5-2019

CADASIL subcortical dementia – A case report

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A Case of CADASIL-related Dementia

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL, is a genetic disease that results in early-onset strokes and dementia. It is one of the most common hereditary causes of strokes and vascular dementia. The mutation involves the NOTCH3 gene, a gene implicated in small vessel proliferation and remodeling. Interestingly, the majority of the small vessel pathology occurs in the vasculature of the subcortical regions of the brain. This is a case of a female with a typical presentation of the disease, presenting with late stage subcortical dementia. Collaborative history from her children revealed a characteristic progression of the disease. The study of her case will help illustrate the distinctive manifestations of the condition often associated with the condition. Information regarding the natural history, diagnosis, and management will also be discussed. CADASIL is assumed to be massively under-diagnosed, and is believed to underlie a much larger proportion of stroke and dementia cases than previously thought.

Introduction

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare autosomal dominant disease characterized by small vessel angiopathy that leads to early-onset strokes and vascular dementia. It is caused by a mutation to the NOTCH3 gene on chromosome 19[1], a gene involved in vascular smooth muscle proliferation and remodeling. The disease was first described and genetically mapped by Tournier-Lasserve et al in 1993[2].

A very rare and invariably fatal disease, CADASIL is estimated to affect 2/100,000 adults based on several epidemiological studies, including one performed in Scotland (with similar rates all around the world), although it is thought to be widely underdiagnosed [3]. CADASIL characteristically manifests with cerebral ischemic episodes, cognitive deficits, migraine with aura, and psychiatric disturbance [4].

Discussion

CADASIL is an autosomal dominant small vessel vasculopathy affecting the small arteries of the brain [1]. A related clinical entity, subcortical vascular dementa (Binswanger's disease) is the sporadic type and presents with very similar dementia symptoms. CADASIL is the first detected hereditary syndrome of vascular dementia, and is one of the most common hereditary causes of stroke. The disease usually presents in early adulthood, at around 30-60 years of age . It is caused by a NOTCH3 gene mutation on chromosome 19 [5].

Case Report

A 54 year old Syrian female presented with several years of progressive cognitive decline, starting with social isolation (4 years), followed by irritability and emotional lability, with episodes of laughing or crying (3 years), began to develop inappropriate social behavior (2.5 years), loss of urinary continence and gait disturbance and falls (2 years), apathy (1.5 year), dysarthria (1 year), finally progressing to total memory loss and disorientation. Prior to the start of her mental deterioration, past medical history included chronic migraines of moderate frequency and occasional episodes of syncope. She was not on any medication at the time but was placed on imipramine and memantine previously for management of her progressive mental illness. Her family history revealed that her father began suffering from very similar symptoms in his fifth decade and died after 3 years. She did not smoke or drink.

On observation and neuropsychiatric inventory, patient was alert but not oriented to person, place, time, or situation. She was restless and extremely irritable. She was mute and avoided eye contact. She was ambulatory but appeared to have a stomping, or sensory, gait. She would sometimes speak to herself or to people not present in the room, indicating that she was hallucinating. Her affect was completely flat. Motor abnormalities included peri-oral dyskinesia and twitching. She had severe psychomotor retardation. The patient could not complete the mini mental state examination (MMSE), short-term memory function (SMFT), or Benton tests because she was completely disoriented. Differential diagnosis included subcortical vascular dementia and normal pressure hydrocephalus due to her early urinary incontinence and gait disturbance, and Lewy body dementia due to her hallucinations and falls.

Diagnosis of subcortical vascular dementia was made based on clinical and radiological findings. A very high likelihood of CADASIL was hypothesized based on characteristic historical findings: early onset, migraines, syncope (likely to be transient ischemic attacks, or TIAs), and positive family history. Genetic testing was not performed and hence a definitive diagnosis of CADASIL was not made.

Photos

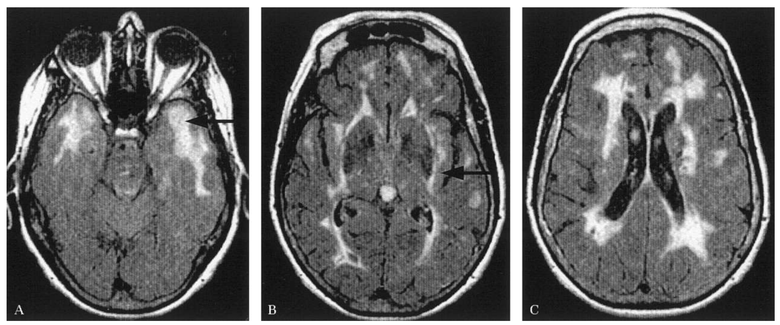

Figure 1. MRI findings associated with CADASIL. First slide shows anterior temporal leukoencephalopathy. Second arrow shows the diffuse periventricular white matter lesions

Laboratory Values and Imaging

Laboratory investigations of hematological, hepatic, renal, endocrine, and urological panels showed decreased serum B12 (99pg/ml, RR 211-911), which was treated with a B12 injection. Imaging could not be completed initially due to the patient's irritability.

Head magnetic resonance imaging (MRI) showed prominent basal cisterns and cortical sulci, with dilated ventricles consistent with involutional brain changes. MRI also showed bilateral symmetrical diffuse periventricular and centrum semi-ovale hyperintensities on T2/FLAIR, consistent with microvascular ischemic changes. Computerized tomography (CT) showed diffuse ventricular dilation in conjunction with widened basal cisterns, sylvian fissures, and cortical sulci, denoting involutional brain changes. CT also showed bilateral periventricular deep white matter hypodensities, predominantly in the anterior region, consistent with subacute atherosclerotic encephalopathy.

Management and Conclusion

Following initial diagnosis of CADASIL, it is recommended patients undergo neurologic evaluation, psychometric studies (focusing on executive function), brain imaging (MRI T2 FLAIR), and genetic counseling. Psychiatric evaluation should also be performed if patients exhibit symptoms of psychiatric illness. Since this patient presented at such a late stage of the disease, no further investigations would have been useful. Genetic testing of the patient and her children may have been worthwhile but was not performed.

There is currently no treatment of proven efficacy for CADASIL. Prophylactic therapies, such as low dose aspirin, have been proposed for secondary prevention of ischemia and infarction; however, no prophylactic treatment has been proven to positively alter the course of the disease. Most treatment options are symptomatic, aiming to improve patients' quality of life.

Bibliography

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