

CJD and prion disease

An introduction and explanation

About the CJD Support Network

The CJD Support Network is the leading care and support charity for all forms of CJD. The CJD Support Network:

- Provides practical and emotional support to individuals, families and professionals concerned with all forms of CJD
- Provides emotional support to people who have been told that they are at a 'higher risk' of CJD through blood or surgical instruments
- Links families with similar experiences of all forms of CJD
- Offers financial support for families in need
- Provides accurate, unbiased and up-to-date information and advice about all forms of CJD
- Provides a national helpline on all forms of CJD
- Promotes research and the dissemination of research findings
- Promotes good quality care for people with all forms of CJD
- Encourages the development of a public policy response for all forms of CJD
- Provides support, education and training to professionals concerned with CJD.

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CJD and prion disease

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Introduction

The prion diseases are a group of rare, and invariably fatal, brain disorders which occur both in humans and in certain animals.

They first came to public attention in the mid-1980s in the form of the BSE epidemic. BSE (bovine spongiform encephalopathy) is a prion disease of cattle. The origin of BSE is still uncertain.

Explanations include a spontaneous disease in British cattle and, possibly, contamination of feed with scrapie from sheep. However, once it began, it was recycled and amplified in cattle feed. Inevitably, concern over whether BSE could pass to humans mounted.

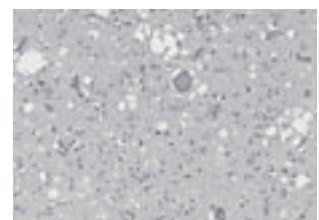
In humans the best-known of the prion diseases is Creutzfeldt-Jakob disease (CJD), which affects around one in a million of the UK population per year, resulting in around 50–60 new cases a year.

CJD exists in four different subtypes. Sporadic CJD, which occurs for no known reason, is the commonest form and accounts for approximately 75% of cases in the UK. Approximately 7% of cases are caused by an abnormal gene and are known as genetic CJD. A few cases (4%) have occurred from contamination via medical procedures and this type is known as iatrogenic CJD. The fourth type of CJD is variant CJD (vCJD) (19%) which was identified in 1996 and is considered to be the result of exposure to BSE in diet.

The two main features of prion diseases are dementia, an irreversible decline in mental faculties, and a range of neurological symptoms including unsteadiness, incoordination and sudden jerky movements (myoclonus).

The brains of people or animals with prion disease show characteristic damage known as spongiform change. When brain tissue is examined under a microscope (usually after death) it looks spongy, because it is punctured by many tiny holes where cells have been lost. For this reason, these diseases are sometimes known as the spongiform encephalopathies, although these days the term prion disease is often preferred.

Most of the prion diseases are transmissible in the laboratory, although the infectious agent (the prion) is not a conventional bacterium or virus. Instead, the infectivity is associated with an abnormal protein called prion protein (PrP). Because prions are so unusual, and because prion diseases are unique in that they can



Microphotograph of spongiform change in brain tissue taken from someone with CJD

both be inherited and transmitted, the area has attracted enormous scientific and medical interest. This provides a ray of hope that all this attention may, one day, lead to a cure for these cruel diseases.

Human prion diseases

| TYPE | CAUSE | DISTINGUISHING FEATURES |
|--|--|---|
| Sporadic CJD | Unknown | Affects mainly over-50s. Ataxia, (staggering gait) dementia, myoclonus. Short duration. Spongiform change and, rarely, plaques ¹ occur in the brain |
| Inherited prion disease Genetic CJD GSS FFI | Inherited mutation in PrP gene | Younger onset pattern than sporadic CJD. Symptom pattern depends largely on type of mutation |
| Iatrogenic CJD | Contamination through brain surgery, corneal transplant, dura mater graft, human growth hormone ² | Growth hormone cases have: <ul style="list-style-type: none"> - younger onset patterns than sporadic CJD - ataxia rather than dementia in the initial phases - show plaques¹ in the brain |
| Variant CJD | Exposure to BSE | Usually young onset. Psychiatric features and longer time course. Distinctive florid plaques ¹ in the brain |

¹ Plaques are characteristic collections of PrP (prion protein) seen on microscopic examination of the brain: see page 17.

² Iatrogenic transmission of vCJD via blood has been reported. Blood has not been implicated in the transmission of other forms of CJD.

