CADASIL Conference at Addenbrooke's Hospital, Cambridge, 30 June 2017

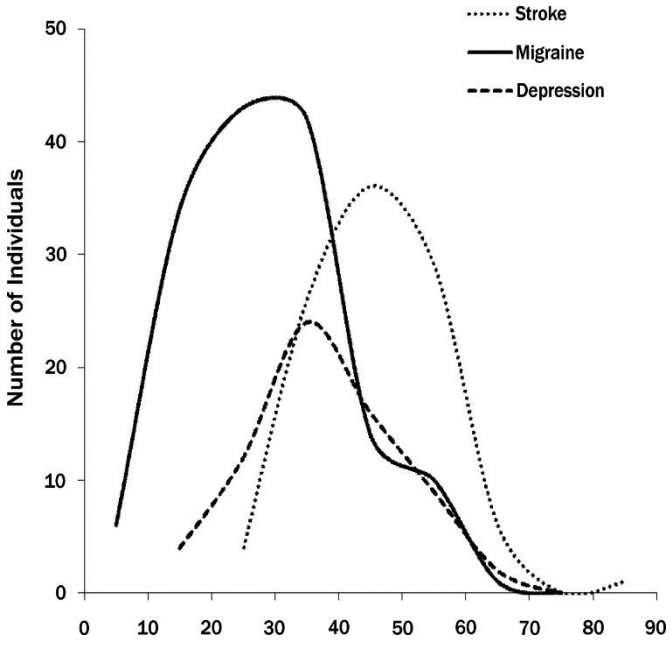
These notes on the medical aspects of CADASIL were made for personal use and are not in any way official. They are intended to capture the main points of the conference from a patient standpoint. Relevant web links have been added in several places.
Phil Jones, 7 July 2017

What is CADASIL? What are the symptoms and treatments?

- CADASIL is a monogenic condition – caused by a mutation in a single gene (as distinct from a polygenic condition, which is dependent upon the simultaneous presence of several genes).
- It's a small (blood) vessel disease associated with a constellation of symptoms (*e.g.* recurrent stroke, migraine, depression, and cognitive impairment progressing to dementia).
- It's autosomal dominant (*i.e*. if a child inherits the mutated gene from just one parent, the child will have the condition).
- If one parent has the condition, then each child has a 50% chance of inheriting it too.
- At a genetic level, the condition is caused by the loss or gain of a cysteine[1] residue, resulting in an uneven number of cysteine residues within epidermal growth factor–like domains of the Notch3 gene. Currently, it's not clear why an uneven number of cysteine residues causes the effects that it does.
- Evidence of damage to small blood vessels may be detected throughout the body, but symptoms only occur within the brain.
- "Perforating arteries" within the brain are where effects are generally observed.
- Over 400 cases have been found within the UK, suggesting a frequency of occurrence of around 1 in 100K. But it may be higher than this, perhaps around 1 in 50K worldwide.
- Migraine is a common feature of the condition, often with associated neurological symptoms such as visual disturbance, numbness down one side of the body or speech impairment. These neurological symptoms are generally short-lived.
- The condition affects cerebral white matter. (White matter connects the various grey matter areas of the brain.)
- CADASIL affects a different part of the brain to that associated with Alzheimer's disease, and the symptoms are different.
- Evidence indicates that CADASIL patients who smoke typically experience stroke about 10 years earlier than would otherwise be the case.

[1] Cysteine is an amino acid, a building block for proteins.

- A graph was presented – similar to the one shown here – showing the age distribution of some CADASIL effects.
- Control of hypertension (high blood pressure) is very important.
- Exercise, control of weight, healthy nutrition and control of cholesterol levels may all help to slow down the rate of progress of the condition. A Mediterranean diet seems to be particularly beneficial in protection against stroke. A healthy mind in a healthy body seems to be advantageous.
- Aspirin has not been tested specifically in CADASIL patients, but does reduce the risk of recurrent stroke in common stroke patients. Most doctors would therefore recommend a small daily dose (typically 75mg a day). An alternative is Clopidogrel (75mg a day), which is very slightly better at preventing stroke.



Source: http://stroke.ahajournals.org/content/41/4/630

Questions and answers (NB. Some Q&As were posted separately)

- Why do some people remain well, even into their seventies, whilst other do not?

  Severity can vary significantly within the same family. We don't really know why this is, but it may be because of the modulating effects of other genes. This is something currently being investigated, in collaboration with researchers elsewhere in Europe.

