



www.cadasil.co.uk

Cambridge CADASIL Clinic

What is CADASIL?

CADASIL is an abbreviation for a long name describing a rare heritable form of stroke (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy). The disease usually presents with multiple small strokes, but migraine can also be a prominent feature. CADASIL is caused by an abnormality (mutation) in a gene called NOTCH3.

What does genetic mean?

In many diseases genetic factors are important. This means that part, or all of the risk, is passed down from one's parents. Certain diseases are caused by an abnormality in one single gene and CADASIL is one of these diseases. Genes produce proteins, which are necessary for normal functioning of the body. Everybody has two copies of each gene, one passed down from their mother, and one from their father.



In CADASIL, an abnormality in one of these two copies results in the disease. We refer to this as autosomal dominant inheritance. A consequence of this is that if you have CADASIL, you have one normal copy and one abnormal copy of the gene. If you have a child, he or she will receive one copy of the gene from you, and one from your partner. Therefore there is a 50/50 chance that any child of yours will inherit the abnormal copy of the CADASIL gene and will be at risk of developing CADASIL.

What causes CADASIL?

We now know that CADASIL results from an abnormality in a gene known as *NOTCH3*. We think that the protein produced by the *NOTCH3* gene is responsible for communication between cells within the body, although much work is still required on this subject. We are beginning to understand how

the abnormalities in the *NOTCH3* gene result in CADASIL, but it will take a number of years before we fully understand this.

Although we don't fully understand the process, we do know that patients with CADASIL suffer from progressive damage within the small blood vessels. This is likely to lead to both reduced



CADASIL causes progressive damage of the small blood vessels in the brain (circled).

brain blood flow, and an inability of the blood vessels to regulate blood flow. Although abnormalities in blood vessels can be found throughout the body, they are most severe in the brain, and only produce problems noticed by the person with CADASIL within the brain.

What are the features of the disease?

Most people with the disease will suffer from strokes. These most commonly first occur in the 30s to 50s although we are discovering that the disease can be very variable, and in some people no problems may occur until their 60s. There are some individuals identified with CADASIL who remain well in their 70s. The strokes are what we refer to as lacunar strokes

(literally meaning a small lake or hole in the brain). Because they are small, they tend to be fairly mild and individuals often recover well. The most common type of stroke causes weakness affecting one side of the body. If recurrent strokes occur, this can lead to persistent disability which is most often arm or leg weakness, or slurring of the speech.



MRI brain scan showing small strokes (indicated by arrow) in CADASIL

Migraine is another common feature of CADASIL. This most commonly starts in the 20s but the age of onset is variable. Usually it is what we call 'complex' migraine. This means that, in addition to the headache, there are short-lived neurological symptoms, most commonly, some disturbance of vision, numbness down one side of the body, or speech disturbance.

Individuals with CADASIL can suffer from anxiety or depression. Not surprisingly, depression is very frequent after any type of stroke and usually improves with time, although treatment may be necessary. Occasionally, depression occurs before any other symptoms of CADASIL.

Rarely, seizures (fits) occur as part of CADASIL. Over time, as the disease progresses, cognitive (memory and other 'thinking') problems may occur most likely in the 50s or 60s.

An unusual feature is of the onset of confusion and reduced consciousness over a period of hours or days, sometimes with fever and seizures; this often follows a migraine attack. This is known as encephalopathy. It recovers completely over 1 to 2 weeks and appears to have no long-term effect on the course of the disease.

Investigations when CADASIL is suspected



1. Brain Scans

A magnetic resonance imaging brain scan (MRI) is usually performed shows and characteristic appearances abnormalities in with the deeper parts of the brain known as the white matter. Involvement of certain brain areas, including a region called the anterior temporal lobe, is a useful guide to the diagnosis. This is a safe scan that involves

no radiation but some people find it rather claustrophobic.





The characteristic involvement of the anterior temporal lobes (left, arrowed) and external capsules (right, arrowed) of the brain seen in CADASIL patients.

