The UK experience of variant Creutzfeldt-Jakob Disease

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Leak to media Feb 2009

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Scientists warn of first ever case of human mad cow disease from blood plasma

The first case of a person being infected with the human form of mad cow disease after receiving contaminated blood plasma has been identified by scientists.

By Patrick Hennessy and Laura Donnelly
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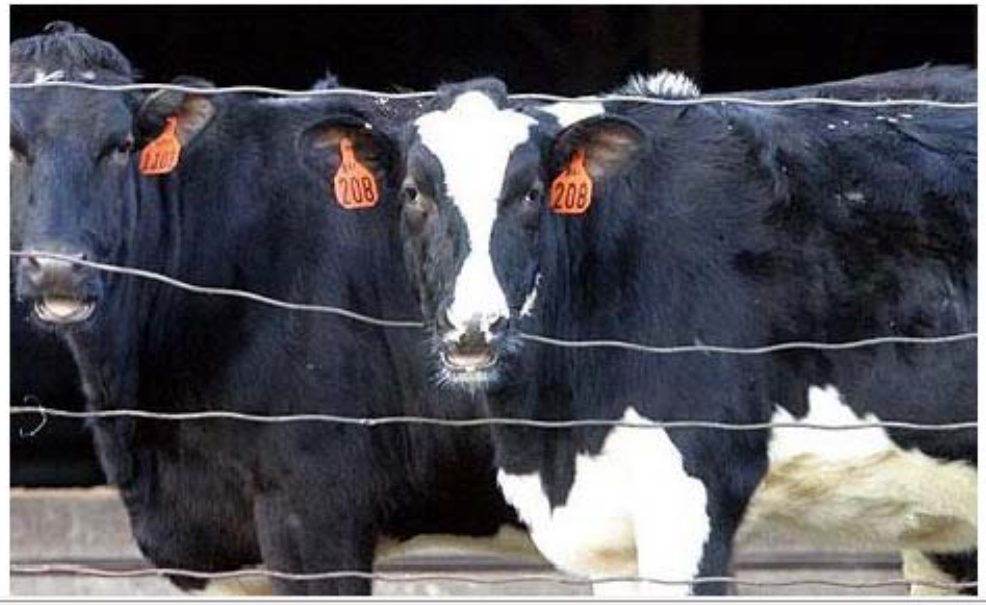

