

# Detection of Early Cognitive Impairment Using AD8 in a Young Patient With Stroke With Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Syndrome: A Case Report

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## Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome is a hereditary disease resulting from *NOTCH3* gene mutation. The clinical presentations include migraine, recurrent stroke, and cognitive impairment. The severity of cognitive impairment varies in different stages, and early recognition poses a challenge. A 47-year-old lady presented with chronic migraine and sudden onset of hemiparesis. Magnetic resonance imaging revealed compatible findings of CADASIL, which was confirmed by mutation analysis of *NOTCH3* gene. Early cognitive impairment was detected by her score of 3 in Ascertain Dementia 8 (AD8) questionnaire and confirmed by detailed neuropsychological assessments. After 21 months of follow-up, deterioration in her cognition and ability to perform instrumental activities of daily living were significant with a follow-up AD8 score of 7. Ascertain Dementia 8 questionnaire is an easy and valid screening tool for early cognitive impairment in patients with CADASIL syndrome.

## Keywords

young stroke, cognitive impairment, CADASIL syndrome, AD8

## Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome is an inherited small vessel disease that is caused by mutation of *NOTCH3* gene.<sup>1,2</sup> In CADASIL, the arterioles penetrating to the cortex have vessel wall thickening and lumen stenosis which compromise circulation of cortex. As a result, the individual who carried mutated *NOTCH3* gene would easily have cerebral infarcts with periventricular white matter change that mimics hypertensive encephalopathy.<sup>3</sup> The clinical manifestations of patients with CADASIL syndrome are characterized by migraine with or without aura, recurrent ischemic stroke, cognitive impairment, and even dementia.<sup>1,2</sup> Cognitive impairment is the second most common manifestation in CADASIL syndrome.<sup>1</sup> Early and recurrent stroke with cognitive impairment in CADASIL may lead to dementia eventually,<sup>4</sup> and about 60% of the patients with CADASIL with stroke become demented after 60 years.<sup>2</sup> Even in the patients with CADASIL who had

not experienced stroke, there was evidence of deficits in short-term memory and working memory.<sup>5</sup> The spectrum of cognitive impairment in CADASIL has been documented, including pronounced impairment in processing speed and error

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monitoring<sup>4</sup> as well as alterations in visuospatial abilities, memory, attention, and executive function.<sup>6</sup> In the patients older than 60 years of age, cognitive impairment will be more profound in all domains, while cognitive impairment in younger patients, especially those less than 50 years old, might begin with abnormal executive functions, including alterations in attention and memory, difficulties in organizing daily activities and thoughts, prioritizing tasks, and decision making.<sup>6</sup> Some patients also had mood problems, that is, depression or apathy.<sup>1,2</sup> Because cognitive impairment is usually insidious as compared to more localized symptoms associated with ischemic stroke, it poses a special challenge to detect the occurrence of neuropsychological decline of the patients.

For patients with Alzheimer's disease, the Ascertain Dementia 8 (AD8) questionnaire<sup>7</sup> has been used to detect very mild dementia in the Western and Asian populations.<sup>7-11</sup> It queries memory, orientation, judgment, and function with 8 questions, and both informant-rated AD8 (iAD8) and participant-rated AD8 (pAD8) could be used easily in the primary care setting.<sup>12</sup> When using cutoff score of 2 in iAD8 and 1 in pAD8, both iAD8 and pAD8 reliably differentiate nondemented individuals from individuals with dementia at the very mild stage,<sup>7-11</sup> and iAD8 seems a relatively good discriminative tool in differentiating between mild Alzheimer's disease and moderate-to-severe Alzheimer's disease.<sup>11</sup> There were no published data using AD8 in patients with CADASIL syndrome in the literature. Here, we reported a case of CADASIL syndrome with early cognitive impairment detected by AD8 questionnaire but not by conventional Mini-Mental State Examination (MMSE).

