59 Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a newly identified cause of stroke and vascular dementia.[1] It is an inherited arterial disease of midadulthood due to mutations of the *NOTCH3* gene on chromosome 19.[2] The disease was first reported in European families. Since 1993, CADASIL has been diagnosed in American, African, and Asiatic pedigrees, suggesting that it is present throughout the world and not limited to Caucasians. Because this disease has been discovered only recently, it is underdiagnosed.

Epidemiology

The exact frequency of CADASIL is unknown. The acronym "CADASIL" was adopted in 1993 after the genetic location of the disease on chromosome 19.[1] Genetic testing to confirm the diagnosis of the disease has been available only since 1996.[3] By 1999, hundreds of affected families had been reported on all continents. The frequency may be much higher than currently thought, because the first sporadic case has recently been identified, pointing to the possibility of neomutations.[4]

Pathophysiology and pathogenesis

CADASIL is a systemic small artery disease involving mainly smooth muscle cells. Because of the presence of severe alterations in the wall of small cerebral arteries and the association of rarefaction of the white matter with small deep infarcts, the presumed mechanism of the cerebral lesions is chronic ischemia.[5,6] Secondary inflammatory processes within the tissue, alterations of exchanges through the arteriolar wall, or wallerian degeneration (or a combination of these) may be associated.[6] Recently, diffusion tensor imaging showed in vivo that the severity of ultrastructural changes in the white matter was associated with the severity of clinical status in CADASIL.[7] We have suggested a threshold of tissue damage above which dementia and severe motor disability might occur in CADASIL.

Genetics

The defective gene in CADASIL is the *NOTCH3* gene located on chromosome 19. This gene encodes a large transmembrane receptor.[2,8] Its exact role in disease occurrence has not been determined. Numerous missense mutations of the gene have been detected in CADASIL patients. These mutations are located in the epidermal growth factor-like repeats in the extracellular domain of the protein. So far, they invariably lead to an odd number of cysteine residues. Most of the causative mutations are clustered within two exons (3 and 4); this clustering is the basis of a genetic test that is able to detect 70% of mutations causing the disease.[3] Only the most frequent mutations of the *NOTCH3* gene (within exons 3 and 4) are easily detected with routine testing (incomplete sensitivity). For the other mutations, the absence of a known target (know mutation within the family) hampers genetic testing, because of the numerous exons that have to be analyzed.

Clinical features

CADASIL is a disease of mid-adulthood. The mean age at the onset of symptoms is 45 years. The duration of the disease varies between 10 and 40 years. The mean age at death is about 65 years, but it varies from 30 to 80 years in the affected pedigrees that have been reported.[9,10]

Stroke is the most frequent clinical manifestation of CADASIL. About 85% of symptomatic subjects have transient ischemic attacks (TIAs) or completed strokes,[11,12] most frequently in the absence of vascular risk factors. The ischemic events occur at a mean age of 49 years (range, 27 to 65 years). All temporal profiles of ischemic manifestations are observed: TIAs, reversible ischemic neurological deficits, and completed strokes. The ischemic deficits are the subcortical type, and two-thirds of them are classic lacunar syndromes: pure motor stroke, ataxic hemiparesis, pure sensory stroke, sensory motor stroke. Some episodes of focal deficits occur in association with headache. During the course of the disease, the total number of TIAs a patient may have varied from one to more than ten. For most patients, the maximal number of completed strokes is less than five. In the largest series of affected families,[11,12] 40% of affected members who had ischemic manifestations had TIAs, 70% had completed strokes, and 10% had both.

