Peer reviewed article

A novel heterozygous mutation in the NOTCH3 gene causing CADASIL

Elisabeth Andreadou, George Papadimas, Constantinos Sfagos

Department of Neurology, Athens National University, "Aeginition" Hospital, Athens, Greece

Summary

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an identifiable cause of inherited stroke among young adults, characterised by diffuse leukoencephalopathy with prominent involvement of the temporal poles and external capsule. The disease is caused by mutations in the NOTCH3 gene encoding a NOTCH3 receptor protein. The clinical course is relentlessly progressive with early transient ischaemic attacks (TIA) or strokes, dementia and finally death in the mid-60s. We describe a 40-year-old patient with clinical features of CADASIL and a positive family history who was a carrier of a new mutation at the exon 4 of the NOTCH3 gene: C162R. Regardless of the distinctive clinical and neuroimaging features one of his siblings had been mistakenly diagnosed as suffering from multiple sclerosis (MS), suggesting that the disease can occasionally be misdiagnosed as MS.

Key words: stroke; CADASIL; mutations; NOTCH3 gene

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered to be a relatively common but underdiagnosed cause of inherited stroke in young patients lacking other well-established cardiovascular risk factors [1]. It is an autosomal dominant microangiopathy due to mutations in the NOTCH3 gene on chromosome 19 [2]. However, rare cases with autosomal recessive inheritance have also been reported, known as CARASIL or Maeda syndrome [3, 4].

The mean age of disease onset is 40.3 ± 13.8 years and the mean age of death is 64.5 ± 10.6 years [1]. Stroke, stroke-like episodes or transient ischaemic attacks, migraine, dementia, neuropsychiatric disorders and especially depression are among the cardinal clinical manifestations of this disorder. Most of the ischaemic events are typical lacunar infarcts in the absence of hypertension or other vascular risk factors [1].

The physiological NOTCH3 gene product encodes a transmembrane receptor primarily expressed in arterial smooth muscle cells [2]. Notch signalling is crucial for vascular development and has an important role in arteriovenous specification [5]. Pathogenic NOTCH3 mutations lead to an odd number of cysteine residues within the NOTCH3 extracellular domain, resulting in progressive degeneration of the smooth muscle layer surrounding cerebral and skin arterioles [2, 5]. Substitution of the medial layer with connective tissue causes fibrosis and narrowing of the vascular lumen [5]. Most of mutations responsible for the disease are missense point mutations identified in exons 4 and 3 [6]. Thus far only two reports have described mutations for CADASIL in the Greek population, one at exon 4 and a new mutation at exon 5 of the NOTCH3 gene [7, 8].

We report on a Greek patient with a novel mutation located at exon 4 of the NOTCH3 gene responsible for CADASIL.

No financial support to declare.

Case report

A 40-year-old male (fig. 1, case II-3) was admitted to our hospital reporting an episode of blurred vision, dysarthria, hypaesthesia and weakness of the right arm which persisted for 20 minutes and resolved completely. His medical history was unremarkable with no vascular risk factors. Neurological examination was normal. Brain MRI revealed multiple confluent hyperintense lesions on FLAIR and T2-weighted images in the periventricular and deep white matter areas of the frontal, parietal, temporal and occipital lobes bilaterally, in the left caudate nucleus, in the cerebellar hemispheres bilaterally and in the cerebral peduncles (fig. 2A), without gadolinium enhancement, whereas cervical MRI was normal. Oligoclonal bands which indicate intrathecal production of immunoglobulins possibly suggestive of multiple sclerosis (MS) were not found on cerebrospinal fluid examination. Laboratory investigations, including blood tests for disorders of haemostasis, carotid Doppler echogram and 24h blood pressure monitoring were normal. The visual fields examination revealed small scotomas of the central region bilaterally. Neuropsychologic tests showed a mild deficit in attention and recall of newly acquired knowledge. A SPECT brain scan with 99m-Tc HMPAO showed reduced perfusion in the gray matter of the left temporal lobe and the adjacent parietal and occipital lobe, compatible with decreased blood flow in the above areas.

