A Two-Year Clinical Follow-Up Study in 80 CADASIL Subjects
Progression Patterns and Implications for Clinical Trials

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Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease causing stroke and dementia. The aim of this study was to explore the patterns of clinical progression in CADASIL, to check for prognostic variables, and to provide sample size estimates for future therapeutic trials.

Methods—Eighty CADASIL subjects (aged 45.7±9.9 years [mean±SD]) were followed prospectively during a mean period of 26.3±1.1 months. Standardized scales on disability (Rankin), activities of daily living (Barthel index), neurological outcome (National Institutes of Health Stroke Scale [NIHSS]), and cognition (structural interview for diagnosis of Alzheimer dementia and multi-infarct dementia [SIDAM] and Mattis dementia rating scale [MDRS]) were assessed at baseline and at follow-up. All but 1 individual completed the protocol. At follow-up, the cohort had deteriorated with respect to all clinical scales: Rankin scores (0.3±0.7 [mean change±SD]; P=0.001), Barthel index (−5.4±15.9; P<0.001), NIHSS scores (1.0±2.6; P=0.001), SIDAM scores (−2.1±6.4; P=0.004), and MDRS scores (−4.3±18.5; P=0.09). The spectrum ranged from marked worsening to some degree of improvement. Seventeen patients experienced a new stroke. Overall, there were 18 strokes within 173 person-years, giving an average incidence rate of stroke of 10.4 per 100 person-years (95% CI, 5.6 to 15.2). Age at baseline was found to be a predictor of clinical progression. Sample size estimates show that the number of individuals needed to include in an interventional trial (assumed duration 2 years, assumed treatment effect 40%) is 602 when using stroke occurrence as an outcome measure.

Conclusions—The clinical course of CADASIL includes periods of acute worsening, chronic progression, stabilization, and improvement. Sample size calculations emphasize the need for surrogate markers of disease progression for future interventional trials. (Stroke. 2004;35:1603-1608.)

Key Words: CADASIL ■ longitudinal studies ■ stroke ■ dementia ■ Notch

Cerebral small vessel disease (SVD) is an important cause of disability and a major contributor to dementia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary variant of ischemic SVD related to mutations in the NOTCH3 gene. The clinical spectrum of CADASIL has been delineated in large cross-sectional studies. These studies have determined the frequency of manifestations such as migraine with aura (20% to 35%), recurrent ischemic episodes (70% to 85%), and cognitive deficits (50%) in mutation carriers of different ages. Yet, little is known about the patterns of disease progression and the incidence rate of acute clinical events such as strokes.

Within the past few years, more than 400 families have been identified in Europe alone, and the number of newly diagnosed cases continuously increases as physicians become aware of the condition. Unfortunately, treatment options are limited. Often, antithrombotic agents such as aspirin are being used. Yet, there are no data to demonstrate efficacy of this or any other agent in CADASIL. In view of the large number of patients, controlled trials are needed. Planning such studies involves the choice of a suitable target population, decisions on outcome measures, and power calculations determining the number of cases needed to include to detect a treatment effect with sufficient power. These questions are best addressed by longitudinal studies that measure the progression of clinical scales and the rate of new clinical events in a given population. Longitudinal data are further critical when looking for prognostic factors modifying disease progression.

The aim of this study was (1) to obtain detailed information on the patterns of clinical progression and the annual inci-
dence rate of stroke in CADASIL, (2) to explore potential prognostic variables influencing the clinical course, and (3) to provide an estimate on the number of patients needed to include in clinical trials.

Methods

Subjects

Study participants were selected on the basis of the following criteria: (1) aged ≥21 years, (2) diagnosis of CADASIL on the basis of a CADASIL-typical NOTCH3 mutation6,7 (76 individuals) and/or a positive skin biopsy result8,9 (53 individuals), and (3) written informed consent according to the criteria of the local ethics committee. Reasons for exclusion were a stroke within the 3 preceding months and severe interfering conditions such as malignancies. Treatment with antithrombotic agents, anticoagulants, statins, and antihypertensive drugs was allowed.