## Case Report

A 47-year-old female, a senior high school graduate and a vendor selling betel nuts for living, presented with migraine for 8 years with visual aura. She was admitted due to sudden onset of left hemiparesis along with numbness over left face, trunk, and limbs in March 2011. She had body mass index of 19.2 and had no previous history of hypertension or diabetes mellitus. Positive family history of stroke (maternal grandfather and grandmother) as well as family history of young stroke at age of 40s (mother, maternal uncle, and aunt) was present. The brain magnetic resonance imaging (MRI) of T2-weighted and axial fluid-attenuated inversion recovery images revealed diffuse hyperintensity of white matter at periventricular and subcortical areas, in particular at both temporal lobes and frontoparietal regions (Figure 1A). The characteristic clinical and neuroimaging findings suggest the diagnosis of CADASIL. Mutation analysis of the *NOTCH3* gene revealing a missense mutation of 406C>T (R110C) in exon 3 confirmed the diagnosis. Of note, she was the first diagnosed case in her family.

She was transferred to rehabilitation ward for further training due to first-ever ischemic stroke. During admission, we paid special attention to her symptoms of memory loss and cognitive impairment, since insidious decline in cognition usually happens to patients with CADASIL. Before the ischemic event, she still could work without problems in cash deal with

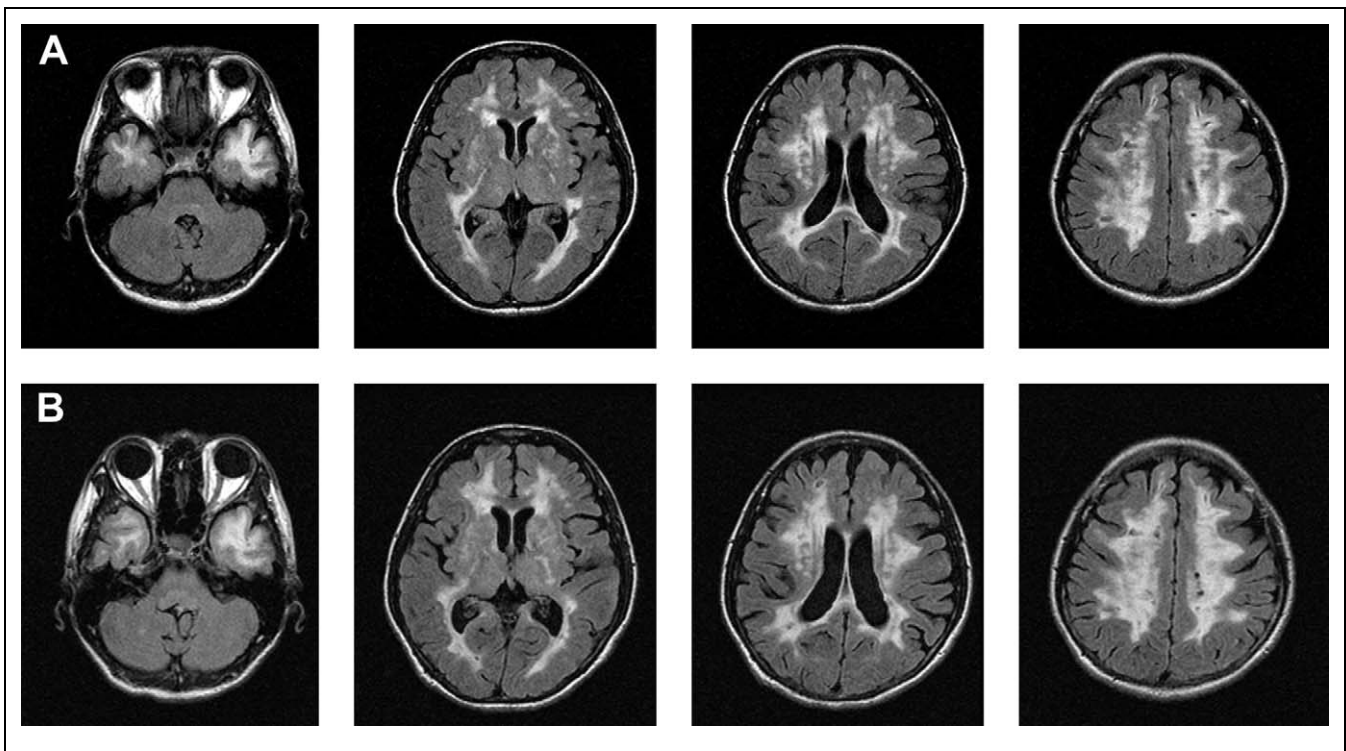
customers. In recent months, even the patient herself did not have any subjective cognitive complaint; some odd behavior and poor memory had been noticed by her husband. She sometimes gave irrelevant answers to questions, and she lost interest in her previous hobby including dancing gradually. Initial screening with MMSE<sup>13</sup> (score of 28) failed to show the evidence of dementia. The iAD8 questionnaire<sup>7</sup> was then used for screening. The score of 3, slightly above the cutoff value of 2, indicates that she had prodromal stage of dementia as well as mild cognitive impairment. The endorsement of each question was as follows: question 2: reduced interest in hobbies/activities, question 7: trouble remembering appointments, and question 8: consistent problems with thinking and/or memory.

