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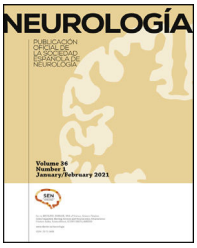

ORIGINAL ARTICLE

Non-convulsive status epilepticus as the initial manifestation in a family with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

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KEYWORDS
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy;
CADASIL;
Epilepsy;
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Status epilepticus

Abstract Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant small-vessel disease caused by mutations of the *NOTCH3* gene. It typically presents with migraine, recurrent brain ischaemia, and cognitive disorders. Seizures rarely present as the initial manifestation, with non-convulsive status epilepticus being even less frequent. We present a series of 3 related patients with this arteriopathy, 2 of whom presented status epilepticus as a manifestation of the disease.

PALABRAS CLAVE
Arteriopatía cerebral con infartos subcorticales y leucoencefalopatía;
CADASIL;
Epilepsia;

Status epilepticus no convulsivo como manifestación inicial en una familia con arteriopatía autosómica dominante cerebral con infartos subcorticales y leucoencefalopatía (CADASIL)

Resumen La arteriopatía autosómica dominante cerebral con infartos subcorticales y leucoencefalopatía es una enfermedad autosómica dominante de pequeños vasos causada por mutaciones del gen *NOTCH3*. Típicamente se presenta con migraña, eventos isquémicos

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NOTCH3;
Status epilepticus no convulsivo;
Status epilepticus

cerebrales recurrentes y trastornos cognitivos. Las crisis epilépticas son inusuales como manifestación inicial, pero aún más infrecuente es su presentación como *status epilepticus* no convulsivo. Se presenta una serie familiar de 3 casos con esta arteriopatía, entre los cuales 2 de ellos tuvieron *status epilepticus* como manifestación de la enfermedad.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant small-vessel disease caused by mutations of the *NOTCH3* gene. It typically presents with migraine, recurrent brain ischaemia, and cognitive disorders. Seizures rarely present as the initial manifestation, with non-convulsive status epilepticus (NCSE) being even less frequent.[1] We present a series of 3 related patients with CADASIL, 2 of whom presented status epilepticus as a manifestation of the disease.

Case description

Patient 1

The index patient was a 67-year-old woman with a 5-year history of migraine and cognitive disorders (Fig. 1). She consulted due to sudden onset of expressive aphasia and altered awareness. Brain MRI revealed spontaneous T2/FLAIR hyperintensity in the supratentorial region, thalamus, midbrain, and pons, with normal findings on diffusion-weighted sequences (Fig. 2). EEG initially showed epileptiform activity in the left hemisphere, and subsequently detected activity compatible with status epilepticus (Fig. 3). Symptoms improved with levetiracetam and the patient was discharged. However, she presented several recurrences, and was therefore readmitted. A genetic study detected the R1006C *NOTCH3* mutation.

Patient 2

Patient 2 was a 65-year-old woman, the sister of patient 1, who consulted due to confusional syndrome and expressive aphasia, before diagnosis of CADASIL was confirmed in patient 1. Brain MRI detected multiple T2-/FLAIR-hyperintense subcortical lesions, with normal results on diffusion-weighted sequences. EEG findings were compatible with status epilepticus. The patient was treated with levetiracetam, which improved symptoms. In the light of the patient's family history, we suspected CADASIL.

Patient 3

Patient 3 was a 72-year-old man, the brother of patient 1, with history of headache and a stroke 10 years prior to consultation. He reported that his mother had presented similar symptoms to his own. He consulted due to 7 years' progression of cognitive impairment. Physical examination revealed disorientation in time, with impaired memory and attention, bradykinesia, and retropulsion. Brain MRI detected multiple T2-/FLAIR-hyperintense subcortical lesions in the frontal, parietal, and temporal regions, with normal results on diffusion-weighted sequences. In the light of the patient's family history, we suspected CADASIL.

Discussion

We describe the cases of at least 2 patients with confirmed NCSE as the initial manifestation of CADASIL, a very unusual form of presentation at the time of diagnosis. To our knowledge, only one case has previously been described of NCSE at onset; that patient presented a different genetic mutation than the one detected in our series. The patient was a 65-year-old woman with a 40-year history of migraine and depression; the initial manifestation of CADASIL was migraine, and the patient presented 3 episodes of sudden onset of language, gait, and sensory alterations, which led to diagnosis of NCSE. That patient presented the C583 T *NOTCH3* mutation (Table 1).[1]

