Creutzfeldt-Jakob Disease

This disease is notifiable in the UK, see NOIDs article for more detail.

Description

Creutzfeldt-Jakob disease (CJD) is the best known of the human prion diseases. Prion disease is thought to arise from the transformation of normal host-encoded prion proteins to aberrantly folded protease resistant isoforms.[1]

Prion diseases are neurodegenerative illnesses due to the accumulation of small infectious pathogens containing protein but apparently lacking nucleic acid, which have long incubation periods and progress inexorably once clinical symptoms appear.[2]

The gene prion protein (PRNP = PRioN Protein) is the major genetic determinant of susceptibility; however, several studies now suggest that other genes are also important.[3]

A new or new variant prion, called nCJD or nvCJD, is recognised. There is much evidence to suggest that it is spread to humans by eating meat that has been infected with bovine spongiform encephalopathy (BSE) in cattle. This was thought to have originated as scrapie in sheep but may then have been modified.

Variants

There are four variants of the disease:

- **Sporadic**: about 85% of cases.[4] It is rare at around one case per million population per year. It is found throughout the world, and is thought to be due to a spontaneous mutation of the prion protein. It is not transmitted.
- **Hereditary**: a little under 15% of cases. This variant occurs in family clusters with a dominant pattern of inheritance.[4]
- **Iatrogenic CJD**: may be transmitted by instruments used in neurosurgery, tissue grafts, and hormones derived from cadaveric pituitary glands.[5] Other healthcare workers have also been affected.[6]
- **nvCJD**: is linked with BSE discovered in cattle in 1986 and is believed to be transmitted through eating infected meat products, especially through parts of the central nervous system (CNS). It was first recognised in 1996 and no cases had been identified with infection before 1994.

There is also **Gerstmann-Sträussler-Scheinker syndrome (GSS)** - a rare inherited prion disease characterised by adult onset of memory loss, dementia, ataxia, and pathological deposition of amyloid-like plaques in the brain. It is classified as a transmissible spongiform encephalopathy (TSE)

Epidemiology

There is a National CJD Surveillance Unit (NCJDSU) based at the Western General Infirmary in Edinburgh, which brings together a team of clinical neurologists, neuropathologists and scientists specialising in the investigation of this disease. Between 1990 and up to Nov 2009, the number of recorded deaths in the UK from the various forms, based on NCJDSU information, were:

- Sporadic - 1,099.
- Iatrogenic- 61.
- Familial - 73.
- nvCJD - 166.
- Total - 1,438 (includes 39 cases of GSS).

Press coverage of this issue gave the impression that the streets would be littered with the dead of nvCJD and many people were very concerned about the possibility of catching the disease. This was based on the assumption of wide exposure to BSE infection in cattle, producing estimates of eventual total numbers of cases of nvCJD in the UK in excess of 100,000. In 2004 it was estimated that the total number of cases would not exceed 2,000.[8] Worldwide there have been 25 cases in France, 4 in Ireland, 3 in USA and Italy, 5 in Spain and 3 in the Netherlands.

Notification

Clinicians caring for patients with CJD or suspected CJD of all types, should inform the local Consultant in Communicable Disease Control or their equivalent in Scotland. Cases should also be reported jointly to the NCJDSU and the National Prion Clinic.

Presentation
Clinical findings include myoclonus, visual disturbances and cerebellar, pyramidal and extrapyramidal signs in addition to rapidly progressive cognitive and functional impairment. These findings are all nonspecific and it is often difficult to diagnose before death.\textsuperscript{[8]} The incubation period usually appears to be between 4 and 30 years.\textsuperscript{[10]}

