

PPTA Backgrounder: Variant Creutzfeldt Jakob Disease (vCJD) and the Safety of Plasma Protein

Variant Creutzfeldt Jakob Disease (vCJD) is one of a group of diseases called transmissible spongiform encephalopathies (TSEs). TSEs are fatal diseases of the nervous system, in which the brain degenerates in a particular way characterized by a sponge-like appearance, hence the name. They are all infectious through various routes. TSEs affect a number of mammals including humans. The most important non-human TSEs include scrapie in sheep, which is a disease which has been known for hundreds of years, and bovine spongiform encephalopathy (BSE) in cattle. BSE appeared in the United Kingdom (UK) in 1986, and by 1993 had peaked to over 1,000 new cases weekly. BSE is thought to have been spread by feeding cattle material including the tissues of BSE infected cattle, thus leading to a considerable increase in the epidemic. This was recognized early in the epidemic and the UK authorities took steps to prevent this practice, so that the epidemic was controlled and the number of cases had decreased considerably by 2000. However, the contaminated cattle feed which is thought to have caused the disease was also used in other countries, including several European countries which experienced their own – considerably smaller- BSE epidemic over the past 8 years. This epidemic is also considered to be under control and the number of BSE cases in Europe is decreasing rapidly.

In 1996, a new human disease was described which had the typical brain damage observed in other TSEs but which differed in several aspects from other human TSEs. This condition was designated as vCJD and was rapidly identified as the human form of BSE, through studies involving the agent thought to be responsible for TSEs. This agent, called a prion, is a natural and benign constituent of many body tissues but in TSEs it assumes a form which causes brain damage and illness. It was determined that the prion in vCJD was similar to the prion in BSE, confirming that BSE had been transmitted to humans through eating beef contaminated with BSE prions. An epidemic of vCJD in the UK has so far caused 168 cases, and about 35 other cases have occurred in other countries. These cases include individuals who lived in the UK and are presumed to have been infected there, and individuals who consumed meat contaminated with BSE, whether imported from the UK or sourced from within countries which also had BSE in their cattle. The vCJD epidemic in the UK appears to have peaked and the number of cases reported in the past few years is very low.

It is worrisome that, despite the low number of vCJD cases, it is likely that many more people have been infected and may be incubating the disease in a form which can be transmitted. Estimates of how many people may be carrying vCJD vary and are clouded by uncertainty, as are many features of this, still mysterious, disease. It is known that human TSEs can be transmitted through contaminated surgical instruments, some tissues used for transplant, and some medicines extracted from human tissues. Before the description of vCJD, no human TSEs had transmitted infection through the

transfusion of blood or any blood products, whether these were transfusion components or derivatives of plasma fractionation.

The particular features of vCJD suggested that the likelihood of this disease spreading through blood and blood products was higher than in other TSEs. In experiments using animals it was shown that blood from animal TSEs similar to vCJD was an efficient route of infection, and that this infectivity was found in the plasma of these animals. Fractions manufactured from the animal plasma, similar to plasma fractions used to make plasma protein therapies, could also transmit disease to other animals. However, it was also observed that the process of making these fractions could also decrease their infectivity considerably, compared to blood or plasma itself. Because of the possibility that blood and plasma donors who had resided in the UK and some other countries could be carriers of vCJD, these individuals have been deferred from donating blood or plasma for the past ten years or so in most countries outside the UK, including the countries where the PPTA members source their plasma.

In 2004, an individual who had been transfused in the 1990's in the UK with blood from a person who subsequently developed vCJD also developed the illness. This seemed to confirm that blood could transmit the disease between humans. In the succeeding years, two other people have developed vCJD under similar circumstances, and one other person has been found to have also been infected, although this person died from other causes and did not develop vCJD. The vCJD prion was found in the person's tissues after the person's death.

Since animal studies had shown that much of the infected TSE blood was in the plasma, the plasma protein industry has examined the capacity of its technology to remove the infective prions. It is considered, using the best science available currently, that in the products of Cohn fractionation technology, for example immunoglobulin and albumin, the process removes much of whatever prion contamination may be present in the plasma. This technology has been broadly universally in place for many years before the BSE epidemic, and it is therefore likely that these products are of low risk in relation to being contaminated by vCJD.

The technologies used to manufacture coagulation factors have evolved and changed considerably over the years, and it is considered that some early methods of purifying Factor VIII and IX had less capacity to remove prions. Technologies currently used by plasma protein therapy manufacturers are well validated for their capacity to do this, and the U.S. Food and Drug Administration (FDA) considers that all the products available in the U.S. have a considerable prion removal capacity and, hence, a very low risk.

Two reports over the past month have received much publicity, despite an incomplete appreciation of all the relevant facts. A person with hemophilia who died of non vCJD causes in the UK was examined for the presence of prions in his tissues. This was

because he had received Factor VIII concentrate made from a pool of plasma which included a donor who subsequently died of vCJD. Currently, most of the patients in this situation are under close study in the UK, and are subject of this examination if they die. It was found that the vCJD prion was in the tissues of this patient. Pending the completion of the necessary investigations, experts in TSEs consider as a serious possibility that the Factor VIII concentrate is the responsible transmission route for this patient. Another patient, who received immunoglobulin which similarly included plasma from a donor who died of vCJD was also examined for the presence of vCJD prion when the patient died from unrelated causes. In this instance, the vCJD prion was not found in the tissues.

What, therefore, is the situation for patients receiving plasma protein therapies today? There is still much that is unknown in this area. But we do know that the products available on the market today are made from plasma which does not include donors with a high risk of exposure to BSE. As stated earlier, no plasma collected in the UK is used for the manufacture of these therapies after the deferral policies came into place. PPTA members have not used UK plasma for their therapies. We do know that the manufacturing methods have high prion removal capacities. It is therefore likely that any risk of vCJD transmission by plasma protein therapies is very low, and much lower than any risks incurred by abstaining from treatment.

Because of the novel nature of this disease, a test to screen blood and plasma donations for the prion agent is not yet available. There is hope that a satisfactory test will be available over the coming year, though other experts believe it may take longer, and any such test will have to undergo considerable regulatory scrutiny. Furthermore, powerful technologies for the deliberate removal of prions from plasma and plasma therapies are under investigation. In the meantime, authorities, treaters and industry will continue to exert precautionary measures and adopt new ones as soon as these become available, thus ensuring the protection of patient well being.