

Variant CJD

Variant CJD (vCJD) was initially named New variant CJD. It is a new form of Creutzfeldt-Jakob disease, which belongs to a group of rare, and always fatal, brain disorders called the prion diseases. vCJD is generally believed to be caused by exposure to BSE, a prion disease found in cattle.

CJD is caused by the accumulation in the brain of an abnormal form of a protein called “prion protein”. PrP can exist in – normal (PrP^C) and abnormal (PrP^{Sc}) forms. We all have normal PrP^C in our brain. The abnormal prion is different because it is folded in an unusual 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 to brain cells

A new type of prion disease

In 1995, two cases of CJD were found among teenagers in the UK. This was extremely unusual, and alarming, for only four cases of CJD (one in Britain) had ever been reported in this age group previously. By 1996 the number had increased to ten, and it was evident that a new type of prion disease, called variant (v) CJD, had arrived in Britain. The occurrence of an epidemic of BSE among UK cattle from 1986 was thought to be no coincidence. vCJD was soon linked to exposure to BSE prior to the 1989 ban on specified offal (brain and spinal cord) from cattle in the human food supply. Exposure may have continued via spinal cord in mechanically recovered meat until 1995.



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

The number of deaths per year due to vCJD in the UK increased from 1995 up to 2000 (when there were 28 deaths) and currently (2008) remains in decline with five deaths in 2007. By January 2008 there had been a total of 163 (definite and probable) deaths from vCJD in the UK (with three patients still alive). Eight countries have reported between one and three cases, the Republic of Ireland has reported 4 and France 23 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 country.

Like all the other prion diseases, vCJD is caused by an unusual infective agent called a prion, which is an abnormal form of a protein called PrP. vCJD was called variant because it differs in several respects from (sporadic) sCJD, the most common of the prion diseases:

- vCJD usually affects significantly younger individuals. In UK, of the 163 cases identified by January 2008, the average age at onset of symptoms was 28 (the youngest at 12 and the oldest 74). There have been approximately 40 deaths from vCJD in other countries around the world.
- 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.
- When the brains of people with vCJD are examined at post mortem, the characteristic spongiform change (spongy appearance) is seen under the microscope. However, these differ from those seen for sCJD.

vCJD and BSE

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 1996, it was shown that PrP can exist in various forms (or strains) and that all the vCJD cases were affected by the same strain of PrP.

This strain had never been seen before in humans and, moreover, it bore a marked similarity to the strain of PrP seen in BSE. Later, laboratory mice were injected with vCJD prions and developed a pattern of disease like that seen in BSE, but unlike that of sporadic CJD. Furthermore, the pattern of the disease resembles that of kuru, a prion disease suffered by the Fore people in Papua New Guinea caused by exposure to infected human brain tissue.

All this is strong evidence that vCJD is caused by exposure to BSE.

But how might these young people have been exposed to BSE? Spinal cord from infected animals may have ended up in mechanically recovered meat, used in the manufacture of sausages, pâtés, meat pies and hamburgers. Both the vCJD cases, and controls without the disease, had consumed these products prior to 1995 - and so had most of the rest of the population. There was no other obvious link between diet and exposure to BSE, nor to occupation or medical history.

An investigation into a cluster of cases of vCJD in Leicestershire published in March 2001 has produced potentially valuable additional information about possible exposure to BSE. It found a biologically plausible explanation suggesting that four out of the five people with vCJD may have been exposed to the BSE agent through the purchase and consumption of beef from a butcher's shop where the meat could have been contaminated with brain tissue. Analysis of the exposure of the cases to this butchering practice indicates an incubation period for the development of vCJD of between ten and 16 years.

In addition, there are a range of laboratory features and experiments providing strong evidence that vCJD is due to the BSE infectious agent. 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. Measures were put in place to protect the human food chain from BSE between 1989 and 1995. It remains uncertain as to how many individuals will develop vCJD due to this dietary route.

Primary transmission

It is not yet known what the likely route of transmission in vCJD is. It may be that young people consume more of whatever foodstuffs carried the most infectivity, or it may be that young people are just more susceptible to the transmission of CJD via BSE. Certainly there is the same genetic susceptibility as found in sporadic CJD. We all carry two copies of the PrP gene, one from our father and one from our mother. The PrP gene can exist in two different forms -people who inherit two identical copies appear to be more susceptible to prion disease. BSE contaminated foodstuffs were also fed to sheep, pigs and poultry, so exposure through their consumption cannot be ruled out.

It is not known how many other people will develop vCJD without knowing the probable route of exposure. However, if it is like kuru, which has an incubation period of up to 40 years (time from exposure to onset of symptoms), there could be many more cases of vCJD in the future

The incubation period (time from exposure to onset of symptoms) for dietary acquired 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.

Secondary transmission

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). The infective prion is extremely resistant to normal sterilization procedures and so special precautions are taken in situations where infection is at an increased risk. These include the use of disposable surgical instruments where appropriate.

In September 2006, three probable instances of transmission of vCJD infection via blood donation had been identified (see leaflet 8 for further information). At this time, no instances of infection via surgical instrument or organ transplantation had been identified.

To minimize the possible effects of secondary transmission, the Department of Health CJD Incidence Panel examines every case of CJD, to identify the risk to public health. Where people have been found to be at an increased risk, they are now always informed.

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. This includes sexual contact. With good nursing practice, there is no additional risk of cross infection.

The symptoms of vCJD

The symptoms of vCJD are typically distinct from those of sCJD. 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:

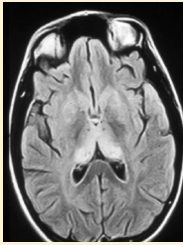
- Unsteadiness in walking, incoordination
- Progressive dementia (loss of mental function, including memory loss)
- Involuntary movements (such as tremor, fidgety movements and myoclonus – jerky movements)
- Swallowing may become difficult
- The patient progressively loses the ability to move or speak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

Diagnosis

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. A definite diagnosis requires the examination of tissue from the brain. This is usually undertaken after death, however, in certain specific situations, a brain biopsy may be considered in life. The hallmarks of CJD (spongiform change, and loss of neurons) are present, but the most striking feature of vCJD is the presence of so-called florid plaques.

The diagnosis of CJD in life is therefore usually a judgement based on the clinical neurological 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.



**MRI scan of vCJD patient
(Pulvinar sign)**

© Prof. John Collinge,
MRC Nat. Prion Unit

Magnetic resonance imaging (MRI)

This is important in excluding other problems, such as tumour and in 80 per cent or more of cases a characteristic abnormality, known as the Pulvinar sign, can be seen which may be very useful in arriving at a diagnosis.

Electroencephalogram (EEG)

An EEG does not show the same characteristic changes as seen in sporadic CJD. Blood and other biochemical tests are usually normal. The presence of certain proteins within the cerebrospinal fluid (particularly a protein called 14-3-3) may be helpful.

Tonsil biopsy

This 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.

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 vCJD at present (January 2008). 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.

The diagnosis of vCJD often takes time, due principally to the lack of a simple straightforward test. A number of neurological conditions can look very similar in the early stages and it is important 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 vCJD?

At present (November 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 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.

Support and care

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

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

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
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