inherited family history of vascular disease, which was found in some Asian populations. Our patient's MRI findings of hyperintensities predominantly in brainstem rather than anterior temporal regions were also more commonly reported in Asians as compared to Caucasians.

The genesis of psychotic symptoms and correlations with brain lesions in CADASIL are not well delineated. Although the current opinion of schizophrenia in association with CADASIL appears anecdotal [8], both CADASIL and schizophrenia are associated with disruption of Notch-dependent transcription critical for many biological processes, which may suggest possible common pathways of dysfunction. Although both conditions could co-exist, this is less likely in our patient with late onset presentation, where there is already significant brain disease. Psychosis is particularly associated with multiple subfrontal white matter infarcts [12], contributing to damage in the cortical-subcortical network, which our patient demonstrated on brain imaging. Nevertheless, whether psychotic symptoms predate the brain lesions or both develop concurrently would necessitate longitudinal follow-up of CADASIL patients with normal brain imaging using structured psychiatric interviews and systematic MRI brain evaluations.

Presence of late-onset psychiatric symptoms and cognitive impairment with white-matter MRI abnormalities should raise suspicion of this complex syndrome. There is a wide range of clinical manifestation seen in CADASIL, of which Asians may present differently. Therefore, its diagnosis should not be made based merely on typically described phenotypes, but rather with a combination of confirmatory investigations while being mindful of its clinical variability.

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Fig. 2. Electron microscopy of skin biopsy showing osmiophilic deposits.

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