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Health
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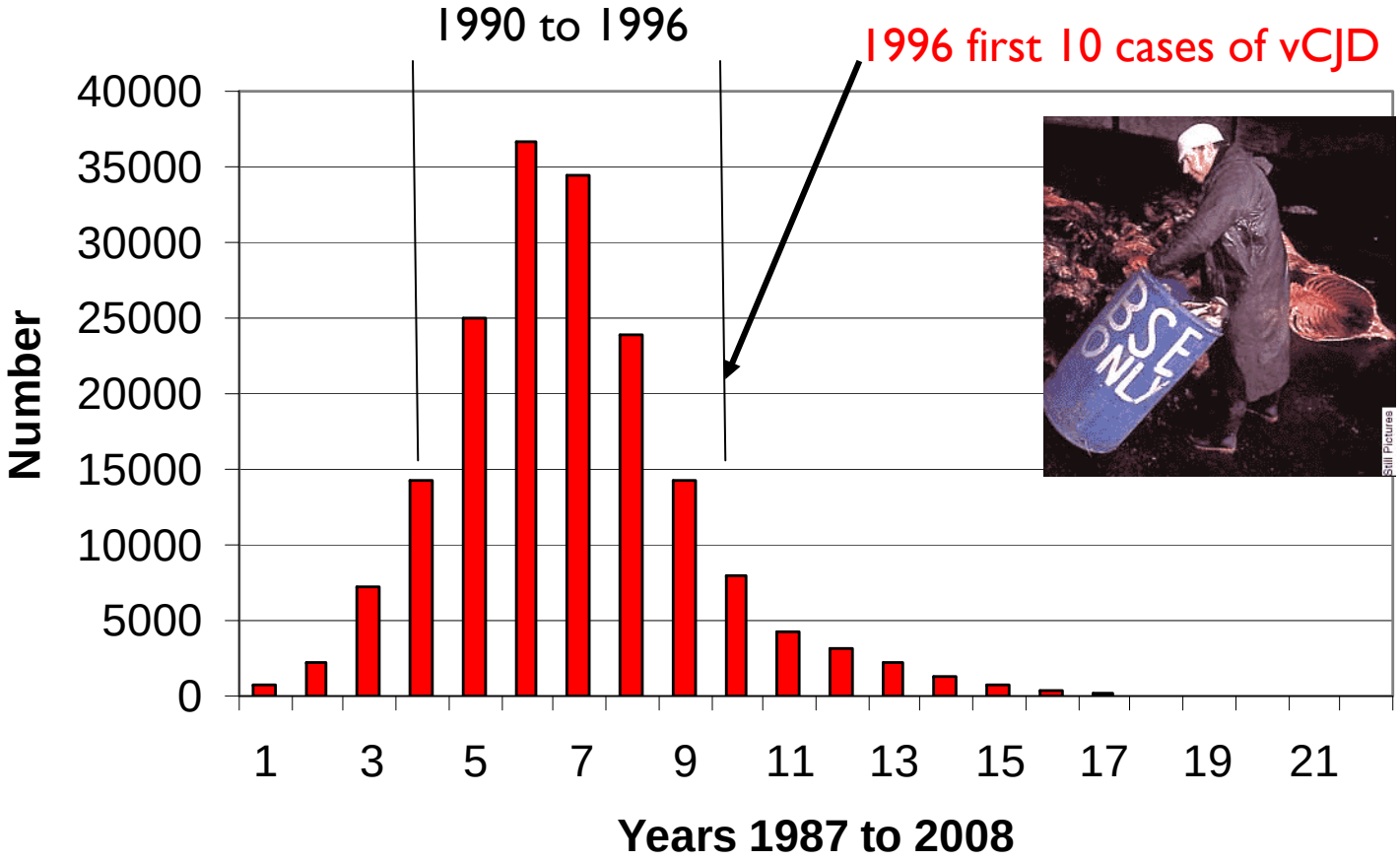
An artist divided

Transmissable Spongiform Encephalopathy (TSE)

- A group of neurodegenerative disorders in many animals including humans
- Prolonged incubation period of years
- Progressive dementia with spongy degeneration of the brain
- Usually fatal within 1-2 years of diagnosis
- Scrapie in sheep and goats, BSE in cattle, wasting disease in elk and deer
- Kuru in humans (cannibals) Fore tribe in Papua New Guinea in 1950s

