

Iatrogenic CJD

Iatrogenic CJD (iCJD) is a form of Creutzfeldt-Jakob disease, which belongs to a group of rare, and always fatal, brain disorders called the prion diseases. This form of CJD arises from contamination with tissue from an infected person, usually as the result of a medical procedure.

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 cell.

The first indication that human prion diseases might be transmissible through infected tissue came with the discovery of a strange disease called kuru among the Fore people of Papua New Guinea in the 1950s. Kuru mainly affected women and children, and began with unsteadiness of gait, shakiness and lack of co-ordination. Behavioural changes followed, although dementia was unusual (making it different from sporadic CJD). Eventually the patient would become unable to move and death would follow, usually within a year of onset of symptoms. The brains of these patients showed severe damage to the cerebellum, the part of the brain which controls movement. There were also spongiform changes (characteristic of prion disease) where the brain tissue has a spongy appearance when viewed under the microscope. A further feature was the appearance of small deposits called plaques within the brain tissue, distinguishing kuru from CJD, where plaques only occur in a minority of cases.



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

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Kuru was eventually linked to the funeral practices of the Fore people, in which it was common for the women and children to handle the body of their dead relatives, including the brain. Whether they practiced cannibalism, as has been widely reported, and actually ate the brain is not known. But if just one member of the tribe had sporadic CJD, any woman or child handling brain tissue could have been contaminated by it merely through scrapes or scratches on their body. Since the victims of kuru went on to be given these funeral rites, the disease perpetuated itself.

Our first awareness of prion diseases

Kuru is almost extinct now, since the Fore people were persuaded to abandon their funeral rites from around 1959. However, since the time from infection to the onset of symptoms is between three and 40 years, there is still the occasional case occurring in older people.

Kuru has been of great importance in helping us to understand the human prion diseases, and in particular the risks of their being transmitted from person to person.

Transmission of CJD by surgery

Brain tissue from a person with CJD contains an abnormal form of a protein called PrP. If this abnormal form comes into contact with normal PrP, which is present in the brains of uninfected people, it can change it into the abnormal form and thereby transmit the disease.

Unless certain precautions are taken, some medical procedures carry a risk of transmitting CJD. For instance, a few people have contracted CJD from brain operations with instruments which were previously used on someone with CJD. In these cases, the infection was delivered intracerebrally, that is, directly into the brain. The prion agent survives the disinfection procedures which normally destroy bacteria and viruses - but this was not known at the time. Now all instruments which have been used on the brain of someone with suspected CJD are destroyed.

Intracerebral transmission of CJD has also occurred with corneal transplants and with grafts of dura mater, the tough membrane which covers the brain, and is used in various kinds of surgery. The incubation time for intracerebral iatrogenic CJD is 19 to 46 months.

Transmission with Human growth hormone

CJD has also been transmitted by treatment with human growth hormone. This is known as peripheral transmission because the route to the brain of the infective agent is through the circulation, not direct into the brain. Human growth hormone, which is used to treat children with short stature, was prepared from human pituitary glands, its natural source. Typically 2,000 glands would be pooled to make one batch of growth hormone which, would be split into many hundreds of doses and distributed. Therefore the inclusion of just one gland from someone with CJD had the potential to infect many people. To date 1,900 people have been treated with this form of growth hormone in the UK and there have been 54 cases of iCJD from 1985 to 2008 arising from this cause. The incubation time for peripheral iatrogenic CJD is longer than for the intracerebral form, and is more like Kuru (itself a peripherally transmitted disease) being in the order of around 15 years. This means there could be more growth hormone related cases to come. Growth hormone is now made synthetically, so there is no longer a risk of iCJD from this treatment.

Risk through blood transfusion

Blood was always thought to be a theoretical risk, but on the 17 December 2003, Health Secretary, John Reid, gave the news to the House of Commons that a patient had died of vCJD after receiving a blood transfusion from a donor who was subsequently found to have developed the disease.

Since that date two further patients have died of vCJD as a result of contaminated blood. One other patient died of an unrelated condition, but on post mortem it was established that abnormal prion protein was present in the body, thought to be as a result of a blood transfusion. It is now understood that blood is a very efficient carrier of vCJD.

As we do not know how many people who live in the UK are incubating vCJD and as there is no available screening test for blood, certain precautionary measures have been put in place in an attempt to protect the national blood bank.

