Chapter 16
Creutzfeldt-Jakob Disease and its Variants

16.1 Introduction: The First Descriptions of Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease or spastic pseudosclerosis was a term applied by Jakob to a set of patients first described by Creutzfeldt (1920).

The course of the disease is usually rapid, death occurring within a few months or rarely years from of onset of symptoms. The disease is characterised by progressive dementia with memory loss, personality changes and hallucinations. Clinically there is dysarthria, spastic weakness of limbs, extra-pyramidal symptoms such as a Parkinsonian tremor, athetosis and pronounced muscular wasting. There is difficulty in talking normally made worse by the concomitant dysarthria.

On post-mortem examination there is global atrophy of cerebral gyri from frontal to parietal regions, widespread demyelination with degeneration of cortico-spinal tracts and destruction of anterior horn cells.

In the 1920's Creutzfeldt-Jakob disease was first described and identified as a debilitating and fatal neurological disease. It is classified into various types such as sporadic, genetic or familial.

Some of these forms are iatrogenic or acquired and more recently variant forms of Creutzfeldt-Jakob disease have been described (Irani 2003).

Only sera from two patients with sporadic Creutzfeldt-Jakob disease (sCJD) were available for analysis in the sera obtained from the Institute of Neurology, Queen Square Hospital, London (Courtesy of Prof. Edward Thompson) which showed elevated levels of antibodies to *Acinetobacter* bacteria. The relevance of this observation must await more extensive studies with a greater number of Creutzfeldt-Jakob disease patients.

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16.2 Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies include Creutzfeldt-Jakob disease and its variants, the genetic disorders Gerstmann-Sträussler-Scheinker (GSS) syndrome, Fatal Familial Insomnia (FFI) and kuru in New Guinea natives.

Other diseases also thought to belong to this group is bovine spongiform encephalopathy (BSE), chronic wasting disease of elk and deer, and scrapie in sheep and goats.

All of these diseases are thought to be caused by misfolded or aberrant prions.

16.3 Sporadic-Creutzfeldt-Jakob Disease

The incidence of sporadic-Creutzfeldt-Jakob disease is about one case per million, per year in the world. Sporadic Creutzfeldt-Jakob (s-CJD) disease accounts for about 85 % of cases.

In the USA there are about 200 cases per year.

In the UK, Creutzfeldt-Jakob disease is monitored by the CJD Surveillance Unit in Edinburgh. Since May 1990, when the surveillance of Creutzfeldt-Jakob disease was started, there have been, till 2013, 1,454 cases of sporadic-CJD.

In 2012, 5 New Zealanders were confirmed to have died from sporadic-Creutzfeldt-Jakob disease, in a country where no cases of bovine spongiform encephalopathy had been reported.

The onset of sporadic-CJD usually appears later in life, around the age of 60 years and it has a rapid course with death within months to years. In some individuals it gives a characteristic pattern on electro-encephalogram examination involving periodic sharp and slow wave complexes.

Symptoms can vary from dementia to disturbance of balance and movement. Early non-specific symptoms include headaches, dizziness, fatigue, sleep disturbances and behavioural changes with mood swings. Visual hallucinations occur frequently in sporadic-CJD (Zerr and Poser 2002).

In Japanese patients with sporadic-CJD there is elevation of neuron-specific enolase in both serum and cerebro-spinal fluid (Kohira et al. 2000).

16.4 Acquired or Iatrogenic Creutzfeldt-Jakob Disease

Acquired Creutzfeldt-Jakob disease is transmitted by exposure to brain or nervous tissue usually by a medical procedure, such as injection of growth hormone extracted from pituitary glands or dura mater grafts.

Since 1990, there have been 74 cases of acquired or iatrogenic cases of Creutzfeldt-Jakob disease in the U.K.

Between 1970 and 2003, seven cases of human dura mater associated Creutzfeldt-Jakob disease were identified in the U.K. One of these was a porcine dura mater graft. The latent period between surgery and onset of neurological symptoms was 6–7 years.

