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SACTTI UPDATE

Recent events have raised awareness of possible theoretical risks of transmission of nvCJD by transfusion. This edition will review current knowledge in this area and provide information on the steps currently being proposed to further assess the risk which this disease might pose to transfusion.

During March of this year the WHO held a Consultation of "Medicinal and other products in relation to Human and animal Transmissible Spongiform Encephalopathies. " On this occasion consideration was given to the risk of transmission of CJD by blood and blood products. The meeting concluded that

> *"there is no proven or even probable instance of transmission of CJD by blood, blood components and blood products".*

It was however acknowledged that clinical and neuropathological observations suggest that nvCJD may behave differently to classical CJD and that further studies were warranted in this area. In particular preliminary evidence was presented which appeared to show that the agent of nvCJD might be detected more easily in lymphoreticular tissue thus raising the possibility that the agent might be more likely to be found in blood. There is increasing scientific evidence that new variant CJD represents the human form of Bovine Spongiform Encephalopathy (BSE). These concerns underpin the recent debate on the possible value of leucodepletion as a mechanism to reduce any theoretical risk of transmission of nvCJD by transfusion.

New variant CJD - the current position

Following the initial announcement of the existence of a new form of CJD in February 1996 considerable effort has been made in attempting to understand the potential impact of this disorder within the UK. Limited information is however currently available whereby the potential risk that this disorder might pose to the blood supply can be assessed.

- The rate of case accrual remains low and currently only 22 confirmed cases have been identified. Given the high profile of the disorder and the effective surveillance system in place within the UK the number of cases reported is likely to be an accurate reflection of the incidence of the disease.
- Current understanding indicates that the risk of exposure to the BSE agent in food occurred during the late 1980s, this risk was eliminated by the introduction of the Specified Bovine Offal ban. Ongoing exposure through food is thus not considered to occur.
- An epidemiological model has been developed which should allow incidence data to be utilised to predict the pattern of future cases. At this stage however insufficient data is available to accurately predict the size of any epidemic within the UK. Whilst the low level of new case accrual is welcome it is too early to be reassuring that the picture will not alter within the next few years.
- No data is available in relation to the transmissibility of new variant CJD by blood transfusion. Data is not available in relation to the transmission of BSE in cow to cow transfusion.
- The distribution of BSE in cattle tissue and preliminary data in relation to the distribution of nvCJD in human tissue suggest that there might be an increased level of the infective agent in lymphoreticular tissue. In particular the prion has been demonstrated in tonsils of patients with nvCJD, this is not seen in cases of classical CJD.
- early clarification of the potential for transmission of nvCJD by transfusion of blood or products derived from blood appears unlikely.

Transmission of TSEs by transfusion

This topic has been extensively reviewed during the past two years. Two reviews are particularly noteworthy, that of Paul Brown (Current opinion in Haematology 1995) and that of Maura Ricketts (Emerging Infectious diseases 1997). The conclusions of these reviews coincide with the opinion developed at the WHO Consultation on Medicinal and other Products in relation to Human and Animal Transmissible Spongiform Encephalopathies held in March 1997. Extracts from the conclusions of the WHO consultation are given below.

- There is no proven or even probable instance of transmission of CJD by blood, blood components and blood products

  Numerous attempts have been made by several different laboratories during the past twenty years to detect the infective agent in the blood of experimentally infected animals. Although some results have been negative, several laboratories have reported the presence of small amounts of infectivity in blood and particularly in buffy coat during both the preclinical incubation period and clinical phase of the disease. It is important to emphasise that the presence of the infectious agent in the blood of either experimentally infected animals or naturally infected humans has been determined by transmission of disease to laboratory rodents only by intracerebral inoculation, and that the single experiment using an intravenous route of

inoculation failed to transmit disease (units of blood from three CJD patients transfused into three chimpanzees).

- Epidemiological studies have yet to identify a single instance in which disease has been actually transmitted by blood.

- Published case control studies have not found an elevated risk of CJD following a transfusion. However case control studies designed specifically to determine the risk from transfusion have yet to be completed.

- While published epidemiological studies give some reassurance that transmission of CJD has not occurred through blood, they are limited in scope, and improved surveillance for CJD is essential.

