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Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients

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Summary

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary angiopathy caused by mutations in the *NOTCH3* gene. The clinical course is highly variable. Little is known about the long-term prognosis and the causes of death in CADASIL patients. Likewise, the impact of gender and *NOTCH3* genotype on disease progression remains largely unexplored. We identified 411 subjects (196 men, 215 women) with a definite diagnosis of CADASIL. Age at onset for stroke, immobilization and death as well as the causes of death and clinical status at onset of the cause of death were determined systematically. Weibull regression models were used to calculate times to event, with gender and *NOTCH3* genotype as covariates. At the time of the study, 73 patients had died. The median age at onset for stroke was 50.7 years [95% confidence interval (CI) = 48.2–53.1 years] in men and 52.5 years (95% CI = 50.0–54.9 years) in women (*P* = n.s.). The median ages at onset for inability to walk without assistance [men 58.9 years (95% CI = 56.6–61.3 years); women 62.1 years (59.7–64.4 years)], bedriddenness [men 62.1 years (59.6–64.7 years), women 66.5 years (63.9–69.1 years); and death [men 64.6 years (61.7–67.6 years); women 70.7 years (67.6–73.9 years)] were significantly lower in men than in women (all $P \leqslant 0.01$). The median survival time of men was significantly shorter than expected from German life tables (64.6 versus 69.3 years, *P* = 0.01). In contrast, the median survival time of women was not significantly reduced (70.7 versus 72.2 years). The C117F mutation was associated with a lower age at death and the C174Y mutation with a lower age at onset for stroke, immobilization and death (adjusted *P* values <0.05). At onset of the cause of death, 78% of the subjects were completely dependent. Sixty-three per cent were confined to bed. Pneumonia was the most frequent cause of death (38%), followed by sudden unexpected death (26%) and asphyxia (12%). We conclude that male sex is a risk factor for early immobilization and death in CADASIL. Our findings suggest possible genotype–phenotype correlations with regard to disease progression. The data presented may serve as source material for counselling CADASIL patients and for designing future interventional trials.

Keywords: CADASIL; prognosis; causes of death; Notch3; genotype–phenotype correlations

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; ICD10 = International Classification of Diseases—Tenth Edition

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a non-amyloid type of small vessel disease caused by mutations in the *NOTCH3* gene (Joutel *et al*., 1996). Manifestations include recurrent strokes, cognitive decline, and psychiatric disturbance as well as migraine with aura (Chabriat *et al*., 1995; Dichgans *et al*., 1998; Amberla *et al*., 2004).

CADASIL usually takes a progressive course and may lead to severe disability and premature death. There is, however, considerable variability in the rate of progression and survival

between individual patients (Chabriat *et al*., 1995; Dichgans *et al*., 1998; Peters *et al*., 2004). Preliminary evidence suggests that male patients have a shorter survival than females (Dichgans *et al*., 1998). However, this study did not account for the known differences in expected survival, and the effects of gender on disease progression were also not evaluated. Few studies have systematically compared the influence of different *NOTCH3* mutations on the disease phenotype (Dichgans *et al*., 1999; Lesnik Oberstein *et al*., 2001).

Precise knowledge of the long-term prognosis is essential for counselling patients and their families. Many patients become immobilized at an early age, which poses a significant burden on both patients and caregivers. This burden is increased by cognitive deficits and other manifestations, such as dysphagia and incontinence, which are both frequent and a source of further complications. Little is known about the frequency of these symptoms in late disease stages and the causes of death in CADASIL.

We therefore undertook the present study to determine the long-term prognosis of patients with CADASIL. Specifically, we examined the following parameters: (i) age at onset for stroke, immobilization and death, including survival compared with the expected survival, drawn from German life tables; (ii) clinical status at onset of the cause of death; and (iii) causes of death. We further investigated the influence of gender and *NOTCH3* genotype on ages at onset.

