



A Case Report: A CADASIL with a New Mutation in NOTCH3

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Abstract

Background: Cerebral autosomal dominant hereditary arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a familiar small-vessel disease, which clinical symptom is an unexplained ischemic event with cognitive impairment and some of these patients have a migraine history. Gene genetic tests have found that the NOTCH3 gene mutation caused CADASIL.

Methods: We report one case of a patient diagnosed with an acute ischemic stroke. One-year after treatment review, who considered to be diagnosed as the CADASIL.

Results: Abnormal cranial MRI may be considered as CADASIL disease, followed by genetic testing of the NOTCH3 gene in patients and their families.

Conclusion: We found the new gene mutation which had never been reported, which demonstrated that the mutation of C.1585 to 1586insT resulted in a change of amino acid synthesis which starting from the 529 amino acid Tyr, which may lead to the occurrence of CADASIL.

Keywords: CADASIL; Leukoencephalopathy; Subcortical white matter; NOTCH3

Introduction

CADASIL is a hereditary disease whose clinical manifestations include a migraine, ischemic stroke, cognitive impairment, but its atypical clinical manifestations are hard to identify or diagnose at a preliminary stage probably. However the cranial magnetic resonance imaging of this atypical CADASIL disease can provide some clinical clues for diagnosis of the disease in the early stage, which was first reported by Sourander P et al., [1] in 1977. This disease had been found in a European family, in which the family members have a progressive cones, medulla oblongata and cerebella neuropsychiatric disorder and all those disorders are evolved into severe dementia. In 1993, Tournier-Lasser Element et al., [2] found that CADASIL is the cause of the stroke, and located on chromosome 19q12 through gene test. The best estimate of the location of the affected genes within 14 organic intervals around the D19S221 and D19S222 loci are established by using Multi-locus analysis of site-point scoring. Joutel A et al have found that the characteristics of the key regions in human Notch3 gene and made the conclusion that this gene mutation caused gene expression abnormal which results in gene interruption, indicating that NOTCH3 may be CADASIL patients defective protein. We recently admitted a case of cerebral infarction patient, whose atypical clinical expression lead to misdiagnosis, but we make a definite diagnosis after one year follow-up visit, all of those processes are reported as follows given below.

Case Presentation

Medical history and clinical examination

A 49-year-old Hui male, who was born in Ningxia Hui Autonomous Region, China, and moved into China's Xinjiang Uygur Autonomous Region when he was ten-years-old, from that time he lived there in a long time. On November 3, 2016, he spoke unclearly suddenly, the outpatient department diagnosed him as a stroke, so admitted him to neurology department ward. The main complaint symptoms were unclear three days, with no headache, dizziness, limb paralysis and cranial nerve palsy symptoms and signs, to further complete the non-contrast enhanced cranial Magnetic Resonance Imaging (MRI), Fluid-Attenuated Inversion Recovery (FLAIR) sequences showed flaky white matter demyelination in the bilateral lateral ventricle and anteroposterior angle. The responsible lesion was considered in the left basal ganglia. The culprit's vessel was considered as the lateral ventricular artery. Admission National Institutes of Health Stroke Scale (NIHSS) score 1 point, Essen Stroke Risk Score (ESSEN) score 1 point. No clear history of hypertension,

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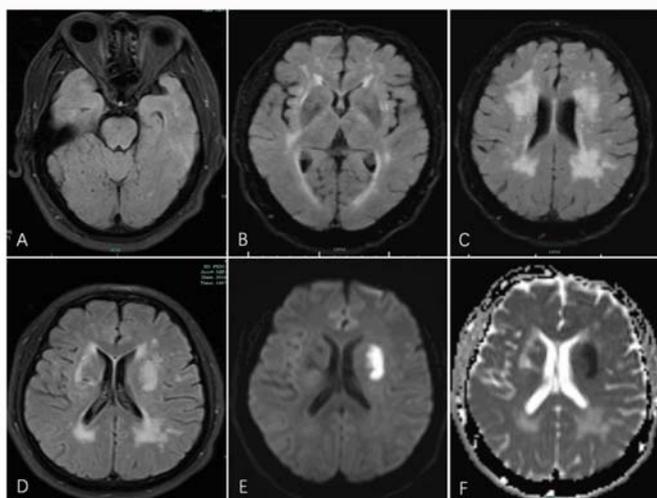


Figure 1: Cranial Magnetic Resonance Imaging (MRI): **A)** The FLAIR axial sequence shows a few flaky high signals of white matter below the bilateral temporal cortex. **B)** The FLAIR axial sequence shows a few flaky high signals of white matter in the bilateral outer balloon region and bilateral frontal cortex. **C)** The FLAIR axial sequence shows a few flaky high signs of white matter in the bilateral anterior and posterior horn of the lateral ventricle. **D)** The FLAIR axial sequence shows an abnormal high signal in the left basal ganglia region. **E)** The DWI sequence shows a high-intensity signal in left basal ganglia region and local spread of lesions is limited. **F)** The ADC sequence shows low-intensity sign in left basal ganglia region, which conform to DWI, considered to be an acute cerebral infarction.

