The Effect of Leucodepletion on Transmission of BSE by Tranfusion of Sheep Blood Components

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Country

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Title of project or programme

The Effect of Leucodepletion on Transmission of BSE by Tranfusion of Sheep Blood Components

Source of funding information

NIHR (PRP projects (NEL: Aug 2007-Jan 2011))

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€ 7,474,314

Start date of award

01/04/2007

Total duration of award in years

10.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract
Background
Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases, which

include Creutzfeldt-Jakob disease (CJD) in man, scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle. A new form of Creutzfeldt-Jakob disease (variant CJD or vCJD) emerged in the mid-1990s, apparently as a result of transmission of BSE to humans. To date, there have been 166 cases of vCJD recorded in the UK, as well as several cases in other countries. More recently are the reported cases of vCJD being transmitted by blood transfusion. While the prevalence of vCJD in the UK population is still unknown, the most recent projections, based on vCJD cases to date and a survey of appendix and tonsil tissues for PrPSc detection, suggest an upper limit of 4000 (Hilton et al. 2004). However, on-going human-to-human transmission could obviously have a significant impact on these estimates Houston et al. (2000, 2008) and Hunter et al. (2002) have demonstrated efficient transmission of BSE when whole blood and buffy coat, from sheep at pre-clinical and clinical stages of the infection, were transfused. This data suggests that levels of infectivity in blood were substantial and also that the route of transmission was efficient. The potential for using sheep as a model for studying the risks of vCJD transmission by blood transfusion was highlighted by the similarity between the distribution of infectivity and PrPSc in sheep infected with TSEs and humans infected with vCJD.

Aims

1) This proposal is intended to further develop the BSE sheep model to study the risks of transmission of variant CJD, in humans, by transfusing clinically relevant BSE-infected blood components in sheep i.e. red cell concentrates, plasma and platelet concentrates.

2) We will determine the of current risk reduction measures i.e. the effectiveness of human leucodepletion filters in removing endogenous infectivity associated with the BSE agent.

3) We will evaluate the titres of infectivity in whole blood and separated components throughout the course of infection, using transgenic mouse lines that over-express ovine PrP.

4) We will assess the potential for secondary transmission of TSE infection, by performing serial blood transfusion experiments from donors to primary and secondary recipients.

5) We will create an archive of blood samples collected from all blood donor sheep and selected recipients (including negative controls) for the validation of potential diagnostic or screening tests. Specially targeted tissue samples, including ocular tissues and dental pulp, will be collected at necropsy for future research / diagnostic analysis.

Plan of Investigation

Sheep, used as ‘blood donors’, were orally dosed with bovine BSE-infected or uninfected brain homogenate. Approximately 900ml was collected from donors at late pre-clinical phase of infection. A unit of blood (450ml blood + 63ml anticoagulant) was prepared into components (red cells, plasma, buffy coat & platelets) using methods routinely employed for human blood by transfusion services. Paired components from the second unit were passed through human leucoreduction filters, prior to transfusion into recipients. A sub sample of all components transfused was also inoculated into transgenic mice. We anticipate positive transmissions from these bioassays around mid 2009 at the earliest. Ten donor sheep have shown clinical signs indicative of TSE infection, 7 have been confirmed. Three donors have died as a result of intercurrent causes.

A single unit of whole blood will be collected at a late pre-clinical timepoint from primary recipients that received BSE infected whole blood and buffy coat. These units will be transfused

to secondary recipients.

Whole blood (100ml) will be collected from all BSE-infected blood donors at 0, 2,4,6,8,10,12,18, months post-infection and when clinical signs appear. Recipients of infected whole blood, red cells, plasma and platelets will be sampled at 3 month intervals starting from 6 months post-transfusion to 36 months or until clinical signs develop. Paired samples from negative controls will also be collected. Aliquots of whole blood, red cells, plasma and buffy coat will be prepared and stored. At post mortem, a range of neuronal and lymphoid tissues will be collected and archived.

Potential Impact
Our research program is based on the presumption that the BSE sheep model is the best available model to determine the potential of transfusion of blood components to transmit vCJD in man.

The study also provides a unique opportunity to collect serial blood samples for assessment of any proposed screening assay on pre-clinical blood components from infected animals, as well as negative controls. The samples would also be used to determine when infectivity appears in blood and how the titre changes during the course of infection.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A