More about prions

Prions are different from bacteria and viruses. The discovery that prion diseases were transmissible led researchers to the natural conclusion that the infective agent had to be a bacterium or a virus. When, however, infectious tissue remained infectious after treatment with both heat (which destroys most bacteria) and ultraviolet light (which should inactivate viruses) the conclusion was that some other kind of infectious agent was responsible.

In 1982, neurologist Stanley Prusiner of the University of California suggested that the infectious agent was actually a protein. (This is where the word 'prion' comes from – proteinaceous infectious particle.) The idea was highly unusual, and even heretical at first – although it has slowly gained in acceptance over the years.

Abnormal prions are infectious proteins

Proteins are essential to life. They are long molecules made up of thousands of smaller chemical units called amino acids, joined together like beads on a necklace. Once formed in a living cell, a protein molecule folds up like ball of wool. Protein molecules are fairly flexible and can adopt a number of subtly different shapes; and this simple chemical fact may lie at the heart of the whole prion enigma.

The prion protein, PrP, can exist in two forms – normal and abnormal. For convenience, these are written PrP^C and PrP^{Sc}. The normal exists in everyone in the human brain and in other parts of the body. It is also found in many other mammals and even in birds. However, its function is unknown. Genetic modification can produce laboratory mice which do not have PrP^C and these seem to be quite healthy, suggesting that it may not be essential to normal life.

The strange behaviour of abnormal prions

The abnormal form of prion protein has unusual properties. First, unlike the normal form, it is not broken down by enzymes. It also forms tiny fibres called scrapie-associated fibrils (SAFs) in the test tube and it has been found that tissue that forms a lot of SAFs is often the most infectious. Finally, the SAFs often clump together to form a chemical structure called amyloid. In some cases of CJD, amyloid deposits, known as plaques, are found in the brain on post mortem. Similar plaques are also found in other diseases such as



A computer model of the structure of a prion molecule. Such models give useful insights into the pathology of CJD, and may point to potential treatments

Alzheimer's disease, and in the normal ageing brain (although the plaques in these cases are not made of prion protein).

The disease process

The precise way in which the disease process in the brain develops is uncertain. The accumulation of the abnormal prion protein (PrP^{Sc}) is associated with disease but it is not necessarily the cause of tissue damage.

Ways in which abnormal prions are transmitted

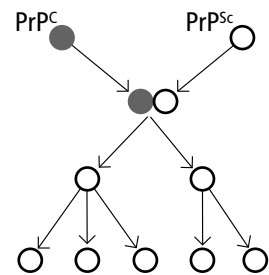
Prusiner's idea is that a single molecule of PrP^{Sc} could convert molecules of PrP^{C} into the abnormal form. And these newly converted molecules could, in turn, 'corrupt' more normal molecules, leading to a cascade effect which would eventually lead to brain damage.

It may be that once in a while (very rarely) a molecule of PrP^{C} spontaneously converts into the abnormal form, setting the scene for sporadic CJD. In genetic CJD it is known that there are mutations in the PrP gene which are inherited from one parent. These may produce forms of the PrP molecule which are less stable and are more likely to be converted into the abnormal form. Finally, in CJD acquired by transmission (iatrogenic and variant), PrP^{Sc} molecules enter the body from an infected source, and may set about corrupting the normal PrP molecules of their 'host'.

The PrP gene can exist in two forms. We each inherit two PrP genes, one from our mother and one from our father. In just over half the general population, one of each form is inherited and these people are called heterozygotes. In all other cases, two identical copies are inherited (of either form); such people are termed homozygotes. However, contrary to the general trend, most people with CJD are homozygotes; it may be that they produce a form of PrP which is more vulnerable to conversion into the abnormal form.

The prion (the infectious agent)

The precise nature of the prion is uncertain. The prion theory states that PrP^{Sc} (the abnormal form of the prion protein) is either the prion itself or a major component of it. Certainly, the accumulation of PrP^{Sc} in disease is associated with infectivity. However, the prion theory awaits final proof.



Conversion of a PrP^{C} molecule to PrP^{Sc} , leading to a cascade of PrP^{Sc} , and eventually brain damage

Sporadic CJD

Sporadic CJD (sCJD) is most common in the 45–75 age group with the peak age of onset being 60–65. In younger age groups it is very rare. The incidence of sCJD in the UK is around one per million per year – that is, there are around 50–60 new cases every year. Between 1990 and 2005 there were a total of 829 deaths from sCJD (as at July 2006).