Data from Veterinary Laboratories Agency website, UK

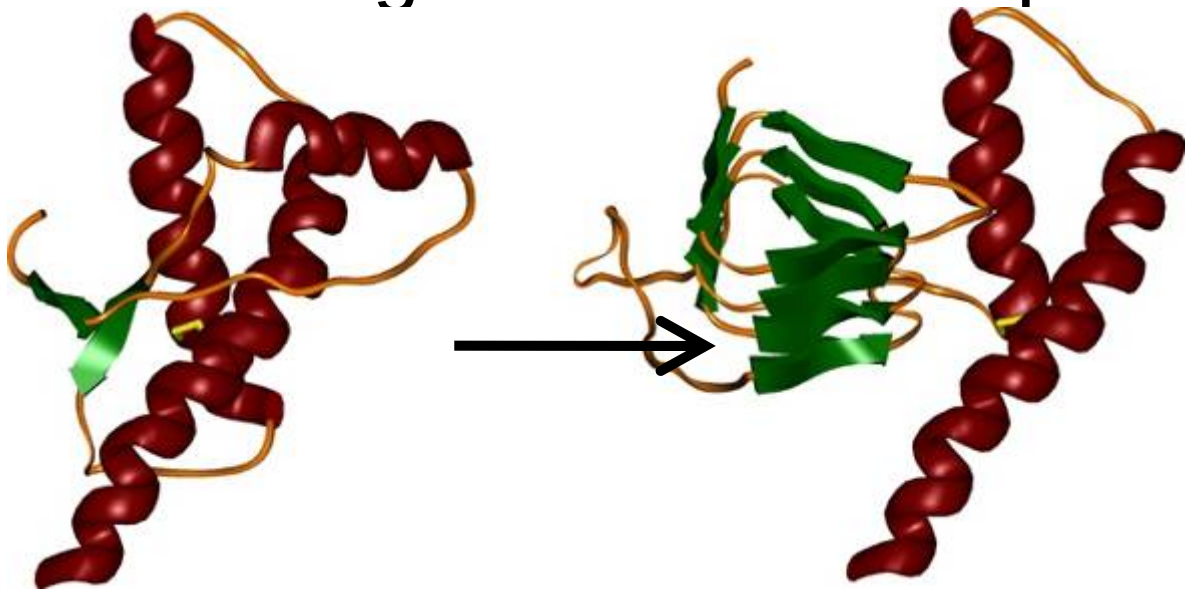
Cattle slaughtered with confirmed BSE

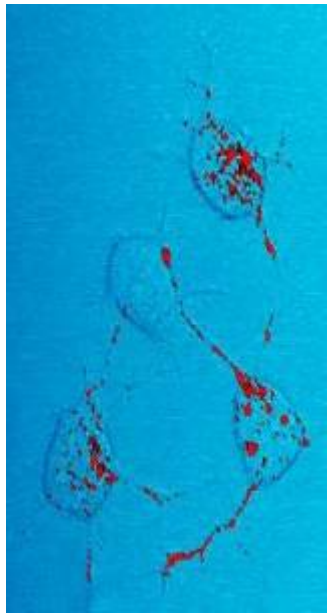


Over 180,000 cases identified, but perhaps 3 million unidentified cattle entered the food chain in the U.K.

Cause of vCJD

- Self-propagating protein ‘prion’
- Misfolding leads to build up in nerve





PrP^{c}

(C – cellular, normal)
Easily broken down

PrP^{Sc}

(Sc – scrapie, pathogenic)
Resistant to break down

Prion?

- A protein
- Very resistant to usual sterilisation methods
- Still not fully understood and controversy over causal agent
- Source of BSE was cattle feed prepared from bovine tissues such as brain and spinal cord contaminated by the BSE agent
- Spontaneous occurrence in cattle thence into food chain, or from sheep carcasses?....

National vCJD surveillance

- Programme set up in 1990 after start of BSE before any cases of vCJD were identified
- First 10 cases reported 1996 with features different to the other 197
- Expert review and collaboration
- Reports to the Department of Health
- www.cjd.ed.ac.uk