Paul Brown has reported the initial results of recent work undertaken in his laboratory at NIH. Data, as yet unpublished, has been presented that demonstrates transmission of experimental TSEs by intracerebral inoculation of blood. Transmission has been seen following inoculation of plasma (and its fractions) as well as red cell and buffy coat. Further studies are in progress involving blood to blood transmission. This data, if confirmed, is of concern. However it is by no means certain that the procedures used to separate individual fractions of blood mirror procedures used in the handling of blood donations. Further information on the timing of separation and the possibility of leucocyte damage during collection and processing of animal blood is needed before the importance of the data can be properly assessed.

Possible mechanisms whereby the theoretical risk of transmission of nvCJD by transfusion might be reduced

Currently the most effective mechanism to reduce the theoretical risk of transmission must be to ensure that unnecessary transfusions are avoided, this will include consideration of alternative therapies when appropriate.

In the manufacturing context practical donor exclusion criteria can not currently be defined and screening tests to identify asymptomatic infected individuals do not currently exist. It might however be possible to improve the safety of individual components by removing those fractions which are most likely to contain the infective agent. It is in this context that the possible value of leucodepletion is being considered. It must be emphasised that currently there is no direct evidence that leucocyte depletion will improve the safety of individual components.

Professor Aguzzi has recently reported (ISBT Frankfurt) studies which demonstrate that the B lymphocyte is essential for the transfer of the prion agent from the periphery into the CNS. This work suggests that there might be an association between the prion and B cell.

Leucodepletion

In assessing the desirability of implementing a policy of leucocyte depletion two main issues must be considered. Firstly is it possible and secondly is it likely to be of any benefit. A preliminary analysis indicates that leucodepletion is feasible and that it could, if necessary, be applied to all components including plasma destined for fractionation. The second question is more difficult. In recognition of the uncertainty the DoH has commissioned a risk assessment to be undertaken. Limited information is however available by which an informed assessment on this issue might be made.

This issue has been considered recently as part of the process by which SEAC have been informed of the feasibility of implementing leucodepletion within the UK. A copy of the paper is included with this issue of Update. This includes an assessment by Dr Lorna Williamson (Chair SACBC) of the clinical and technical aspects of universal leucocyte depletion.

CPMP position on CJD and plasma product withdrawal.

The CPMP has recently reviewed its position on the management of products derived from plasma pools subsequently identified as containing donations derived from donors diagnosed with CJD. Although this has not yet been published the position as currently understood is identified below.

CPMP confirmed their previous view that no action need be taken in respect of reports of donors excluded on the basis of **classical** CJD related criteria.

CPMP have however determined that as a precautionary measure product derived from pools containing donations from donors subsequently diagnosed with confirmed **nvCJD** should be quarantined and product recalled. This decision led to the two recent batch withdrawals undertaken by BPL.

In the light of this changing position the importance of prompt reporting to plasma fractionators of any donors excluded on the basis of CJD criteria is emphasised. Individual fractionators will have mechanisms to review individual reports and institute appropriate action.

Virally inactivated FFP

The policy in relation to the provision of virally inactivated FFP within the NBS has recently been reviewed. A number of issues have been considered.

- The available evidence suggests that initial demand for virally inactivated FFP will be approximately 30% of total FFP issues.

- Significant progress has been made in relation to the availability of technology to support methylene blue treatment of individual FFP components.

The decision to introduce solvent detergent FFP was based on a belief that this was the only feasible mechanism whereby the NBS could confidently meet demand for a virally safer FFP product. The theoretical benefit of a single donor product is recognised.

In the light of the emerging debate on the theoretical risk of nvCJD transmission and awareness that it is likely to be possible to meet predicted demand for virally safer FFP by methylene blue technology, a decision has been made not to pursue negotiations with Octapharma. **Consequently a solvent detergent FFP product derived from UK donor plasma will not be produced.** Instead UK Transfusion Services will work as rapidly as possible towards making methylene blue FFP available. A letter is being sent to all hospitals explaining this decision. It is hoped that an addendum to current BCSH guidelines on this issue will be produced.

This newsletter has been produced by Dr Peter Flanagan on behalf of SACTTI. Any correspondence should be sent to the author at the Leeds Blood Centre. The assistance of Dr Lorna Williamson and Dr Brian McClelland is gratefully acknowledged.