2. Genetic Testing

If we detect an abnormality on genetic testing, we can be 100% sure that someone has CADASIL. In CADASIL the abnormalities that occur are all within one gene which is called *NOTCH3*. However, this gene is made up of many thousands of building blocks (base pairs). In CADASIL, there is an abnormality (mutation) in only one of these. Testing for this can be a very time-consuming process. For this reason routine genetic testing of the whole gene is not always performed in CADASIL.

Most of the abnormalities tend to occur in certain parts of the gene and many laboratories only screen these parts of the gene. We have carried out studies to show that limited screening can pick up about 90% of *NOTCH3* gene changes in a UK population. However, increasingly with new technology laboratories are screening the whole gene to look for abnormalities.

If one member of a family has CADASIL, any other member of the same family who also has CADASIL will have exactly the same underlying genetic abnormality. Therefore, once we've found the underlying abnormality within a particular individual, it is relatively easy to determine whether other family members are affected or may become affected in the future.

3. Skin Biopsy

CADASIL results in characteristic changes in the blood vessels. For obvious reasons it is difficult to look at the blood vessels within the brain. However even though CADASIL itself only produces symptoms within the brain, abnormalities within the blood vessels can be seen elsewhere in the body. The easiest place to look for these is in the skin. A very small skin biopsy is performed using local anaesthetic. This can be carried out as a day case or outpatient procedure.

Because we now carry out more extensive genetic testing, we tend to only perform skin biopsy if the genetic testing has been negative and the diagnosis is still uncertain.

It is important that the skin biopsy is processed in a special way allowing it to be looked at under high magnification

using an electron microscope. Under this magnification, in patients with CADASIL, one can frequently see abnormal collections of material called GOM (Granular Osmiophilic Material).



Granular Osmiophilic Material (GOM) observed on skin biopsy, indicated by arrows.

Is there any treatment for CADASIL?

There is no specific treatment for CADASIL available at the moment. In the long run, we hope that a better understanding of how the underlying genetic abnormality causes CADASIL will allow us to discover how this results in the blood vessel damage, and lead to the development of drugs to prevent this damage. However, this is likely to be a number of years away.

Aspirin has been shown to reduce the risk of recurrent stroke by about 20% for common stroke. Therefore although it has not been tested specifically in CADASIL patients most doctors would recommend that patients with CADASIL take a small dose of aspirin (75-300mg/day). An alternative to aspirin is clopidogrel (75mg/day) which has been shown to be very slightly better at preventing stroke than aspirin. We avoid warfarin, unless required for another medical reason, as this can increase the risk of bleeding within the brain in people with CADASIL.

Recent studies have shown that other risk factors for common stroke such as smoking and high blood pressure are associated with earlier onset of stroke and increased rate of damage on MRI brain scans in CADASIL sufferers. Therefore it is important to address these common stroke risk factors. It is important not to smoke, and that blood pressure and cholesterol are checked and treated if abnormal. It is also advisable not to take the combined oral contraceptive pill or hormone replacement therapy (HRT) as these can increase the risk of blood clotting and could increase stroke risk.

If required during attacks of migraine, standard migraine painkillers can be taken. These include drugs such as Migraleve. However, it may not be advisable to take some of the newer anti-migraine drugs such as Imigran, which act by reducing the blood flow to the brain, although the patients we have seen who have taken these before the diagnosis was made do not seem to have suffered problems in our experience. If migraine attacks are frequent then normal migraine prevention therapies seem effective.

It is important to look for, and treat when necessary, depression in patients with CADASIL. This can be treated with standard anti-depressant drugs and cognitive behavioural therapy.

Should other members of the family be tested for the disease?

