The Natural History of CADASIL
A Pooled Analysis of Previously Published Cases

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Background and Purpose—Although numerous families with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) have been reported, our understanding of the disease remains incomplete. Thus, we performed this study to investigate the phenotypic range and natural history of CADASIL.

Methods—We performed a pooled analysis of previously published cases.

Results—We identified 105 symptomatic patients in 33 families. Vascular risk factors were uncommon, with hypertension reported in only 8 patients. The mean age of symptom onset was 36.7 ± 12.9 years. Stroke or transient ischemic attack was an initial symptom in 45 patients, with a mean age of onset of 41.2 ± 9.2 years. Migraine was also a common initial symptom, reported by 42 patients at a younger mean age of 28.3 ± 11.7 years. Other initial symptoms included depression in 9 patients, cognitive impairment in 6 patients, and seizures in 3 patients. Regarding clinical course, 71 patients experienced a stroke or transient ischemic attack, and 52 of those patients had 1 or more recurrent ischemic events. Dementia was reported in 44 patients. Only 3 additional patients experienced migraine at a later time, while 13 additional patients developed depression. Six patients had seizures. Twenty-two of the 105 patients had died, with a mean age of death of 54.8 ± 10.6 years. Nineteen of those 22 patients had experienced a stroke or transient ischemic attack and 19 patients were demented.

Conclusions—CADASIL typically becomes evident in early or middle adulthood with migraine or an ischemic event, later manifests itself through recurrent subcortical ischemic strokes leading to a stepwise decline and dementia, and results in reduced survival. (Stroke. 1999;30:1230-1233.)

Key Words: cerebral artery diseases ■ dementia ■ genetics ■ migraine ■ stroke

Early reports of the disease that was later termed “cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy” (CADASIL) were sporadic. Families with an apparently hereditary form of vascular dementia were described by Van Bogaert in 1955 and Sourander and Wålinder in 1977, but that disorder received little additional attention until 1991, when the current resurgence of interest in the disease now known as CADASIL began. Despite the numerous case reports that have since been published, however, our understanding of the phenotypic range and natural history of CADASIL remains incomplete. Thus, we performed a pooled analysis of the clinical characteristics of previously reported well-studied symptomatic CADASIL patients to provide a broader perspective on that disorder, with an emphasis on the age and nature of symptom onset and the association between stroke and dementia.

Subjects and Methods
To identify all previously reported well-studied symptomatic patients who were likely to have had CADASIL, we first performed a computerized review of the literature using MEDLINE and a broad group of search terms. We then performed a manual review of the literature that was guided by the reference lists of relevant articles. Finally, we performed a manual review of abstracts that had been presented at major neurological meetings. In certain cases, follow-up publications provided further information regarding patients who had been described previously. In those instances, we incorporated that information into our database, but we did not cite those follow-up publications unless new cases had been reported in order to maintain the clarity of our reference list. It should be noted that we did not extract any additional patients from the cohorts described by Chabriat et al and Dichgans et al.

We constructed a database consisting of families with an autosomal dominant pattern of inheritance of disorders that are typical of CADASIL (eg, stroke, migraine). We first required that 1 or more family members had undergone pathological study with results consistent with CADASIL. Alternatively, families were required to have undergone a genetic analysis with results supportive of linkage to the CADASIL locus. Individual members of each of those families were then required to have brain imaging features or pathological findings typical of CADASIL as well as an adequate clinical description (eg, age of symptom onset, nature of first symptom) to be eligible for inclusion in our final database.
Results

Background Characteristics
We identified 105 eligible patients in 33 families. Although we did not extract any additional patients from the cohort studies of Chabriat et al and Dichgans et al, we did include patients whom they had presented in other publications. Unfortunately, Chabriat et al and Dichgans et al failed to state explicitly whether any of the patients that they presented in those other publications had been included in their cohort studies. After careful review of their descriptions of those cohorts, however, we infer that no more than 11 of our 105 patients (10.5%) overlap with the cohort of Chabriat et al and that no more than 7 of our 105 patients (6.7%) overlap with the cohort of Dichgans et al.

Regarding our eligibility criteria, pathological findings consistent with CADASIL were reported in 1 or more members of 24 of the 33 families, the results of genetic testing were consistent with CADASIL in 17 families, and both forms of supportive information were available in 8 families. Brain imaging findings consistent with CADASIL were reported in 100 patients, pathological findings consistent with CADASIL were reported in 34 patients, and both forms of supportive information were available in 29 patients. It should be noted that pathological findings consistent with CADASIL were reported in each of the 5 patients for whom brain imaging was not available.

Thirty-four of the 105 patients were from France, 16 were from Italy, 39 were from other European countries, 13 were from the United States, 2 were from El Salvador, and 1 was from Japan. The sample was evenly divided by sex, with 55 males and 50 females. Vascular risk factors were uncommon, with hypertension reported in only 8 patients.