Dementia, the second commonest clinical manifestation of CADASIL, has been reported in one-third of symptomatic patients. It is observed at a mean age of 60 years, and 90% of the patients will become demented before they die.[10,12] Of CADASIL patients

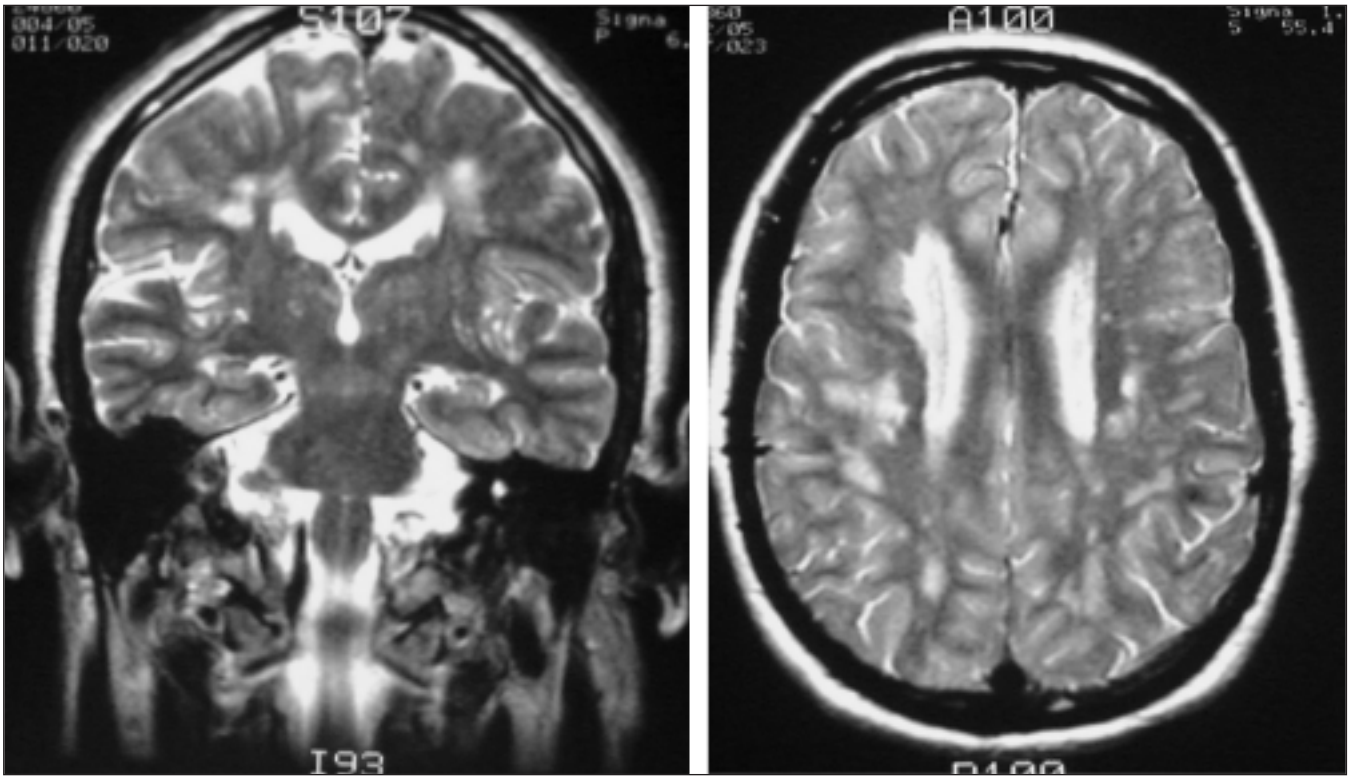

Figure 59.1 T_2-weighted magnetic resonance image of patient with CADASIL showing typical hyperintensities predominately in deep and periventricular white matter. *A*, Coronal and, *B*, axial sections.

older than 65 years, 80% are demented. The exact time of onset of cognitive impairment in CADASIL has been difficult to ascertain. Taillia et al.[13] showed that nondemented symptomatic patients (the youngest of whom was 35 years old) had altered performances on the Wisconsin Card Sorting test, a task very sensitive to frontal dysfunction. In 90% of patients, the cognitive impairment occurs step-by-step and is associated with recurrent strokes. In 10% of patients, the neuropsychological decline is isolated, mimicking the course of Alzheimer's disease.[11,12] The cognitive deficit is the subcortical type, with predominately frontal symptoms and memory impairment. Dementia is often associated with pyramidal signs, pseudobulbar palsy, gait difficulties, or urinary incontinence (or a combination of these).