His father (I-1) had a first stroke when he was 45 years old and a second in his 60s. He progressively became demented and died aged 65 after complete deterioration. The patient's mother is 69 years old and has hypertension under medication.

Table 1

Data of the index case and his brothers.

Patient	Age	Clinical features	MRI
II-1	45	–	+
II-2	43	+	+
II-3	40	+	+
II-4	37	–	+
II-5	34	+	N/D
II-6	26	–	–

+ Clinical features or MRI compatible with CADASIL
– Absence of symptoms or MRI abnormalities
N/D MRI not performed

The patient is the third among five other brothers (fig. 1, table 1). The first (II-1), 45 years old, has an unremarkable medical history with normal neurological examination. However, his brain MRI revealed multiple confluent hyperintense white matter lesions on T2 and FLAIR images involving the frontal and temporal lobes bilaterally, without gadolinium enhancement (fig. 2B). His first daughter, aged 14, had when she was 6 years old a spontaneous intracerebral haemorrhage of undetermined cause with full recovery.

The patient's second brother (II-2), aged 43, was diagnosed 12 years ago as having multiple sclerosis on the basis of an episode of right hemiparesis and hemisensory deficit lasting less than 24 hours, combined with white matter changes in brain MRI. He also reported a transient episode of blurred vision and paraesthesia of the right hand, lasting for a few minutes, one year ago. Neurological examination revealed only a brisky right achilles tendon reflex. He recently underwent a second brain MRI which was unchanged, showing diffuse white matter lesions and involvement of the temporal poles of both hemispheres (fig. 2C, 2D).

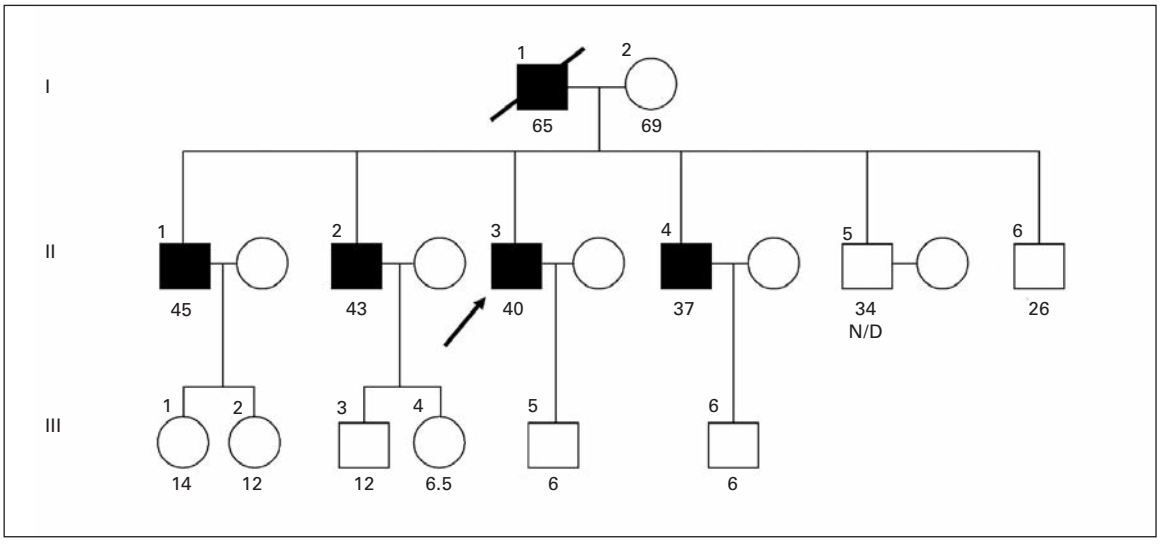
The fourth brother (II-4) aged 37, with an unremarkable medical history, underwent brain MRI similarly revealing confluent and discrete, fairly symmetric T2 hyperintense foci in the deep and subcortical white matter of both hemispheres, with characteristic involvement of the temporal poles.