CADASIL is a genetic disease caused by mutations to the *NOTCH3* gene, located on chromosome 19p13, which encodes a membrane protein containing epidermal growth factor—like repeat domains; the protein is involved in cell signalling and is extremely important in cell migration during embryogenesis, in arteriovenous differentiation, and in controlling muscle tone in small arteries.[2,3] Several mutations have been described in the different exons encoding these domains, some of which appear as clusters associated with ethnicity or geographic origin.[4—6] The R1006C mutation was observed in families from a small area of central Italy, extending from the city of Ascoli Piceno to the Adriatic coast, along the river Tronto.[7] According to the description of these families, nearly all patients presented the typical initial manifestations of CADASIL, with the exception of one patient who presented psychotic symptoms at onset.[8] The main clinical manifestations are recurrent ischaemia, migraine, and progressive cognitive impairment. Seizures are infrequent. They are usually secondary to previous ischaemic lesions, and rarely appear as the initial manifestation of the disease.[9—11] They have also been reported in patients with history of migraine or in the context of encephalopathy or coma.[12,13]

In an extensive series of 102 patients, Dichgans et al.[14] report 10 patients with history of seizures, 9 of whom had previously had strokes. Nine of these patients presented generalised tonic-clonic seizures, and one presented focal seizures. Seizures were recurrent in 5 patients, and 3 cases were successfully treated with standard antiepileptic drugs.[14] Our series includes 2 related patients who presented NCSE as the initial manifestation of CADASIL.

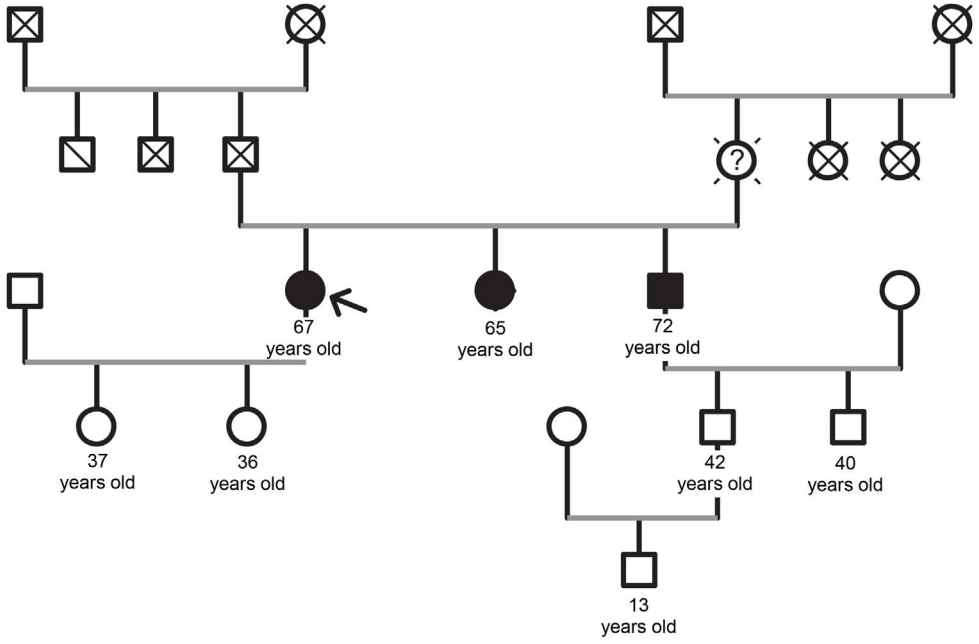

Figure 1 Pedigree chart.

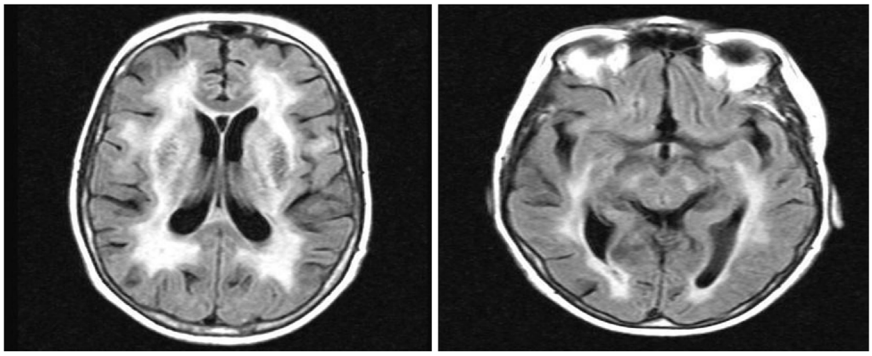

Figure 2 Brain MRI, T2/FLAIR sequence.

Table 1 Summary of patients with epilepsy as the initial symptom of CADASIL.