From 20% to 30% of affected subjects have attacks of migraine with aura. This symptom is present in 40% of CADASIL families, but its frequency varies from zero to 85% of the patients within the affected pedigrees. When present, migraine with aura is the earliest clinical manifestation of the disease, with a mean age at onset of 30 years. As usually observed in migraine with aura, the most frequent neurological symptoms associated with headache are visual or sensitive (or both). However, according to the diagnostic criteria of the International Headache Society, the frequency of attacks with basilar, hemiplegic, or prolonged aura is noticeably high. In some families, several members have migraine with aura as the main and sole symptom of the disease.[14,15]

Nearly 20% of CADASIL patients present with severe mood disturbances. The frequency of such manifestations varies widely among families. Most patients have a severe depression of the melancholic type, sometimes alternating with typical manic episodes. The diagnosis of bipolar mood disorder was considered in some subjects until a magnetic resonance imaging (MRI) examination was performed.[16] The exact cause of mood disturbances in CADASIL is unknown, but the location of ischemic lesions in the basal ganglia or frontal lobe white matter may be important.[17]

MRI is essential for the diagnosis of CADASIL. The findings are always abnormal in symptomatic subjects. In addition, signal abnormalities can be detected during a presymptomatic period of variable duration. MRI signal abnormalities are observed as early as age 20 years. After age 35, all subjects who have the affected gene have abnormal MRI findings.[1]

T_1-weighted images show punctiform or nodular hyposignals in the basal ganglia and white matter, and T_2-weighted images show hypersignals in the same regions, associated with widespread areas of increased signal in the white matter (Figure 59.1).[18] In one-third of affected subjects, the hypersignals are observed in the absence of lesions seen on T_1-weighted images.[19] The severity of the lesions increases dramatically with age. The frontal and occipital periventricular lesions are constant. The frequency of signal abnormalities in the external capsule (two-thirds of patients) and the anterior part of the

temporal lobes is noteworthy. Brainstem lesions are observed mainly in the pons. The mesencephalon and medulla are usually spared. Cerebral cortical or cerebellar lesions are exceptional.

The results of ultrasonographic and echocardiographic studies are usually normal. Cerebral angiographic findings are normal; rarely, a narrowing of small arteries is seen. The results of cerebrospinal fluid analysis are usually normal, but oligoclonal bands with pleocytosis have been reported. A monoclonal immunoglobulin was detected in two affected members of our first family but not in other affected pedigrees.[20]

Macroscopic examination of the brain shows a diffuse myelin pallor and rarefaction of the hemispheric white matter, with sparing of the arcuate fibers. Lesions predominate in the periventricular areas and centrum semiovale.[5] Lesions are associated with lacunar infarcts in the white matter and the basal ganglia. In the brainstem, the lesions are most marked in the pons and are similar to the pontine rarefaction of myelin of ischemic origin.

Microscopic investigations have shown that the wall of cerebral and leptomeningeal arterioles is thickened and the lumen is significantly reduced. These abnormalities can be detected also in leptomeningeal biopsy specimens.[21] The media is thickened and contains abnormal smooth muscle cells, often degenerated, with multiple nuclei and an eosinophilic nonamyloid material. Sometimes, smooth muscle cells cannot be detected because they have been replaced by collagen fibers. In contrast, the endothelium is usually spared. On electron microscopy, the eosinophilic material appears dense, granular, and osmiophilic. Staining for amyloid substance and elastin is negative.[5] Recently, Ruchoux et al.[22,23] made the crucial observation that the vascular abnormalities observed in the brain can be detected also in other organs. The granular material surrounding the smooth muscle cells seen on electron microscopy is also present in the media of arteries in the spleen, liver, kidneys, muscle, and skin (Figure 59.2). The presence of this material in arteries in skin, muscle, and nerve has been used to confirm the diagnosis of CADASIL in several patients.[10,22,24]