Up to 2012, some 200 cases of dura mater associated Creutzfeldt-Jakob disease have been reported world wide. Autopsy carried out on some of these cases showed widespread spongiform changes with variable neuronal loss and extensive gliosis.

16.5 Genetic Creutzfeldt-Jakob Disease

Approximately 5–10 % of Creutzfeldt-Jakob disease are hereditary and occur in families having a genetic predisposition for developing the condition.

The two main genetic or familial conditions which produce a clinical and pathological pattern similar to Creutzfeldt-Jakob disease are Gerstmann-Sträussler-Scheinker (GSS) disease and Fatal Familial Insomnia (FFI).

Since 1990, there have been 155 cases of genetic or familial cases of Creutzfeldt-Jakob disease in the U.K.

Gerstmann-Sträussler-Scheinker syndrome is a rare autosomal dominant genetic disorder characterized by dysarthria and cerebellar ataxia. A change in codon 102 from proline to leucine on chromosome 20 has been found in the prion protein gene of most affected individuals.

Fatal Familial Insomnia is a rare autosomal inherited disease of the brain. It involves progressively worsening insomnia which leads to hallucinations, delusions and dementia. Death occurs within 2 years of onset of symptoms.

It also occurs as a rare mutation of the PrP^C protein gene which is found on the short arm of chromosome 20.

The disease has been described in 40 families, involving some 200 individuals throughout the world.

These are inherited neurological disorders similar to Huntingdon's chorea. The question arises to what extent do environmental factors contribute to the causation of these genetic disorders.

16.6 Variant Creutzfeldt-Jakob Disease

The median age for variant-CJD is 28 years whilst for sporadic-CJD is 60 years.

Up to 2013, there have been 177 cases of variant-CJD reported by the CJD Unit in Edinburgh. These consisted of 122 confirmed cases and 55 probable variant-CJD, awaiting neuro-pathological confirmation.

The neuropathological features comprise at post-mortem examination, spongiform changes, neuronal loss, astrocytic and microglial proliferation with accumulation of abnormal prion proteins.

The proposed link of Creutzfeldt-Jakob disease, particularly the variant form (v-CJD), with bovine spongiform encephalopathy (BSE), especially in young people below the age of 40 years, was a source of considerable concern to the government and public in the U.K., as well as throughout the world (Will et al. 1996). This young age of occurrence of variant-CJD suggested that it might be due to the consumption of meat derived from BSE affected animals.

As a consequence of these observations, the use of British beef for human consumption was drastically curtailed. This led to a widespread decline in meat consumption in the mid 1990's, in the U.K. and to a lesser throughout the world.

The suggested maximum incubation period of more than 20 years for variant-Creutzfeldt-Jakob disease has passed since the possible entrance of "infected" beef into the human food chain in the 1980's. However this expected epidemic never occurred. The incidence rate of Creutzfeldt-Jakob disease are fairly similar in many European countries and no such epidemic located mainly in the U.K. has been observed (Will et al. 1998).

The distribution of variant-CJD in the UK shows the highest incidence in Scotland but this does not tally with the distribution of BSE affected cattle which was highest in the south of England.

Furthermore, a meta-analysis of control studies, in the UK, Japan and USA failed to show an increased frequency of CJD among professional groups involved in handling animal and cattle products such as farmers, butchers and veterinary workers (Wientjens et al. 1996).

In 2004, a report appeared that a person had died from a non-neurological condition but had preclinical markers of variant-Creutzfeldt-Jakob disease after receiving a blood transfusion from a person who subsequently developed Creutzfeldt-Jakob disease (Peden et al. 2004).

This led to a comprehensive restriction on the use of individuals who had spent some time in the U.K. from donating blood in the USA, Canada, New Zealand, Australia, Switzerland, Poland and the Czech republic.

It was presumed that such potential blood donors may have been exposed to the agent involved in variant-CJD whilst visiting the UK.

The number of patients who have died from variant-CJD has continued to increase over the years. Although it had been suggested that consumption of meat from BSE-affected animals may have caused the disease but nutritional studies from the "CJD Surveillance Unit" in Edinburgh failed to show a higher consumption of meat by variant-CJD patients when compared to controls (Table 16.1).

