Research paper

Is there evidence of vertical transmission of variant Creutzfeldt–Jakob disease?

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ABSTRACT

Objectives The possibility of vertical transmission of variant Creutzfeldt–Jakob disease (vCJD) has been raised because of the widespread distribution of infectivity in vCJD and the demonstration that this condition can be transmitted through blood transfusion. The aim of this study is to search for evidence of this type of transmission of vCJD.

Methods A national surveillance system for CJD has been established in the UK since 1990. Through this register, details were extracted of all children born to vCJD cases up to March 2009. This list was checked against the CJD register and cases identified through the UK study of Progressive Intellectual and Neurological Deterioration in children to determine whether any of the children of vCJD cases had themselves developed a progressive neurological disorder or vCJD.

Results 125 children were born to parents with a diagnosis of vCJD. Nine of these children were born to females with vCJD who were symptomatic at conception, birth or within a year of clinical onset. Only one woman was known to have breast fed her child. None of the children of vCJD cases have been referred to the National CJD Surveillance Unit as suspected vCJD and none have been classified as suffering from a progressive neurodegenerative disorder through the Progressive Intellectual and Neurological Deterioration study. One of the children has been investigated by the National Prion Unit (see accompanying case report).

Interpretation To date there is no evidence of vertical transmission of vCJD. However, the incubation period through this mechanism might be prolonged and it will be many years before observational data can exclude this possibility.

Transmissible spongiform encephalopathies (TSEs) are a group of neurodegenerative diseases including scrapie, bovine spongiform encephalopathy (BSE) and the human forms, Creutzfeldt–Jakob disease (CJD) and kuru. There are four main types of CJD defined by aetiology. Sporadic CJD is of unknown cause. Familial CJD is associated with mutations of the prion protein gene. Iatrogenic cases are caused by transmission of infected material inadvertently during medical or surgical procedures—for example, human pituitary hormone injections and human dura mater grafts. Variant CJD (vCJD) was first identified in 1996 and is due to infection with the BSE agent. To date, there have been 168 cases of vCJD in the UK with a mean age of onset of 28 years. Unlike sporadic CJD, which tends to affect an older population, the majority of the variant cases have been of reproductive age and concerns have been raised about the possibility of vertical transmission of infection from mother to child.[1]

There is a weight of epidemiological evidence in both kuru and sporadic CJD suggesting that these diseases are not vertically transmitted. However, vertical transmission may be more likely in vCJD. Prion protein is readily detectable in lymphoreticular tissues, including tonsil, spleen, lymph nodes and appendix in vCJD whereas in sporadic and iatrogenic cases it is not detectable extraneurally using comparable methods. There is also evidence of transmission of vCJD via blood transfusion[2–4] whereas epidemiological data do not implicate blood transfusion as a mechanism of transmission in sporadic CJD.

These concerns stimulated a review of the available UK data to assess the possibility of vertical transmission of vCJD.

METHODS

A prospective surveillance system was set up in 1990 at the National CJD Surveillance Unit (NCJDSU) with the identification of all suspected cases of CJD in the UK as a primary objective. Following the emergence of vCJD in 1996, an enhanced surveillance system was established and this included the Progressive Intellectual and Neurological Deterioration (PIND) study aimed at identifying cases of vCJD in the paediatric population. Methods for case ascertainment and classification have been described previously.[5 6] For this report, the NCJDSU register was used to identify all probable or definite cases of vCJD as defined by published diagnostic criteria. A list of children born to these cases was obtained from questionnaires completed by relatives at the time of referral to the surveillance unit. The date of clinical onset of vCJD was established from the questionnaires and medical records and, if this was within 1 year of a child's birth, for children born to affected women the obstetric notes were requested. Detailed information was obtained on children born to women rather than men because there is no evidence in TSEs of paternal transmission of infection. No further medical details were available on the children unless they were subsequently referred to the NCJDSU or to the PIND study.

RESULTS

A total of 125 children were born to parents with a diagnosis of vCJD. In one of the 168 vCJD cases we have no information on whether they had children (a case diagnosed outside of the UK). In 57%, the affected parent was the mother (71/125)