Methods

Case ascertainment

Subjects were selected from a register of CADASIL families set up at the authors' institution in 1993. This register contains clinical, genealogical and genetic data on 215 families with CADASIL. Data were continuously updated over a 10-year period. Index cases were identified through the authors' institution and referrals from outside physicians. In all cases an attempt was made to contact additional family members. Families were approached using a proband-initiated contact method. The study was approved by the local ethics committee (ethics commitee of the faculty of medicine, Ludwig Maximilians University, project 214/99).

In order to be included in the study, individuals had to have a definite diagnosis of CADASIL as defined by the following criteria: a pathogenic mutation in the *NOTCH3* gene, a positive biopsy or autopsy result (electron-dense deposits within small blood vessels), or an obligate carrier status by pedigree position (Ruchoux *et al*., 1995; Joutel *et al*., 1997; Markus *et al*., 2002). A total of 411 subjects (196 men and 215 women) from 215 families met the criteria. The authors personally saw and examined 255 of the patients.

Data acquisition and analysis

Between November 2002 and March 2004, we contacted all families who had previously agreed to an interview. At that time, 73 subjects fulfilling the inclusion criteria had died. A personal, structured interview was conducted with the patients, or with relatives and caregivers if the patient was unable to participate or had difficulties remembering. This information was compared with that provided by medical records and by private practitioners. If necessary, the date of birth and death were obtained from the registry office. If a particular question could not be answered or if the answer was felt to be unreliable, the information was classified as unknown.

Time-to-event for stroke, immobilization and death

We systematically determined the age at onset for stroke, inability to walk without assistance, bedriddenness and death. Stroke was defined as a neurological deficit of sudden onset with focal dysfunction and symptoms lasting more than 24 hours that were presumed to be of a vascular origin. If symptoms had been transient we asked for symptoms typical of migraine with aura (MA) to exclude attacks of MA or complications of migraine. Age at onset curves were estimated by Weibull regression models for interval-censored data. These models account for both right-censoring (no event until last follow-up) and left-censoring (event has occurred, but the onset is unknown) (Cox and Oakey, 1984). Gender and *NOTCH3* genotype were included in the models to explore the possible influence of these factors on age at onset. Specifically, the eight most frequently occurring mutations (all present in more than 10 subjects) were analysed separately and compared with all remaining mutations (Table 1). All reported *P* values were adjusted for multiple testing as confirmed by closed test procedures (Pigeot, 2000). Hence, for each time to event analysis the probability of reporting a false positive effect is $\leqslant 5\%$. The calculated medians for age at death were compared with life expectancies drawn from German life tables. These were calculated as standardized medians with gender and date of birth as stratification factors. To avoid a selection bias for a survival cohort, standardization was based on life expectancies of those who had reached an age of 20 years.

All analyses were done using SAS/STAT® software with the LIFETEST and MULTTEST procedures (SAS Institute, Cary, NC, USA).

Clinical status at onset of the cause of death

To characterize the late disease stages of CADASIL, we systematically obtained information on the clinical status at onset of the cause of death. In particular, we asked about the presence or absence of the following: confinement to bed, dementia according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition), dysarthria, dysphagia, pathological laughing or crying, urinary incontinence, faecal incontinence, and decubital ulcer. We also asked whether the patient had had transcutaneous gastric feeding or a suprapubic catheter. Finally, we determined the time between becoming bedridden and death. Data were obtained from the sources described above. Eighteen of the deceased individuals had personally been seen by the authors prior to their death.

Causes of death

Data on cause of death were obtained by using all available information from the following sources: autopsy reports, death certificates, medical records, notes from general practitioners, and interviews with proxies. Some patients died following a series of events, e.g. a fracture after a fall, complicated by fatal pneumonia. In such cases the initial event was recorded as the primary cause of death and the final complication leading to death as the secondary cause. Stroke was not considered a cause of death, since it is the main manifestation of CADASIL and the majority of the deceased had experienced one

Table 1 *NOTCH3 mutations in the 371 individuals in whom a mutation was identified*