However a subsequent study showed a higher consumption of meat products. Ward et al. 2006.

The fact that some variant-CJD patients had been vegetarians for a number of years would appear not to be compatible with the hypothesis that the disease was started by the consumption of "infected meat".

Venters who investigated the *E.coli 0157* epidemic in Lanarkshie has cast some doubt that there was a link between bovine spongiform encephalopathy and variant-CJD (Venters 2001).

The scientific problem relating to the origin of variant-CJD is the question to what neurological group did the variant-CJD patients who died from the disease belong?

Table 16.1 Meat consumption in 51 cases of patients with variant-CJD compared to 27 controls

	% of cases (n = 51)	% of controls (n = 27)
Beef	98	96
Sausages	88	93
Burgers	88	88
Meat pies	86	87
Venison	25	22
Veal	18	35
Brain	0	4

See Ward et al. (2006)
Eighth Annual Report 1999, the National CJD Surveillance Unit, Western General Hospital, Edinburgh

Is variant-CJD a separate autonomous disease, "sui generic" or does it belong to a larger group?

Since both patients with sporadic-CJD in our studies had antibodies to *Acinetobacter,* the hypothesis is proposed that variant-CJD patients may also have antibodies to this microbe. If they do have such antibodies, the probability arises that variant-CJD as well as sporadic-CJD could be a severe form of multiple sclerosis. A preliminary study with a small number of sera from variant-CJD patients gave an inconclusive result and it should be repeated with a larger number of patients.

Approximately, 700 persons per year die in England and Wales from multiple sclerosis, which is about 2 persons per day (Department of Health Statistics, UK; 1995; 685, 1996; 712, 1997; 703, 1998; 801, 1999; 758, 2000; 696).

Some 7 % of multiple sclerosis patients die before the age of 40 years, which is approximately one person per week (Fig. 16.1). However the 7 % of young patients who died from "multiple sclerosis" did not have a post-mortem examination to determine whether they had similar pathological features to patients who died from Creutzfeldt-Jakob disease.

Since the majority of variant-CJD patients were aged below 40 years, could they have belonged to the group of multiple sclerosis patients who died before the age of 40 years?

Professor Scholz from Munich has pointed out that the distribution of variant-CJD in the UK shows an unequal regional prevalence.

The highest incidence of variant-CJD would appear to be in Scotland which does not tally with the distribution of BSE-affected cattle which occurred predominantly in the south of England (Fig. 16.2).

However the distribution of variant-CJD does fit quite well the distribution of multiple sclerosis in the UK. It is well known that there is more multiple sclerosis in Scotland compared to England.

The observation that multiple sclerosis is commoner in countries further away from the equator, also known as the "latitude effect", would appear to explain the higher prevalence of multiple sclerosis in Scotland and this could be related to the observation that there is a higher frequency of variant-CJD in Scotland.

