Creutzfeldt–Jakob disease and urinary gonadotrophins

Dear Sir,

Recent contributions to the debate regarding the use of urinary gonadotrophins and their potential risk of transmission of variant Creutzfeldt–Jakob disease (vCJD) have prompted us to clarify some issues. In their letter, Matorras and Rodriquez-Escudero (2003) wrongly cite the incidence of vCJD as 1 per million. The annual mortality in the UK (where 93% of the cases have occurred worldwide to date) is 0.3 cases per million of the population. In their letter, they state that, although there is theoretical risk of transmission of vCJD based on the work done by Shaked *et al*. (2001), uncertainty cannot be resolved until a 'systematic search of a history of urinary gonadotrophins among patients with vCJD' has been addressed. At the National CJD Surveillance Unit, we obtain a detailed medical history from relatives, which is corroborated using hospital and primary care records.

Of 143 cases of vCJD to date in the UK, 63 were females and one of these cases had a history of treatment for infertility from 1998 to 1999, with a latency of 20 months from the start of treatment to the onset of clinical symptoms. The treatment included clomiphene, four cycles of treatment with Normegon and Pregnyl, three cycles of Puregon and Pregnyl, and finally treatment with Suprecur and Puregon. Two additional cases are reported as having attended gynaecological out-patients for menorrhagia and carcinoma of the cervix. This compares with two community controls (out of 95 women) with a history of treatment for infertility. Both are known to have received clomiphene and, although one regularly attended for infertility treatment, no further details are available. One additional control had a history of attending gynaecological out-patients and had a dilatation and curettage.

Thus there is a history of treatment with both urinary-derived and recombinant gonadotrophins in a single case of vCJD in comparison with a history of infertility treatment in two community controls who received clomiphene and possibly no other therapy. Approximately 2% of live births occur in the context of infertility treatment, and that a single case of vCJD out of 63 cases had a history of infertility treatment is not surprising. The question arises as to whether the infertility treatment and, in particular, urinary-derived gonadotrophins may have been the cause of vCJD in this case. The minimum incubation period in iatrogenic CJD related to peripheral

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inoculation with human growth hormone (and in kuru) is 4.5 years (Brown *et al*., 2000) and involved sourcing of infectivity from the pituitary gland, in which there are high levels of infectivity. The potential incubation period in the case of vCJD undergoing infertility treatment was a maximum of 20 months and urinary gonadotrophins are likely to contain very low levels of infectivity, if any. There is an inverse relationship between dosage and incubation period in prion diseases, and the very short potential incubation period in this case indicates that infertility treatment is very unlikely to have been the source of infection. It is also of note that the urine used for the extraction of gonadotrophins and bovine serum used in the production of recombinant gonadotrophins currently are sourced from countries free of bovine spongiform encephalopathy and vCJD (Balen, 2002).

The question also arises as to whether sporadic CJD could have been transmitted through urinary gonadotrophin treatment, which has been used widely over the last 40 years, long before the advent of vCJD. Sporadic CJD typically occurs in those over the age of 60 years (median age at death is 67 years), although the range is wide (20–95 years) and, therefore, there is the potential for some cases to have donated urine while pregnant or post-menopausally. The data gathered on 169 female cases of sporadic CJD referred to the National CJD Surveillance Unit show that none had a reported history of treatment for infertility, nor a history of receiving urinary gonadotrophins.

In conclusion, we are continuing to collect data at the National CJD Surveillance Unit on a wide range of potential mechanisms of secondary transmission of CJD, including infertility treatment. To date, there is no strong evidence to support the suggestion that vCJD (or in fact sporadic CJD) has been acquired through receiving urinary gonadotrophins.

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References

Balen A (2002) Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? Hum Reprod 17,1676–1680.

Brown P, Preece M, Brandel JP, Sato T, McShane L, Zerr I, Fletcher A, Will RG, Pocchiari M, Cashman NR et al. (2000) Iatrogenic Creutzfeldt–Jakob disease at the millennium. Neurology 55,1075–1081.

Matorras R and Rodriguez-Escudero FJ (2003) Prions, urinary gonadotrophins and recombinant gonadotrophins. Hum Reprod 18,1129–1130.

Shaked GM, Shaked Y, Kariv-Inbal Z, Halimi M, Avraham I and Gabi R (2001) A protease-resistant prion protein isoform is present in urine of animals and humans affected with prion diseases. J Biol Chem 276,31479–31482.

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