

A novel CADASIL-causing mutation in a stroke patient

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Summary

Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an uncommon autosomal dominant genetic disease due to mutations in the Notch3 gene on chromosome 19. The major clinical characteristics of CADASIL are migraine, recurrent ischaemic strokes and dementia.

Case report: We describe the case of a 58-year-old man who presented with a minor stroke that occurred in the absence of significant vascular risk factors. His family history included stroke, dementia and early death. An MRI brain scan demonstrated hyperintensities in the white matter on FLAIR images with prominent involvement of the area of the external capsule bilaterally. Based on

the family history and the MRI findings, CADASIL was suspected. Mutational analysis of the Notch3 gene disclosed a novel mutation substituting cysteine for glycine at codon 251 in exon 5, confirming the diagnosis of CADASIL.

Conclusion: This case suggests that CADASIL should be suspected in patients with stroke that arises in the absence of known vascular risk factors, especially if there are typical MRI findings. A strong family history of stroke and dementia are also supportive.

Key words: CADASIL; ischaemic stroke; autosomal dominant arteriopathy; Notch 3 gene; exon 5; Cys251 Gly mutation

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare autosomal dominant genetic disease due to mutations in the Notch3 gene on chromosome 19 [1]. Ischaemic events, transient or permanent, are the most common disease characteristics overall [1–3]. Most patients experience multiple recurrent subcortical ischaemic events leading to a stepwise decline and a vascular demen-

tia syndrome. Migraine, usually with aura, is another common manifestation of CADASIL. Worldwide, families with CADASIL from many ethnic populations [1–3] and at least 70 Notch3 disease-causing mutations have been identified [4]. We herewith report a novel Notch3 mutation causing CADASIL in a stroke patient from Greece.

Case report

We describe the case of a 58-year-old right-handed man who presented with a minor stroke, consisting of sudden-onset dysarthria and weakness of left extremities. His past medical history included memory problems and personality change for two years and non insulin-dependent diabetes mellitus, which was well controlled with medication. He had no history of hypertension or smoking. His family history was significant for dementia, stroke and early death. Both his father and grandfather had a similar progressive illness of few years' duration with strokes, memory problems and cognitive impairment resulting in death in their early 60s. No personal or family history of headaches was reported. The patient reached a score of 27/30 at Mini-Mental Status Examination. His neurolog-

ical examination revealed brisk tendon reflexes bilaterally and extensor plantar response on the left side. Routine blood examination including homocysteine levels, chest x-ray, ECG and carotid Doppler studies were normal. An MRI brain scan showed extensive hyperintensities on FLAIR images located in periventricular, subcortical and deep white matter of the cerebral hemispheres and the brainstem (figure 1). The area of the external capsule was particularly involved bilaterally. As recent studies have suggested that this finding is highly suspicious of CADASIL in patients with leucoencephalopathy [5] and given the strong family history, the possibility of CADASIL was considered and genetic studies were performed. After informed consent was given, genomic DNA

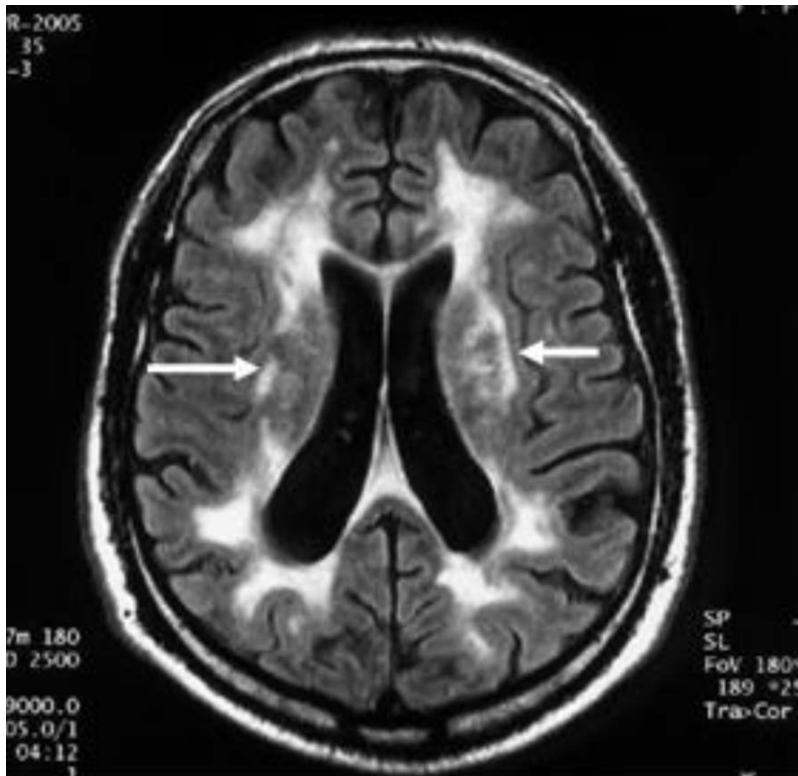


Figure 1
MRI brain scan of our patient (FLAIR images). Involvement of the external capsule can be noticed.

