What is CADASIL?

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy) is an inherited form of cerebrovascular disease that occurs when the thickening of blood vessel walls blocks the flow of blood to the brain. The disease primarily affects small blood vessels in the white matter of the brain. A mutation in the Notch3 gene alters the muscular walls in these small arteries. CADASIL is characterized by migraine headaches and multiple strokes progressing to dementia. Other symptoms include cognitive deterioration, seizures, vision problems, and psychiatric problems such as severe depression and changes in behavior and personality. Individuals may also be at higher risk of heart attack. Symptoms and disease onset vary widely, with signs typically appearing in the mid-30s. Some individuals may not show signs of the disease until later in life. CADASIL - formerly known by several names, including hereditary multi-infarct dementia - is one cause of vascular cognitive impairment (dementia caused by lack of blood to several areas of the brain). It is an autosomal dominant inheritance disorder, meaning that one parent carries and passes on the defective gene. Most individuals with CADASIL have a family history of the disorder. However, because the genetic test for CADASIL was not available before 2000, many cases were misdiagnosed as multiple sclerosis, Alzheimer's disease, or other neurodegenerative diseases.

There is no treatment to halt this genetic disorder. Individuals are given supportive care. Migraine headaches may be treated by different drugs and a daily aspirin may reduce stroke and heart attack risk. Drug therapy for depression may be given. Affected individuals who smoke should quit as it can increase the risk of stroke in CADASIL. Other stroke risk factors such as hypertension, hyperlipidemia, diabetes, blood clotting disorders and obstructive sleep apnea also should be aggressively treated.

Full article: NINDS CADASIL Information Page http://www.ninds.nih.gov/disorders/cadasil/CADASIL.htm

CADASIL is characterized by a history of migraine with aura (30%-40% of individuals), mid-adult (30s-60s) onset of cerebrovascular disease, mood disturbance, apathy, cognitive disturbance progressing to dementia, and diffuse white matter lesions and subcortical infarcts on neuroimaging.

The pathologic hallmark of CADASIL is electron-dense granules in the media of arterioles that can often be identified by electron microscopic (EM) evaluation of skin biopsies. More than 90% of individuals have mutations in *NOTCH3*, the only gene in which mutations are known to cause CADASIL.

Agents to avoid: Angiography and anticoagulants may provoke cerebrovascular accidents; smoking increases the risk of stroke. Thrombolytic therapy (intravenous thrombolysis) is contraindicated because of the presumed increased risk for cerebral hemorrhage.

Full article: NCBI Gene Reviews http://www.ncbi.nlm.nih.gov/books/NBK1500/

Precautions: In a CADASIL patient, migraine should be treated like most other patients of migraine, except the use of a group of medications called triptans (e.g. Imitrex) is usually contraindicated due to increased risk of stroke.

In the event of an acute stroke-like episode, patients with CADASIL should not be treated with a thrombolytic agent (clot dissolving medication). This medication is usually used in patients with acute stroke within the first three hours. Patients with CADASIL have an increased risk of bleeding in the brain. Therefore, the current consensus is that this type of medication should be avoided.
Full article: ULF/United Leukodystrophy Foundation
http://ulf.org/cerebral-autosomal-dominant-arteriopathy-with-subcortical-infacts-and-leukoencephalopathy-cadasil

The onset of cognitive deficit is usually mild and insidious, and its exact time is often difficult to ascertain. The cognitive changes may appear a long time before transient ischemic attacks (TIAs) or stroke.
Lesnik Oberstein SA., van den Boom R., Middelkoop HA., et al. Incipient CADASIL. *Arch Neurol.* 2003;60:707–712. Full article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181851

Cross-sectional studies have shown that early in the disease, cognitive functions, most frequently attention and executive functions, may be impaired.
Above source: Taillia H., Chabriat H., Kurtz A., et al. Cognitive alterations in nondemented CADASIL patients. *Cerebrovasc*. Dis. 1998;8:97–101.
Amberla K., Waljas M., Tuominen S., et al. Insidious cognitive decline in CADASIL. *Stroke.* 2004;35:1598–1602.
Full article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181851

CADASIL occurs when thickening of blood vessel walls blocks blood flow in the brain. The early manifestation is migraine headaches, progressing to strokes and mini strokes, depression, apathy, motor disability and executive dysfunction (inability to plan and organize everyday activities.) The final symptom is dementia.

"It is a terrible disease that runs in families, and unfortunately we as yet don't have effective treatments," said Dr. José Biller, senior author of the study and chairman of the Department of Neurology of Loyola University Chicago Stritch School of Medicine.

There are several reasons why CADASIL is misdiagnosed as MS. Both diseases tend to strike young adults. There are similarities in brain MRIs, and both diseases can cause focal neurologic signs and symptoms.
Full article: News Medical Net http://www.news-medical.net/news/20110310/Vascular-disorder-of-the-brain-most-frequently-misdiagnosed-as-multiple-sclerosis.aspx

Cognitive impairment amounting to a dementia syndrome occurs in about half of people with CADASIL. Of these, 6–10% will have dementia at the onset of the disease. After 10 years of disease evolution, at least 50% of CADASIL patients will have exhibited motor deterioration, pseudobulbar signs and dementia.
Full article: Advances in Psychiatric Treatment http://apt.rcpsych.org/content/14/5/350.full