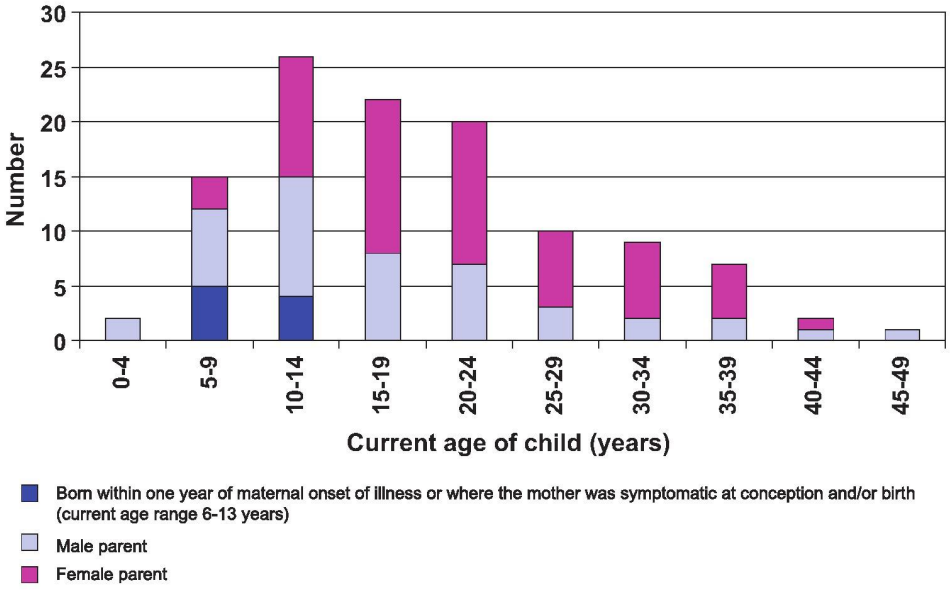

Figure 1 Current age of children of variant Creutzfeldt–Jakob disease (vCJD) cases.

and in 43% the father (53/125). For nine of these individuals we have limited information and they are not included in the following analyses.

The current age range of the remaining 116 children is 3–45 years (figure 1). Seventeen children were born within a year of parental onset of vCJD (table 1) but in only eight cases was the parent symptomatic at birth and in only four cases were they symptomatic at conception. Figure 1 includes the current age of nine children born to female vCJD cases who were symptomatic at conception, birth or within a year of onset. These children range in age from 6 years to 13 years. Regarding the obstetric history of the nine women who were symptomatic within a year of giving birth, five of the nine deliveries involved surgical instrumentation, including three Caesarean sections. Seven of the nine required sutures post delivery. The baby's condition was good in eight of the nine cases, with only the child born to case No 5 causing ongoing concern. Only one of the nine women was known to have breast fed. There is no available information on placenta from these cases.

Table 1 Children born to vCJD cases within a year of parental onset of symptoms

Case No	Gender of parent	Classification	Symptomatic at conception?	Symptomatic at birth?
1	F	Definite	Yes	Yes
2	F	Definite	No	No
3	F	Definite	No	No
4	F	Definite	No	No
5	F	Definite	Yes	Yes
6	F	Probable	No	Yes
7	F	Probable	No	Yes
8	F	Probable	No	Yes
9	F	Probable	No	No
10	M	Definite	No	No
11	M	Definite	No	Yes
12	M	Definite	No	No
13	M	Definite	No	No
14	M	Definite	No	No
15	M	Definite	Yes	Yes
16	M	Definite	No	No
17	M	Probable	Yes	Yes

vCJD, variant Creutzfeldt–Jakob disease.

None of the children of vCJD cases has been referred to the NCJDSU as suspected vCJD and none has been classified as cases suffering from progressive intellectual and neurological deterioration through referral to the PIND surveillance system. One child has been investigated by the National Prion Unit (see accompanying case report in press).

DISCUSSION

We have found no evidence to indicate vertical transmission of vCJD based on data collected in the UK. This is consistent with animal models of TSEs and epidemiological evidence in both kuru and sporadic CJD in which there is no evidence of vertical transmission of infection. The higher incidence of kuru in women and children is explained by greater exposure to high titre tissues during ritual cannibalism in comparison with men who were less likely to consume CNS tissue.[7]

In scrapie the evidence is controversial. There is a high frequency of scrapie in lambs born to infected ewes but it is unclear whether this relates to transmission in utero or to horizontal transmission of infection post partum. A study of pregnant scrapie infected ewes demonstrated PrP^{sc} positivity only in the endometrium and chorioallantoin.[8] The fetus may be protected in utero due to separation from the chorioallantoin by PrP^{sc} negative amnion. Lambs may be infected soon after birth by lateral transmission via close contact, ingestion of PrP^{sc} positive placenta or possibly via milk.[9] However, studies do indicate the possible occurrence of in utero transmission of scrapie in sheep.[10] In BSE, the possibility of vertical transmission was examined in a cohort study which produced equivocal results.[11] However, there is a restricted peripheral pathogenesis of the BSE agent in cattle which contrasts with clear evidence of prion protein immunostaining and infectivity in lymphoreticular tissues in vCJD. The probability that blood contains infectivity in vCJD[12] enhances concerns about the possibility of vertical transmission of infection although there is no evidence to date of vertical transmission of BSE in sheep despite transmissibility through blood transfusion.[13]

While current UK data on vCJD do not provide evidence of vertical transmission, there are a number of caveats. In animal models, PrP^{sc} titres rise through the incubation period with the highest levels around the time of clinical symptoms and it is

likely that progeny born closer to disease onset will be at higher risk of infection. In this study, only nine women had children within a year of vCJD onset and if vertical transmission was possible, but rare, the observed population may be too small to identify transmission by this route.