Design

The study protocol was approved by the local ethics committee. Patients were enrolled at the authors’ institution between September 1999 and October 2000. All patients were seen and examined by a trained neurologist. Patients were examined twice: at baseline and at the end of the follow-up period. At both time points, patients underwent a comprehensive protocol that included a detailed history, a complete physical and neurological examination, and neuropsychological assessment. Disability was rated according to the modified Rankin scale (a 7-point scale that assesses overall function with a strong accent on physical disability; death is rated 6),10,11 the Barthel index (a 100-point scale that assesses activities of daily living),12 and the National Institutes of Health Stroke Scale (NIHSS; a 12-item scale that assesses neurological deficits).13 Neuropsychological assessment was done using the following 2 screening instruments on global cognitive functioning: the Mattis dementia rating scale (MDRS; maximum score 144)14 and the structural interview for diagnosis of Alzheimer dementia and multi-infarct dementia (SIDAM; maximum score 55).15 Psychiatric disturbances were assessed both at baseline and at follow up and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

Blood pressure was measured. Hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or use of antihypertensive medication together with a past diagnosis of hypertension. Laboratory investigations were done at baseline and included plasma homocysteine and fibrinogen. Information of smoking, hypercholesterolemia, diabetes mellitus, and education were obtained by questionnaire. At the end of the baseline visit, patients and their proxies were instructed to carefully document new clinical events that might occur between baseline and follow-up visits.

At follow-up, the authors performed a systematic inquiry regarding new clinical events within the study interval. In particular, patients were asked for the occurrence of transient ischemic attacks, strokes, cognitive worsening, migraine attacks, psychiatric disturbances, epileptic seizures, and other neurological symptoms that had occurred since baseline. They were also asked whether deficits had evolved in an acute or slowly progressive manner. Information from patients and their proxies was compared with medical records when possible. New clinical events were classified as “stroke” if symptoms were those of an “acute stroke” and at least 1 of the following 3 criteria was fulfilled: a documented new infarct on diffusion-weighted images at the time of the event, a diagnosis of acute stroke made by the primary hospital, or corresponding new neurological signs at follow-up examination.

Statistical Methods

Statistical inferences regarding changes of clinical scores during the study interval were based on Wilcoxon tests for dependent samples. Bivariate exploration of determinants of clinical deterioration was based on Spearman rank correlation coefficients (SRCCs) and the corresponding tests. Independent variables were selected on the basis of epidemiological data suggesting a role for age, systolic blood pressure, homocysteine levels, and fibrinogen levels in SVD.16-19 We also included clinical status at baseline and gender. Multivariate analysis was done using stepwise logistic regression. For this purpose, the dependent variables were dichotomized (clinical deterioration/stroke versus no deterioration/stroke). Regressors with a probability value <0.05 (Wald test) were included in the respective models. Statistical analyses were done with SPSS version 11.5.1 for Windows (SPSS Inc).

Because of the exploratory nature of this study, probability values <0.05 were regarded as “significant,” and no correction for multiple testing was performed.

Sample Size Estimates

Sample sizes were calculated according to standard methods using a validated protocol (PS program version 2.1.30; available online at http://www.mc.vanderbilt.edu/prevmed/ps). Calculations were done assuming a treatment effect of either 20% or 40%. These assumptions are based on results from large trials on secondary stroke prevention.20,21

For dichotomous outcome measures (stroke occurrence and Rankin [dichotomous]), the alternative hypothesis was expressed as a relative risk (0.8 or 0.6) using an uncorrected χ2 test (independent observations, prospective design). For continuous variables (clinical scores), the expected difference in population means (δ) was calculated by multiplying the observed mean change of the clinical score with a factor of 0.2 (treatment effect 20%) or 0.4 (treatment effect 40%).

Results

Demographic Characteristics

Eighty CADASIL subjects from 56 unrelated families were included in the study. Their demographic characteristics are shown in Table 1. All but 2 subjects had developed classical manifestations of CADASIL. One patient died during the study interval, and 79 subjects completed the study. Follow-up examinations were done after a mean interval of 26.3±1.1 months (range 24 to 31 months).