- Sporadic CJD usually affects middle-aged or older people, whilst nvCJD affects young adults; however, there are overlaps. The oldest case of nvCJD was aged 74 and sporadic and hereditary cases have affected those in their teens and twenties. Why nvCJD should have a predilection for young people is unknown.
- The duration of illness is not a rigid guide but usually cases of nvCJD have durations of a year or more. The duration of sporadic CJD is typically a few months, and, in a few cases, a few weeks.
- The symptoms of sporadic and nvCJD tend to be different. Sporadic CJD usually presents with a clearly neurological illness that is very rapidly progressive. In nvCJD, the initial presentation is often with psychiatric or behavioural changes and it may not be clear that there is neurological illness until several months after the onset. An experienced neurologist can normally distinguish the clinical patterns of sporadic and nvCJD but there is some overlap in the symptoms of the two forms, and, on occasions, it may be difficult to be certain as to the classification of the type of CJD if this were based on the clinical symptoms alone.
- Neurological features include progressive ataxia, dementia and involuntary movements that may be choreiform or dystonic, often changing into myoclonus.
- In the hereditary form, clinical features differ between families and the disease lasts longer than in the sporadic form.
- In the iatrogenic form, clinical features and the course of the disease depend upon route of transmission. Where there is implantation into the CNS, most cases present with progressive dementia similar to the sporadic form. With peripheral transmission, as with injections of pituitary hormones, it presents with progressive cerebellar ataxia with cognitive impairment appearing later. With inoculation into the CNS, symptoms can appear after around 18 months but, with other routes, it is around 12 years and may be up to 30 years.

**Differential diagnosis**

Other types of dementia, multiple system atrophy and also GSS. It is unusual for patients with sporadic CJD to survive for longer than 2 years. Illness durations of ≥3 years that are gradual in progression are most likely due to non-prion neurodegenerative brain diseases.\textsuperscript{[11]}

**Investigations**

Brain biopsy is only considered if there is a good chance of another diagnosis. Tonsil biopsy in nvCJD can help with diagnosis.

Electroencephalography (EEG) shows periodic wave complexes in sporadic CJD unlike nvCJD. Further biochemical markers in the CSF, namely 14-3-3, may be useful in sporadic CJD where the clinical manifestations have been present for under 2 years.\textsuperscript{[12]}

MRI can help distinguish between sporadic CJD and nvCJD. In nvCJD there is changes including high signal in the posterior thalamus (has high sensitivity and specificity). On the other hand, in sporadic CJD there is increased intensity in the caudate and putamen.\textsuperscript{[12, 13]}

The neuropathological features of sporadic CJD and nvCJD are quite distinct and this is the only definitive way to distinguish between the two. Therefore, if there has been neither a brain biopsy in life, nor at post-mortem, then the diagnosis cannot be made with absolute certainty. However, where a diagnosis of probable sporadic CJD has been made in life, it has been correct in 95% of cases and, at post-mortem, the in vivo diagnosis of probable nvCJD is yet to be proved wrong.

**Management**

There is currently no cure for the disease and so management is purely supportive. The outcome is invariably fatal.\textsuperscript{[4]} However, much work has been done and analysed in a systematic review.\textsuperscript{[14]} There may well be hope for the future.

**Prevention**

**Sporadic**

There is nothing known that can be done to prevent the sporadic variant. Both tetracycline and vaccination may have potential for the future but there is no effective treatment yet.\textsuperscript{[15]}

**Iatrogenic**

Iatrogenic transmission of the prion is now an important public health issue but standard disinfection methods do not inactivate the prion.\textsuperscript{[16]} Special measures are now required for patients at high risk of CJD. Disposable instruments are now used for tonsillectomy and neurosurgical procedures. A review of 2,000 tonsillectomy specimens, published in 2004, did not reveal a single case of prion infection.\textsuperscript{[17]}

There is a theoretical risk that the disease could be spread by blood transfusion but with an incubation period of perhaps 40 years or more.\textsuperscript{[18]} There is currently no way of screening blood donors. There is also the ethical issue of what, if anything, to tell the donor.\textsuperscript{[19]}

“You carry an incurable disease that may or may not strike you in 40 years’ time.”