Forms of CJD

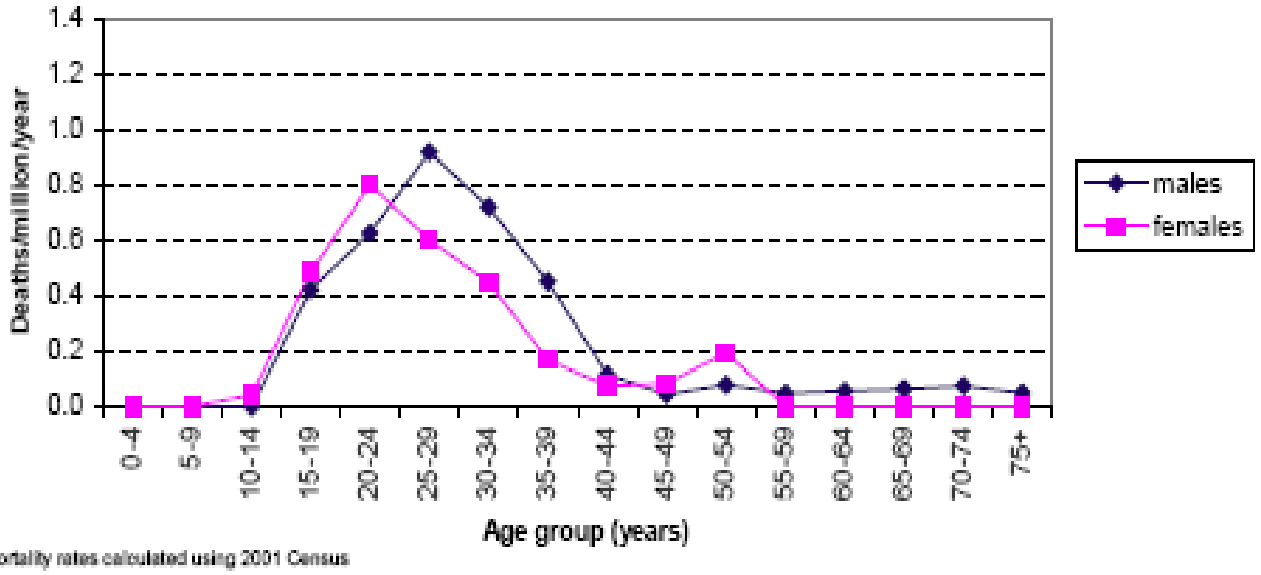
- Sporadic CJD – rare, recognised throughout the world, older age (65y), 1 per million people (85-90%) – described 1920s, death in 6 months
- Familial - associated with gene mutation (5-10%)
- Iatrogenic CJD – accidental contamination via neurosurgical instruments (6), cornea (2), dura mater transplants (192), or human growth hormone from pituitaries (198)

Variant CJD

- First recognised in 1996
  - Symptoms started in 1994
- Young people
  - (average age 29y range 14-75)
- Longer duration of illness
  - (14 months vs 4.5)
- Linked with BSE in cattle
- Infectious agent not confined to brain, also found in lymphoid tissues

vCJD affects younger people

Figure 6 Age- and sex-specific mortality rates from vCJD in the UK
1 May 1995 - 31st December 2007



Mortality rates calculated using 2001 Census

Incidence of vCJD onsets and deaths from January 1994 - December 2007

Differences in types of CJD

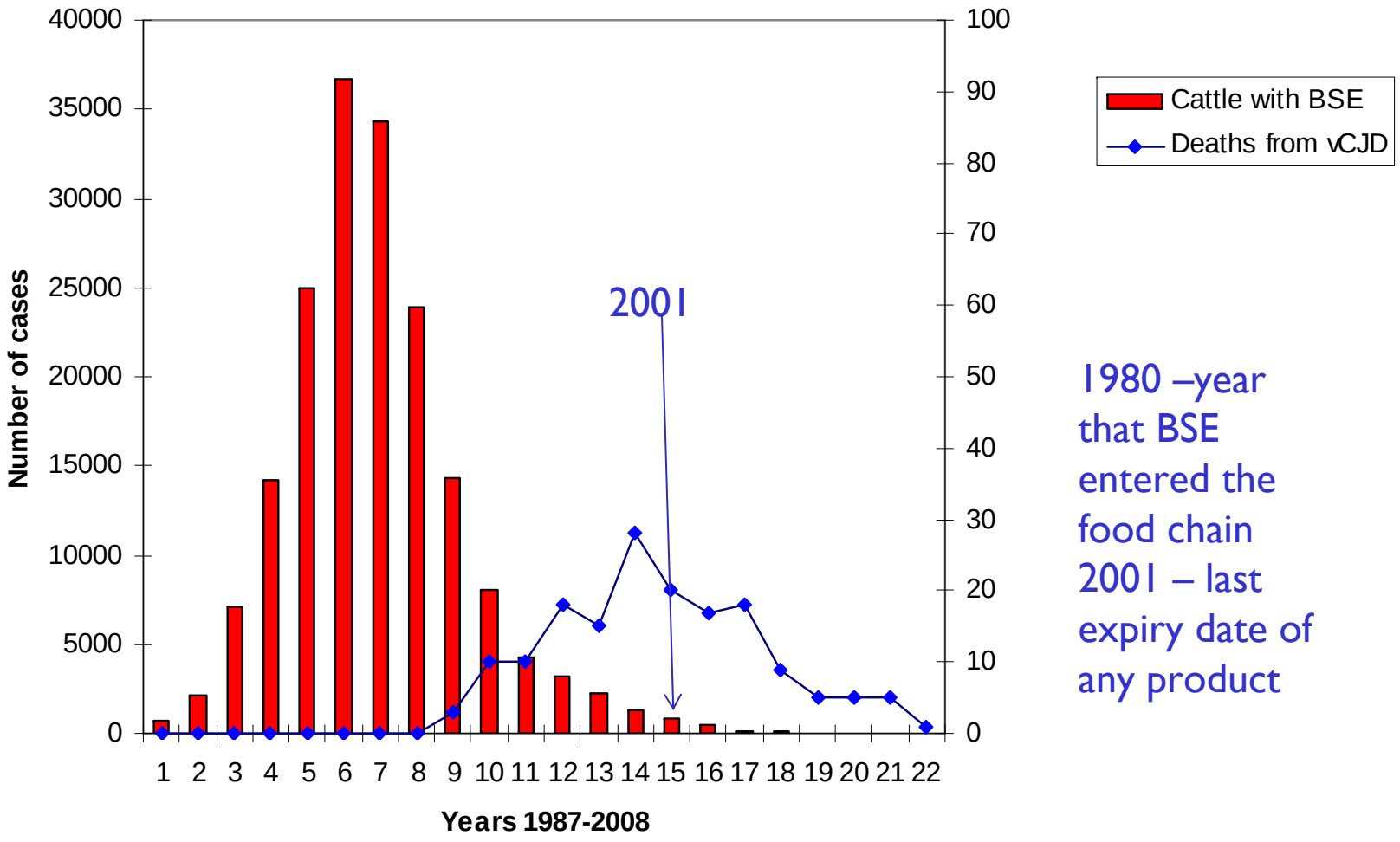
Table 5. Comparison of sporadic and variant Creutzfeldt-Jakob disease

