CJD SUPPORT NETWORK

# Genetic CJD

Genetic CJD (previously called familial CJD and sometimes referred to as inherited CJD) is an inherited form of Creutzfeldt-Jakob disease, which belongs to a group of rare, and always fatal, brain disorders called the prion diseases. These occur in both humans and animals, and include BSE and scrapie in animals.

## Introduction to genetic CJD

CJD is caused by the accumulation in the brain of an abnormal form of a protein called a "prion protein". PrP can exist in two forms – normal ($PrP^{C}$) and abnormal ($PrP^{Sc}$). We all have normal $PrP^{C}$ in our brain. The abnormal prion is different because it is folded in a different way and has a different shape to the normal. Abnormal prion protein can cause normal prion protein to change shape and become abnormal. This leads to a chain reaction which, in turn leads to damage of brain cells

**Microphotograph of spongiform change in brain tissue taken from a person with CJD**



Genetic CJD accounts for around 15 per cent of all cases of CJD. There are fewer than five new cases occurring in the UK each year. Like the other forms of CJD, genetic CJD is characterised by dementia (mental decline with symptoms such as memory loss) and neurological problems such as unsteadiness. The brain of someone with genetic CJD will also show the spongiform change which is the hallmark of all forms of CJD - the brain tissue has a spongy appearance when viewed under a microscope.

Genetic CJD is caused by a genetic mistake where a mutation in the PrP gene seems to make the conversion into the abnormal form more likely. Several different mutations have now been identified. There are also two other, even rarer, inherited brain diseases which resemble genetic CJD. These are Gerstmann Straussler Scheinker disease (GSS) and fatal familial insomnia (FFI). Like genetic CJD, they are associated with mutations of the PrP gene. The distinction between these different forms of disease (GSS, FFI and genetic CJD) is partly historical and currently many experts tend to class these diseases together under 'genetic prion diseases'.

## Inheriting a risk of CJD

We all inherit two copies of the PrP gene – one from our mother, and one from our father. Genetic CJD, GSS and FFI are all inherited in an autosomal dominant fashion. That is, you need to possess just one mutated copy of the PrP gene to develop the disease. A person carrying the mutated gene has a 50 per cent chance of passing it on to each child. Since CJD does not usually strike until later in life, people carrying the gene may not realise that they may have passed it on to their children, although they may well be aware of a problem with neurological disease within the family.

However, before CJD was recognised as a well as it is now, and before diagnostic tests were available, some family members may have been wrongly diagnosed as having a psychiatric illness or maybe some other neurological disease such as Huntington's chorea or another type of dementia.

Research on genetic CJD in the UK found that one third of affected families report a history of dementia and another third a history of CJD itself. The remaining families have no history of any similar disease. Given the fact that genetic abnormalities are inherited, it is not entirely clear why some individuals with genetic disease have no family history of the disease. However, one possible explanation is that new mutations in the gene can arise in individuals. The majority of affected families remain unaware of their risk of developing CJD.

## How CJD can be transmitted

CJD is unique in that it can be both inherited and transmitted. However, it is not infectious in the usual way, as the causative agent is not a bacteria or a virus. The only way that the disease could be transmitted from someone with genetic CJD is if infected tissue (mainly the brain) is passed into the body of someone else. This has happened on a few occasions in the past when, unknowingly, contaminated surgical instruments were re- used, giving rise to so-called iatrogenic cases of CJD. Those identified at an increased risk of CJD, including people with a family history of genetic CJD are asked not to give blood to minimise any potential risk to public health.

## Symptoms of genetic CJD

The symptoms of the genetic form of CJD vary, largely depending on the type of PrP mutation involved. However, there may even be great variation in the symptoms within affected members of the same family who all have the same mutation. Sometimes the symptom pattern is similar to that found in sporadic CJD, namely:

- Initially, depression, memory lapses, maybe unusual fatigue
- Within weeks, unsteadiness and lack of coordination (cerebellar ataxia) and dementia.
- Difficulties with speech and/or swallowing
- Sudden jerky movements, rigid limbs, maybe blindness and incontinence.

Genetic CJD often strikes at an earlier age than the sporadic form: the average age of onset is 52, compared to 65. The course of the disease is also longer, and the patient may survive for several years after the onset of symptoms.

## Symptoms of GSS and FFI

GSS usually starts with cerebellar ataxia and progresses to dementia. The patient may survive for several years.

In FFI the main symptom is a progressive and untreatable form of insomnia. FFI differs from the other prion diseases in that brain damage is mostly confined to the thalamus, the area which is involved in relaying information to and from the brain, and plays a part in controlling sleep-wake cycles. Eventually FFI leads to a complete breakdown of the brain's control of bodily functions, coma, and death.

## Genetic testing and diagnosis

Mutations in the PrP gene can now be detected via a blood test. People with a relative who has or had CJD could therefore opt to find out whether they are at risk before any symptoms develop.