Sporadic means 'occurring here and there' – no obvious cause has been discovered

Extensive research has shown no obvious cause for sCJD. Men are as likely to get it as women and there is no link with any particular occupation. Indeed, it occurs all over the world and it is important to emphasise that it is not thought to be related to BSE. Sporadic CJD occurs with roughly the same frequency in all countries regardless of the occurrence of BSE in those countries. Individuals developed sCJD in the UK well before BSE was identified in cattle. There is also no known link between sCJD and scrapie (a disease of sheep). On present evidence there is no causal link between animal prion diseases and sCJD.

What are the typical symptoms of sporadic CJD?

Sporadic CJD usually comes out of the blue, although the pattern of symptoms may vary from person to person.

- Early symptoms may be like those of depression – mood swings, memory lapses, social withdrawal and lack of interest. However, rapid progression to dementia and obvious neurological symptoms distinguish CJD from depression.
- Often within weeks the patient becomes unsteady on their feet, lacking in coordination, and markedly clumsy. This pattern of symptoms is known clinically as cerebellar ataxia, because it is caused by damage to the cerebellum – the part of the brain which controls movement. In some people, these are the first symptoms.
- Later symptoms may include blurred vision or even blindness, rigidity in the limbs, sudden jerky movements, and incontinence.
- Speech may become more difficult, or slurred. Swallowing may become difficult, and feeding by tube may eventually become necessary.
- Eventually the patient loses the ability to move or speak and they will require full-time nursing care. In this state, known clinically as akinetic mutism, the patient's eyes can still move and they may appear to be following what is going on around them, but in fact they are not aware of their surroundings at this stage. The average duration is 4–5 months; 70 per cent of patients die within six months of the onset of symptoms and some within a few weeks. Rarely, sporadic CJD lasts for several years. It is thought that most people with CJD eventually lose insight into their condition.

Genetic 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. In genetic CJD, there is a mutation in the PrP gene which 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 familial 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 the 'genetic prion diseases'. Both are associated with PrP mutations.

Genetic means 'occurring in families' – some families have a mutated gene which makes the development of abnormal prion protein more likely

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 in years past may have been wrongly diagnosed. Their condition might have been thought to be 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.

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.

Ante-natal 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.

What are the symptoms of genetic prion disease?

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. 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 sleepwake cycles. Eventually FFI leads to a complete breakdown of the brain's control of bodily functions, coma, and death.

Iatrogenic CJD

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 was similar to CJD except that ataxia was the predominant symptom and dementia was rare. The brains of these patients showed severe damage to the cerebellum, the part of the brain which controls movement, along with the spongiform change so characteristic of prion disease. A further feature was the appearance of characteristic deposits called kuru plaques within the brain tissue.

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. If just one of the group had had sporadic CJD then 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.

The incubation time for kuru is between three and 40 years. When the Fore people stopped these funeral rites, when the country was taken over by Australia, the number of new kuru cases went down dramatically but there is still the occasional case occurring in an older person in whom the disease has had a very long incubation time. 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. Brain tissue from a person with CJD contains prions and if it comes into contact with normal PrP, in the body of an uninfected person, it can change it into the abnormal form, with transmission of disease.'

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

Iatrogenic means 'caused by medical treatment' – but more generally this form of CJD is transmitted by direct contact with infected tissue from someone with the disease

Intracerebral transmission of CJD has also occurred with corneal transplants and with grafts of dura mater, the tough membrane which covers the brain and has been used in various kinds of surgery. The incubation time for dura mater associated iatrogenic CJD has ranged from six to 30 years range (Brown P et al, 'Iatrogenic CJD at the Millennium'; *Neurol* 2000 55:1075-1081). In the UK it is 45 – 177 months (mean 93 months). Ref: Heath CA et al 'Dura Mater – associated CJD: experience from surveillance in the UK' *JNNP* 2006 77:880-882.

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 body, not direct into the brain. Human growth hormone, which is used to treat children with short stature, used to be prepared from human pituitary glands, its natural source. Typically 2,000 glands would be pooled to make one batch of growth hormone which, in turn, 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. Around 2000 people were treated with this form of growth hormone in the UK and there have been 46 cases of CJD arising from this cause since between 1990 and 2006. The incubation time for iatrogenic CJD when infection occurs via peripheral route is longer than when it occurs by intracerebral route. Therefore, there could be more growth hormone related cases to come. Growth hormone is now made synthetically, rather than being extracted from pituitary gland, so there is no current risk from this source.

