

the p.A383V substitution demonstrates consistent variability in expressivity ranging from late onset with mild neuropathy to early onset with more severe phenotype. In addition, the mutation was detected in two asymptomatic subjects, thus supporting the incomplete penetrance of *MFN2* mutations, as already reported by Lawson and collaborators.⁵

The clinical variability and the incomplete penetrance underline the importance of other factors in defining the phenotype. Indeed, the presence of two non-penetrant cases in the same family branch corroborate the importance of the genetic background suggesting that an interacting gene(s) may modulate the CMT2A phenotype or protect it against pathological mutations.

Mitofusin 2 (MFN2) is a mitochondrial transmembrane GTPase which is located on the outer mitochondrial membrane and regulates the mitochondrial network architecture by fusion of mitochondria. Most of the mutations previously reported are within or immediately upstream of the GTPase domain (residues 103–261) or within the two coiled coil domains (residues 408–433 and 724–752, respectively). The mutation p.A383V described here is located on exon 11 of the *MFN2* gene. Nine additional mutations have been identified in this exon^{2–5} and two of them (p.H361Y and p.R364W) have been reported in families affected by axonal CMT associated with optic atrophy. In our patients no visual impairments were observed.

Interestingly, all of the mutations identified in exon 11 involve amino acids highly conserved across different species. In particular, the alanine at position 383 is conserved in both mouse *Mfn2* and the cognate protein mitofusin 1 (*Mfn1*). Together, these findings suggest that, even if exon 11 is not located in a functionally characterised domain, the region it encodes plays a crucial role for the function or stability of the protein. From this standpoint, it remains to be established whether the mutation exerts its noxious effect by a dominant negative mechanism or haploinsufficiency. Further investigations, including the study of heterozygous *MFN2* knock-in mouse, are necessary to clarify the function of normal and mutated *MFN2* gene.

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M Muglia

Institute of Neurological Sciences, National Research Council, Mangone, Cosenza, Italy

G Vazza

Department of Biology, University of Padova, Italy

A Patitucci

Institute of Neurological Sciences, National Research Council, Mangone, Cosenza, Italy

M Milani, D Pareyson, F Taroni

Division of Biochemistry and Genetics, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

A Quattrone

Institute of Neurological Sciences, National Research Council, Mangone, Cosenza, Italy

M L Mostacciolo

Department of Biology, University of Padova, Italy

Correspondence to: Dr Maria Muglia, Institute of Neurological Sciences, National Research Council, 87050 Mangone (Cosenza), Italy; m.muglia@isn.cnr.it

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Non-convulsive status epilepticus causing focal neurological deficits in CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessel disease caused by mutations of the *Notch3* gene. Clinical manifestations include migraine with or without aura, psychiatric disorders, recurrent ischaemic strokes and cognitive decline. Brain MRI shows confluent hyperintense signal alterations involving characteristically the anterior part of the temporal lobes and widespread areas of the deep and periventricular white matter. Focal or generalised seizures represent a rare neurological manifestation in CADASIL with a frequency of 6–10% in two large series.^{1,2} Status epilepticus, however, has not been reported so far. Herein we describe a patient with CADASIL with an acute focal neurological deficit following a prolonged migraine attack. The symptoms were first interpreted as an ischaemic stroke but subsequently diagnosed to be due to a non-convulsive status epilepticus.