Clinical Scales

The mean clinical scores obtained in the overall cohort at baseline and at follow-up are shown in Table 2. At follow-up, all clinical scores had deteriorated when compared to baseline. Significant changes were found for the Rankin scale, the Barthel index, the NIHSS, and the SIDAM. A nonsignificant trend for deterioration was found for the MDRS.

Individual longitudinal changes of disability scores (Rankin) are shown in Figure 1. Sixteen (20%) subjects deteriorated, 2 (3%) improved, and 62 (78%) remained stable. Thirteen (81%) of the patients who deteriorated had experienced a new stroke.

Longitudinal changes of cognitive scores (SIDAM) are shown in Figure 2. Three (4%) subjects showed marked worsening (>10 points), 8 (10%) subjects showed moderate worsening (6 to 10 points), and 68 (86%) subjects showed no or minor changes (0 to 5 points) of their cognitive scores. In 4 (36%) of the subjects with moderate to marked worsening of cognitive scores, onset of cognitive worsening had been acute. A SIDAM score of <33 (cut-off for “dementia”) was found in 1 individual at baseline and in 7 individuals at follow-up.
To assess the relationship between disability and cognitive status on a longitudinal scale, we looked at the relationship between Rankin and SIDAM scores. Longitudinal changes of the Rankin correlated with longitudinal changes of the SIDAM (SRCC /H11002 0.43; P/H11021 0.001). This correlation remained when controlling for age at baseline (partial correlation coefficient [PCC] /H11002 0.43; P/H11021 0.001). A similar correlation was found between the NIHSS and SIDAM (PCC /H11002 0.54; P/H11021 0.001).

New Clinical Events During Follow-Up
Seventeen (22%) of the 79 subjects who completed the study experienced a new stroke. The total number of strokes was 18 and occurred within 173 person-years, which gives an average incidence rate of stroke of 10.4 per 100 person-years (95% CI 5.6 to 15.2). At follow-up, 13 (76%) of the patients with a new stroke had deteriorated with respect to their Rankin scores.

In 4 (5%) cases, patients or proxies reported an acute cognitive event with marked and persistent worsening of cognitive performance. At follow-up, all of them had deteriorated with respect to their SIDAM scores (19.5±18.6, range 2 to 41 [mean change±SD]). New clinical events are summarized in Table 3.

Prognostic Factors
To determine potential prognostic factors that would predict clinical worsening, we looked at the following dependent variables: changes of the Rankin score, changes of the SIDAM score, and the number of newly occurring strokes. Independent variables included age at baseline, gender, clinical status at baseline, systolic blood pressure, homocysteine level, and fibrinogen level.

In bivariate correlations, age at baseline was found to be a significant predictor of clinical worsening as assessed by the Rankin scale (SRCC 0.38), the SIDAM (SRCC 0.31), and the number of new strokes (SRCC 0.36; all P<0.005). Rankin scores at baseline correlated with changes of the Rankin score (SRCC 0.31; P<0.01). Fibrinogen levels correlated with the number of newly occurring strokes (SRCC 0.23; P<0.05), and there was a trend for a correlation with changes of the Rankin score (P<0.07). Finally, there was a trend for a correlation between systolic blood pressure and the number of new strokes (P=0.05). On multivariate analysis, age was the only significant predictor of clinical worsening as assessed by the Rankin scale (odds ratio [OR] per year, 1.10; 95% CI, 1.03 to 1.17), the SIDAM scale (OR per year, 1.07; 95% CI, 1.02 to 1.13), and the number of newly occurring strokes (OR per year, 1.10; 95% CI, 1.03 to 1.18).