Blood has not been shown to be a route of transmission for most forms of CJD such as sporadic, genetic and human growth hormone related cases. However, variant CJD has resulted in transmission via blood. These represent iatrogenic transmission of vCJD and details are to be found on page 19.

What are the symptoms of iatrogenic CJD?

Where transmission is intracerebral, the symptoms are like sporadic CJD. However, human growth hormone CJD is more like kuru, with symptoms of ataxia predominating, and dementia being a rare or late feature.

Variant CJD

In 1996 a new form of CJD was identified in the UK, initially named 'new variant CJD' but later re-named 'variant CJD' (vCJD). The number of deaths due to variant CJD in the UK increased from 1995 up until 2000 (when there were 28 deaths) and currently (2006) remains in decline with five deaths in 2005. By September 2006 there had been a total of 162 definite and probable cases of vCJD identified in the UK. At September 2006, eight countries had reported either one or two cases, the Republic of Ireland had reported four and France had reported 18 cases. Some of these non-UK cases are thought to have arisen during stays in the UK, while others are thought to have arisen within the relevant other country.

Variant CJD is thought to be due to exposure to BSE infectivity in diet following the development of the BSE epidemic in UK cattle in the 1980s. The fact that vCJD appeared in the nineties and has predominantly affected the UK are facts that support the causal link with BSE in cattle. In addition, there are a range of laboratory features and experiments providing strong evidence that vCJD is due to the BSE infectious agent. Measures were put in place to protect the human food chain from BSE between 1989 and 1995. Prior to these measures, infectivity may have ended up in food, probably mostly from contamination of so-called 'mechanically recovered meat' used in the manufacture of various pre-prepared food stuffs such as sausages, patés, pies and hamburgers. A case control study undertaken in the UK was published in 2006 and this study provided some evidence supporting the idea of transmission through foodstuffs containing mechanically recovered meat. It remains uncertain as to how many individuals will develop vCJD due to this dietary route. The incubation period (time from exposure to onset of symptoms) for dietary vCJD is unknown but it is likely that the minimum is around five years and the maximum may possibly be as long as 40 years. During this incubation period, it is possible that individuals might pass on infection to others via certain specific routes (such as donation of blood or organs and via surgical instruments). In September 2006, three probable instances of transmission of vCJD infection via blood donation had been identified. At this time, no instances of surgical instrument or organ transplantation had been identified. It should be emphasised that there is no risk from ordinary contact with individuals with vCJD either in the incubation period or in the disease period.

Variant CJD is so-called because it differs in some ways from other forms of CJD (including that it principally occurs in younger people). It was first identified in 1996. The earliest identified onset of symptoms was in 1994.

vCJD differs from sporadic CJD in several aspects. It affects significantly younger individuals. In 162 UK individuals identified by September 2006, the average age at onset of symptoms was 28 (the youngest having symptom onset at 12 and the oldest at 74). The course of the illness is longer than in sCJD, typically being around 14 months. The initial symptoms are generally different, typically being more of a psychiatric than a neurological type. Finally, the brains of people with vCJD, when examined at post mortem, show characteristic appearances which are somewhat different from those of sCJD.

What are the symptoms of vCJD?

The symptoms of vCJD are typically distinct from those of classical CJD. The most characteristic initial symptoms are:

- Anxiety, depression, withdrawal and behavioural changes. The patient may be referred initially to a psychiatrist rather than to a neurologist
- Persistent pain and odd sensations in the face, trunk and limbs.

After several weeks or months, more clear-cut neurological symptoms occur, including:

- Unsteadiness in walking, incoordination
- Progressive dementia (loss of mental function including memory loss)
- Involuntary movements (such as tremor, fidgety movements and myoclonus – jerky movements)
- The patient progressively loses the ability to move or speak and will generally require 24-hour nursing care in the later stages. Death occurs at around an average of 14 months after the onset of symptoms.

Investigation and diagnosis of CJD

CJD is a rare disease. While general practitioners should be aware of the condition, most of them will never see a case during their professional life. However, progressive neurological symptoms should lead to appropriate referral to a clinical neurologist and then detailed neurological assessment including investigations.