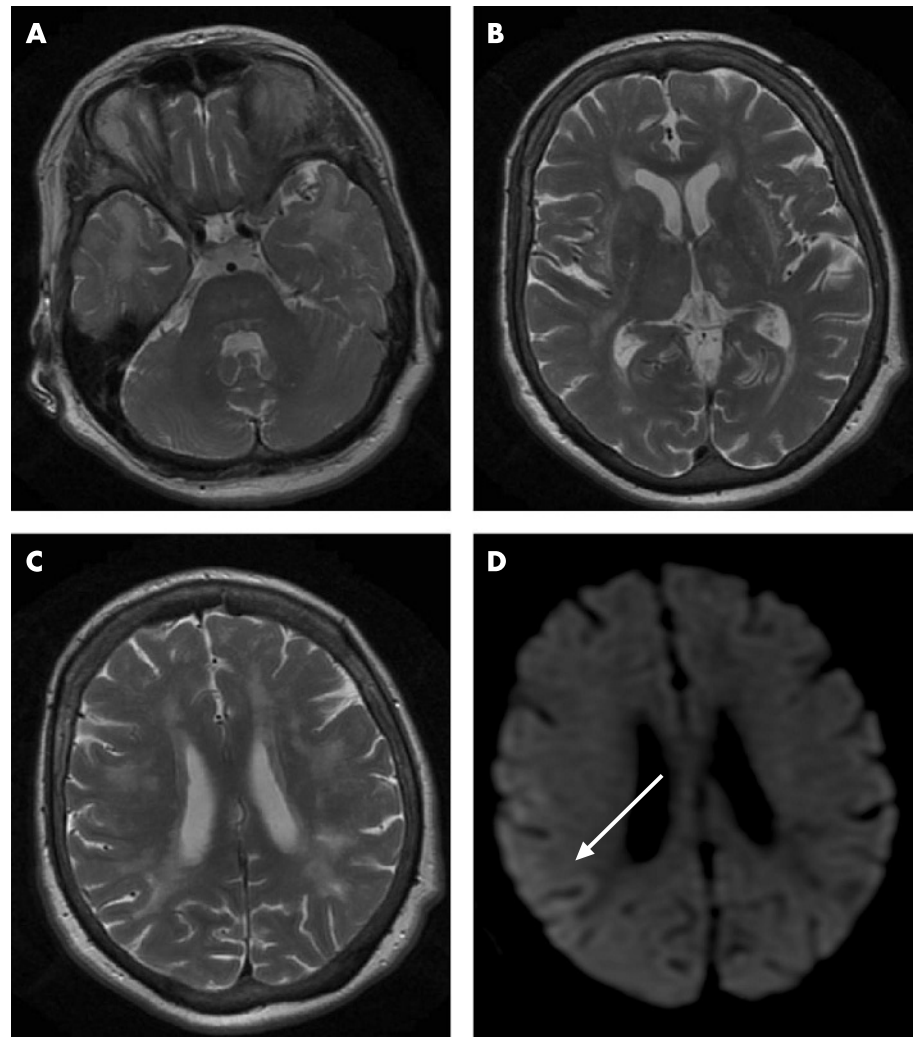


Figure 1 T2 weighted MRI scans showing diffuse hyperintense signal abnormalities with prominent involvement of both temporal lobes (A), both thalami, external and extreme capsules (B), as well as widespread areas of the white matter (C). Diffusion weighted imaging does not show evidence of an acute ischaemic strokes but demonstrates a weak and diffuse signal alteration in the right parieto-occipital cortex 24 h before the first EEG (arrow; D).

Case report

The 63-year-old right-handed female had a history of severe and longlasting migraine attacks with visual aura since the age of 40 years. The patient's father died at age 63 years after a history of progressive behavioural changes interpreted as the result of recurrent strokes. At age 59 years, the patient underwent a neurological examination because of a 2 year history of depression and generalised anxiety. Neurological examination revealed unspecific mild subcortical neuropsychological deficits but was otherwise normal. Cerebral MRI showed confluent hyperintense signal abnormalities with prominent involvement of both temporal lobes, both thalami, external and extreme capsules, as well as widespread areas of the white matter (fig 1). The diagnosis of CADASIL was confirmed by detection of characteristic granular osmiophilic material in the skin biopsy and detection of an already described mutation in the *Notch3* gene (C583T) (Professor E Tournier-Lasserre, Hôpital Lariboisiere, Paris, France).³

Between age 61 and 63 years, the patient had three episodes with sudden onset lasting for several hours up to 2 days with transient neurological symptoms, such as speech and gait disturbances, decreased responsiveness and recurrent vomiting. Because she was hospitalised in regional hospitals, no neurological examination or electroencephalography (EEG) were performed. Brain CT after the first episode demonstrated a new thalamic lesion suggesting an ischaemic origin of this particular episode, but the aetiology of the other episodes remained unclear. At age 63 years, she had migraine headaches without aura but recurrent vomiting lasting for 3 days. She was described as being confused, agitated, dysarthric and incoherent in her thoughts. At admission to our department, neurological examination revealed psychomotor slowing, confusion, neglect to the left and hemianopia to the left as well as right hemispheric neuropsychological deficits including visual ataxia and apraxia. An acute stroke was suspected. Diffusion weighted MRI (DWI), however, did not show any acute ischaemic lesion but revealed a weak, diffuse hyperintensity of the right parieto-occipital cortex (fig 1). EEG recordings disclosed widespread right hemispheric attenuation and periodic frontally accentuated focal epileptic discharges consistent with the diagnosis of a non-convulsive status epilepticus (NCSE) (fig 2). Antiepileptic treatment with phenytoin 300 mg daily was initiated and led to prompt and persistent clinical and electroencephalographic recovery (fig 2).

