Creutzfeldt-Jakob disease

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

What is Creutzfeldt-Jakob disease?

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive, fatal and transmissible neurodegenerative disease associated with the accumulation of misfolded prion protein in the CNS.[1]

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.[2]

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.[3]

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.[4]

International CJD surveillance programmes have been active since the emergence, in the mid-1990s, of variant CJD (vCJD), a disease linked to bovine spongiform encephalopathy.[1]

Variants

There are four variants of the disease:

- **Sporadic**: about 85% of cases.[5] 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.[5]
- **Iatrogenic CJD**: may be transmitted by instruments used in neurosurgery, tissue grafts, and hormones derived from cadaveric pituitary glands.[6] . Other healthcare workers have also been affected[7]
- **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)

How common is Creutzfeldt-Jakob disease? (Epidemiology)[8]

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.

The annual NCJDSU report in 2021 reported:

- Between 1st January 1970 and 31st December 2021, 2909 cases of sCJD were identified in the UK.
- The annual mortality rate for sporadic CJD (sCJD) was 1.97 cases/million in 2021.
- Up to 31st December 2021, 178 cases of definite or probable vCJD had been identified in the UK.

- Since 1970, up to 31st December 2021, 89 cases of CJD attributable to iatrogenic exposure have been identified, 8 in individuals receiving dura mater implants, 80 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) who was treated in Australia.

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.

Symptoms of Creutzfeldt-Jakob disease (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.[9] The incubation period usually appears to be between 4 and 30 years.[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.[11]

Investigations[12]

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.[13]

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.[13] [14]

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 of Creutzfeldt-Jakob disease

There is currently no cure for the disease and so management is purely supportive. The outcome is invariably fatal.[5] However, much work has been done and analysed in a systematic review.[15] There may well be hope for the future.

Prevention of Creutzfeldt-Jakob disease

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.[16]

Iatrogenic

Iatrogenic transmission of the prion is now an important public health issue but standard disinfection methods do not inactivate the prion.[17] 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.[18]

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.[19] There is currently no way of screening blood donors. There is also the ethical issue of what, if anything, to tell the donor.[20]

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 poliodystrophy), 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 recombitant growth hormone, CJD was responsible for a number of deaths, starting in the USA in 1985, in children treated for growth 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 cannibals. 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.[21]

Further reading

- Creutzfeldt-Jakob Disease, CJD; Online Mendelian Inheritance in Man (OMIM)

- Gerstmann-Straussler Disease, GSD; Online Mendelian Inheritance in Man (OMIM)
- Narula R, Tinaz S; Creutzfeldt-Jakob Disease. N Engl J Med. 2018 Jan 25;378(4):e7. doi: 10.1056/NEJMicm1710121.
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