THE DIFFERENT TYPES OF HUMAN PRION DISEASE (INCLUDING CJD)

Human Prion Diseases exist in three main forms, essentially distinguished by the cause of the illness in each case. However, in addition, the symptoms and course of the illness tend to be relatively different in the different forms. Also, the neuropathological features (what one sees under the microscope) tend to be different in the different forms.

The three main forms are: Genetic, Sporadic and Acquired.

Genetic disease is caused by an abnormality in a gene (specifically a mutation in the prion protein gene, *PRNP*). Sporadic disease is of unknown cause. Acquired disease results from the transmission of disease from an animal or another human disease. The precise terminology of these diseases has changed over the years with earlier terminology being based often on the names of those who first described them.

Variably protease sensitive prionopathy (VPSPr) is a relatively newly described (in 2008) human prion diseases of unknown aetiology. Its precise relationship with other prion diseases is uncertain.

Please click on the following to find out more about:

Genetic Disease | Acquired Disease | Sporadic Disease | VPSPr | Differences between sCJD and vCJD

GENETIC PRION DISEASE

Genetic prion disease is very rare. In this form, the disease is caused by an inherited abnormal gene (a mutation in the human prion protein gene, *PRNP*). There are many identified different mutations and the different mutations tend to be associated with different clinical pictures (such as age of disease onset, rapidity of disease progression and particular symptoms). The illness is therefore not "caught" in any way and there is no causal relationship between this form and BSE. In most cases, the illness is known within the family because of the family history and the mode of inheritance is termed 'Autosomal Dominant' (which means that if an individual has the abnormal gene, then any of their children have a 50% chance of inheriting the abnormality). However, genetic cases are also seen in which no previous family history is identified .The definitive test in relation to genetic disease is a blood test in order that the gene can be analysed to see whether there is any genetic abnormality. The United Kingdom has a population of around 62 million and there are only a few deaths due to genetic prion disease in a year.

Within the group of genetic prion diseases, there are three main disease entities. These have been separated because of differences in their clinical features and the neuropathological findings. They relate, in general, to different underlying genetic abnormalities but they are all genetic diseases relating to mutations in *PRNP*.

The three entities are **Genetic CJD**, **Fatal Familal Insomnia (FFI)**, and **Gerstmann Sträussler-Scheinker Syndrome (GSS)**.

ACQUIRED PRION DISEASE

Acquired Prion Disease is prion disease that is transmitted to a person from an animal or other person. There are three main forms of acquired human Prion Disease:

- **Kuru**: A disease confined to Papua New Guinea, of historical importance.

- **Variant CJD**: A human disease resulting originally from BSE (Bovine Spongiform Encephalopathy) contamination of food.

- **Iatrogenic CJD**: CJD transmitted accidentally during the course of medical or surgical procedures.

IATROGENIC CJD

The diagnosis of these cases is usually clear from the history of a relevant medical or surgical treatment in the past. Worldwide, most cases have arisen through the use of accidentally contaminated Human Growth Hormone treatment in childhood or Human Dura Mater Grafts used in surgery (in the UK, the greatest number of cases have related to Human Growth Hormone). A very few cases have resulted from corneal transplantation, neurosurgery and specialized brain electrode techniques. Currently, there are very few deaths per year due to iatrogenic CJD in the United Kingdom. In a few instances, the source of the initial infection is known, but not in the vast majority. However, in the above described instances, it must have arisen from sporadic CJD (or, possibly, genetic CJD).

More recently, iatrogenic cases have been reported resulting from transmission of variant CJD. While these are indeed 'iatrogenic' in nature, 'Iatrogenic CJD' tends to be used to describe the instances listed above and the instances related to variant CJD are discussed in the variant CJD section as cases of 'secondary transmission'.

VARIANT CJD

Variant CJD was first reported in 1996. To date, the NCJDRSU has not seen any cases of variant CJD with symptoms that began before 1994. The majority of cases have been in the UK but other countries, particularly France, have been affected (see http://www.eurocjd.ed.ac.uk/). There is good (although indirect) evidence that variant CJD originated from transmission of infection from BSE in cattle to humans via infectivity in food. This transmission from cattle to man, via diet, is referred to as the 'primary' transmission of variant CJD. The timing of the appearance of variant CJD and its geographical distribution in the world strongly suggested a connection with BSE in cattle. Laboratory scientific work has shown that the protein agent involved in variant CJD agent is very like that of BSE.

There has been concern about 'secondary' transmission, from human-to-human, with many protective measures being established. Secondary transmission of vCJD has been reported via blood and blood products (see http://www.cjd.ed.ac.uk/TMER/TMER.htm).