	Sporadic CJD	Variant CJD
Mean age at death (years)	67	29
Mean duration of illness (months)	4	13
Psychiatric symptoms at onset	Rare	Common
Rapidly progressive dementia	Common	Rare
Sensory symptoms	Rare	Common
PrP^{Sc} distribution	Central nervous system	Central nervous system and lymphoid tissues

See WFH monograph vCJD by James Ironside (www.wfh.org)

Relationship between 2 epidemics

The BSE and vCJD time course



1980 –year that BSE entered the food chain

2001 – last expiry date of any product

vCJD

- No screening test currently
  - Test in the process of validation
- No treatment
- No cure
- So, are people with bleeding disorders at higher risk of
  - being infected with the prion agent?
  - Getting symptomatic disease?

vCJD Timelines in UK

- 1980
  - First year BSE assumed to have entered human food chain
- 1998
  - Last year BSE in food chain
  - Last year that products were made from U.K. plasma
- 2001
  - Final expiry date of factor manufactured in 1998

CJD Known Transmission

- BSE contaminated beef
- Medication (growth hormone)
- Contaminated medical equipment from high risk procedures
- Infected transplant material (dura mater)

More recently,

- Blood transfusion (4 cases)

VARIANT CREUTZFELDT-JAKOB DISEASE CURRENT DATA (JULY 2009)

COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	CUMULATIVE RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	165 (4)	3 (0)	168
France	25 (1)	-	1
Republic of Ireland	4 (0)		
Italy	1 (0)		
USA	3† (0)		
Canada	1 (0)		
Saudi Arabia	1 (1)	-	0
Japan	1* (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0

The total number of cases is very small in relation to the UK population of 61 million many of whom will have consumed infected meat

Transfusion safety in the UK

- Withdrawal and recall of any blood components or plasma derivatives obtained from any individual who subsequently develops vCJD from Dec 1997
- Use of non-UK plasma for fractionation by October 1999
- Importation of frozen plasma for children born since 1996
- White blood cell removal for all red cell units implemented autumn 1999 – estimated remove 40% infectivity
  - All 4 cases were related to non-leucodepleted blood
- Exclusion of donors who have received transfusion in UK since 1980