Discussion

The epileptic origin of focal neurological deficits in this patient with CADASIL is suggested by the EEG findings, a DWI pattern consistent with a NCSE without evidence of acute ischaemic lesions and the good response to antiepileptic therapy. The DWI alterations, in addition, argue against the hypothesis of a persistent migraine aura.

The incidence of epileptic seizures in CADASIL is estimated to range between 6 and 10%. Nine of 10 patients with CADASIL with epileptic seizures in one study had generalised tonic-clonic seizures, and only one had focal seizures.² In another study, all three CADASIL patients had generalised seizures.¹ The incidence of seizures in patients with CADASIL seems to be lower compared with first time seizures in common stroke, affecting 12–15% of patients. In contrast,

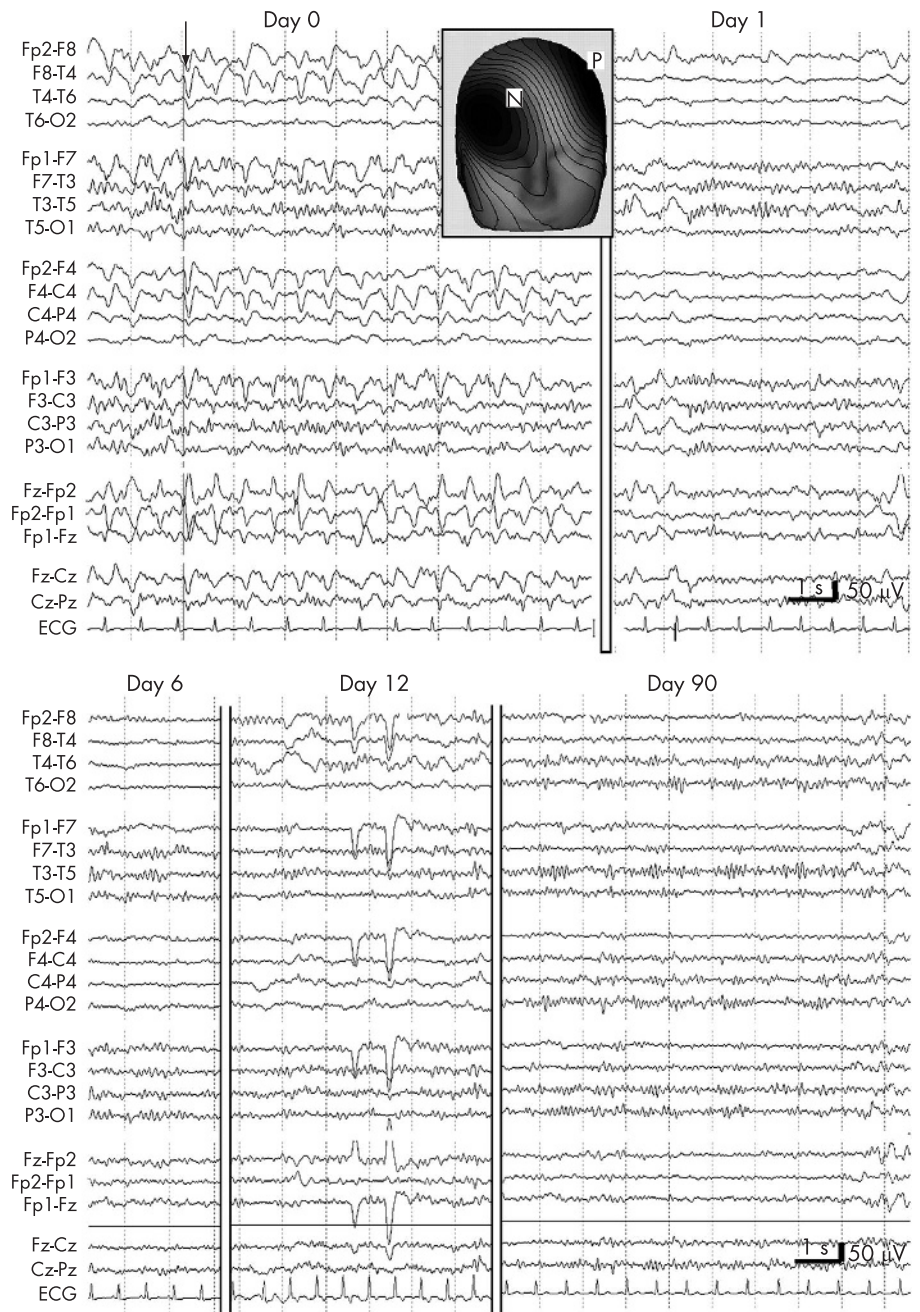


Figure 2 EEG during non-convulsive status epilepticus (NCSE) (day 0 = 24 h after diffusion weighted MRI) demonstrates periodic right frontal 1.5/s epileptic discharges with right frontal predominance. The insert shows the voltage map of the sharp waves marked by the arrow (N, negative, P, positive). Intravenous midazolam controlled the NCSE (day 1), and subsequent treatment with phenytoin 300 mg daily led to cessation of the NCSE seizure activity but persisting right hemispheric attenuation which normalised later on (day 90).

status epilepticus has been reported to occur in 14–19% of all patients with post-stroke epileptic seizures.⁴ On the other hand, almost 10% of patients with CADASIL in a British survey developed a reversible acute encephalopathy with headache at onset, confusional state, fever, epileptic attacks and coma, similar to the clinical presentation of patients with familiar hemiplegic migraine.³ However, EEG in these patients revealed no epileptiform discharges.

The aetiology of epileptic seizures and reversible coma in CADASIL is still a matter of debate. A post-stroke aetiology origin has been postulated, as in nine of 10 patients of one series, epileptic seizures occurred after stroke onset.² In the absence of acute ischaemic lesions in the