The precise incubation period for vCJD contracted by oral ingestion of BSE contaminated food is unknown but estimated to be 12–23 years.[14] There are no data to allow predictions of the incubation period from vertical transfer. In iatrogenic cases, the route of transmission influences incubation periods, which range from under 2 years with direct CNS contamination to over 30 years with infection by a peripheral route.[15] Many of the children born to vCJD parents are relatively young, with 17 currently less than 10 years of age and all of the children born to mothers within a year of clinical onset less than 14 years of age. Furthermore, the genotype at codon 129 of the prion protein gene may influence susceptibility and incubation period. To date, all clinical cases of variant CJD have been methionine homozygous but vCJD has been transmitted to a codon 129 heterozygote via blood transfusion[12] and it is possible that heterozygote offspring could have a more prolonged incubation period. No data are available on the codon 129 genotype in the offspring of vCJD cases. A longer period of follow-up is necessary to exclude the possibility of vertical transmission of vCJD.

Irrespective of the issue of vertical transmission in vCJD there are implications related to pregnancy. Seven of the deliveries reviewed in detail required surgical instrumentation or sutures but in only one case was the diagnosis of vCJD suspected at the time of the delivery. In most cases the instruments will have undergone routine sterilisation and may have been reused.

To date there is no evidence to indicate vertical transmission of vCJD in the UK but data are limited and the period of observation in children of vCJD cases is relatively short. Evidence from natural and experimental BSE does not indicate vertical transmission of infection but an extended period of follow-up will be necessary to exclude this possibility in vCJD.

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Competing interests None.

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Contributors KM and JP extracted and collated the information in this paper, LS, AMW and CV manage the PIND study, RGW initiated, planned and supervised the study. All authors were involved with the writing of the paper.

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REFERENCES

1. **Gore SM.** Bovine Creutzfeldt–Jakob disease? *BMJ* 1996;**312**:791–3.
2. **Llewelyn CA,** Hewitt PA, Knight RSG, *et al*. Possible transmission of variant Creutzfeldt–Jakob disease by blood transfusion. *Lancet* 2004; **363**:417–21.
3. **Hewitt PE,** Llewelyn CA, Mackenzie J, *et al*. Creutzfeldt–Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. *Vox Sang* 2006;**91**:221–30.
4. **Wroe SJ,** Pal S, Siddique D, *et al*. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt–Jakob disease associated with blood transfusion: a case report. *Lancet* 2006;**368**:2037–9.
5. **Cousens SN,** Linsell L, Smith PG, *et al*. Geographical distribution of variant CJD in the UK (excluding Northern Ireland). *Lancet* 1999;**353**:18–21.
6. **Verity CM,** Nicoll A, Will RG, *et al*. Variant Creutzfeldt–Jakob disease in UK children: a national surveillance study. *Lancet* 2000;**356**:1224–7.
7. **Will RG,** Wilesmith JW. Response to the article: 'Vertical transfer of prion disease' by Lacey and Dealler. *Hum Reprod* 1994;**9**:1792–800.
8. **Tuo W,** Zhuang D, Knowles DP, *et al*. PrPc and PrPsc at the fetal-maternal interface. *J Biol Chem* 2001;**276**:18229–34.
9. **Konold T,** Moore SJ, Belworthy SJ, *et al*. Evidence of scrapie transmission via milk. *BMC Vet Res* 2008;**4**:14–24.
10. **Foster J,** Goldmann W, Parnham D, *et al*. Evidence for the in utero transmission of scrapie in sheep. *First International Conference of the European Excellence NeuroPrion* 2004;**83** (Abstract).
11. **Donnelly CA,** Gore SM, Curnow RN, *et al*. The bovine spongiform encephalopathy maternal cohort study: its purpose and findings. *Appl Stat* 1997;**46**:299–304.
12. **Peden AH,** Head MW, Ritchie DL, *et al*. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004;**364**:527–9.
13. **Foster JD,** Goldmann W, McKenzie C, *et al*. Maternal transmission studies of BSE in sheep. *J Gen Virol* 2004;**85**:3159–63.
14. **Valleron A-J,** Boelle P-Y, Will R, *et al*. Estimation of epidemic size and incubation time based on age characteristics of vCJD in the United Kingdom. *Science* 2001;**294**:1726–8.
15. **Brown P,** Preece M, Brandel J-P, *et al*. Iatrogenic Creutzfeldt–Jakob disease at the millennium. *Neurology* 2000;**55**:1075–81.