For the reasons explained above, if one member of a family has CADASIL, there is a 50/50 chance that close relatives will also be at risk of the disease. If the underlying genetic abnormality is known it is relatively simple to look for it in other family members. This will allow us to be 100% sure whether or not an individual carries the CADASIL gene, and is at risk from the disease. Before testing family members for CADASIL, it is very important that a careful discussion of the pros and cons is carried out. This is usually performed by a genetics counsellor. The knowledge that a healthy person is likely to develop CADASIL can obviously be very distressing, and it is possible that it could influence a number of factors including things such as life insurance. Therefore we would normally only test other family members if they are absolutely certain that this is what they want. It would be extremely unusual for us to test children.

A potential advantage of being tested for the disease is that if you are having children it is possible to determine whether the foetus carries the disease. If you have the abnormal gene, any children you have also have a 50/50 chance of having the abnormal gene. However, if the abnormal gene has not been passed to you, neither you nor your children are at risk.

If tests do show that you have the abnormal gene, it is now possible to determine whether the baby has a genetic abnormality fairly early in the pregnancy. If you wished, if the abnormality was present, you could then have a termination. This testing is very similar to the testing which is provided for Down syndrome. For some people this raises important ethical issues, and individual people have different views on how they would like to address these. It is now becoming possible to select embryos which are free from genetic diseases such as CADASIL before implantation. This process involves IVF. This means that an embryo without a CADASIL mutation can be selected and therefore prenatal testing does not rely on termination. This technology is only offered in a few places and is not yet widely available on the NHS. If you are keen on having such genetic testing during pregnancy, it is very important that you discuss this well before you plan to become pregnant.



Cambridge and CADASIL

At Cambridge we have a particular interest in CADASIL. We have a research programme and run a clinical service for patients with CADASIL.

A) Research

We have an active research programme in CADASIL. If you attend our clinic we may ask you whether you would like to take part in research studies. If you are interested, we will explain the specific details of any individual study and it is always entirely up to you as to whether you take part. Before we plan any study, it is always approved by the local hospital ethics committee.

Funded by a National Health Service Research & Development grant we carried out a British CADASIL prevalence study to find out how common CADASIL is in Great Britain. This showed it had been underdiagnosed. We have identified brain imaging (MRI) features which are now widely used to diagnose the disease. We worked out the best way to screen for the disease using genetic tests in the UK population and then set up testing available to all NHS patients via the South West Thames Genetics unit based at St George's.

More recently we have been involved in studies looking at why the disease is so variable between different CADASIL sufferers, and have shown that smoking is associated with earlier onset of stroke. We have also been involved in a trial of CADASIL looking at whether the drug Donepezil helps patients with memory impairment. Results from this study did not show a significant benefit of taking the drug. We are currently looking at genetic factors which may determine why the severity of the disease is so different between different people.

If you wish to support our CADASIL research, donations can be made to the "University of Cambridge (CADASIL fund)" and sent to Professor Markus at the address at the end of the leaflet. You can also donate directly via this website (www.cadasil.co.uk)

B) Clinical Service

At Addenbrooke's Hospital in Cambridge we have a CADASIL clinic at which we see patients suspected of having CADASIL, or family members who wish to have genetic screening. Referrals can be made by your neurologist/stroke physician or your GP to the address at the bottom of this page.

If you only want to organise genetic testing then this can be organised directly with a number of molecular genetics labs. These include the Department of Molecular Genetics, St George's Hospital, London.

How can I find out more information about CADASIL?

Because CADASIL is a rare disease, and because much of the information on it is very new, it is quite difficult to access accurate information. Some of the information found on the internet is misleading or incorrect. The website **www.cadasil.co.uk** is a reliable source of information for patients and relatives alike. On this site there is a wealth of information written in lay language along with links to other helpful websites.

One further site which gives details about medical aspects of CADASIL is: http://www.geneclinics.org/profiles/cadasil. This site is maintained on a regular basis so information found there should be up to date.

We are always happy to see patients and members of families with CADASIL at the Cambridge CADASIL clinic- see above or go to www.cadasil.co.uk for further information.

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For information about the Cambridge CADASIL clinic, or to download copies of this leaflet, visit **www.cadasil.co.uk**