Currently, there is no simple absolute test for CJD in life. An absolutely definite diagnosis requires the examination of tissue from the brain. This is usually undertaken after death. In certain specific situations, a brain biopsy may be considered in life. Therefore, the diagnosis of CJD in life is usually a judgement based on the clinical features of the illness along with the results of investigations. In most cases, this will allow a very confident clinical diagnosis and, certainly, the exclusion of other potentially treatable conditions.

The clinical diagnosis rests on three elements:

- the recognition of typical symptoms and signs of CJD
- the exclusion of other possible diagnoses (usually involving investigations)
- certain characteristic test abnormalities (detailed below).

Some investigations may have more than one role; for example, a brain scan and a lumbar puncture may both help exclude other illnesses and provide results that support a diagnosis of CJD.

The following investigations may show characteristic abnormalities that help support the diagnosis of CJD:

Magnetic resonance imaging (MRI)

This type of scan produces a detailed image of the brain. It is important for ruling out other conditions (such as brain tumour) but it may also show relatively characteristic changes which aid diagnosis. This may be useful in all forms of CJD but it is particularly useful in vCJD.

Electroencephalogram (EEG)

This involves placing electrodes on the scalp to measure the electrical activity of the brain. It may show non-specific abnormalities indicating some form of brain disease. However, in sCJD there may be specific changes which can be very useful in diagnosing this disease.

Lumbar puncture (LP)

In a lumbar puncture, a sample of the cerebrospinal fluid (CSF) which surrounds the brain and spinal cord is taken by inserting a hollow needle under local anaesthetic into the lower part of the spinal column. This may be very important in excluding certain other diseases. However, it is possible to measure the levels of certain proteins in the CSF that may be helpful in diagnosis, particularly in sCJD. One protein is of particular importance and is called 14-3-3.

Blood tests

There is no specific blood test for CJD diagnosis at present (March 2007). Blood is generally taken to explore other possible diagnoses. However, blood can be taken to undertake genetic analysis of the prion protein gene to see whether there is any abnormality associated with genetic CJD.

Tonsil biopsy

A tonsil biopsy may be useful in the diagnosis of vCJD. In vCJD, unlike other forms of CJD, the abnormal prion protein can be readily detected in tissues outside the brain, including the tonsil. In cases where the diagnosis of vCJD remains significantly uncertain, despite other investigations, tonsil biopsy may be considered.

Brain biopsy

Taking a sample of tissue from the brain may be useful in helping reach a diagnosis. This involves a neurosurgical procedure (brain operation). This is not a routine procedure and would usually be done in certain specially selected cases, particularly those individuals who might have a potentially treatable condition, other than CJD, that could be confirmed only on brain biopsy. Certainly,

NOTE 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 including the CJD Support Network and the Human BSE Foundation.

brain biopsy could also confirm the diagnosis of CJD, although there is a small possibility of a negative result even in individuals with CJD.

Neuropathological changes in the brain

There are four main features which may be found when brain tissue from someone with CJD is examined under a microscope:

Spongiform change

The brain tissue has the appearance of a sponge when seen under a microscope. It is nearly always present in the brain of someone with CJD and affects the grey matter rather than the white matter.

Increased number of astrocytes

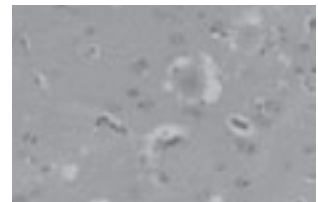
The astrocytes are cells in the brain which support and supply nutrients to neurons and increased astrocytic activity is often seen in CJD.

Loss of neurons

The neurons are the main cells in the nervous system which are responsible for its function. In CJD, as in some other neurological diseases, the neurons undergo disease and are lost.

Deposition of prion protein

The characteristic abnormality in CJD is deposition of the abnormal prion protein in the tissues. This may be seen relatively diffusely in the brain but can also be seen in characteristic deposits called plaques. Plaques are not often seen in sCJD but are seen in some cases of genetic CJD, in human growth hormone associated iatrogenic CJD and characteristically in vCJD (where they have a particular characteristic and are named florid plaques).



Microphotograph of florid plaques in brain tissue from someone with vCJD

Treatment for CJD

At present (September 2006), there is no proven treatment for CJD. However, there are a number of possible treatments being investigated in the laboratory. One potential treatment, Quinacrine, is being 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.