SPORADIC CJD

Sporadic CJD is numerically the most common form of CJD. It is not confined to the United Kingdom and, indeed, has been found in every country in the world where it has been looked for. In general, it affects about 1-1.5 person(s) per million of the population. There are generally some fifty to sixty deaths per year due to sporadic CJD in the United Kingdom. The cause of sporadic CJD remains uncertain but detailed investigation over many years has failed to provide any evidence to suggest that it is related to diet. It was first described many years before the BSE epidemic, and is found in countries throughout the world regardless of the presence of animal diseases such as scrapie and BSE. There is therefore no evidence to suggest that sporadic CJD is in any way the result of BSE. However, the most favoured current theory suggests that the normal prion protein in the brain undergoes a spontaneous change to the abnormal form, thereby resulting in disease. If this theory is correct (and it has not been proven at this point) then the disease arises simply as a chance event inside the brain. On this basis, it would not be "caught" in any way.

Note: Although the current evidence is as stated above, it is in principle possible to transmit sporadic CJD as has happened in iatrogenic CJD and as can be done in laboratory animal experiments.

VPSPr

Variably protease sensitive prionopathy (VPSPr) is a relatively newly described (in 2008) human prion disease of unknown aetiology. Its precise relationship with other prion diseases is uncertain but no mutations have been found in the *PRNP* coding sequence and the patients have no (known) risk factors for iatrogenic CJD. The reported cases have clinico-pathological profiles and protein biochemical characteristics that differ from those seen in variant or sporadic CJD (Gambetti et al. A novel human disease with abnormal prion protein sensitive to protease. Ann Neurol 2008; 63(6):697-708).

DIFFERENCES BETWEEN SPORADIC CJD AND VARIANT CJD

The age of onset is generally different in variant and sporadic CJD. Variant CJD has tended to affect younger individuals with an average age of onset of around 28. Sporadic CJD has tended to affect middle-aged and elderly individuals. However, this difference is not absolute. There are those with variant CJD with a relatively older onset (including one case aged 74). Sporadic CJD may also affect very young individuals on occasions, including those in their teens and twenties. There is therefore a small overlap in the age group affected by variant CJD and sporadic CJD. The age of an individual is not an absolute guide to the type of CJD.

The duration of illness is generally different in variant CJD and sporadic CJD. Many cases of variant CJD 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. However, there is again no absolute distinction. There are cases of variant CJD who have died after an illness of only a few months and there are occasional cases of sporadic CJD with durations of one or two years or even longer. Therefore, the duration of illness is not an absolute guide to the form of CJD.

The symptoms of sporadic and variant CJD tend to be different. In particular, sporadic CJD tends to present with a clearly neurological illness that follows a very rapidly progressive course. In variant CJD, the initial presentation is often with psychiatric or behavioural symptoms and it may not be clear that the individual has neurological illness until several months after the onset. An experienced neurologist can generally distinguish the clinical patterns of sporadic and variant CJD. However, 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.

Some investigations which are undertaken in CJD may be of great help. In particular, the EEG, the MR scan and tonsil biopsy may be useful. The EEG shows a typical pattern in the majority of cases of sporadic CJD. This typical abnormality is generally not seen in variant CJD, although it may sometimes be seen very late in the disease. The cerebral MRI shows a typical abnormality in the majority of cases of variant CJD which is generally distinct from the changes seen in sporadic CJD. Tonsil biopsy may show a positive abnormal prion protein test in variant CJD and this is not found in sporadic CJD.

The neuropathological features of variant and sporadic CJD are different. In determining whether an individual has CJD or not, the only absolute test at present is that of neuropathology. Therefore, if an individual has not had neuropathology undertaken on either a brain biopsy in life or at a post mortem, then one cannot be absolutely sure as to the diagnosis. In addition, the neuropathological features of sporadic CJD and variant CJD are quite distinct and this would represent the main definitive method of distinguishing between the two forms of CJD.

Note: There are individuals who do not undergo brain biopsy in life and do not have an autopsy. These individuals may be diagnosed on the basis of "probable sporadic CJD" or "probable variant CJD". Although this does not represent an absolutely definitive diagnosis, if an individual is considered as having "probable" CJD, then it is very likely indeed that this is what they had.

The abnormal prion protein in variant and sporadic CJD has different properties. Certain laboratory tests (that require tissue samples) can generally distinguish the abnormal protein in variant CJD from that in sporadic CJD.

The experimental transmission characteristics of the two diseases are different. In the laboratory, experimental transmission of disease to animals can be undertaken. The characteristics of these experimental transmissions (such as incubation period and the resulting brain changes) are different for sporadic and variant CJD.