**Variant**
When the occurrence of BSE in British cattle was confirmed, the world banned the export of British cattle and meat, including from herds that had never been infected and had never been given artificial feed.

Beef and steak were removed from many menus, including removal of roast beef from school meals. The problem originated from the CNS, and practices such as cutting through the spinal column with a chainsaw could disseminate the prion. It was not really cuts of meat that posed the risk so much as electronically recovered meat that may be included in sausages or burgers, and gelatine as used in jelly. There was a small risk from bone marrow and for a while T-bone steaks were banned.

There have been massive changes in the beef industry with measures such as selective culling of animals of high risk, removal of brain and spinal cord from carcasses and 100% veterinary inspection of meat.

**Historical aspects**

- The earliest reference to scrapie, the first of the TSEs in sheep, dates back to a description in England in 1732, although it was not until 1938 that it was shown to be transmissible. Only New Zealand and Australia are regarded by the USA as now being scrapie-free.
- CJD was identified in 1920, and linked to scrapie in the 1950s. Alfons Jakob (1884-1931) a German neurologist, who early in his career worked under Alois Alzheimer, was also the first to describe Alpers’ disease (an autosomal recessive progressive infantile poliiodystrophy), and did important work on multiple sclerosis and Friedreich's ataxia. Hans Creutzfeldt (1885-1964), was a psychologist and neurologist and was actually the first to describe a patient with "pseudoparalysis", predating Jakob's cases of "spastic pseudoparalysis" by a few months. However, Creutzfeldt's case does not meet the criteria for TSE, and so the honour for the first case of TSE belongs to Jakob alone. The disease used to be called Jakob-Creutzfeldt disease but then it was reversed.
- Other human TSEs include GSS (a very rare inherited TSE), kuru, and fatal familial insomnia. Before the introduction of recombinant growth hormone, CJD was responsible for a number of deaths, starting in the USA in 1985, in children treated for hormone deficiency.
- Carleton Gajdusek was an American physician of immigrant parents, who won the Nobel Prize in 1976 for his work in the 1950s and 1960s into kuru, and later demonstrated that both this and CJD could be transmitted to monkeys and was therefore contagious. He was co-discoverer of kuru and he lived among the Fore people of New Guinea, concluding that the disease was transmitted in a funeral custom of the ritualistic eating of the brains of the deceased. With the abolition of cannibalism, the disease has become virtually extinct.
- It is thought that changes to the rendering processes from batch to continuous processing and the abandonment of solvent extraction of tallow, in the 1970s and early 1980s may have led to a ten-fold increase in infectivity in meat and bone meal (MBM) in cattle feed which coincided with its introduction into rations for calves from the first or second week of age. It is not thought that an unmodified scrapie agent was the responsible agent, but that it was a novel agent from a new prion mutation in cattle, or possibly sheep. Cattle are herbivores but feeding them meat and bone meal enforces them to become carnivores and possibly even canivans. The practice was stopped in 1988. Herds such as Aberdeen Angus that graze in pastures and are not fed this artificial concoction have never had a case of BSE.
- Stanley Prusiner won the Nobel Prize in Physiology or Medicine for the discovery of prions in 1997. An American neurobiologist, he had first introduced the term prion in an article in 1982 which set off a storm of criticism, but he persevered and, by the early 1990s, the existence of prions was gaining acceptance.
- The Government and government scientists have been accused of being slow to react and more concerned with political and economic aspects of the BSE crisis than public health. This assertion is easy to make with the benefit of hindsight but the slow response was because the evidence was not available at the time. Even in 2004, the link between nvCJD and BSE was contentious. [20]

**Further reading & references**

- **Creutzfeldt-Jakob Disease, CJD**: Online Mendelian Inheritance in Man (OMIM)
- **Gerstmann-Strassler-Scheinker Syndrome (GSS)**: Online Mendelian Inheritance in Man (OMIM)
- Trevitt CR, Collinge J; As systematic review of prion pathogenesis in experimental models.; Brain. 2006 Jul 1;.

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