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.

The Chief Medical Officer has requested that individuals suspected of having CJD should be notified to two research organisations, namely 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.

Emerging issues

Blood was always thought to be a theoretical risk, but on the 17 December 2003, the then 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 and a third patient diagnosed 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 screening test for blood available, 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), to be implemented spring 2004.
- Promotion of appropriate use of blood and tissues and alternatives throughout the NHS.

Animal prion disease

Prion diseases may affect a variety of animals. Scrapie, a prion disease in sheep, has been known since the 18th century and is found in many parts of the world. There is no current evidence that scrapie has caused prion disease in humans. Recently, new atypical forms of scrapie have been identified and their significance is uncertain. Chronic wasting disease is a disease of certain species of deer and, to date, has been confined to North America. At present there is nothing to definitively link it with human health.

BSE is a prion disease of cattle. The origin of the BSE epidemic in the UK is uncertain. However, it is agreed that the epidemic grew and spread because of the use of carcasses of ruminants (sheep and cows) in preparing animal feed. Initial BSE cattle therefore contaminated foodstuff production and led on to further cases of BSE in other cattle. The ruminant feed ban, put into place in 1988, forbade the feeding of ruminant derived protein to cattle and sheep. The number of cases of BSE in the UK peaked in 1993 at 3500 per month. The subsequent decline in BSE mainly reflected the long incubation period of the illness. BSE has affected a number of other countries. The disease was also transmitted via contaminated food to a number of other animals including domestic cats and certain zoo animals. There is no evidence of transmission to humans from these other species including cats.

CJD figures

Deaths of definite and probable cases in the UK

These figures show the number of suspect cases referred to the CJD surveillance unit in Edinburgh, and the number of deaths of definite and probable cases in the UK, up to 8th February 2011.

| REFERRALS OF SUSPECT CJD | | DEATHS OF DEFINITE AND PROBABLE CJD | | | | | | |
|----------------------------|-----------|-------------------------------------|----------|------------|----------|-----|------|--------------|
| Year | Referrals | Year | Sporadic | Iatrogenic | Familial | GSS | vCJD | Total Deaths |
| 2000 | 178 | 2000 | 50 | 1 | 2 | 1 | 28 | 82 |
| 2001 | 179 | 2001 | 58 | 4 | 4 | 2 | 20 | 88 |
| 2002 | 163 | 2002 | 72 | 0 | 4 | 1 | 17 | 94 |
| 2003 | 162 | 2003 | 79 | 5 | 4 | 2 | 18 | 108 |
| 2004 | 114 | 2004 | 50 | 2 | 4 | 2 | 9 | 67 |
| 2005 | 124 | 2005 | 66 | 4 | 8 | 5 | 5 | 88 |
| 2006 | 112 | 2006 | 69 | 1 | 6 | 3 | 5 | 84 |
| 2007 | 119 | 2007 | 64 | 2 | 9 | 1 | 5 | 81 |
| 2008 | 150 | 2008 | 88 | 5 | 2 | 3 | 1 | 99 |
| 2009 | 153 | 2009 | 78 | 2 | 3 | 5 | 3 | 91 |
| 2010 | 147 | 2010 | 72 | 2 | 5 | 1 | 3 | 83 |
| 2011* | 14 | 2011 | 8 | 0 | 0 | 1 | 0 | 9 |
| Total referrals since 1990 | 2745 | Total deaths since 1990 | 1210 | 64 | 82 | 44 | 170 | 1570 |

*As at 8th February 2011

Summary of vCJD cases

Deaths

| | |
|---|-----|
| Deaths from definite vCJD (confirmed): | 119 |
| Deaths from probable vCJD (without neuropathological confirmation): | 51 |
| Deaths from probable vCJD (neuropathological confirmation pending): | 0 |
| Number of deaths from definite or probable vCJD: | 170 |

Alive

| | |
|---|-----|
| Number of definite/probable vCJD cases still alive: | 4 |
| Total number of definite or probable vCJD cases (dead and alive): | 174 |

Up-to-date figures can be found at the following website: <http://www.cjd.ed.ac.uk/figures.htm>

