Clinical Case Reports

CASE REPORT

Recurrent transient global amnesia as presenting symptoms of CADASIL

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Key Clinical Message

Despite transient global amnesia is considered unusual in Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and causal relation is still unclear, this report suggests to consider CADASIL in those patients with recurrent transient global amnesia, especially when MRI shows multifocal hyperintensities affecting the cerebral white matter or when it is followed by cognitive decline.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a systemic arteriopathy due to missense mutations of NOTCH3 gene. Early-onset ischemic strokes and vascular dementia are the main clinical features. Migraine, psychiatric disorders, and epileptic seizures are additional features [1]. Asymptomatic cerebral microbleeds are also frequent, while spontaneous lobar hemorrhages are very rare [2]. Vascular dementia generally follows recurrent strokes, while progressive subcortical dementia without strokes is rare [3, 4]. Cognitive decline generally starts with alterations in attention and executive functions and is the result of dysfunction within the subcortical/frontal network. In contrast, visuospatial abilities, recognition, and semantic memory generally remain spared until the late stages [5].

The pathological hallmarks of CADASIL are the degeneration of vascular smooth muscle cells (VSMCs) and extracellular accumulation of granular osmiophilic materials (GOMs) [6]. NOTCH3 gene mutations are stereotyped and alter the odd number of cysteines in one of the 34 EGF-like repeats (coded by exons 2-24) of *Notch3*. Earliest studies suggested that NOTCH3 gene mutations were mainly clustered in some exons, but the increasing number of new mutations out of these exons strongly weakens this assumption, with relevant meanings about the molecular diagnosis. In fact, due to the high costs, the mutation screening covering the whole region coding for EGF repeats is not generally performed in all cases [7].

We report a CADASIL patient carrying a NOTCH3 gene mutation involving exon 24 and presenting with recurrent transient global amnesia (TGA) and atypical cognitive decline.

Case Report

A 73-year-old woman underwent our observation for recurrent TGA, cognitive impairment, psychiatric disorders, and delirium. Her father experienced his first stroke at age of 52 and suffered from recurrent cerebrovascular events. Her personal history revealed several antidepressant treatments and a suicide attempt. Migraine with typical aura onset in sixth decade. Hypertension and hypercholesterolemia were both present, but they were well controlled. About 10 years ago she experienced two transient amnestic episodes. In both cases, the amnesia involved both anterograde and retrograde memory, consciousness was spared, and neurologic deficits were absent. The episodes endured, respectively, 18 and 10 h. A gradual and spontaneous recovery occurred. At electroencephalographic registrations, epileptic discharges were absent. Acute cerebral lesions were absent at brain MRI, although some focal white matter hyperintensities were noticed in FLAIR and T2-dependent images. According to the criteria of Hodges and Warlow [8], a diagnosis of TGA was made in both cases. About 2 years later, memory difficulties, disturbs in spatial and temporal orientation and name anomia onset. Then, a very slow progressive cognitive decline arose. MMSE score was 22/30, and MODA score was 72/100. 18F-FDG PET revealed a reduction of perfusion in the left temporal lobe, in the right parietal lobe and in the both frontal lobes. A suspect of Alzheimer's disease was made, and she was treated with donepezil first, then with memantine and finally with rivastigmine without any improvement. Five years later, she started suffering from recurrent vascular events, including a transient visual deficit and a transient global aphasia. Sporadic right fronto-temporal epileptiform abnormalities were also noticed. Finally, she was admitted in hospital for an acute worsen of her orientation, attention, and language disturbance, recovered spontaneously in 24 h. The neurologic examination was
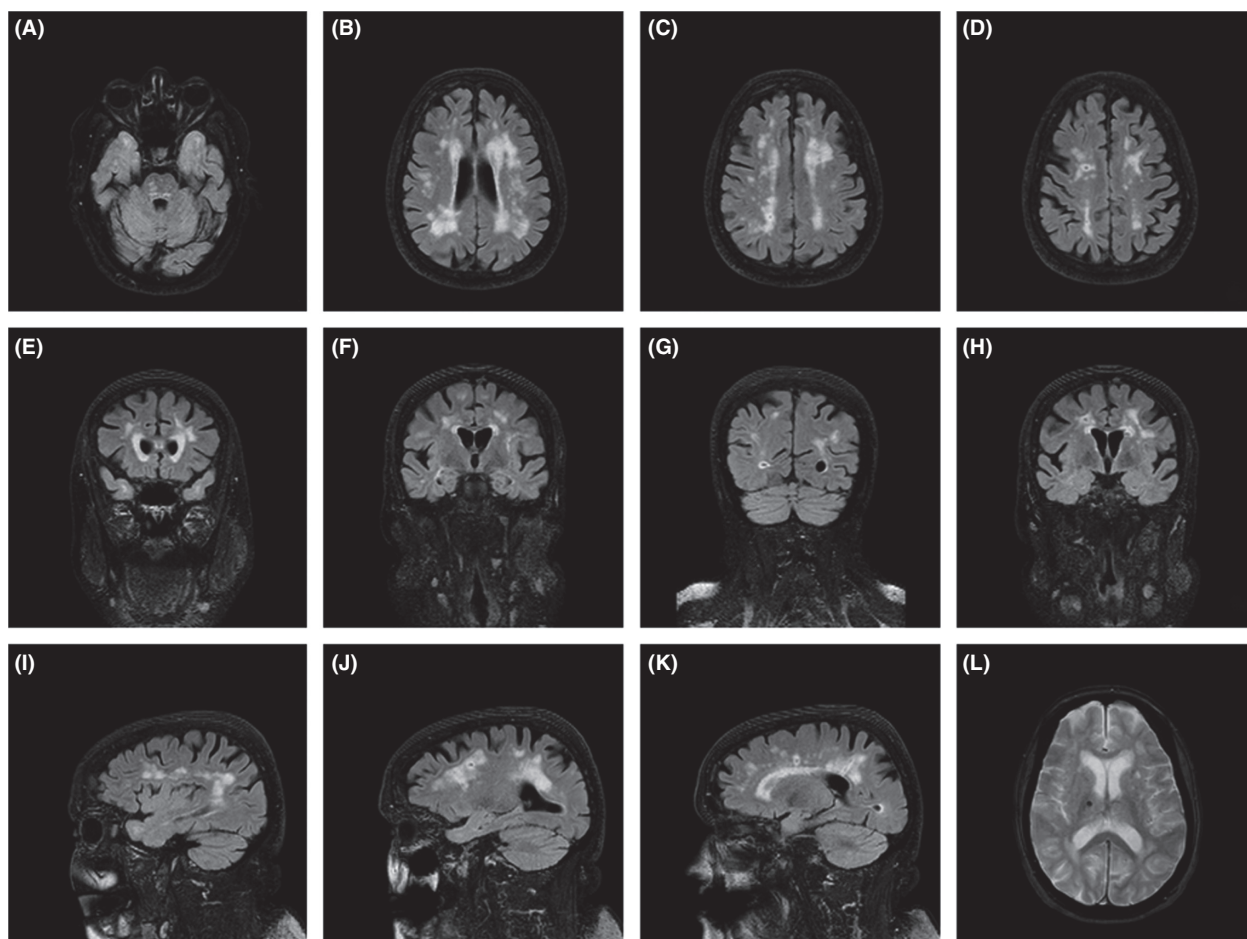