Retrospective review of haemophilia

- HIV positive haemophiliacs with consent for post mortem were restudied for prions (RFH, Oxford, Edinburgh)
- 33 patients treated with concentrates 1962-1995
- No prion protein found and no evidence of spongiform encephalopathy
- To date (October 2009) no cases reported in haemophiliacs

Lee et al. Thromb Haemost 1998; 80: 909-911

Prion transmission by blood transfusion-1

- Clearly demonstrated in experimental animals (sheep) in pre-clinical stage of disease at rate of at least 36%
- Human transmission in 5 cases so far
  - Patient developed vCJD in 2003. The patient was transfused in 1996 from a donor who developed vCJD in 1999
  - July 2004 – patient transfused in 1999 from a patient who developed vCJD 18 mo later. Recipient died of unrelated causes 2004 and prion found in spleen and one lymph node at post mortem. No evidence of brain disease.
  - **These two cases led to change in policy**

vCJD Risk for Recipients of UK Plasma Products

- “All patients with bleeding disorders…who have received clotting factors derived from UK-sourced plasma between 1980-2001 should be considered at risk for vCJD for public health purposes.”
- 4,000+ U.K patients notified

vCJD risk assessment 2004

- Have recipients of British plasma products 1980-2001 been exposed to the infectious agent?
  - Therefore have increased risk of developing vCJD
  - Could pass the agent on to others
- Level of risk unknown but likely to be low
- Complex risk assessment
- Concluded that such people have an additional 1% increased risk compared to the rest of the British population.

vCJD risk assessment 2004

- At risk
  - Haemophilia A and B
  - FXI deficiency
  - Recipients of intravenous immunoglobulin
  - Antithrombin deficiency
- Obligatory notification and special precautions related to surgery and endoscopy to avoid potential transmission

What advice?

- Do not donate blood
- Do not donate organs or tissues
- Tell doctors, surgeons, dentists
- Best to also tell family in case of emergency surgery
- Note made in hospital records and GP notes
- Care should not be compromised in any way

Prion transmission by blood transfusion- 2

- February 2006 – patient developed vCJD 8 years after receiving blood from a donor who developed CJD 20 months after donating
- January 2007 Patient developed symptoms of vCJD 8 yrs after blood transfusion from donor who developed vCJD 17 mo after donation
- January 2009 A man with haemophilia investigated at autopsy found to have prion in his spleen. (Death unrelated to vCJD). He had received batches of UK FVIII concentrate to which a donor who subsequently developed vCJD had contributed

vCJD and UK

- 18 blood donors later developed vCJD
- Their blood / components went to 66 recipients
- 4 cases of vCJD from these blood transfusions
- Of the 18 blood donors, the plasma components of 11 have contributed to 25 plasma pools from which 191 plasma product batches have been made
- 16 batches of FVIII and 8 batches of FIX were manufactured containing plasma from these donors between 1980 and 2001

Are plasma derivatives likely to be infectious?

- '..experimental spiking studies show that there are steps in the manufacturing process which remove prions...'
- 'the starting level of infection in plasma from UK donors remains unknown'
- 'The risk from UK plasma products is likely to have been low but it cannot be assumed that the risk is zero'

Joint UKBTS/NIBSC Professional advisory committee Position statement March 2009

February 15, 2009

guardian.co.uk

Haemophiliac caught CJD from plasma donor

Patient given clotting factors from UK blood is first haemophiliac thought to have human form of BSE

Health Protection Agency

- Confirmation of likely infection by blood transfusion caused assessment of transmission by other blood products
- First information to patients - Sept 2004
- Second information to patients - Feb 2009 following prions found in haemophiliac at autopsy
- Interference with surgery
  - Problems with endoscopy
  - Need for dedicated endoscopes

vCJD and UK - 2009

- Person with Hemophilia A died of cause unrelated to vCJD in late 2008
- > age 70
- Person did not have vCJD
- Person received UK plasma derived “implicated” batch of FVIII
- Heterozygous M/V genotype
- Autopsy carried out (Part of haemophilia study)

vCJD and UK - 2009

- Autopsy – Prions observed in spleen
  - Not in the gut, stomach, brain, tonsils
- Low amount – observed in 1 of 14 samples
- Risk Factors
  - UK FVIII (multiple treatments, some from implicated batches)
  - Blood (15 units - none known from donor who later developed vCJD)
  - Surgery
  - Diet ?
- Decided that most likely source was FVIIIC infusions from non-implicated batches

What Does This Mean?