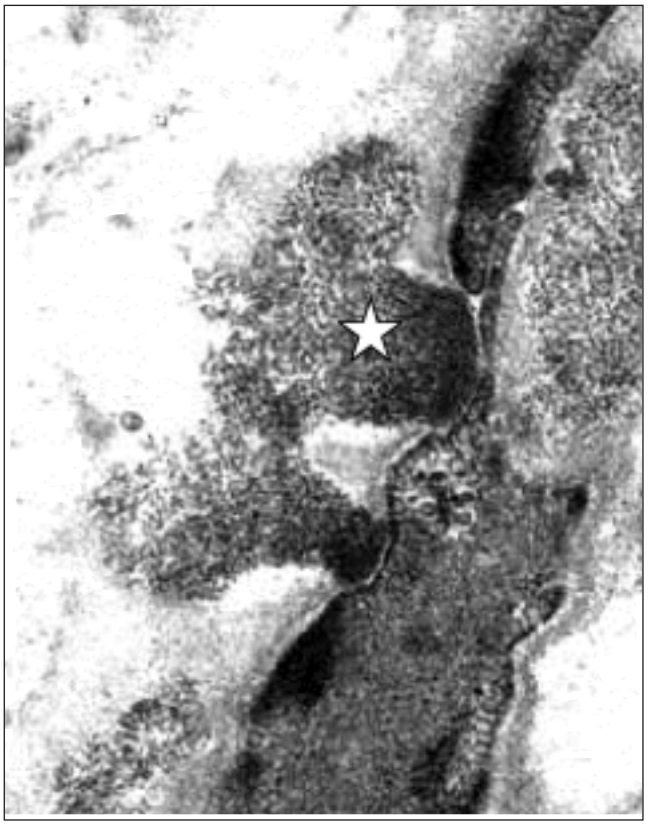

Figure 59.2 Electron micrograph of skin biopsy specimen showing granular material at external surface of smooth muscle cells (*star*). (Courtesy of P. R. Ruchoux, CHRU, Lille, France.)

Classification

There is no classification of CADASIL. The relation between the clinical phenotype and the genotype needs to be investigated further. Previous reports have not favored a specific clinical presentation or course of the disease according to the type of mutation. Also, the radiological features do not seem to differ in families according to the type of *NOTCH3* mutation.[25]

Diagnostic criteria

Some authors have proposed diagnostic criteria for CADASIL.[26] However, the complete clinical and radiological spectrum of all *NOTCH3* mutations is unknown. The diagnosis of CADASIL should be considered for all patients with symmetrical and periventricular white matter lesions on T_2-weighted MRIs and a history of attacks of migraine with aura, ischemic events, dementia, or mood disturbances during midadulthood. A positive familial history is useful but not essential, because a case of neomutation has been reported recently.[4] The diagnosis is confirmed with genetic testing or skin biopsy. In the very near future, diagnostic testing with immunostaining using anti-*NOTCH3* antibodies might be easier and more sensitive than genetic analysis or electron microscopic examination of tissue.[27]

If the diagnosis of CADASIL is suspected, angiography with contrast agents should be avoided, because confusion or coma have been reported as secondary effects in several affected subjects.[28]

Differential diagnosis

The diagnosis of CADASIL usually is considered if the patient has a familial history of stroke or dementia and MRI shows diffuse white matter signal abnormalities on T_2-weighted images. Differentiating CADASIL from other diseases associated with signal abnormalities in the white matter may be difficult. Binswanger disease usually is reported in patients with hypertension, but it is not hereditary and does not cause migraine[29] and it is associated with atherosclerosis of large arteries. Amyloid angiopathy, which