no antihypertensive medication drugs, non-alcoholic drinks and other special hobbies. Doctors made the prescription, the drug therapy, during his hospitalization; including aspirin tablets 100 mg, once daily, antiplatelet therapy, stable vascular endothelium, antihypertensive drugs to control blood pressure, and patients with high levels of Homocysteine (HCY) admission, not to folic acid tablets and mecobalamin drugs treatment. Ten days after the above treatment, all of those symptoms were relieved and discharged. After discharge, oral antiplatelet and statin drugs were administered and monitor the change in blood pressure. After 12 months, the patient was re-examined on November 4, 2017, and re-admitted. Review of non-contrast enhanced cranial MRI showed intracranial white matter demyelination was significantly increased compared with the previous, Diffusion Weighted Imaging (DWI) prompted negative, because of the patient were found fewer words after admission, did not like to communicate with other people, unresponsive. By asking history closely, The Similar symptoms appeared a year ago, mainly manifested as memory loss, do not like communicating with other people, after the stroke occurs, all these above symptoms are more severe than before. We have found that patient's cognition disorder by cognitive evaluation.

MRI examination

The patient's Magnetic resonance imaging FLAIR images demonstrated a small number of anomalous signals visible on both sides of temporal lobes. The white matter demyelinating main appears in the lateral para-ventricular region, showing bow fiber involvement characteristically, unfortunately, the patient's family members did not perform brain MRI and could not obtain family information (Figure 1).

Genetic testing

Afterwards, we carried out a series of gene test of the NOTCH3 gene and gene genetics test of some gene which associated with leukoencephalopathy. The results of all test above revealed that NOTCH3 gene C.1585 to 1586insT resulted in altered amino acid synthesis starting from the 529 amino acid Tyr and termination of the 10th amino acid at the beginning of the change, (PubMed

and HGMD Pro, 1000 Genomes, dbSNP) patient's family map, as shown in Figure 2, by genetic testing, the patient's oldest son, and the youngest daughter has genetic variation, which is heterozygosity status, indicating that may cause disease.

Discussion

Non-Contrast-enhanced nuclear magnetic resonance scans indicate the multiple demyelination of subcortical white matter, and at the same time, there is also need to exclude the possibility of subcortical arteriosclerotic encephalopathy, adrenoleukodystrophy and some diseases like that, atypical clinical manifestations, and special MRI manifestations [1]. The specialty of this case was diagnosed with the acute ischemic stroke on the first hospitalization. During that time neurologists have initially ignored the patient's deterioration of memory and lack of communication with others. Patients denied the history of a migraine, and non-contrast enhanced cranial MRI Atypical intracranial multiple white matter demyelinations did not arise doctors' attention, so the initial clinical diagnosis of the disease is not correct. The first hospital blood test Homocysteine levels were significantly higher, the data showed 62.56 mmol/l, The doctor did not give folic acid and mecobalamin drug treatment to patient, the second hospital HCY levels are still high, the data showed 56.76 mmol/l, meanwhile we found that review non-contrast enhanced cranial MRI showed that intracranial white matter demyelinating lesions are significantly increased compared with previous. Patient's family members have initiative told the doctor that the patient's memory is significantly decreased, easy to forget things, unable to work properly, loss of some self-care ability. The incidence of ischemic stroke of CADASIL at the age of 45-50 years old. It has been reported that after a mean duration of about 23 years, the average age of death is 61 years [3,4]. Less than half of patients over the age of 60 can walk without help [5]. Almost 80% of patients need to be completely dependent on other people's help to live before death [6]. Multiple intracranial white matter demyelination changes in the clinical indicating specialty to some extent, which cannot be explained by used lacunar infarction or single cause of cerebral arteriosclerosis, at the same time rheumatoid immune-related indicators were prompted negative,

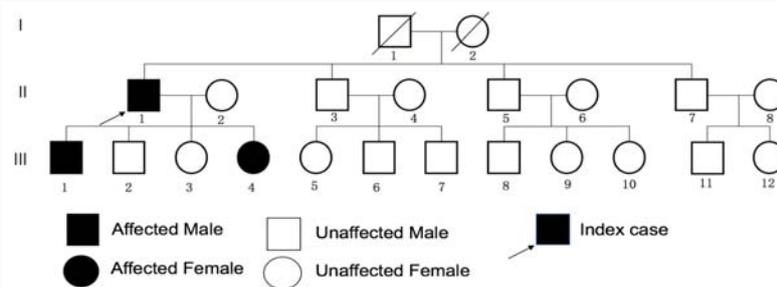


Figure 2: Family map: Affected family members are marked in black. Family members with no clinical symptoms are marked in white. Index patients (II.1) are marked with black arrows.

meanwhile lesions Morphology does not accord with the common manifestations of multiple sclerosis or optic neuromyelitis, and the accompanying symptoms are vomiting words unclear only, no other signs of neurologic symptom to help to position, the radiologist did not report the diagnosis of clinical disease prompted the diagnosis of CADASIL may have increased difficulties to diagnosis, so the misdiagnosis and missed diagnosis is inevitable. This CADASIL patient with typical characteristics of the temporal pole and outer capsule lesions. It is rare to find these two cases both completely performance in the early stages of this disease. T2-weighted images showed high signal combined with FLAIR high signal may be able to help to diagnose disease to some extent [7,8]. For some clinical neurologists ignore the reading of the magnetic resonance imaging or over-reliance on the radiologist's report, resulting in some CADASIL patients difficult to diagnose and be found. For such patients, Radiologists should remind clinicians of implementing gene genetics test on these patients promptly, for the sake of diagnosing of CADASIL in early time.

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