The fifth (II-5), aged 34, reported transient episodes of blurred vision and vertigo but he refused to be examined. The youngest brother (II-6) is 26 years old, symptom-free and with normal neurological examination. Brain MRI revealed one non-specific white matter lesion in the right precentral gyrus.

Bearing in mind the possibility of CADASIL, genetic studies were performed after obtaining written consent. The NOTCH3 gene was analysed by complete sequencing (Prof. A. Rolfs, Rostock, Germany). A novel heterozygous NOTCH3 mutation was detected with substitution of thymidine for cytocine (T>C) at position 484 in exon 4 which caused an amino acid change (C162R).

Figure 1

Pedigree of the family. The index case is indicated by an arrow. Black-filled symbols indicate affected members, N/D = not examined.



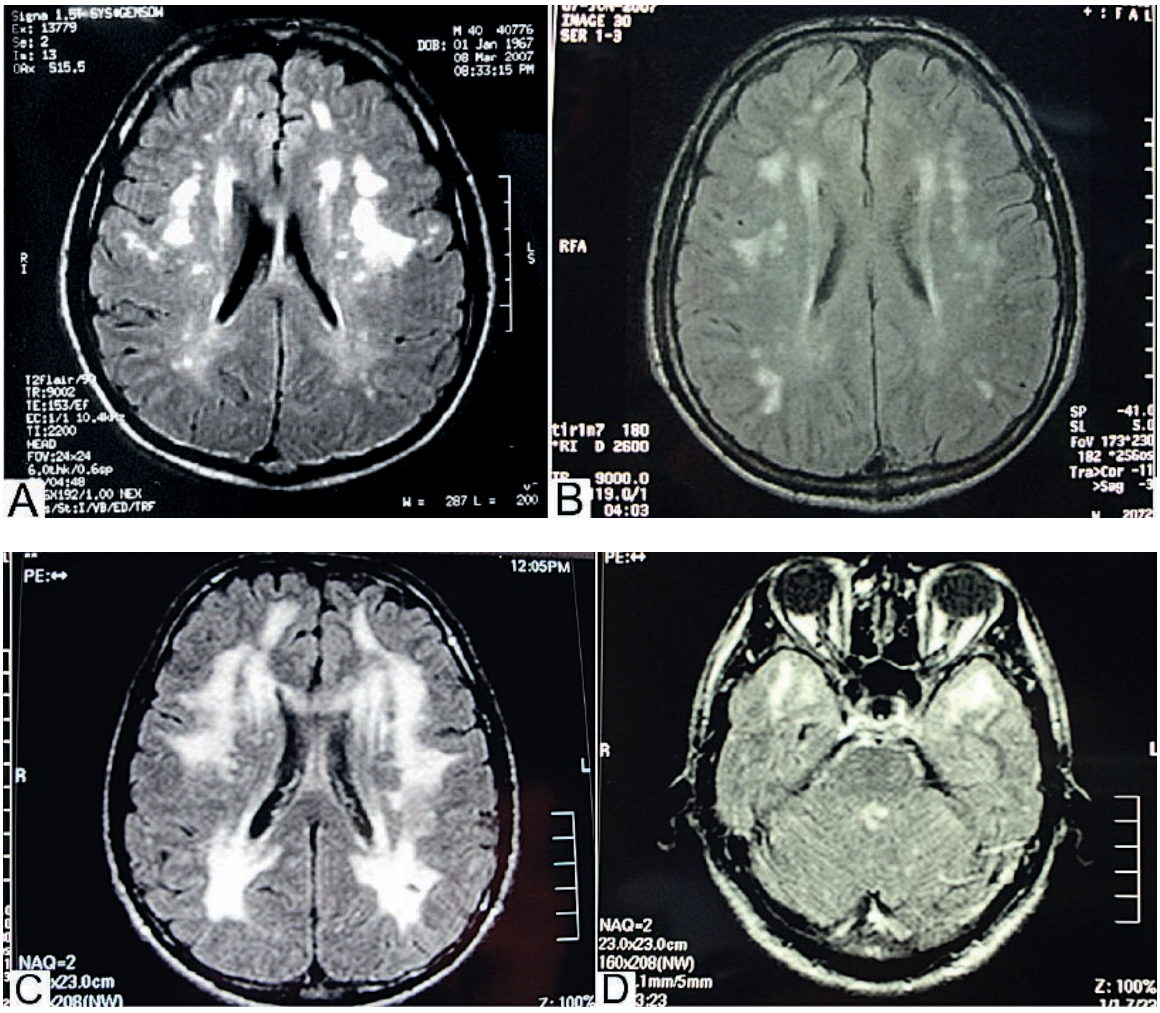


Figure 2

Transverse FLAIR MRI: **A** of the patient showing abnormal hyperintense signal in the subcortical and periventricular white matter of both hemispheres, **B** of the asymptomatic patient II-1 showing multiple white matter lesions, **C** of patient II-2 who was mistakenly diagnosed as suffering from MS, showing diffuse and confluent symmetrical white matter lesions and **D** of the same individual as C, showing the characteristic involvement of the temporal poles.

Discussion

The patient's symptoms, the atypical brain MRI abnormalities with no spinal cord involvement and the absence of oligoclonal bands in CSF ruled out multiple sclerosis as a possible diagnosis. In addition, the absence of vascular risk factors and the family history consistent with autosomal dominant inheritance raised the possibility of CADASIL. Genetic testing revealed a novel mutation located in exon 4 of the NOTCH3 gene, which is considered the most common mutation site in individuals with CADASIL [6] and confirmed the diagnosis. Two other mutations at the same position (C162S and C162W) have been described previously [9–10].