is rarely familial,[30] is often associated with dementia of Alzheimer type, and it is responsible for recurrent lobar hemorrhages more frequently than for subcortical ischemic strokes.[31] The lack of involvement of the optic nerve and medulla and the presence of lesions in the basal ganglia are useful for differentiating CADASIL from multiple sclerosis, a great mimic of CADASIL. Other hereditary arteriolar diseases have specific features different from those of CADASIL: alopecia, skeletal abnormalities, and a recessive pattern of transmission in the vascular disease reported in Japanese pedigrees by Fukutake and Hirayama,[32] palmoplantar keratodermia and increase in skin collagen in hereditary leukoencephalopathy reported by Lossos et al.,[33] and capillary abnormalities in the retina and prominent meningeal thickening in familial oculoleptomeningeal amyloidosis related to transthyretine mutations.[34,35]

Treatment

No treatment has been evaluated for CADASIL. Because of the variability in the natural history of the disease, a large number of subjects will have to be included in a randomized trial. The use of MRI abnormalities as surrogate markers needs to be explored, because there is some degree of correlation between the severity of the clinical presentation and MRI changes.

Because CADASIL is a vascular disease that causes cerebral ischemic events, we prescribe aspirin for secondary prevention, but its benefit in the disease has not been proved.

The report of cerebral hemorrhage in a patient just before death is noteworthy.[20] It indicates that anticoagulant therapy may be dangerous. In the presence of severe ultrastructural alterations of the vascular wall, as observed in CADASIL.

Some drugs are useful in relieving specific symptoms during the course of CADASIL. For migraine, all vasoconstrictive drugs such as ergot derivatives and triptans are contraindicated. Cortical oligemia has been reported in one asymptomatic patient.[36] Also, the blood-brain barrier might be altered because of the vascular lesions.[6] Therefore, we cannot exclude some deleterious effects of triptans on the cerebral circulation. Treatment of migraine should be restricted to analgesic agents and nonsteroidal anti-inflammatory drugs.

All treatments (e.g., neuroleptic agents and antihypertensive drugs) that decrease blood pressure should be used with caution because hypoperfusion, which is the presumed mechanism of cerebral lesions in CADASIL, may be aggravated.

As reported for other ischemic diseases, all rehabilitation procedures are crucial after a stroke occurs in a patient with CADASIL. If stroke occurs at an early stage of the disease, recovery is often complete.

Psychological support for the patient and family is crucial. Not only the psychological consequences of the neurological deficits but also those related to the hereditary nature of the disease should be considered. The diagnosis of a familial disorder may have important consequences within the family and modify relationships among close relatives. Genetic testing raises important ethical problems similar to those encountered in families with Huntington disease, particularly for asymptomatic members at risk for having the deleterious mutation. Genetic counseling and testing should be performed only at specialized centers that have the necessary experience.

References

1. Tournier-Lasserve E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. Nat Genet 1993;3:256–259
2. Joutel A, Corpechot C, Ducros A, et al. *NOTCH3* mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 1996;383:707–710
3. Joutel A, Vahedi K, Corpechot C, et al. Strong clustering and stereotyped nature of *NOTCH3* mutations in CADASIL patients. Lancet 1997;350:1511–1515
4. Joutel A, Dodick D, Parisi J, et al. De novo mutation in the *NOTCH3* gene causing CADASIL. Ann Neurol 2000;47:388–391
5. Baudrimont M, Dubas F, Joutel A, et al. Autosomal dominant leukoencephalopathy and subcortical ischemic stroke. A clinicopathological study. Stroke 1993;24:122–125
6. Ruchoux MM, Maurage CA. CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neuropathol Exp Neurol 1997;56:947–964
7. Chabriat H, Pappata S, Poupon C, et al. Clinical severity in CADASIL related to ultrastructural damage in white matter. In-vivo study with diffusion tensor MRI. Stroke 1999;30:2637–2643
8. Joutel A, Tournier-Lasserve E. Notch signalling pathway and human diseases. Semin Cell Dev Biol 1998;9:619–625
9. Chabriat H, Joutel A, Vahedi K, et al. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [French]. J Mal Vasc 1996;21:277–282
10. Chabriat H, Joutel A, Vahedi K, et al. CADASIL. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [French]. Rev Neurol (Paris) 1997;153:376–385
11. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 1998;44:731–739
12. Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lancet 1995; 346: 934–939
13. Taillia H, Chabriat H, Kurtz A, et al. Cognitive alterations in non-demented CADASIL patients. Cerebrovasc Dis 1998;8:97–101
14. Verin M, Rolland Y, Landgraf F, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. J Neurol Neurosurg Psychiatry 1995; 59:579–585
15. Chabriat H, Tournier-Lasserve E, Vahedi K, et al. Autosomal dominant migraine with MRI white-matter abnormalities mapping to the CADASIL locus. Neurology 1995;45:1086–1091
16. Kumar SK, Mahr G. CADASIL presenting as bipolar disorder. Psychosomatics 1997;38:397–398