Reference	Age of onset (years)/sex	Type of seizures	Treatment	Mutation
Haan et al.[10]	42/F	Generalised tonic-clonic	Carbamazepine	ARG182CYS
Velizarova et al.	30/F	—	Levetiracetam	—
Haddad et al.[11]	80/F	Focal/status epilepticus	Levetiracetam/valproate	—
Oh et al.[9]	43/M	Generalised tonic-clonic	Oxcarbazepine/topiramate	R544C
Chen et al.[12]	12/F	Generalised tonic-clonic	Valproate/lamotrigine	CYS446TYR
De Freitas et al.	69/F	Focal/generalised tonic-clonic	—	—
Malandrini et al.	47/F	Generalised tonic-clonic	Phenytoin/phenobarbital	—
Valko et al.[1]	61/F	NCSE	Phenytoin	C583T
Chen et al.[12]	61/F	Focal/generalised tonic-clonic	Midazolam/phenytoin	CYS446TYR
Chen et al.[12]	25/M	Focal/generalised tonic-clonic	Lamotrigine/levetiracetam	CYS446TYR
Sacco et al.	34/F	Generalised tonic-clonic	BZD	R141C
Gonzalez et al.	67/F	NCSE	Levetiracetam	R1006C
Gonzalez et al.	65/F	NCSE	Levetiracetam	R1006C

BZD: benzodiazepines; NCSE: non-convulsive status epilepticus.

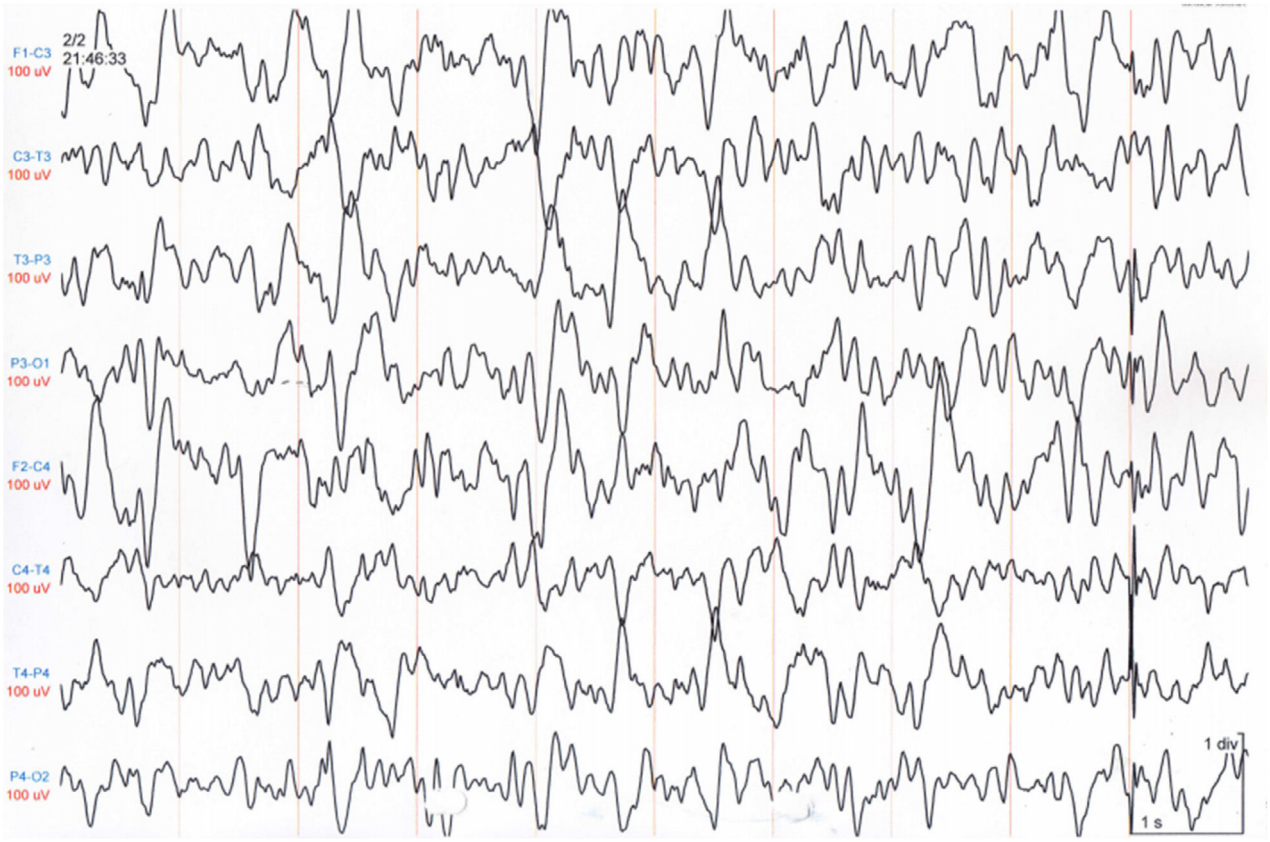

Figure 3 Electroencephalography study.

Conclusion

Seizures are rare in patients with CADASIL, and typically present after stroke. Cases of CADASIL presenting with epilepsy as the initial manifestation are even rarer in the literature. This is the first reported family with CADASIL presenting with NCSE at onset, with a different mutation to that previously described in the only other patient with this clinical picture reported to date.

Conflicts of interest

The authors have no conflicts of interest to declare.

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