Figure 1. Brain MRI findings of the proband. The FLAIR images (A–K) demonstrated the multifocal damage of the white matter involving the brainstem (A), the temporal poles (A, E, I), the left external capsule (F), the periventricular regions (E, J, K), the subcortical regions apparently sparing the U-fibers (B–K). The gradient-echo image (L) showed one microbleed in the right basal ganglia region.

consistent for a progressive subcortical dementia with mild pyramidal and extrapyramidal involvement. Brain MRI disclosed a multifocal hyperintense damage of the white matter, mainly subcortical, apparently sparing the U-fibers and with the typical involvement of the temporal poles (Fig. 1). Also the left external capsule was involved. As the clinical features and the MRI findings were suggestive for CADASIL, skin biopsy and NOTCH3 gene analysis were performed.

Microscopic Skin Analysis

The microscopic investigation of skin arteries was performed as previous reported [4]. A severe degeneration of VSMCs and PAS-positive material was found in the tunica media. At electron microscopy, GOMs were detected in several arteriolar vessels, as well as VSMC degeneration, loss of adherence between VSMCs, and abundant cellular debris.

NOTCH3 Gene Analysis

Genomic DNA was extracted from peripheral blood leukocytes and amplified by PCR with 23 sets of primers specific to investigate coding sequences and intron–exon boundaries of exons 2-24 of NOTCH3 gene. The PCR products were sequenced in both directions using the ABI Prism Big-Dye Terminator Cycle Sequencing Ready Reaction Kit and ABI Prism 377 (Applied Biosystems). Transcript NOTCH3-001 (Ensembl Genome Browser entry # ENST00000263388) was used as standard sequence. The
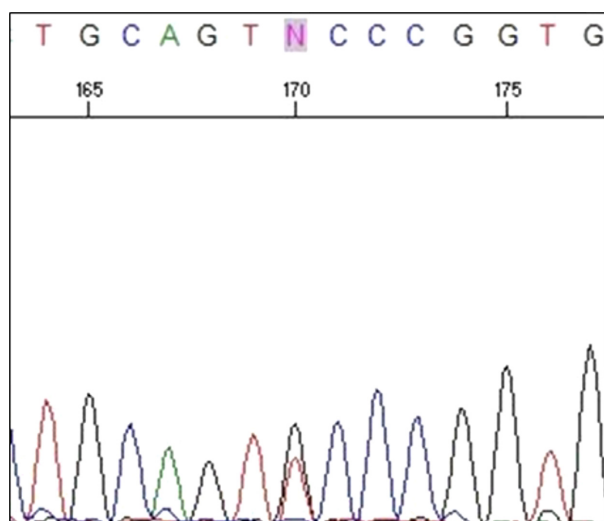

Figure 2. NOTCH3 gene analysis. The forward sequence of the exon 24 disclosed the heterozygous G→T substitution at the second position of the codon 1298 (TGC→TTC). The affected nucleotides were indicated by the N letter.