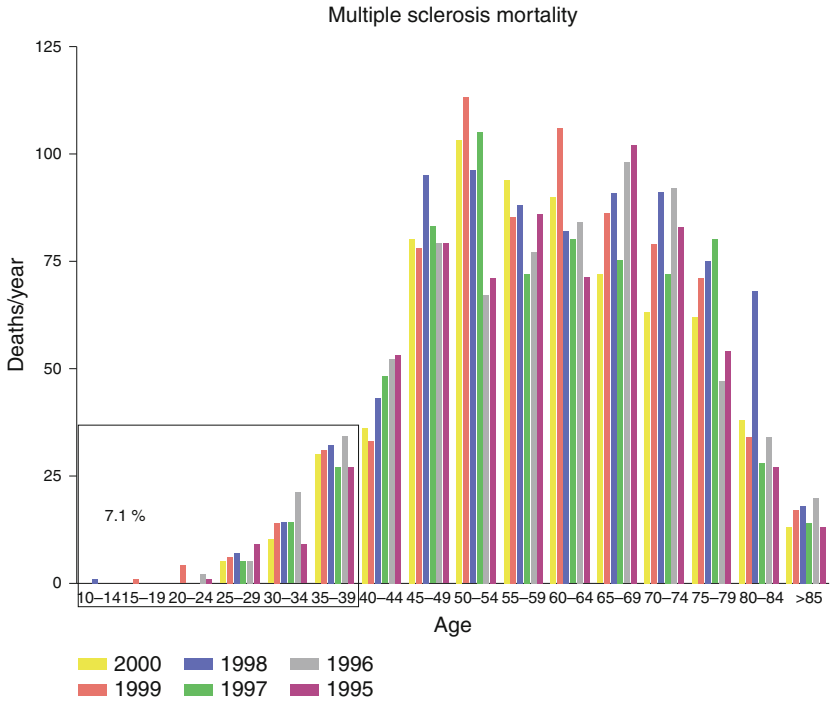

Fig. 16.1 Age and frequency distribution of patients who died from multiple sclerosis in England and Wales over the years 1995–2000 (Department of Health Statistics. Courtesy Dr. Lucy Hughes)

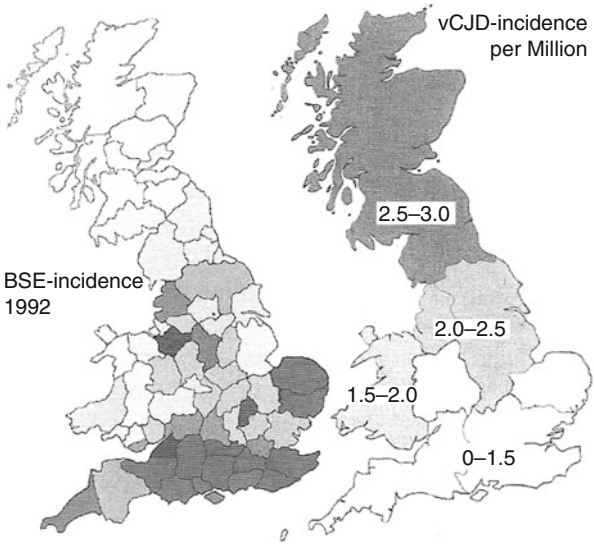

Fig. 16.2 Left-side of figure shows incidence of BSE in the U.K. according to Anderson et al. 1996. Right-side of figure shows incidence of variant-CJD per million, according to Cousens et al. (2001) (From "Phantom-BSE Gefahr" with permission)

Furthermore the reverse is found in the Southern Hemisphere. Multiple sclerosis is seven times more common in Tasmania and southern New Zealand than in tropical Queensland, in populations coming from predominantly Anglo-Celtic stock.

It is possible that the latitudinal effect could be linked to greater prevalence of respiratory infections during winter months with super-infection by environmental bacteria present in nasal sinuses such as *Acinetobacter/Pseudomonas.* Only further epidemiological and field studies can resolve these questions.

16.7 Kuru in the Fore Tribe of New Guinea and Gajdusek

Kuru was a neurological disease, also known as the "laughing disease" because of "risus sardonicus" among some patients and was prevalent among the Fore tribe people of New Guinea in the 1950's and 1960's.

Daniel Carleton Gajdusek, an American paediatrician and neurologist connected the disease to the spread of funerary cannibalism involving the consumption of the brains of diseased relatives.

He then transmitted the disease to primates by drilling holes in the skulls of chimpanzees and injecting homogenized brain matter from the affected dead individuals into the cerebellum. The animals then developed a disease resembling kuru and it was claimed that this proved the transmission of an infectious agent (Gajdusek et al. 1967).

The possibility that Gajdusek's group were repeating Pasteur's mistake of half a century earlier and producing "experimental allergic encephalomyelitis" or EAE in the chimpanzees was not considered.

Further studies showed that heterogeneic autoantibodies against axonal neurofilament proteins were detected by indirect immunofluorescence in 13 % of chimpanzees infected with kuru material and in 35 % of sera from sheep affected by scrapie (Aoki et al. 1982).