In most (but not all) cases, if the mutation is found the affected person is certain to develop the disease. Furthermore, it may also be possible to tell, from the form of the PrP gene carried, whether the person is likely to have early or later onset disease. Obviously, undergoing PrP gene testing is a serious matter because, at present, there is no way of preventing or curing CJD. So testing should not be done without the full consent of the person involved, and full pre and post test support and counselling by specialist staff. The results will have an impact on other family members, and they should also be involved in discussions.

Antenatal testing where a foetus is at risk of carrying a PrP mutation is also possible. This gives the couple a chance to opt for termination, and so avoids passing the disease on. But this also involves a difficult ethical decision – for a child born carrying a mutated PrP gene is likely to enjoy normal health for many years before the onset of disease. Mutations in the PrP gene are not seen in other forms of CJD.

For people with symptoms of genetic CJD, the investigations are the same as for any other prion disease. However, in addition, a simple blood test should confirm the presence of a PrP gene mutation. EEG often but not always shows characteristic changes. Magnetic Resonance Imaging (MRI) will be done to eliminate other conditions such as a tumour. Blood and other biochemical tests are likely to be normal. The only definite diagnosis comes, as with sporadic CJD, by examining the brain for spongiform change after death. However, in the case of inherited prion disease, the family history of neurological disease will be a very important pointer in the diagnosis.

The diagnosis of CJD often takes time, due principally to the lack of a simple straightforward diagnostic test. It is important to stress that a number of neurological conditions can look very similar in the early stages and it is important, on occasions, to see how the illness develops over time before making a definitive diagnosis. In addition, clinicians do not wish to perform unnecessary distressing investigations on individuals. This time to make diagnosis can be a very distressing period for the family, particularly as their relative or friend may be deteriorating very rapidly. It is important that clinicians support families and friends through this difficult period and additional support is available from organisations such as the CJD Support Network.

## Is there a cure for genetic CJD?

At present (January 2008), there is no proven treatment for CJD. However, there are a number of possible treatments being investigated in the laboratory. One potential treatment, Quinacrine, has been assessed (Prion-1 Trial funded by the UK Medical Research Council and co-ordinated by the London National Prion Clinic). Entry into this trial ceased in 2006. Another possible treatment, Pentosan Polysulphate (PPS), has been given to a number of CJD patients on an individual basis. This needs to be administered directly into the brain and therefore the treatment involves a neurosurgical operation. The Medical Research Council (MRC) commissioned a review of these individuals who have received PPS. Further information about possible treatment development can be obtained from the MRC and the National Prion Clinic.

## Support and care

There are a number of drugs which can relieve some of the symptoms of the illness and make the patient more comfortable – for example, treatments for psychiatric symptoms, pain and the jerking movements.

General support and care for the patient, family and friends is equally important. Social services should be involved in an early stage to advice on financial matters, respite and long term care. Various therapists – including speech and language therapists, physiotherapists and occupational therapists – will provide help with specific problems. Community nursing may provide more general nursing care outside of hospital.

There is now a national care package based at the National CJD Surveillance Unit in Edinburgh that provides advice and support for individuals with CJD, their families and also local health professional. The national care package is able to provide help with organising care and, in certain circumstances, with funding of this care.

What happens on admission to hospital varies. Much depends on the type of hospital, the particular type of patient and the views of the family. Following admission there will be investigation and tests to establish the diagnosis and general supportive care.

## Notification

The Chief Medical Officer has requested that individuals suspected of having CJD should be notified to two research organisations, the National CJD Surveillance Unit and the National Prion Clinic. Involvement with these research organisations is entirely voluntary for the patients and their families. Aside from their research functions, these organisations are able to provide additional information, help and advice.

## Research

There is much research underway into the causes of CJD and potential treatments. For instance, it may be possible to develop drugs to stop the conversion of normal PrP into prions, or to turn off the PrP gene. The function of PrP is unknown and laboratory animals have been shown to survive quite well without it.

## Glossary

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| **Cerebellar ataxia** | **Shaky movements, unsteady gait and clumsiness caused by damage to the cerebellum – a part of the brain which controls movement and balance.** |
| **Myoclonus** | **Jerking movements of the limbs caused by sudden muscle spasms.** |
| **Akinetic mutism** | **A state of complete physical unresponsiveness caused by damage to the base of the brain.** |
| **Spongiform change** | **Brain damage characterised by a spongy appearance of brain tissue seen under a microscope.** |
| **Encephalopathy** | **Any disease in which the overall functioning of the brain is impared** |

## Further information and Contacts

Further information about CJD may be found on the CJD Support Network website at *www.cjdsupport.net* and in the booklet "CJD and Prion Disease" obtainable on the website and from the Network.
Support and information may be obtained from the organisations below.

**CJD Support Network**
**Helpline:** 01630 673 993

**CJD Support Network**
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**National Prion Clinic**
Po Box 98
National Hospital for Neurology
and Neurosurgery
Queen Square
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Tel 0207405 0755 (direct line)
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**National CJD Surveillance Unit**
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