Nucleotide change	Amino acid change	Exon	EGF repeat	No. of individuals
205T>G	C43R	2	1	2
224G>T	C49F	2	1	2
257C>G	S60C	2	1	3
272G>C	C65S	2	1	2
306T>G	C76W	3	1	1
309_326del	Q77_C82del	3	1 + 2	1
317_331del	D80_S84del	3	2	1
337T>C	C87R	3	2	1
338G>A	C87Y	3	2	1
346C>T	R90C	3	2	38*
356G>T	C93F	3	2	4
396C>G	C106W	3	2	1
401G>A	C108Y	3	2	1
406C>T	R110C	3	2	10
428G>T	C117F	4	2	11*
446G>T	C123F	4	3	5
475C>T	R133C	4	3	52*
480C>G	C134W	4	3	2
499C>T	R141C	4	3	17*
509G>C	C144S	4	3	1
509G>A	C144Y	4	3	3
512C>G	S145C	4	3	1
523G>T	G149C	4	3	5
527A>G	Y150C	4	3	6
537_545del	R153_C155del	4	3	1
535C>T	R153C	4	3	12*
542G>C	C155S	4	3	1
583C>T	R169C	4	4	32*
598T>C	C174R	4	4	2
599G>A	C174Y	4	4	20*
622C>T	R182C	4	4	60*
625T>C	C183R	4	4	1
625T>A	C183S	4	4	2
626G>T	C183F	4	4	3
631T>C	C185R	4	4	8
659G>T	C194F	4	4	1
680G>A	C201Y	4	5	1
697C>T	R207C	4	5	4
776G>A	C233Y	5	5	1
792_836del	D239_D253del	5	6	8
797G>C	C240S	5	6	1
811T>C	C245R	5	6	1
857G>A	C260Y	5	6	2
1033_1034 GC>TG	A319C	6	8	2
1072C>T	R332C	6	8	4
1082C>G	S335C	6	8	2
1088A>G	Y337C	6	8	5
1214G>C	C379S	7	9	1
1261T>C	C395R	7	10	1
1339C>T	R421C	8	10	1
1361G>A	C428Y	8	10	1
1396T>C	C440R	8	11	1
1415G>C	C446S	8	11	5
1529G>A	C484Y	9	12	4
1562G>A	C495Y	9	12	1
1609T>C	C511R	10	13	1
1724G>A	C549Y	11	14	1
1750C>T	R558C	11	14	2
3031C>T	R985C	18	25	6
3860G>A	C1261Y	23	32	1

*Mutations that were separately analysed by Weibull regression models. EGF = epidermal growth factor-like.

or multiple strokes during the course of their illness. Instead, we documented whether the patient had had a stroke prior to death.

Results

Demographic data

We identified 411 subjects (196 men, 215 women) with a definite diagnosis of CADASIL. Subjects belonged to 215 families. The size of the families ranged from 1 to 14 definitely affected individuals. At the time of this study 35 men and 38 women had already died.

Time-to-event analyses

The results of the time-to-event analysis for first stroke, immobilization and death are presented in Fig. 1 and Table 2. The median age at onset for stroke was lower in men (50.7 years) than in women (52.5 years), but this difference was not significant. In contrast, median age at onset for inability to walk without assistance was significantly lower in men (58.9 years) than in women (62.1 years) ($P = 0.01$). The difference between men and women was even more obvious as regards median age at onset for bedriddenness (62.1 years in men, 66.5 years in women, $P = 0.002$). The difference was most pronounced for median age at death, which was 64.6 years in men and 70.7 years in women ($P < 0.001$).

The observed minimum age at onset for stroke was 19 years and the maximum was 67 years. The observed minimum age