  Differences in smoking habits and blood pressure account for some of the variation, but not all.

- How can one tell the difference between migraine and TIA's[2] or stroke?

  Often, it's a matter of looking for clues in how symptoms present. A stroke will typically occur very suddenly, perhaps with several symptoms occurring all at the same time. There may be a sudden weakness down one side of the body.

  A migraine will typically occur more slowly, with a gradual spread of bodily symptoms. "Productive aphasia", an inability to find the correct words (as distinct from an inability to

[2] Transient Ischaemic Attack: a "mini stroke" caused by a temporary disruption in the blood supply to part of the brain.

pronounce some words) would indicate migraine rather than stroke. If the patient is young, that would probably indicate migraine.

- What about pre-natal testing for CADASIL?

  There are two possible approaches:

  (1) If a patient is already pregnant, a small sample of cells can be taken from the placenta and tested. Alternatively, a sample of amniotic fluid can be taken and tested. If the CADASIL mutation is found, termination of the pregnancy is an option.

  The implications and risks of taking such a test is best discussed beforehand with your GP or local Clinical Genetic Service.

  (2) A more recent test, known as "pre-implantation genetic diagnosis" (PGD) involves IVF[3] treatment. Several embryos are developed until they reach the stage where they each contain about eight cells. One of these cells would be tested for the CADASIL mutation: if the mutation is found, that embryo would not be implanted.

  The availability of this option varies across the UK. Up to three PGD tests for one pregnancy may be funded by the NHS, but this will depend on where you live. Age and BMI (body-mass index) limitations may also apply.

  More information on pre-natal testing can be found at:
  http://www.cambridgestroke.com/prenataldiagnosis.php

- Should I convince my family to be tested?

  Different people cope with uncertainty in different ways, so what is appropriate for one person may not be appropriate for another. But it is perhaps important for individuals to be aware if the condition exists within a family, because individuals can then reach a decision that is appropriate for them.

  There are several psychological and emotional consequences of genetic testing and it may be helpful to consider these before going through the procedure.

  More information on genetic testing can be found at:
  http://www.cambridgestroke.com/genetictesting.php

- Can CADASIL cause problems with gait?

  Yes, connection problems within the brain can cause difficulty with walking, sometimes called "gait apraxia" – but it's not that common.

- Can CADASIL cause problems of dizziness?

  The difficulty with dizziness is that there are lots of possible causes (e.g. low blood sugar, labyrinthitis, viruses) but – yes – it can be a symptom.

[3] In-vitro fertilisation: a process of fertilisation whereby an egg is combined with sperm outside the body, in vitro ("in glass").

- Is CADASIL related to deep vein thrombosis?

  No. Thrombosis is a condition of large blood vessels. CADASIL is a condition of small vessels.

- How often should one have an MRI?

  With a normal MRI scan, changes are often not detectable within a 4-year time-frame.

- Is it possible to donate one's brain for research?

  Yes. Access to brain tissue is important, because it's possible to analyse it in ways that are not possible with an MRI scan. The donation of post-mortem brain tissue is an important aid in the further understanding of disorders and their treatment.

  More information on the Cambridge Brain Bank can be found at:
  http://www.cuh.org.uk/for-public/cambridge-brain-bank

CADASIL research

There's a lot of research going on. Some examples are shown below:

- *Cognitive testing*

  Current cognitive testing is based on tests appropriate for Alzheimer's disease. In CADASIL, it's more appropriate to focus on planning, multi-tasking and processing speed, so new tests are being developed.

  A Brief Memory and Executive Test (BMET) has been devised to detect the cognitive deficit seen in patients with cerebral small vessel disease. It's been designed for use by clinicians and researchers, but can be accessed by anyone via the Cambridge website:

  http://www.cambridgestroke.com/bmetcognitivetesting.php

- *The prevalence of apathy in patients*

  Apathy (loss of motivation) is a common feature of CADASIL, and can be a particular problem for families of CADASIL patients. Funding has been obtained from the Stroke Association for more research into this aspect of CADASIL.