Given the neuroimaging findings, four brothers have probably inherited the disease. The brother who refused evaluation mentioned some symptoms possibly related to the disease, while the younger one thus far presents neither radiological nor clinical evidence of being affected. Although this mutation has not been previously reported, the clinical features of the symptomatic family members are similar to those usually described. Moreover, disease onset and progression in our patient's father matched expectation. Although some mutations have been associated with age of stroke onset and survival time, most studies have failed to demonstrate a phenotype-genotype correlation [6].

MRI findings in CADASIL include symmetrical and extensive white matter hyperintense foci on T2-weighted images and well defined non-enhancing hypointense lesions on T1 images. Involvement of the temporal pole and the confluent hyperintensity of the external capsule are considered highly sensitive and specific for CADASIL and may distinguish it from ischaemic leukoaraiosis [12]. The symptomatic members of our family had these distinctive white matter hyperintensities in the anterior temporal lobes. The asymptomatic members aged 45 and 37 also had characteristic MRI abnormalities. This is consistent with previous reports where abnormal MRI may be observed in about 20% of apparently asymptomatic carriers irrespective of age [11].

It should be mentioned that none of the patient's brothers, including case II-2, accepted genetic testing, despite being informed. Regardless of this limitation it is noteworthy that case II-2 already showed the characteristic neuroradiological findings (i.e. involvement of the temporal poles and the external capsules) at first presenta-

tion; however, he had been diagnosed as having MS. Although the diagnosis could not be genetically confirmed, the radiological abnormalities combined with the clinical evolution are sufficient in our opinion to rule out the possibility of MS. Misinterpretation of MRI abnormalities may not be uncommon, in view of the absence of factors predisposing to atherosclerosis and the relatively early onset of symptoms in the affected individuals.