Gajdusek obtained the Nobel Prize in medicine in 1976.

16.8 The Role of Inflammation in Creutzfeldt-Jakob Disease

Although there have been extensive studies into the aetiology of multiple sclerosis, few similar investigations into the aetiology and pathogenesis of transmissible spongiform encephalopathies have been carried out, despite the fact that diseases like scrapie were known for several centuries, especially in Europe.

Unlike multiple sclerosis, the search for the involvement of autoimmunity in the pathogenesis of transmissible spongiform encephalopathies is surprisingly lacking.

However several groups have shown evidence of immune responses in a number of "transmissible spongiform encephalopathies":

1. Scrapie infectivity accumulates in lymphoid tissues (Mabbott and Bruce 2001).
2. Sera from scrapie infected sheep were found to react with a 62 kDa neurofilament preparation obtained from mouse brain (Toh et al. 1985).
3. Immuno-deficient mice injected with 1 % homogenate of brain tissues prepared from mice with scrapie, failed to produce a clinical disease when B lymphocytes were not present (Klein et al. 1987).
4. There have been increased values of total IgG, IgA and C3 complement in the CSF and serum of patients with Creutzfeldt-Jakob disease when compared to healthy controls (Galvez et al. 1979).
5. Patients with Creutzfeldt-Jakob disease and kuru have high titres of anti-neurofilament antibodies (Sotelo et al. 1980).
6. Microglial cells have been observed to accumulate in and around the brain lesions of animals affected by transmissible spongiform encephalopathies (Giese et al. 1998) and in patients with Creutzfeldt-Jakob disease (Van Everbroeck et al. 2002).
7. Elevated plasma levels of C-reactive proteins and Il-6 cytokines, which are indicative of ongoing inflammation somewhere in the body have been found in Creutzfeldt-Jakob disease patients (Volkel et al. 2001).
8. In a study from California, brain tissues from 5 out of 6 patients with sporadic-Creutzfeldt-Jakob disease, as well as from scrapie infected mice were found to be infiltrated with inflammatory cells and lymphocytes (Lewicki et al. 2003).
9. Active components C1q and C3b of the complement proteins have been detected in the lesions of patients with sporadic and variant Creutzfeldt-Jakob disease (Kovacs et al. 2004).

Clearly the proposal that there is limited inflammation in transmissible spongiform encephalopathies can no longer be sustained in view of these extensive reports demonstrating inflammatory and immunological processes in these diseases.

16.9 Problems Associated with Variant-Creutzfeldt-Jakob Disease

The "mad cow disease" crisis which erupted in England in the 1980's and 1990's has become notorious for the controversial science used to investigate this problem.

The German book by Scholz and Lorenzen (2005) entitled "Phantom-BSE Gefahr" (Phantom-BSE Danger) describes the inadequate and faulty advice given to government which led to worse political decisions that almost destroyed the meat industry and caused a world hysteria about meat consumption which continues to this day.

Some six million cattle were slaughtered and approximately one million cows deemed to have "bovine spongiform encephalopathy" or BSE entered the human food chain in the U.K.

Millions of people throughout the world have become concerned that they might develop some neurological disease such as variant-Creutzfeldt-Jakob disease (v-CJD).

However there is no valid scientific evidence that patients with variant-CJD consumed more meat products than the rest of the population when examined by careful nutritional studies. In their Eigth Annual Report 1999, the National CJD Surveillance Unit investigated 51 patients with variant-CJD and compared them to 27 controls (Table 1). Almost all cases and controls reported to have eaten beef, sausages, burgers and meat pies. Their careful conclusion was that these findings were consistent with there being no association between meat consumption and variant-CJD, but "we cannot exclude the possibility that such an association exists".

Some 150 patients have died from variant-CJD over the last 10 years. However over this same period of time some 7,000 patients in the U.K. have died from multiple sclerosis but the majority have not undergone a post-mortem examination. Whether there are post-mortem pathological similarities between v-CJD patients and those who have died from multiple sclerosis is at the moment unknown.