was isolated from EDTA-stabilised whole blood, using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). Notch3 exon-fragments were amplified by PCR using primer pairs in the flanking intron sequences and purified from agarose gel slices using the Easy Pure DNA purification kit (Biozym Diagnostik GmbH, Hess. Oldendorf, Germany). Fragments were sequenced double-stranded using the ABI Prism BigDye Terminator cycle sequencing kit (Applied Biosystems, Darmstadt, Germany) and analysed on an ABI capillary electrophoresis genetic analyser. No mutation was detected in the initially screened exons 3 and 4 of the Notch3 gene, where most CADASIL-causing described mutations are located. Therefore we proceeded with the screening of other exons where mutations have been described. In exon 5, a heterozygous T>G base change was detected. This base change affected codon Cys251 (TGC) that changed to Glycine (GGC). A T>C base change in this codon resulting in a Cys251Arg mutation has been reported and is listed as CADASIL causing mutation [4]. The base change in exon 5 in our patient follows the stereotyped nature of most Notch3 mutations, leading to either the (heterozygous) loss or gain of a cystein residue [1, 4]. After these results were obtained, interest was focused on the patient's close family members and especially his two children and two siblings. The patient's sister, aged 56 has had a diagnosis of multiple sclerosis for about 15 years and had received disease modifying treatment for this. Despite the fact that her MRI brain scan findings were indicative of CADASIL and she was explained the strong possibility of having been misdiagnosed, she declined genetic testing. The younger brother of the patient and the two children of the patient, aged 51, 33 and 25 respectively, refused other examination than history taking and clinical examination that were unremarkable in all three cases.

Discussion

Although numerous families with CADASIL have been reported [1-3], particularly during the last decade, its prevalence remains unclear. Nevertheless, more widespread testing has suggested that the disease is probably underdiagnosed. The case we present suggests that the possibility of CADASIL should be considered in any stroke patient whose imaging demonstrates multiple abnormalities (especially if the area of external capsule is particularly affected) that arise in the absence of hypertension or other recognised vascular risk factors. A personal history of migraine or mood disorder and a family history of similar disease and early death are supportive, if present. It must be noted that a false-negative family history was shown to have been commonly documented in a recent series of CADASIL patients by Razvi et al [6].

Whenever there is suspicion of CADASIL, genetic testing or skin biopsy should be considered to establish diagnosis. The relatively low sensitivity of skin biopsy gives the diagnostic key of this disorder to the molecular genetic screening [4]. Given that the majority of CADASIL-causing mutations have been observed in exons 4 and 3, the most efficient approach would be to initially screen these two

exons. If the results are negative and the index of suspicion is high, screening of the remaining exons should be performed, starting with exons 2, 4-6, 8, 11 and 19, where relatively higher numbers of mutations have been found [4, 7, 8]. In this clinical setting, if no known CADASIL-causing mutation is present, an investigation for a novel mutation should be undertaken.

A limited amount of data is available to date on the clinical course of CADASIL. In a recent publication, Peters and colleagues [9] prospectively followed 80 CADASIL subjects for a mean period of about two years. They observed that progression varied significantly among patients; some patients deteriorated rapidly, while others remained stable or even improved. In this cohort, most patients with increases in disability had experienced a new stroke, indicating that stroke is a major determinant of disability progression in CADASIL.

As far as therapy regards, there is no proven specific treatment for CADASIL up to date. Antithrombotic agents such as aspirin are usually used but yet, there are no data to prove efficacy of this or any other agent in CADASIL [6-10]. The current treatment approach includes aggressive man-

agement of the major cerebrovascular risk factors such as hypertension, diabetes, hyperlipidaemia and smoking.

In conclusion, the case we present suggests that CADASIL should be suspected in patients with stroke that arises in the absence of known vascular risk factors, especially if there are typical MRI findings. A strong family history of stroke and dementia is also supportive. Awareness of the clinical manifestations and radiological features of CADASIL shall increase diagnostic accuracy. It is crucial to confirm diagnosis of CADASIL not only for the prognosis of symptomatic patients but also for the counselling of asymptomatic family members who may be at risk.

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