Further information

CJD Support Network

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PO Box 346, Market Drayton, Shropshire TF9 4WN
Telephone (admin) 01630 673993 CJD Helpline 0800 0853527
Email info@cjdsupport.net Website www.cjdsupport.net
Charity registration number 1097173

National CJD Surveillance Unit

Western General Hospital, Crewe Road, Edinburgh EH4 2XU
Telephone 0131 537 1980
Website www.cjd.ed.ac.uk

National Prion Clinic

Box 98, National Hospital for Neurology and Neurosurgery
Queen Square, London, WC1N 3BG
Help Line 020 7405 0755 Fax 020 7061 9889
Email help.prion@uclh.org Website www.nationalprionclinic.org

Institute of Child Health

Leah Davidson, 30 Guildford Street, London WC1N 1EH
Telephone 02074040536 Email Leahdavidson@ich.ucl.ac.uk

BOOKS

Fatal Protein. The Story of CJD, BSE, and Other Prion Diseases,
by Rosalind M Ridley and Harry F Baker, Oxford University Press,
1998. A readable account of human and animal diseases for the
non-specialist.

Prion Diseases, edited by John Collinge and Mark S Palmer,
Oxford University Press, 1997. A more technical account, with
contributions on all aspects of human prion diseases.

INTERNET

Information from the National CJD Surveillance Unit is available
at www.cjd.ed.ac.uk. The site also has a number of useful links to
other CJD-related sites.

Some frequently asked questions about CJD

1 Can you catch CJD from someone?

Prion diseases are not infectious in the usual way. For example, they are not spread by airborne droplets like colds and flu, or by blood or sexual contact like HIV. The overall evidence suggests that there is no increased risk of developing CJD from contact with a person suffering from the condition. There has been one case of the spouse of a patient developing CJD (with no evidence that this was due to direct contact) but no case involving a family member or friend. No special precautions are required by anyone coming into contact with someone with CJD. However, it is sensible for anyone who might be exposed to the blood of a CJD patient (usually medical staff) to wear gloves.

There should be no concerns about hugging or touching affected individual.

2 How can we be sure that the diagnosis of CJD is the correct one?

Each individual case of CJD can be assigned to one of the four types: sporadic, genetic, iatrogenic or variant. Diagnosis varies depending on the type.

In all types of CJD, a definite diagnosis can be given only by examination of brain tissue under the microscope. This is usually done at post mortem although, in some circumstances, clinicians may feel it reasonable to undertake a brain biopsy. The National CJD Surveillance Unit in Edinburgh has been gathering information on suspect cases of CJD since 1990. Of all the cases referred, only about half are finally confirmed as having CJD. The rest have a range of differing diagnoses including Alzheimer's disease. While a doctor may not be able to give an absolutely certain diagnosis of CJD in life, investigations should be able to exclude other potentially treatable diseases. In addition, it is often possible to give a very confident diagnosis of CJD in life based on the clinical picture and investigation results.

In sporadic CJD the 14-3-3 test has improved diagnosis in life and recent studies have confirmed that the MRI brain scan can also be useful.

In genetic CJD, a family history is important but the relevant gene abnormality can be detected by genetic analysis on a blood sample.

Iatrogenic CJD is diagnosed on the basis of a CJD illness developing in someone with a relevant previous exposure.

The diagnosis of variant CJD in life is greatly helped by certain abnormalities which usually (but not always) appear of the MRI scan. In some cases, a biopsy of the tonsil may provide help in the diagnosis.

3 Is the blood supply safe from CJD?

There is no evidence that sporadic or genetic CJD has been transmitted to humans through blood. However, three individuals have been identified who developed vCJD probably through blood transfusion (as at January 2007). A third individual has been identified as having been infected by a blood donation, but they did not actually develop vCJD in life. There is also experimental evidence to suggest that vCJD could be passed on through blood transfusion. Precautions are now in place to minimise this risk. At present, donors cannot be tested for CJD and blood donations cannot be screened for infection. In the UK, donated blood is now no longer used for the preparation of blood products. This is to protect recipients of clotting proteins and other treatments made from blood plasma from the risk of CJD. Donations of plasma are pooled to make plasma products and one infected donation could therefore affect thousands of people. By contrast, vital components of blood such as red cells come from a single donor and the risk to the recipient is less. In any case, a transfusion may be life-saving so the benefit outweighs any tiny risk that the blood may be contaminated. White blood cells are now removed from blood for transfusion (leucodepletion) as this may lower the risk of infection. Since 2004, transfusion recipients have been excluded from donating blood to further minimise any onward transmission risk.