### TABLE 1. Demographic Characteristics and Frequency of Clinical Manifestations in 80 CADASIL Subjects at Baseline

| Age, in years, mean±SD (range) | 45.7±9.9 (24–64) |
| Gender (male/female) | 37/43 |
| Body mass index, in kg/m², mean±SD | 26.6±4.8 |
| Years of education | 10.5±1.3 |
| CADASIL-related symptoms |
| Transient ischemic attack/stroke, n (%) | 62 (78) |
| Cognitive impairment, n (%) | 35 (44) |
| Migraine with aura, n (%) | 27 (34) |
| Major depression, n (%) | 10 (13) |
| Epileptic seizures, n (%) | 4 (5) |
| Vascular risk factors |
| Hypertension, n (%) | 20 (25) |
| Hypercholesterolemia, n (%) | 18 (23) |
| Diabetes mellitus, n (%) | 2 (3) |
| Smokers, n (%) | 29 (36) |
| Homocysteine, in μmol/L, mean±SD (range) | 11.0±5.4 (5.5–35.4) |
| Fibrinogen, in mg/L, mean±SD (range) | 325.0±60.1 (200–512) |

### TABLE 2. Clinical Scales at Baseline and at Follow-Up (2 Years)

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD; Range)</th>
<th>Follow-Up Mean (SD; Range)</th>
<th>P (Wilcoxon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin score</td>
<td>0.7 (1.0; 0–4)</td>
<td>1.0 (1.5; 0–6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Barthel index</td>
<td>98.4 (5.0, 70–100)</td>
<td>93.0 (18.7, 0–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.9 (1.4, 0–5)</td>
<td>1.9 (3.4, 0–16)</td>
<td>0.001</td>
</tr>
<tr>
<td>SIDAM score</td>
<td>48.1 (6.1, 19–55)</td>
<td>46.0 (9.8, 7–55)</td>
<td>0.004</td>
</tr>
<tr>
<td>MDRS score</td>
<td>133.8 (12.2, 70–144)</td>
<td>129.5 (23.6, 12–144)</td>
<td>0.090</td>
</tr>
</tbody>
</table>
TABLE 3. New Clinical Events During Follow-Up (2 Years) in the 80 CADASIL Subjects

<table>
<thead>
<tr>
<th>Event</th>
<th>Individuals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Recurrent symptoms (unclassified)*</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Acute cognitive worsening</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Attacks of migraine with aura</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Psychiatric disturbance†</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Recurrent symptoms such as gait disturbance that could not be classified. †Included mood disorder (n=3), personality change (n=3), and other symptoms (n=4).

Figure 2. Longitudinal changes of cognitive scores (SIDAM). Each line represents 1 individual. Note that changes occurred mostly in individuals aged >40 years.

Sample Size Estimates
To explore the role of clinical outcome measures for future therapeutic trials in CADASIL, we performed sample size calculations using longitudinal data from the present study. Table 4 gives the numbers needed to include in a treatment trial, assuming a trial duration of 2 years, a power of 80%, and a type I error probability of 0.05. As shown in Table 4, the number of patients was lowest when using stroke occurrence as an outcome measure and was highest when using global cognitive scores (SIDAM) as an outcome measure.

Discussion
This study provides prospective data on the patterns of disease progression in a large and representative cohort of CADASIL subjects. We found that the extent and mode of progression varied largely among subjects. Some patients showed a marked and rapid deterioration, whereas others remained stable or even improved. This observation reflects in part the stepwise progression that is typical of ischemic SVD.1,22,23 In fact, most subjects improved. This observation reflects in part the stepwise progression that is typical of ischemic SVD. Possible structural correlates include (1) strategic lesions within regions critically involved in multiple functions (e.g., thalamic and cingulate gyrus), and (2) a parallel progression of widespread tissue changes such as incomplete ischemic lesions and microinfarcts. However, studies correlating clinical and neuroimaging data are required to solve this issue.

Our data indicate that the occurrence of disability is intimately connected to the occurrence of new strokes. In contrast, deterioration of cognitive scores was associated less strongly with acute clinical events. These findings suggest differences in the mechanisms of disability and cognitive impairment in CADASIL. Nevertheless, we found a significant correlation between cognitive scores and Rankin scores as well as NIHSS scores on a longitudinal scale that was independent of age at baseline. This finding agrees with retrospective studies in pathologically confirmed Binswanger’s disease, showing that in many patients, dementia developed parallel to the occurrence of focal neurological deficits.28 Together, these findings emphasize a close relationship between cognitive performance and physical disability in ischemic SVD. Possible structural correlates include (1) strategic lesions within regions critically involved in multiple domains such as the thalamus, and (2) a parallel progression of topographically distinct lesions.