  More information can be found at: http://www.neurology.cam.ac.uk/neurology-unit-research-groups/stroke-research-group/clinical-studies/apathy-and-outcome-after-stroke

- *The prevalence of encephalopathy in CADASIL*

  Sometimes referred to as "CADASIL coma", encephalopathy is a less common presentation of CADASIL. Symptoms can include confusion, fever, seizures, hallucinations and coma. Patients presenting with such symptoms risk being misdiagnosed as suffering from conditions such as meningitis or viral encephalitis. Research was commissioned in 2016 in the hope of understanding the condition and developing treatments for those affected.

More information can be found at:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911105/

and at:
http://www.hra.nhs.uk/news/research-summaries/familial-cerebral-small-vessel-disease/

- *Migraine and its treatment*

  Migraine is common in CADASIL, but the efficacy of treatment, and its relationship to stroke risk, is unclear.

  It was previously thought that triptans (drugs commonly used to treat migraine) were contraindicated in patients with stroke or TIA (*i.e.* CADASIL patients), because of the theoretical risk that they might exacerbate cerebral ischaemia; but a recent study found no evidence of this. So established views on this may be changing.

  More information can be found at:
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911105/

- *The possible beneficial effects of historically low blood pressure in patients*

  How exactly do blood vessel abnormalities damage the brain? Does low blood pressure early in life confer enduring beneficial effects? A new, ultra-high field strength, 7 Tesla (7T) MRI scanner will give researchers a better understanding of what's going on within the brain, by providing enhanced imagery of perforating arteries.

- *Blood-brain barrier permeability in cerebral small vessel disease*

  The blood-brain barrier is the lining of the brain blood vessels that separates them from the brain structures. Research is taking place to see whether leakiness of the blood-brain barrier is important in cerebral small vessel disease. If it is, might we be able to switch this leakage off?

  Might leakage be taking place near the edges of white matter regions? And what role might inflammation play in all this? Might it be possible to use drugs to prevent localised inflammation and therefore prevent this leakiness from occurring?

  MRI can be used to image this leakiness, whilst PET[4] imaging is used to investigate the inflammation.

- *The development of mouse models in order to understand changes at a molecular level*

  The process by which genetic mutation leads to CADASIL remains unclear. If the process could be more clearly understood, then there's a better chance of developing treatments. By inducing the CADASIL genetic mutation in mice, research has suggested that brain damage might be caused by an inability of the blood vessels to regulate blood flow normally – and hence to brain damage following a shortage of blood (and oxygen) supply.

  If this proves to be correct, might we be able to slow the process down?

[4] Positron emission tomography

More information can be found at:
http://www.cambridgestroke.com/anewanimalmodelforcadasil.php

- *The possible application of genetically-based therapy*

  Gene therapy is a possible avenue of treatment – either at the pre-implantation stage in the context of IVF, or perhaps even after birth. This might involve replacing the mutated genetic code sequence with the "normal" genetic sequence.

  Given that NOTCH3 mutations are caused by an uneven number of cysteine residues, might it be possible to employ genetic techniques to correct this cysteine anomaly? Research into this is currently at the "proof-of-concept" stage, so a definitive answer is a long way off.

  More information can be found at:
  https://www.ncbi.nlm.nih.gov/pubmed/26912635

- *The use of stem cell research in order to model blood vessel cells and cells of the blood-brain barrier so that drugs can be tested for their effectiveness*

  Current research is focussing on investigating human stem cell development as a possible route to developing relevant therapies. The work involves using patient-derived human induced pluripotent stem cells.[5] It's possible to transform such cells into those normally found in vascular smooth muscle. If the cells have been derived from a CADASIL patient, then these cells will have the same abnormalities as those found in CADASIL patients. This process is sometimes referred to as creating "a disease in a dish".

  This technique could help speed up the process of drug testing, and hence the possible discovery of effective therapy.

  More information can be found at:
  https://www.medschl.cam.ac.uk/research/research-themes/stem-cells-and-regenerative-medicine/

- *Telemedicine*

  Telemedicine involves a consultation using a video-call service, such as Skype. It allows patients to have follow-up consultations from their own home, eliminating the need to make long journeys to attend a specialist clinic.

  At Addenbrooke's, a telemedicine trial has been funded for two years. Feedback so far has been very positive from both staff and patients, and so it's hoped that the service will be made part of usual NHS care in due course.

  More information can be found at:
  http://www.cambridgestroke.com/telemedicine.php

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[5] An "induced pluripotent stem cell" is a human cell that is genetically modified to behave like an embryonic stem cell. These cells are pluripotent, meaning that they have the potential to transform into any adult cell type.