Initial Symptoms
The mean age of symptom onset was 36.7±12.9 years, with a range of 10 to 59 years. Stroke or transient ischemic attack (TIA) was an initial symptom in 45 patients, with a mean age of onset of 41.2±9.2 years (range, 20 to 58 years). Migraine was also a common initial symptom, reported by 42 patients at a significantly younger mean age of 28.3±11.7 years (range, 10 to 54 years; P<0.001). Thirty of those 42 patients had experienced migraine with aura, 6 had experienced migraine without aura, and 6 had experienced unspecified migraine. Other initial symptoms included depression in 9 patients, cognitive impairment in 6 patients, and seizures in 3 patients. Given that our report of learning disorders as the initial symptom of 3 patients in another publication was novel, it should be noted that we considered depression to be the initial symptom of the patients coded as III-1 and IV-5 in that pedigree and migraine to be the initial symptom of patient IV-3 for the purposes of the preceding analysis. Initial symptoms stratified by decade of age of onset are presented graphically in the Figure.

Clinical Course
Seventy-one of the 105 patients experienced a stroke or TIA, and 52 of those 71 patients went on to experience 1 or more recurrent ischemic events. Forty-four of the 105 patients were reported to be demented, and 16 of those 44 patients exhibited characteristics clearly typical of frontal lobe involvement (eg, disinhibition, perseverative behavior). An additional 19 patients exhibited cognitive impairment but were not reported to have frank dementia, suggesting that 63 of the patients exhibited at least mild cognitive deficits. Thirty-six of the 44 demented patients (81.8%) had experienced a stroke or TIA, and 31 of those patients (70.5%) had 1 or more recurrent ischemic events, while 35 of the 61 nondemented patients (57.4%) had experienced a stroke or TIA, and 21 of those patients (34.4%) had 1 or more recurrent ischemic events. We determined by \( \chi^2 \) analyses that patients reported to have dementia had significantly more frequently experienced a stroke or TIA (P=0.008) and 1 or more recurrent ischemic events (P<0.001) than nondemented patients. Only 3 additional patients experienced the new onset of migraine later in their clinical course, suggesting that migraine is unlikely to occur if it is not the initial symptom. Thirty additional patients went on to experience at least 1 episode of depression, however, suggesting that depression is more likely to occur later in the course of the disease than as an early manifestation. Six patients had seizures. Among patients who were living at the time of their case report, the mean maximum age reported was 47.6±12.6 years (range, 19 to 76 years). Twenty-two of the 105 patients were reported to have died, with a mean age of death of 54.8±10.6 years (range, 30 to 75 years), and the mean time from symptom onset to death was 12.8±13.1 years (range, <1 to 65 years). Nineteen of those 22 patients (86.4%) had experienced at least 1 stroke or TIA and 19 patients were demented.

Discussion
Our findings are consistent with the results of the cohort studies of Chabriat et al and Dichgans et al in suggesting that CADASIL becomes evident in young or middle adulthood with migraine or an ischemic event. Later, it manifests itself through recurrent subcortical ischemic strokes leading to a stepwise decline and a dementia syndrome with frontal lobe features, thus exemplifying the stereotypic course of vascular dementia. Finally, although we noted wide variabil-
ity in the time from symptom onset to death, CADASIL typically results in reduced survival.

Our presentation is unique because it is based on a large multinational sample of symptomatic patients, but we recognize that it suffers from the methodological weaknesses of the studies from which those patients were drawn. Those methodological weaknesses include the incomplete reporting of background characteristics (eg, vascular risk factors other than hypertension), leading to our inability to use an accurate “denominator” for the calculation of the true frequency of those characteristics in patients with CADASIL, as well as the underrecognition of certain subtle clinical manifestations (eg, mild cognitive impairment, mild depression). In addition, many of the studies of CADASIL that have thus far been published have been compelled to rely on clinical and pathological findings for case identification because of the unavailability of testing for Notch3 mutations, the molecular cause of CADASIL, potentially resulting in diagnostic errors.

Although numerous families with CADASIL have been reported, particularly during the last decade, its prevalence remains unclear, in part because of the challenges of differential diagnosis and case identification. In particular, questions persist regarding the apparent difference in prevalence between Europe and North America. Thus, methods for the epidemiological study of CADASIL are worthy of discussion. Our pooled analysis found that affected individuals typically present with migraine or an ischemic event between the ages of 10 and 58 years, suggesting that the brain imaging studies of such patients should be examined for abnormalities typical of CADASIL when they are performed. When such abnormalities are identified, each patient’s pedigree should be reviewed and conventional laboratory studies should be conducted to exclude alternative etiologies. Patients with an autosomal dominant pattern of transmission of clinical features characteristic of CADASIL should undergo a skin biopsy with electron microscopy. Whenever possible, DNA should be examined for the determination of Notch3 mutation status, but it should be noted that this test is not yet commercially available. Alternatively, linkage analysis could be informative if DNA is available from many family members. Finally, given that our pooled analysis suggested that dementia is an essentially universal end-state for patients with CADASIL, neuropsychological testing should be performed to detect the subtle cognitive disturbances that may be present at the onset of the disease and gain information relevant to patient prognosis. Although our analysis of the clinical characteristics of a pooled sample of previously published cases is instructive, the formation of a patient cohort by these diagnostic methods would permit more accurate and definitive conclusions to be drawn regarding the prevalence, phenotypic range, and natural history of CADASIL.

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References


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