From the number of strokes that occurred within the study interval, we calculate an average incidence rate of stroke of 10.4 per 100 person-years. Molko et al followed 14 patients with MRI during a mean interval of 31.5 months.29 Two patients were mentioned to have had a new clinical event, which gives an incidence rate of 5.8 per 100 person-years. This number is somewhat lower than our estimate. Yet, the CI is large and thus fully compatible with our findings.

Previous cross-sectional studies have shown that the prevalence of manifestations increases with advancing age.3,4 The present study extends those findings by showing that age is a predictor for clinical progression. The robustness of this finding is emphasized by the fact that the ORs for clinical deterioration were almost identical for all outcome measures. We also found that Rankin scores at baseline were associated with clinical worsening during follow-up in bivariate analyses. These findings may relate to MRI findings from Molko et

TABLE 4. Sample Size Calculations

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Minimum Treatment Effect 20% (No. of Subjects Needed)</th>
<th>Minimum Treatment Effect 40% (No. of Subjects Needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke occurrence</td>
<td>2646</td>
<td>602</td>
</tr>
<tr>
<td>Rankin scale (dichotomous*)</td>
<td>2894</td>
<td>658</td>
</tr>
<tr>
<td>Rankin scale scores</td>
<td>5514</td>
<td>1380</td>
</tr>
<tr>
<td>Barthel index</td>
<td>6696</td>
<td>1676</td>
</tr>
<tr>
<td>NIHSS scores</td>
<td>5926</td>
<td>1484</td>
</tr>
<tr>
<td>SIDAM scores</td>
<td>7488</td>
<td>1874</td>
</tr>
</tbody>
</table>

*Deterioration vs no deterioration.
al, who found that the extent of tissue damage within the brain correlates with the progression of tissue changes during follow-up. Together, these findings suggest an acceleration of the disease over time.

The observed impact of age on clinical progression may have implications for the selection of patients in future therapeutic trials. Preventive treatments should be initiated before symptoms evolve. Yet, the inclusion of young and presymptomatic cases will enhance the number of individuals needed to document a treatment effect. Among many other aspects, this issue needs to be considered when planning a trial.

Bivariate analyses also revealed a correlation between systolic blood pressure and the number of newly occurring strokes. This finding, although statistically not significant, suggests that hypertension that has been established as a main risk factor for lacunar stroke and white matter lesions may suggest that hypertension that has been established as a main risk factor for lacunar stroke and white matter lesions may enhance the risk of stroke in CADASIL. The observed trend for a correlation between fibrinogen levels and clinical deterioration is in line with previous studies suggesting a role for elevated fibrinogen levels as a risk factor for SVD. Yet, these observations need to be confirmed in a larger study.

A possible limitation of our study is the selection of symptomatic individuals and the exclusion of severely disabled patients. Also, the use of cognitive screening instruments rather than targeted neuropsychological tests (such as tests on executive function) may have resulted in a low sensitivity with regard to changes in mildly affected patients. Our sample size estimates show that the number of subjects needed to include in an interventional trial is in the range of 650 patients, provided that the assumed treatment effect is strong and dichotomous outcome variables are used. These numbers highlight the need for collaborative studies and for developing more sensitive surrogate markers of disease progression such as MRI. In fact, diffusion tensor imaging has been shown to be highly sensitive in demonstrating the progression of tissue damage even in the absence of clinical deterioration. Potential MRI measures further include the volume of lesions, brain atrophy rates, and the number of new ischemic lesions. Yet, clinical end points will set the ultimate standard for interventional trials. In the present study, the Rankin scale and the NIHSS were more sensitive than global cognitive scores in detecting changes over time. This finding suggests that global cognitive scores are less suitable as outcome measures for future interventional trials. Longitudinal studies including selected neuropsychological items known to be altered in subcortical ischemic vascular dementia are warranted to determine the role of targeted cognitive test batteries in future interventional trials.

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References

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