

FACT SHEET: CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFACITS AND LEUKOENCEPHALOPATHY (CADASIL)

Before we go into detail about CADASIL, let's break down its complex name so that we understand what it means. Although complex the name is self-explanatory and gives an exact medical description regarding the location, mode of inheritance, causative factors and the pathological outcome.

Cerebral: relating to the brain; thus implying that other systems in the body are relatively unaffected

Autosomal dominant: a method of inheritance, whereby a single abnormal copy of a gene causes disease, despite the fact that the other good copy of the gene is present.

Arteriopathy: disease of the arteries, usually medium to small size arteries

Subcortical: relating to the portion of the brain immediately below the cerebral cortex. White matter and the deep gray structures constitute the subcortical region. They play an important part in most higher functions such as sensation, voluntary muscle movement, thought, reasoning, memory, etc.

Infarcts: areas of tissue that have undergone a type of cell death (called necrosis), as a result of loss of blood supply.

Leukoencephalopathy: a disease of the brain caused by damage to the white matter

What is the cause of CADASIL?

CADASIL is an inherited disorder caused by mutations in a gene called *Notch3*, which is a protein that is involved in determining cell fate during fetal development. For example, it might determine whether a particular cell will ultimately be a smooth muscle cell in the wall of a blood vessel, or it will be a liver cell. Post developmental function of *Notch3* includes maintaining the integrity of the arterial vessel wall.

Mutation in *Notch3* causes the arterial wall to disintegrate, which leads to a loss of blood supply in the region supplied by that blood vessel. The abnormal *Notch3* protein accumulates in blood vessels of the brain as well as in other parts of the body. The white matter and deeper parts of the brain are predominantly affected leading to infarcts.

CADASIL is an autosomal dominant disease, which means that a single abnormal copy of the *Notch3* gene overrides the other "good" copy, producing disease (see our *Genetic*

Inheritance fact sheet for more information). This means that if a parent is affected, every child of that parent has a 50% chance of having the disorder as well. If the child receives the abnormal copy, the child has a 100% chance of developing CADASIL.

What are the symptoms of CADASIL?

Initial symptoms of CADASIL, in the twenties or thirties, include migraine (a type of headache) and mood disorders, which may occur in 30-40% of patients. MRI abnormalities can be seen in the twenties and thirties as well. Strokes occur in the 40s and 50s. Over the next few decades as the disease advances, strokes and dementia are common symptoms. Death generally occurs 10-20 years after the onset of strokes and dementia.

The most common symptoms of CADASIL include:

- **Migraine with aura:** a migraine is a vascular headache resulting from changes in the sizes of the arteries in the brain. An aura refers to an abnormal sensation that the migraine is going to occur.
- **Psychiatric disturbance:** any number of mood disorders can occur as a result of CADASIL, including depression
- **Ischemic episodes:** Loss of blood flow to the brain, causing symptoms similar to those of a stroke
- **Cognitive deficits:** these might include deficits in memory, attention, multi-tasking and personality; the cognitive abilities generally decline as the disease worsens.
- **Progressive memory loss and dementia**
- **Multiple strokes leading to hemiparesis** (paralysis of one side of the body), walking difficulty and visual impairment.
- **Rarely, epileptic seizures**

How can CADASIL be diagnosed?

Currently, the most reliable method of diagnosis is sequencing the *Notch3* gene. This method can diagnose >95% of cases of CADASIL with certainty. The method involves a blood test sent to a specialized laboratory. Availability of the test result makes diagnosis of other family members relatively easy.

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Prior to availability of the gene tests, skin biopsy was used to diagnose CADASIL. A technique called electron microscopy was used to look for the characteristic accumulations of granular material (called granular osmiophilic material, or GOM) commonly seen in CADASIL. Presence of the material can positively diagnose CADASIL, though a negative result does not necessarily mean that the disease is not present. Additionally, a skin biopsy tissue can be tested for the accumulation of Notch3, using a molecule that specifically detects this protein. The accumulation occurs well before any symptoms and therefore it can be used to diagnose other family members. At this time, skin biopsy may be used to confirm doubtful cases.

Magnetic Resonance Imaging (MRI) may show characteristic alterations in the brain, but the alterations do not appear to be specific only to CADASIL. Therefore, brain MRI should not be considered as a single diagnostic tool.

How is CADASIL treated?

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.

Several medications are used to prevent migraine in patients who have frequent and/or severe migraine attacks and these should be used as recommended by the neurologist. Some examples of preventative medications are valproic acid, topiramate, gabapentin, propranolol and tricyclic antidepressants. Acetazolamide has been used in the past due to its property of dilating blood vessels.

Most neurologists agree to the use of low dose daily aspirin in patients with CADASIL. Aspirin is used in patients who have other risk factors for stroke such as diabetes and heart disease as a prophylactic (preventative) medication.

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.

Smoking and use of birth control pills are risk factors for stroke. We encourage patients with CADASIL to limit their use. Healthy lifestyle with adequate exercise and control of other risk factors for stroke such as high blood pressure, diabetes and high cholesterol are highly recommended.

Recently, a randomized trial that tested Donepezil (Aricept), a drug recommended for Alzheimer's disease, did not find it to be effective in CADASIL. However, some patients may benefit in terms of improved concentration and attention.

Other forms of supportive therapies such as physical therapy and speech therapy are instituted for rehabilitation from stroke.

Other Clinical Names for CADASIL

- Hereditary multi-infarct dementia
- Chronic familial vascular encephalopathy
- Familial disorder with subcortical ischemic strokes
- Agnogenic medial arteriopathy
- Familial Binswanger's disease