NOTCH3 gene analysis disclosed an alteration of the coding sequence within the exon 24. This variation consisted in the substitution of a guanidine with a thymine at the second position of the codon 1298 and leaded to the replacement of a cysteine with a phenylalanine (p.Cys1298Phe), causing the loose of a cysteine in the EGF-like domain 33 (Fig. 2). This mutation was not found in 100 healthy individuals and was recently reported to cause CADASIL [9].

Discussion

The clinical features of the case reported here were suggestive for a slow progressive subcortical dementia onset in seventh decade and proceeded by recurrent TGA and psychiatric disorders. In CADASIL, TGA is very unusual, although there are many factors which potentially could cause TGA, such as migraine, seizures, cerebrovascular events, and mood disorders. Transient global amnesia is considered a benign disorder which recurs rarely. Diagnosis is clinical, although diffusion-weighted images can reveal focal signal alterations in CA-1 field of hippocampus, when MRI was performed 2 days after the event [8, 10]. In our case, clinical criteria were present, but no diffusion abnormalities were noticed, although there was evident the involvement of the white matter very close to the hippocampus. In recurrent TGA patients, an increase prevalence of hippocampal lesions was reported, suggesting preexisting vulnerability of memory network [11]. In CADASIL, temporal white matter involvement is frequent and very early, even in presymptomatic subjects and in pediatric cases, where temporal lobe was the second most involved after frontal lobe [1, 12]. Our report suggest to consider CADASIL in those cases with recurrent TGA, especially when MRI shows multifocal hyperintensities affecting the cerebral white matter or when it is followed by cognitive decline.

Cognitive impairment in CADASIL is similar to that reported for sporadic subcortical ischemic vascular dementia and is thought to the result of dysfunction within the subcortical/frontal network due to the leukoaraiosis, although a multi-infarction origin based on the accumulation of cerebral infarcts was also proposed [5, 13, 14]. Cognitive decline preceding strokes is unusual in CADASIL, but several cases were reported [1, 3, 4]. In these cases, it is not clear whether the cognitive impairment is due to the accumulation of focal asymptomatic ischemic lesions rather than the disconnection mechanism due to the diffuse white matter damage. In our patient, the cognitive decline correlated better with leukoaraiosis: MRI showed diffuse white matter damage, with the typical involvement of temporal lobe, while lacunar infarcts were rare. Moreover, only one microbleed was found and the involvement of the white matter near U-fibers supported a disconnection

mechanism. These findings were similar to our previous case report of vascular dementia preceding strokes [4].

In our patient, there were several stigmata addressing toward CADASIL diagnosis: the family history, the psychiatric disorders, the migraine with typical aura but with the atypical late onset, the EEG alterations, and, at the end, the recurrent vascular events. Despite these features, the late onset of the cognitive decline, the slow gradual progression, and the presence of amnestic deficits probably were misleading. Otherwise, CADASIL suspect was strongly supported by the MRI findings. Temporal pole involvement, which is rare in chronic hypertensive encephalopathy, is high specific for CADASIL, especially when bilateral, as well as the external capsule involvement [7].

The p.Cys1298Phe mutation was recently reported, but there is no information about the clinical presentation [9]. Until now, only two mutations were reported within the exon 24, both in Italian patients. It must be stressed that in this case the recognition of the pathogenetic mutation has required necessarily the analysis of the whole sequence coding the 34 EGF-like repeats. A partial study would fail to identify the mutation, hindering the diagnosis of CADASIL and the following genetic counseling in other family members. Due to the high cost of a complete screening, NOTCH3 gene analysis frequently is limited to those cases with strong suspect [7]. Thus, patients carrying unrecognized NOTCH3 mutations with unusual clinical presentation can miss the diagnosis. So, it should be considered that even when the partial NOTCH3 gene analysis is normal, CADASIL is still possible and, in the presence of concrete suspect, skin biopsy is necessary to achieve the correct diagnosis.

In conclusion, the striking features of this case were the atypical late onset of the vascular dementia, the recurrent TGA preceding cognitive decline, and the identification of a NOTCH3 gene mutation affecting the exon 24 that is rarely involved in CADASIL. Furthermore, at this moment, considering the absence of a defined genotype–phenotype correlation, the incomplete description of the distribution of CADASIL mutations in the different populations and the lack of sensitive biomarkers, in the presence of a clinical suspect, the diagnosis of CADASIL can be excluded only completing the mutational analysis of the whole sequence coding the 34 EGF-like repeats.

Conflict of Interest

None declared.

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