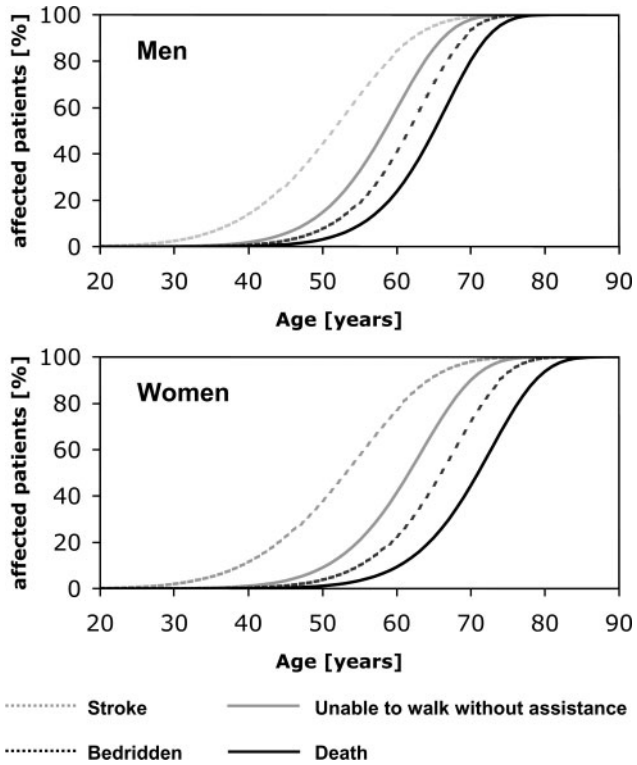

Fig. 1 Age at onset curves for stroke, immobilization and death in 411 CADASIL patients.

at death was 28 years and the maximum was 88 years. The median time between first stroke and death was 19.3 years in men [95% confidence interval (CI) 17.3–21.3 years] and 25.9 years in women (95% CI 19.8–32.0 years), showing a trend towards a significant difference ($P = 0.17$).

Survival compared with life expectancies

The median survival time of men was significantly shorter than expected from German life tables (64.6 versus 69.3 years, $P = 0.01$). The median survival time of women was slightly shorter than expected (70.7 versus 72.2 years), but the difference was not significant.

Influence of NOTCH3 genotype on age at death

The causative mutation was known in 371 of the 411 individuals (Table 1). To explore the influence of specific *NOTCH3* mutations on age at onset, we analysed the eight most frequently occurring mutations, using all other mutations as a reference (Table 3). The C174Y mutation (20 individuals from five families) was associated with a significantly lower median age at onset for stroke, immobilization and death (all $P < 0.01$). The C117F mutation (11 individuals from one family) was associated with a significantly lower median age at onset for death ($P < 0.05$) and a non-significant trend for a lower median age at onset for bedriddenness ($P = 0.11$). In contrast, none of the other six mutations were associated with a lower or higher median age at onset for stroke, immobilization, or death (all $P > 0.1$).

Both the C174Y and C117F mutations replace a cysteine residue with another amino acid (AA). We therefore compared all mutations leading to the loss of cysteine residue (CysAA, $n = 96$ subjects) with all mutations generating a new cysteine residue (AACys, $n = 264$ subjects). There was no significant difference in median age at onset for stroke, immobilization or death between the two groups (all $P > 0.05$).

Table 2 *Age at onset for stroke, immobilization and death*

	Age in years (95% CI)	
	Men	Women
Stroke		
10% percentile	37.2 (35.5–38.9)	38.5 (36.7–40.3)
Median	50.7 (48.2–53.1)	52.5 (50.0–54.9)[ns]
90% percentile	61.7 (58.3–65.2)	63.9 (60.5–67.4)
Unable to walk without assistance		
10% percentile	48.3 (46.4–50.2)	50.9 (48.9–52.8)
Median	58.9 (56.6–61.3)	62.1 (59.7–64.4)*
90% percentile	66.9 (63.8–69.9)	70.4 (67.5–73.4)
Bedridden[§]		
10% percentile	51.9 (49.8–54.1)	55.6 (53.4–57.8)
Median	62.1 (59.7–64.4)	66.5 (63.9–69.1)*
90% percentile	69.7 (66.4–72.9)	74.6 (71.3–77.9)
Death		
10% percentile	54.8 (52.3–57.3)	60.0 (57.3–62.7)
Median	64.6 (61.7–67.6)	70.7 (67.6–73.9)**
90% percentile	71.7 (68.1–75.4)	78.6 (74.7–82.4)

[§]Completely bedridden, needing constant nursing care and attention; [ns]not significant; *$P < 0.01$; **$P < 0.001$.
CI = confidence interval.