17. Aylward ED, Roberts-Twillie JV, Barta PE, et al. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. Am J Psychiatry 1994; 151:687–693
18. Skehan SJ, Hutchinson M, MacErlaine DP. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR findings. AJNR Am J Neuroradiol 1995;16:2115–2119
19. Chabriat H, Levy C, Taillia H, et al. Patterns of MRI lesions in CADASIL. Neurology 1998;51:452–457
20. Tournier-Lasserve E, Iba-Zizen MT, Romero N, Bousser MG. Autosomal dominant syndrome with strokelike episodes and leukoencephalopathy. Stroke 1991;22: 1297–1302
21. Lammie GA, Rakshi J, Rossor MN, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)—confirmation by cerebral biopsy in 2 cases. Clin Neuropathol 1995; 14:201–206
22. Ruchoux MM, Chabriat H, Bousser MG, et al. Presence of ultrastructural arterial lesions in muscle and skin vessels of patients with CADASIL. Stroke 1994;25: 2291–2292
23. Ruchoux MM, Guerouaou D, Vandenhautte B, et al. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Acta Neuropathol 1995;89:500–512
24. Goebel HH, Meyermann R, Rosin R, Schlote W. Characteristic morphologic manifestation of CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, in skeletal muscle and skin. Muscle Nerve 1997;20:625–627
25. Dichgans M, Filippi M, Bruning R, et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. Neurology 1999;52:1361–1367
26. Davous P. CADASIL: a review with proposed diagnostic criteria. Eur J Neurol 1998;5:219–233
27. Joutel A, Andreux F, Gaulis S, et al. The ectodomain of the *NOTCH3* receptor accumulates within the cerebrovasculature of CADASIL patients. J Clin Invest 2000;105:597–605
28. Dichgans M, Petersen D. Angiographic complications in CADASIL. Lancet 1997;349:776–777
29. Babikian V, Ropper AH. Binswanger's disease: a review. Stroke 1987;18:2–12
30. Greenberg SM, Vonsattel JP, Stakes JW, et al. The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. Neurology 1993;43: 2073–2079
31. Gray F, Dubas F, Roullet E, Escourolle R. Leukoencephalopathy in diffuse hemorrhagic cerebral amyloid angiopathy. Ann Neurol 1985;18:54–59
32. Fukutake T, Hirayama K. Familial young-adult-onset arteriosclerotic leukoencephalopathy with alopecia and lumbago without arterial hypertension. Eur Neurol 1995;35:69–79
33. Lossos A, Cooperman H, Soffer D, et al. Hereditary leukoencephalopathy and palmoplantar keratoderma: a new disorder with increased skin collagen content. Neurology 1995;45:331–337
34. Goren H, Steinberg MC, Farboody GH. Familial oculoleptomeningeal amyloidosis. Brain 1980;103:473–495
35. Petersen RB, Goren H, Cohen M, et al. Transthyretin amyloidosis: a new mutation associated with dementia. Ann Neurol 1997;41:307–313
36. Chabriat H, Bousser MG, Pappata S. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a positron emission tomography study in two affected family members. Stroke 1995;26:1729–1730