Scholz emphasises that "Zweifel ist das Salz der Wissenschaft" (Doubt is the salt of science). The book by Scholz and Lorensen discusses the limited scientific evidence which is proposed to describe where "bovine spongiform encephalopathy" or BSE came from and forcefully criticise the "prion theory".

According to Scholz and Lorensen the "prion hypothesis" which has received wide publicity is incompatible with the laws of biochemistry and immunology, as we know them today.

Furthermore Scholz points out there is a significant difference in the distribution of BSE in the U.K. and the regional distribution of v-CJD cases. There are more v-CJD cases in Scotland compared to the south of England (Cousens et al. 2001) whilst the majority of BSE cases occurred in the south of England (Anderson et al. 1996) (Fig. 16.2).

This distribution however fits well with the known prevalence of multiple sclerosis which is found more frequently in Scotland compared to England (Pugliatti et al. 2002).

Although Prusiner obtained the Nobel Prize for his theory in 1997, it is still quite controversial and other explanations may be found to explain "transmissible spongiform encephalopathies" as happened with "prefrontal lobotomy".

Previously the operation of "prefrontal lobotomy" in the 1940's was considered as the solution for some difficult psychiatric problems.

However the operation irreversibly damaged thousands of psychiatric patients unfortunate to fall under the scalpel of neurosurgeons.

Egaz Moniz, the surgeon who introduced the operation obtained the Nobel Prize in Medicine in 1949 but today it is banned in many countries and very few doctors favour its use since powerful drugs are available to treat many psychiatric conditions.

16.10 The Autoimmune Theory as an Alternative Hypothesis to the Prion Theory

The first clinical case of "bovine spongiform encephalopathy" was detected in April 1985. The disease peaked in 1992 and has resulted in the slaughter of thousands of infected and unifected cows when one case was present in the herd and cost the British taxpayer millions of pounds.

The cause of the origin of this epidemic has been investigated by several groups. The origin of this epidemic is to some extent unknown but it would appear to be associated with a change in the processing and preparation of the animal feed. A new form of "meat-and-bonemeal" (MBM) preparation consisting of abattoir materials from brain and other offals including as well as the intestinal contents was introduced to increase the protein content of the feeds to provide an extra source of protein.

The abattoir material was also called "green offal" due to the high content of grass found in the gut which also included large quantities of saprophytic microbes and their breakdown products.

The use of this "meat-and-bonemeal" was prohibited in 1988, and from early 1993 onwards the number of "bovine spongiform encephalopathy" cases in the U.K. has sharply declined.

One cause for this epidemic was thought to be due to "prions". Other groups suggested that the use of organo-phosphates may have been responsible.

A viral theory was another possibility (Manuelidis et al. 2007).

The role of the organo-phosphate theory in the development of "transmissible spongiform encephalopathies "is difficult to sustain, since scrapie has been known in England for 300 years, well before the discovery of organo-phosphates by the chemical industry.

The autoimmune theory implies that "bovine spongiform encephalopathy" and other "transmissible spongiform encephalopathies" are caused by external agents showing molecular mimicry to neuronal tissues similar to the situation of Sydenham's chorea and its link to *streptococcal* antigens.

Repeated exposures to such triggering agents, probably through an upper respiratory infection, will cause the production of cross-reactive bacterial antibodies against the targeted auto-antigens. Thus the development of inflammatory and degenerative lesions in the central nervous system could occur through exposure to bacteria showing molecular mimicry with brain antigens and especially with myelin. The microbes *Acinetobacter* and possibly *Pseudomonas* possess chemical sequences which resemble myelin. Consumption of bacterial fragments containing these molecular mimicry sequences may have evoked immune responses involving IgG1 and IgG3 antibodies which can cross the blood-brain barrier and caused damage to the nervous tissues containing myelin. The elevated levels of antibodies to *Acinetobacter* bacteria in BSE affected animals and in two patients with sporadic-Creutzfeldt-Jakob Disease is compatible with this hypothesis.

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