Clinical status at onset of the cause of death

At onset of the cause of death, 89% of the subjects had spastic tetra- or hemiparesis, 77% were demented and 77% had dysarthria, mostly in combination with dysphagia (73%, Table 4). Fifty-four per cent of the cases had a history of pathological laughing or crying, mostly in combination with dysarthria. However, in many cases pathological laughing or crying had been present for only a few months to years and had spontaneously remitted. Eighty per cent of the individuals had urinary incontinence and 72% were doubly incontinent. At onset of the cause of death, 78% of the subjects were completely dependent and required constant nursing care and attention; 63% were confined to bed (Table 4). In the latter, the mean time between becoming bedridden and death was 13.7 ± 25.2 months (range 0–144 months).

Causes of death

The causes of death could be determined in 50 of the 73 deceased subjects (Table 5). Pneumonia was the primary

Table 3 *Influence of the eight most frequently occurring NOTCH3 mutations on age at onset*

Event	Difference in median age in years (95% CI) compared with all other mutations ($n = 129$ subjects)							
	R90C ($n = 38$)	C117F ($n = 11$)	R133C ($n = 52$)	R141C ($n = 17$)	R153C ($n = 12$)	R169C ($n = 32$)	C174Y ($n = 20$)	R182C ($n = 60$)
Stroke	3.0 (−2.5 to 8.4)	−2.2 (−12.3 to 7.9)	1.5 (−3.3 to 6.2)	−1.6 (−11.1to 7.9)	−0.2 (−8.2 to 7.8)	1.4 (−3.8 to 6.6)	−6.6 (−12.0 to −1.1)*	−0.7 (−5.5 to 4.1)
Unable to walk without assistance	2.9 (−2.3 to 8.1)	−2.6 (−11.9 to 6.7)	2.8 (−1.9 to 7.4)	3.3 (−9.6 to 16.1)	−1.9 (−8.3 to 4.5)	−0.3 (−4.7 to 4.2)	−6.0 (−10.9 to −1.1)*	−0.7 (−5.1 to 3.6)
Bedridden	0.7 (−4.9 to 6.3)	−7.4 (−16.7 to 1.8)	3.4 (−1.7 to 8.4)	−0.9 (−13.4 to 11.6)	−1.0 (−7.9 to 5.8)	1.4 (−3.3 to 6.2)	−7.9 (−13.2 to −2.5)**	0.6 (−4.1 to 5.3)
Death	−2.7 (−8.5 to 3.1)	−9.7 (−19.0 to −0.4)*	1.8 (−3.6 to 7.2)	−4.9 (−17.2 to 7.5)	−2.0 (−9.7 to 5.8)	3.2 (−2.7 to 9.0)	−10.5 (−16.7to −4.3)***	2.5 (−3.5 to 8.4)

*$P < 0.05$; **$P < 0.005$; ***$P < 0.001$.

Table 4 *Clinical status at onset of the cause of death*

Sign/symptom	No. of subjects* (%)
Spastic tetra-/hemiparesis	55/62 (89)
Dementia	49/64 (77)
Dysarthria	47/61 (77)
Dysphagia	41/56 (73)
Transcutaneous gastric feeding	18/59 (31)
Pathological laughing or crying	30/56 (54)
Urinary incontinence	48/60 (80)
Suprapubic catheter	12/58 (21)
Faecal incontinence	42/58 (72)
Decubital ulcer	18/55 (33)
Requiring constant nursing care and attention	51/65 (78)
Bedridden	41/65 (63)

*Number of subjects with symptom/number of subjects for which the respective information could be obtained reliably.