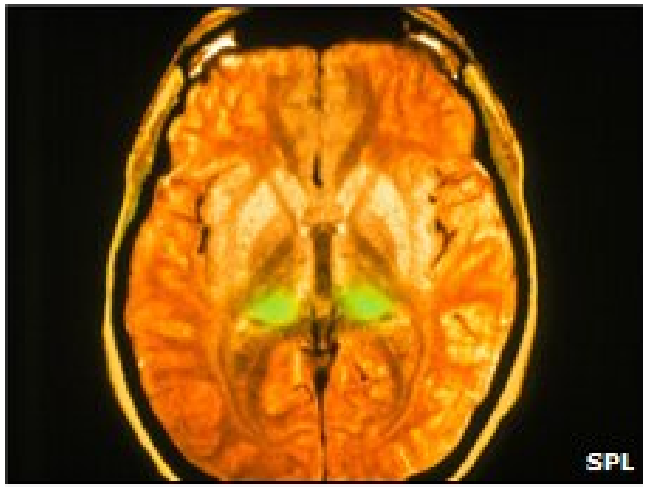
- Likely that plasma-derived factor concentrates containing donations from infected donors can transmit vCJD
- Risk relevant to those who received UK plasma-derived factor in the UK between 1980 and 2001
- Whether or not the patient would have gone on to develop vCJD is unknown
- Surveillance is critical

UK Health Protection Authority Statement

- This new information does not change he way any patients with bleeding disorders will be treated.
- Although this case suggests that those patients exposed to contaminated products in the past may be at risk for vCJD, it does not mean that current plasma-derived products on the market today carry such a risk.

vCJD carrier risk 'overestimated'

Far fewer people may have the human form of mad cow disease in the UK than previously feared, Health Protection Agency researchers have said.



There have been 168 definite or probable cases of vCJD in Britain

There have been 168 definite or probable cases of variant Creutzfeldt-Jakob disease (vCJD) since 1995.

Previous calculations had suggested thousands of people could be incubating the disease.

But the new research, in the British Medical Journal, found no evidence of vCJD in 63,000 tonsil tissue samples.

The researchers said the results, reported in the British Medical Journal, were "reassuring".

A government advisor said the study suggested that the number of future cases would be low.

There has been much debate over how many people in the population might be harbouring vCJD.

Impact on Patients

- Suffering discrimination due to being ‘at risk for health purposes’
- Yet another infection following HIV and HCV – “....will it never end?”
- Uncertainty over vCJD and the risks
- Are haemophilia patients are being singled out as an easily identifiable group?

Blood test for vCJD

- A test has been developed (Amorfix)
  - Run on >1600 UK samples
  - >30,000 French samples
- 99.9% specificity
- Contract signed with UK DH
- Likely to be introduced for blood donor screening
- Patients have heard about it and have already requested screening

Data presented at the WFH Global Forum Sept 2009

Issues

- What are the expectations of patients in the UK?
- Do they want to be tested and if so to know the results?
- Who will do the tests?
- What support will be available?
- What would be the implications of a positive test in terms of health care?

UK Haemophilia Society Position

- We call for any test for vCJD to be brought in as soon as available and with proven efficacy
- “Gold standard” Pre and Post Test Counselling and funding for on-going helpline support

vCJD – Future Meeting with Department of Health

Purpose:

- for people with haemophilia to
  give their views and experiences as
  people at risk of vCJD
- to inform people with haemophilia, and those responsible for their care of current vCJD issues
- describe opportunities for participation in research studies

Hope to see you there