brain MRI, it remains hypothetical whether a transient ischaemic attack may have triggered an epileptic seizure or status epilepticus. In analogy to reversible coma and epilepsy in calcium channel disorders, epileptogenic changes in CADASIL could be primarily related to altered properties of the *Notch3* signalling system. On the other hand, the association of migraine, reversible cognitive alterations and epileptic seizures resembles the clinical pattern found in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). A few reports suggest that *Notch3* mutations in CADASIL might predispose to mitochondrial abnormalities. This hypothesis is based on the observation of an increased sequence variation of

mitochondrial DNA in CADASIL pedigrees compared with healthy controls, and of muscle mitochondrial abnormalities in several CADASIL patients.⁵

In conclusion, our report demonstrates that a NCSE may mimic an ischaemic stroke or a prolonged migraine aura in patients with CADASIL. We propose that EEG should be performed in CADASIL patients with acute neurological deficits, particularly when no acute ischaemic alterations are found in DWI. In addition, evaluation of anticonvulsants as possible prophylactic treatment is warranted in a larger series of CADASIL patients.

**Philipp O Valko, Massimiliano M Siccoli,
Andreas Schiller, Heinz-Gregor Wieser,
Hans H Jung**

Department of Neurology, University Hospital of Zurich, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland

Correspondence to: Dr Hans H Jung, Department of Neurology, University Hospital Zurich, 8091 Zurich, Switzerland; hans.jung@usz.ch

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Prevalence of cluster headache in Germany: results of the epidemiological DMKG study

Cluster headache is a primary headache disorder diagnosed according to the criteria of the International Headache Society.¹ Previous epidemiological studies have shown prevalence rates of 0.056–0.38%. These were lifetime prevalence rates which are subject to recall bias. No population based prevalence rates for Germany have been published to date. Despite the use of common criteria, sociocultural influences on the classification of cluster headache may be significant. Thus it is important to compare epidemiological study results from different countries to elucidate such relations.

We conducted a population based survey on the prevalence of cluster headache in Germany which was part of a larger epidemiological study on the prevalence of different headache types and which was coordinated by the German Migraine and Headache Society (DMKG).