Several detailed neuropsychological assessments were further exercised. She had poor short-term memory with Digit Span Test,<sup>14</sup> which included backward test (her score of 5 of 14) and forward test (her score of 13 of 16). Impairment in visual conceptual and visuomotor tracking was also demonstrated by Trail Making Test,<sup>15</sup> particularly with excessive time consumed in timed tasks (type A/type B, processing time: 220s/348s, errors: 0/1). Moreover, the Knox's Cube Imitation Test<sup>16</sup> revealed forward score of 9 and backward score of 3, showing that her ability to accomplish the number sequences equaled to the performance of a 7-year-old children. In Wisconsin Card Sorting Test,<sup>17</sup> we observed that no specific matching rule is followed when she matched response cards to key cards. When performing card sorting with a total of 128 cards, the number of psychometric scores obtained was as follows: total errors of 65 cards, perservation response 56 times, perservation errors 49 times, and nonperservation errors 16 times. The percentile norms in both perservation response and perservation errors were below first percentile. All of the above-mentioned tests confirmed cognitive impairment of the present case.

During 21 months of follow-up, additional symptoms of emotional problems, childish personality change, and poor social skills gradually appeared. She could not perform daily household activities as she did before. She closed the stall due to frequent faults in cash deal. The follow-up MMSE score of 25 and informant AD8 score of 7 suggested decline in her cognitive function. This time only the question 5: "Forgets correct month or year" in the informant AD8 questionnaire was adequately answered. The brain MRI also revealed deterioration of white matter lesions compared with 1 of the 21 months before, especially at periventricular area and frontoparietal lobes (Figure 1B).

## Discussion

The characteristics of CADASIL syndrome include a history of migraine headaches, midadult onset of cerebrovascular disease progressing to dementia, and diffuse white matter lesions and subcortical infarcts on neuroimaging.<sup>1,2</sup> The histopathological feature of CADASIL is the presence of electron-dense granules in the media of arterioles that can be identified by electron microscopy of the skin biopsies. More than 90% of patients have mutations in *NOTCH3*, the only gene known to be



**Figure 1.** MRI FLAIR imaging demonstrates (A) white matter hyperintensity involving bilateral temporal lobes, frontoparietal lobes, and periventricular areas, and (B) deterioration of white matter hyperintensity after 21 months of follow-up, especially at both periventricular areas and frontoparietal lobe. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

associated with CADASIL.<sup>1,2</sup> Differential diagnosis for CADASIL is wide and includes sporadic small vessel disease such as Binswanger's disease, hereditary small vessel diseases, multiple sclerosis, mitochondrial encephalopathy, and familial hemiplegic migraine. Our patient is normotensive, and the results of her neurological image study and mutation analysis could help reach the diagnosis.

The AD8 questionnaire is developed as a quick screening tool for early diagnosis of dementia in the primary care setting.<sup>7</sup> The AD8 scores correlated well with the MMSE and Clinical Dementia Rating<sup>18</sup> to assess cognitive functions in dementia.<sup>7-11</sup> In Asian population, the use of AD8 questionnaire shows minimal limitation due to ethnicity.<sup>9-11</sup> In a Taiwanese study, informant-rated AD8 questionnaire yield a sensitivity of 97.6% and a specificity of 78.1% with a cutoff value of 2.<sup>10</sup> In the present case, although MMSE score of 28 indicates no cognitive deficits, her iAD8 score of 3 reveals early impairment of cognition. In the first AD8 scores of our patient, the endorsement of the questions was question 7: trouble remembering appointments and question 8: consistent problems with thinking and/or memory. These 2 questions were mainly related to decline in short-term memory. The other one was question 2: reduced interest in hobbies/activities, which would remind us that she might have apathy, mood disturbance, or depression, which is also a characteristic manifestation in patients with CADASIL.<sup>1</sup> Once there is no accompanying informant, AD8 questionnaire could also be participant rated. However, the utility of pAD8 may be greater in patients with very mild cognitive impairment, since