- Withdrawal and recall of any blood components, plasma derivatives or tissues obtained from any individual who later develops vCJD (December 1997).
- Import of plasma from the US for fractionation to manufacture plasma derivatives (announced May 1998, implemented October 1999).
- Leucodepletion of all blood components (announced July 1998, implemented Autumn 1999).
- Importation of clinical FFP from the US for patients born on or after 1 January 1996 (announced August 2002), implemented spring 2004.
- Promotion of appropriate use of blood and tissues and alternatives throughout the NHS.
- People who have received a blood transfusion since 1980 are no longer able to donate blood.

When a person is diagnosed with CJD, their health history is examined to see if they have had surgery or donated blood in the past. The risk to public health is determined and anyone who is identified to be at a increased risk of contracting CJD, through for instance, a blood transfusion, is informed via their GP.

Receiving this information, can be very distressing. Support and advice can be sought from the person's GP or agencies such as the CJD Support Network and those listed at the end of this fact sheet.

Risk through Organ transplant

The risk of contracting CJD from organ transplants is uncertain, but believed to be small. A woman later shown to have been suffering from CJD did provide material for three eye operations (cornea and sclera). Unfortunately, a transplant usually has to be done before a full post mortem, so this risk cannot be completely eliminated. However, it will usually be known if a potential donor is suspected of having CJD. In the vast majority of cases, the benefit of having the transplant far outweighs the risk of CJD.

Ways CJD cannot be transmitted

It is important to realise that CJD is not infectious in the usual way -by airborne droplets, like colds and flu, or by skin contact, or by blood or sexual intercourse, like HIV. Therefore there are no special risks from normal contact with a person with CJD.

Inherited risks

As with sporadic CJD, there appears to be a genetic predisposition to contracting iatrogenic CJD. We all have two copies of the PrP gene, one from our mother and one from our father. These copies can exist in two different forms; people who inherit two identical forms appear to be at greater risk. It may be that this form of PrP is more susceptible to changing into the abnormal form.

Symptoms of iatrogenic CJD

Where transmission is intracerebral, the symptoms are like sporadic CJD:

- Initially, depression, memory lapses, maybe unusual fatigue. However, rapid progression to dementia and obvious neurological symptoms distinguish CJD from depression.
- Within weeks, unsteadiness and lack of co-ordination. (Sometimes these symptoms are the first to appear)
- Sudden jerky movements, rigid limbs, maybe blindness and incontinence.
- Difficulty in speaking and swallowing.
- Eventually the patient loses the ability to move or speak, and will need full-time nursing care.

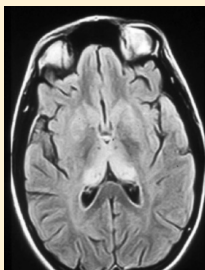
Peripherally acquired CJD is more like kuru:

- Symptoms of ataxia (unsteadiness and lack of co-ordination) predominating, and dementia being a rare feature.

Diagnosing CJD

As at January 2008, there is no absolute test for CJD. A definitive diagnosis is currently only possible by post-mortem examination of the brain for spongiform change. Plaques are commonly seen in growth hormone related CJD.

All GPs should be aware of CJD, although most of them will never have seen a case. A prompt referral to a neurologist should follow the reporting of any suspicious pattern of symptoms, where a number of investigations will be carried out including:



MRI scan of vCJD patient (Pulvinar sign)

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- **Magnetic resonance imaging (MRI)** This scan produces an image of the brain. It is mainly useful for ruling out other conditions such as a brain tumour. However, in some cases, a characteristic abnormality may be present, which aids diagnosis in all forms of CJD
- **Electroencephalogram (EEG)** may show characteristic changes present in non-specific brain disease
- **Lumbar puncture** The presence of a particular proteins, particularly 14-3-3 in the cerebrospinal fluid may be helpful in diagnosis.
- **A brain biopsy** (taking a sample of brain tissue) may be done to look for evidence of spongiform change, which would be diagnostic of sporadic CJD. This would only normally be carried out in specially selected cases, often to exclude CJD from a diagnosis.
- **Blood and other biochemical tests.** As at January 2008, there is no specific blood test for CJD

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.

The symptoms of vCJD

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 on 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.

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 abnormal 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

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 impaired

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
Gillian Turner
National CJD Co-ordinator
CJD Support Network
Po Box 346
Market Drayton
Shropshire TF9 4WN

Tel/fax 01630 673 993
www.cjdsupport.net
Email Info@cjdsupport.net

National Prion Clinic
Po Box 98
National Hospital for Neurology
and Neurosurgery
Queen Square
London WC1N 3BG
Tel 0207405 0755 (direct line)
Fax 020 7061 9889
www.nationalprionclinic.org
email help.prion@uclh.org

National CJD Surveillance Unit
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Tel 0131 537 1980 (Pathology)
Tel 0131 537 2128 (Clinical office)
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