4 Is there a risk in contracting CJD from organ transplant surgery?

The risk of contracting CJD from organ transplants is uncertain, but believed to be small. Unfortunately, a transplant usually has to be done before full post mortem, so the risk of the donor having

CJD cannot be completely eliminated – although, of course, all precautions are taken to try to avoid this event.

In the vast majority of cases, the benefit of having the transplant far outweighs the risk of contracting CJD from a donor who has no symptoms but could be in the incubation period for CJD. Note also that there is a risk of infection in any transplant.

5 I had to have a lumbar puncture. Am I at risk?

Lumbar puncture is now done using a single-use kit which is destroyed after the test, so there is no risk of CJD transmission.

6 What about brain surgery?

Instruments used on the brain or nervous tissue of someone with CJD are always destroyed after use. If the patient is suspected of having CJD, the instruments are ‘quarantined’ and will not be used until the patient is in the clear. If diagnosis is confirmed, the instruments are then destroyed.

7 My child has to have his tonsils out. Is there a risk of him contracting CJD?

In people who have vCJD, the prion protein is found in the tonsil and other lymph tissues. There is a theoretical risk that tonsillectomy instruments could be contaminated during surgery and then pass on infection to others during re-use, despite routine hospital sterilisation procedures. To date (November 2006) this risk remains theoretical and no instance of such transmission has been identified. Despite the fact that this risk is thought to be very low, health bodies in the UK have considered the issue in detail and have taken precautionary actions. The precise actions taken vary from region to region in the UK.

8 Is the person with CJD in pain?

Clinical experience of people in the later stages of CJD indicates that they lose awareness of their condition as the disease progresses. Obviously this saves them – but not their families – much mental suffering. In the early stages, patients with CJD occasionally develop marked fear, which can be very distressing and is probably associated with visual hallucinations.

Some of the symptoms of the disease – such as myoclonus, sudden jerking of the limbs – are distressing for carers to

witness. However, neurologists believe there is, in general, no pain associated with the disease itself although in variant CJD uncomfortable sensations such as numbness, tingling or pain can be an early feature.

9 Is a post mortem necessary in CJD?

Post-mortem examination is not compulsory when CJD is suspected – the doctor will need the permission of the next of kin. However, in some circumstances, the case may be referred to the coroner or procurator fiscal and this authority may decide an autopsy should be under taken.

It often helps the family if they can have a definite cause of death, which at present is only possible after post mortem, and the findings may help research into the disease.

10 Is sporadic CJD increasing in the UK?

Since 1990, the numbers of sporadic CJD cases in the UK have shown some increase. However, this is probably due to greater awareness of CJD among the medical profession and also better diagnostic methods. Similar increases in identified cases of sCJD have occurred in other countries.

11 Will there be many more cases of variant CJD?

From the 2000 to October 2006, the number of deaths due to variant CJD in the UK fell. However, it is impossible currently to predict how many more cases of vCJD there will be. Most authorities believe that the number of individuals contracting vCJD through dietary contamination will, fortunately, be limited.

12 Can CJD be confused with Alzheimer's disease?

Some cases of CJD do have symptoms which can be similar to those of Alzheimer's disease. However, the two diseases are usually readily distinguishable by experienced clinicians.

13 What is being done to protect us from CJD?

At present there is no way of protecting people from sporadic or genetic CJD.

Iatrogenic CJD is guarded against by destroying surgical instruments that have been used on people with CJD, and by not using their organs for transplant. There have also been recent

measures, described above, for safeguarding the blood supply. The risk of exposure to BSE has been minimised by the Specific Offal's Ban in 1989, which forbade the use of brain and spinal cord from all cattle, whether they had BSE or not, in human food. In 1997, the government also banned the inclusion of other nerve tissue in the human food supply (the beef on the bone ban) because that too was thought to carry a risk of infectivity, although lower than that in brain and spinal cord. This ban was lifted in November 1999. Muscle (beef) and milk are thought to carry negligible risk so these have not been restricted. There are also plans to eradicate scrapie in sheep in the UK.

Glossary of clinical terms used in CJD

| | |
|--------------------------|---|
| 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 functioning of the brain is affected. |

CJD
SUPPORT
NETWORK