patients with more severe dementia may be unaware of their symptoms.<sup>8,11</sup> Our case report is the first one to use AD8 questionnaire for detecting mild cognitive impairment in patients with CADASIL and in facilitating standardized neuropsychological evaluation and thus early intervention.

Several cognitive screening measures are currently in use, some of those are performance based, like MMSE and Montreal Cognitive Assessment (MoCA),<sup>19</sup> and others are informant based, including Functional Activity Questionnaire (FAQ)<sup>20</sup> and the AD8 questionnaire.<sup>12</sup> The widely used MMSE is a useful global assessment of cognition in mild-to-moderate dementia but it may be culturally insensitive and may fail to identify very mild dementia in high-functioning individuals.<sup>21,22</sup> Montreal Cognitive Assessment, which addresses decline in frontal and executive function, is a 10-minute screening tool for early-stage cognitive impairment and is sensitive in detecting mild dementia in patients with normal scores of MMSE.<sup>23</sup> On the other hand, FAQ, an informant-based functional assessment with only 10 questions, is developed from the instrumental activity of daily living (IADL) scale.<sup>12</sup> As a standardized assessment of IADL, FAQ also help distinguish mild cognitive impairment from mild Alzheimer's disease.<sup>24</sup> Although it works well in different ethnicity,<sup>25,26</sup> the application of this questionnaire on Asian population is still lacking. Also, the cultural factors that may influence scores are not studied intensively yet.<sup>26</sup>

These cognitive deficits in CADASIL can be detected by some standardized neuropsychological assessments such as Trail Making Test, Digital Span Test, Knox's Cube Imitation

Test, and Wisconsin Card Sorting Test.<sup>4,6</sup> Trail Making Test type A and Digit Span Forwards Test can reflect attention span and temporary memory storage abilities.<sup>27</sup> Trail Making Test type B and Digit Span Backwards Test are more related to higher executive functions.<sup>27</sup> The performance of Trail Making Test and Digit Span Test is thought to be sensitive to brain damage.<sup>27</sup> The Knox's Cube Imitation Test is a nonverbal test of intelligence, with satisfactory reliability in attention, concentration, and executive efficiency.<sup>28</sup> The Wisconsin Card Sorting Test is another test particularly sensitive to changes in executive performances, especially frontal lobe damages.<sup>29-31</sup> The Digit Span Test, Trail Making Test, and Knox's Cube Imitation Test revealed her cognitive impairment in processing speed, attention, memory, visuospatial abilities, and executive functions, while the Wisconsin Card Sorting Test indicated that she had disturbed strategy and deficits in her executive functions, abstract thinking, and planning skill as she completed the tasks. These findings are consistent with previous reports of CADASIL.<sup>4,6</sup> However, these standardized neuropsychological assessments are time consuming and are not routinely used by physicians in daily practice.

Mild cognitive deficits may have vital influences on activities of daily livings and social life. Intervention for early cognitive impairment may help intrinsic neuroplasticity and improve outcome.<sup>32</sup> Patients with CADASIL may not be aware of their cognitive deficits until the symptoms become obvious. We suggest routine screening for the mild cognitive impairment with the AD8 questionnaire in patients with suspected CADASIL syndrome.

## Conclusions

Our case shows that cognitive impairment may appear very early without cognitive complaints in patient with CADASIL. We suggest that in young patients with migraine and recurrent ischemic strokes, the possibility of CADASIL syndrome should be considered, and an easy and valid screening test such as the AD8 questionnaire may be exercised promptly before standardized neuropsychological assessments.

## Author's Note

I-Ling Lin and Yu-Ching Lin contributed equally to this work. No previous presentation of this manuscript or abstract is given in any form. All authors have read the final manuscript draft and approved it for submission.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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