Whether the episode of intracerebral haemorrhage in the daughter of case II-1 could be attributed to this genetically transmitted entity is questionable. Although there are recent reports correlating CADASIL with intracerebral haemorrhage [13–14], it is doubtful whether the disease can be manifested so dramatically in childhood.

In conclusion, a novel mutation in exon 4 of the NOTCH3 gene has been identified in a Greek family with clinical features and MRI abnormalities typical of CADASIL. The disease is probably underdiagnosed. Restriction of family history to premature stroke alone may be insufficient for the detection of affected individuals. The diagnosis should be suspected not only in patients with recurrent subcortical infarcts leading to dementia, but also in patients presenting with transient ischaemic attacks, migraine with aura and mood disturbances, in the presence of prominent MRI signal abnormalities, especially in the subcortical white matter and basal ganglia. Since there is no specific treatment for CADASIL and prenatal diagnosis is already available [15], genetic counselling is of major importance.

Correspondence:
Elisabeth Andreadou
Department of Neurology
"Aeginition" Hospital
74, Vas. Sophia's Ave.
11528 Athens, Greece
E-Mail: eandread@med.uoa.gr

References

1 Davous P. CADASIL: a review with proposed diagnostic criteria. Eur J Neurol. 1998;5:219–33.
2 Monet M, Domenga V, Lemaire B, Souilhol C, Langa F, Babinet C, et al. The archetypal R90C CADASIL NOTCH3 mutation retains NOTCH3 function in vivo. Hum Mol Genet. 2007;16(8):982–92.
3 Razvi SS, Bone I. Single gene disorders causing ischaemic stroke. J Neurol. 2006;253(6):685–700.
4 Arima K, Yanagawa S, Ito N, Ikeda S. Cerebral arterial pathology of CADASIL and CARASIL (Maeda syndrome). Neuropathology. 2003;23(4):327–34.
5 Hofmann JJ, Iruela-Arispe ML. Notch signalling in blood vessels. Who is talking to whom about what? Circ Res. 2007; 100:1556–68.
6 Federico A, Bianchi S, Dotti MT. The spectrum of mutations for CADASIL diagnosis. The spectrum of mutations for CADASIL diagnosis. Neurol Sci. 2005;26:117–24.
7 Mandellos D, Limbitaki G, Papadimitriou A, Anastasopoulos D. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in Greek family. Neurol Sci. 2005;26:278–81.
8 Vikelis M, Papatriantafyllou J, Karageorgiou K. A novel CADASIL-causing mutation in a stroke patient. Swiss Med Wkly. 2007;137:323–5.
9 Escary JL, Cécillon M, Maciazec J, Lathrop M, Tournier-Lasserve E, Joutel A. Evaluation of DHPLC analysis in mutational scanning of Notch3, a gene with a high G-C content. Hum Mutat. 2000;16:518–26.
10 Lesnik Oberstein SA, van Duinen SG, van den Boom R, Maat-Schieman ML, van Buchem MA, van Houwelingen HC, et al. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. Acta Neuropathol. 2003;106:107–11.
11 Kim Y, Choi EJ, Choi CG, Kim G, Choi JH, Yoo HW, et al. Characteristics of CADASIL in Korea. A novel cysteine-sparing Notch3 mutation. Neurology. 2006; 66:1511–6.
12 O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology. 2001; 56:628–34.
13 Choi JC, Kang SY, Kang JH, Park JK. Intracerebral hemorrhages in CADASIL. Neurology. 2006;67:2042–4.
14 Maclean AV, Woods R, Alderson LM, Salloway SP, Correia S, Cortez S, et al. Spontaneous lobar hemorrhage in CADASIL. J Neurol Neurosurg Psychiatry. 2005;76:456–7.
15 Milunsky A, Konialis C, Shim SH, Maher TA, Spengos K, Ito M, et al. The prenatal diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) by mutation analysis. Prenat Diagn. 2005;25:1057–8.