Table 5 *Primary causes of death in 50 CADASIL subjects (classified according to ICD10)*

Cause	No. of subjects (%)
Pneumonia (ICD10: J12–18)[§]	13 (26)
Aspiration pneumonia (ICD10: J69)	5 (10)
Asphyxia (ICD10: T17)	6 (12)
Sudden unexpected death (ICD10: R96.0)*	13 (26)
Postprocedural cardiovascular failure (ICD10: I97)**	2 (4)
Accident (ICD10: V01–X59)***	4 (8)
Infectious diseases/septicaemia (ICD10: A00–B99)**	1 (2)
Suicide (ICD10: X60–X84)	1 (2)
Failed attempted abortion (ICD10: O007)	1 (2)
Malignant neoplasms (ICD10: C00–C97)****	4 (8)
Total	50 (100)

[§]Excluding aspiration pneumonia; *includes two patients with an autopsy diagnosis of pulmonary embolism (International Classification of Diseases—10th Edition, ICD10: I26.9); **includes one case with an autopsy diagnosis; ***falls (three patients), overdose of insulin (one patient); ****glioblastoma multiforme (n = 2); leukaemia (n = 1); gastric cancer (n = 1).

cause of death in 13 (26%) patients and a secondary cause in six (12%) patients (five with aspiration and one with a fracture). Thus, pneumonia accounted for 38% of all deaths. Pneumonia was also the cause of death in 33% of the autopsies (n = 6). Of the subjects who died of pneumonia, 83% had been confined to bed and 83% had had difficulties swallowing. In six (12%) subjects the cause of death was asphyxia following aspiration of food or gastric contents; all had had difficulties swallowing. Sudden unexpected death occurred in 13 subjects (26%). Sixty-nine per cent of them had been confined to bed; autopsies in two revealed that the cause of death was pulmonary embolism. Two other subjects had died immediately after a meal, although there was no evidence for asphyxia. Two patients died following surgery for transcutaneous gastric feeding. Malignant neoplasms were responsible for four deaths (8%). Other causes of death are shown in Table 5.

Discussion

To our knowledge, this is the first study to systematically evaluate the long-term prognosis and causes of death in CADASIL. The main findings are as follows: (i) age at onset for immobilization and for death was significantly lower in male than in female CADASIL subjects; (ii) in comparison with the general population, survival was reduced in CADASIL subjects, but the difference was significant only for male individuals; (iii) both the C117F and C174Y mutations were associated with a shorter survival; (iv) at onset of the cause of death more than 75% of the patients had been completely dependent, requiring constant nursing care and attention; and (v) pneumonia (with or without aspiration) was the most frequent cause of death.

Time-to-event analysis is more appropriate for estimating time spans than averaging the observed ages at onset, as it permits inclusion of follow-up information on all subjects, irrespective of whether they have reached the end-point (right-censoring). The models employed in this study further allow for left-censoring, thus maximizing the information extracted from the available data.

Our finding that male CADASIL subjects have a shorter survival than female CADASIL subjects is not explained by differences in life expectancy. Instead, our findings suggest an effect of sex on disease progression. In support of this, we found a lower age at onset for stroke and immobilization in men compared with women. A more rapid disease progression in men is further supported by a shorter interval between first stroke and death in male than in female CADASIL subjects. Interestingly, a recent neuroimaging study in CADASIL patients found significantly more lacunar infarcts in men compared with women, which is fully in line with our results (van den Boom *et al*., 2003). There is no simple explanation for these observations. Sex hormones might play a role. Indeed, studies in experimental stroke models have demonstrated favourable effects of oestrogen on cerebral blood flow, ischaemic tolerance and infarct size (Alkayed *et al*., 1998; Rusa *et al*., 1999; Sawada *et al*., 2000). However, studies in sporadic stroke patients have shown a less favourable short-term outcome in women compared with men and no significant effect of sex on long-term survival (Dennis *et al*., 1993; Wyller 1999; Glader *et al*., 2003; Kiyohara *et al*., 2003). Thus, the role of oestrogen remains unclear. Other factors that might contribute to our observations include sex differences in risk factor control, medical management, social support, and consequences for socio-economic status, which are known to affect outcome in stroke patients (Kapral *et al*., 2002).