Methods

A sample of 3425 inhabitants of the city of Dortmund, Germany, aged 25–75 years, was randomly selected and invited to participate in a larger epidemiological study in 2005. In total, 2291 individuals (67%) responded, 979 subjects by answering a standardised questionnaire and 1312 through participation in a face to face interview. This analysis was restricted to the latter group. A standardised set of questions was used to assess headache symptoms, characteristics and time pattern.

For cluster headache classification, we chose a two step approach and recontacted all participants who fulfilled the following criteria:

- untreated headache attacks shorter than 6 h,
- unilateral headache,
- at least one of following accompanying symptoms: lacrimation, rhinorrhoea, ptosis, reddening of the face or restlessness during headache.

The second contact was done by a neurologist trained in headache diagnosis. This expert made a final diagnosis according to the criteria of the International Headache Society.

Results

In total, 33 subjects (2.5%) fulfilled the criteria for a personal interview by the neurologist (17 males, mean age 55 years, mean age at headache onset 33 years). A diagnosis of cluster headache was made in two subjects. In the other individuals, the diagnoses were sinusitis (two subjects) and migraine without aura (one subject); the remaining subjects fulfilled the criteria of episodic tension-type headache. They stated unspecific autonomic symptoms such as warmth and reddening in the whole head or feeling hot in the body in the first interview which were revealed as not fulfilling the criteria for trigemino-autonomic cephalalgias in the second interview.

The two cluster headache patients represent a 12 month prevalence of 0.15% (95% CI 0.01 to 0.55). Both patients were male. One was 37 years old, with cluster headache onset at the age of 22 years. The other was 55 years, with cluster headache onset at the age of 37 years. Both suffered from episodic cluster headache with one bout per year and a bout duration of 6–10 weeks. In both patients, daily right sided attacks occurred with typical autonomic features. Only one of the two patients was informed about the diagnosis and treated his attacks with oxygen.

No other neurological or medical disease was apparent in either patient. Interestingly, both had a migration background, with their parents having migrated to Germany.

Discussion

The prevalence in this study falls within the range of the few cluster headache prevalence rates reported in previous studies. They centre around a prevalence of 0.1%, as shown in table 1.^{2–5} We can also confirm the male preponderance of this disorder. It is important to note that the results of several epidemiological studies on cluster headache are more consistent when compared, for instance, with epidemiological studies on migraine. This supports the assumption that cluster headache is a biological disorder with little influence of ethnic or socioeconomic factors.

Our prevalence rate transforms to an estimation of approximately 120 000 cluster headache cases in Germany in the year 2005. This high value contrasts with the number of patients treated for cluster headache in Germany. Based on the German DRG registry in 2005, only 716 German patients were treated as inpatients for cluster headache. Thus underdiagnosis of this headache disorder is likely.

A limitation of our study was that we may have overlooked individual patients with rare cluster headache types, such as bilateral cluster headache, cluster headache bouts not remembered by the patient and cluster headache without autonomic features. However, as these cases are very rare, we believe that our prevalence rate is valid and realistic. Another limitation was the low number of subjects in the sample, resulting in a large confidence interval and making it impossible to define subgroups. This is a problem with all rare diseases. Therefore, additional epidemiological studies on large samples of cluster headache sufferers are warranted.

Stefan Evers, Marthe Fischera

Department of Neurology, University of Münster, Germany

Arne May

Department of Systems Neuroscience, University of Hamburg, Germany

Klaus Berger

Department of Epidemiology and Social Medicine, University of Münster, Germany

Correspondence to: Dr Stefan Evers, Department of Neurology, University of Münster, Albert-Schweitzer-Str 33, 48129 Münster, Germany; evers@uni-muenster.de

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Table 1 Previous epidemiological studies on the incidence or prevalence of cluster headache

Study	Country	Results
This study	Germany	0.15% (12 month prevalence)
Ekblom <i>et al</i> 2006 ⁶	Sweden	0.15% (lifetime prevalence)
Torelli <i>et al</i> 2005 ⁴	Italy	0.28% (lifetime prevalence)
Sjaastad and Bakkeiteig 2003 ³	Norway	0.38% (lifetime prevalence)
Tanon <i>et al</i> 2002 ²	San Marino/Italy	0.056% (lifetime prevalence)