Both the C174Y and C117F mutations were associated with a markedly shorter survival. These findings suggest possible genotype–phenotype correlations with respect to disease

progression in CADASIL. However, our observations should be interpreted cautiously. The majority of carriers of the C174Y and C117F mutations originated from two large families (data not shown). Thus, we cannot exclude the possibility of modifying influences from environmental factors or other sequence variants unique to these families. Also, our results await confirmation by other studies. A few reports in the literature give evidence of genotype–phenotype correlations in CADASIL (Joutel *et al*., 2000; Lesnik Oberstein *et al*., 2001; Arboleda-Velasquez *et al*., 2002). Only two studies have systematically compared the effects of different mutations (Dichgans *et al*., 1999; Lesnik Oberstein *et al*., 2001). One found no obvious effect of single mutations on the volume of lesions seen on brain MRI (Dichgans *et al*., 1999), and the second study detected an increased number of cerebral microbleeds in carriers of the R153C mutation (Lesnik Oberstein *et al*., 2001). In the present study there was no evidence for a more rapid disease progression in carriers of the R153C mutation. This suggests that despite its effects on microbleeds, the R153C mutation has no significant impact on long-term prognosis.

Our findings demonstrate that although some CADASIL patients survive until their late seventies, the long-term prognosis of the disease is poor, and the majority of patients finally experience severe deficits. By the time of onset of the cause of death, most patients were completely dependent and required constant nursing care and attention. Almost three of four patients were also demented, a finding that emphasizes the impact of cognitive deterioration on the long-term prognosis of CADASIL. Our findings further demonstrate that pathological laughing or crying, which is frequent in CADASIL, is often transient. Patients who develop this symptom should be informed of this positive finding. In contrast, many of the other complications do not tend to improve, thus adding to the burden of the caregiver.

Pneumonia was found to be the most frequent cause of death, followed by sudden unexpected death (SUD) and asphyxia. Obvious potential causes for SUD include pulmonary embolism, asphyxia, brainstem infarctions and myocardial infarction, which has been reported as a possible complication of CADASIL (Lesnik Oberstein *et al*., 2003). In the present series, both patients with SUD who underwent autopsy were found to have died from pulmonary embolism, suggesting that pulmonary embolism accounts for a significant proportion of cases. This view is further supported by the fact that the majority of patients had been completely immobilized before death. However, additional studies are needed to clarify the causes of SUD in CADASIL. Our findings also emphasize the importance of swallowing difficulties as a predisposing factor for fatal complications, in particular aspiration pneumonia and asphyxia. Transcutaneous gastric feeding, which is frequently applied in advanced disease stages, may in part prevent these complications. Our findings, however, also suggest a high rate of postprocedural complications among those receiving the procedure. Thus, particular attention should be given to the scheduling of the procedure, perioperative care and monitoring. Interestingly, only a minority of patients died from a fall, although there was an excess rate of falls compared with causes of death in the general population. In contrast, there was no evidence for an excess mortality due to malignancies, accidents or suicide.

Our study has some methodological limitations that need to be addressed. First, data were obtained retrospectively, and this raises the question of inaccurate information. This limitation is, however, unlikely to affect our finding of a significant influence of gender and genotype, since imprecise measures tend to reduce rather than enhance actual differences. Moreover, effects were most pronounced for the time to death, which is an accurate measure. Secondly, we cannot exclude the possibility of a selection bias for symptomatic cases—and thus earlier age at onset—or a survival cohort. However, we think that these biases are limited, because cases were ascertained in several independent ways, e.g. by family studies and regular follow-up. Selective follow-up was also limited: only one individual from our original cohort of 102 patients was lost to follow-up (Dichgans *et al*., 1998). We also took the selection bias for a survival cohort into account by comparing the observed survival with the life expectancies of those who had reached adulthood. Overall, we are fairly confident that our data are representative of the actual situation. Thirdly, our time-to-event analyses did not include aspects of cognition, which are an important determinant of the long-term prognosis of CADASIL. The reason for this was the difficulty of obtaining reliable information on the onset of cognitive deficits retrospectively. Therefore, prospective studies with repeated investigations over several years are needed to resolve this methodological problem.

In conclusion, this study demonstrates an influence of gender and *NOTCH3* genotype on clinical progression in CADASIL. It further provides detailed information on the long-term prognosis and causes of death in CADASIL. The data presented may serve as source material for counselling these patients and for designing future therapeutic trials.

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