

Iatrogenic Creutzfeldt–Jakob disease in Australia: time to amend infection control measures for pituitary hormone recipients?

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In Australia, from 1967 to mid 1985, treatment for short stature and infertility with cadaver-acquired pituitary hormones (human growth hormone [hGH] and human pituitary gonadotrophin [hPG], respectively) was provided through the Australian Human Pituitary Hormone Program (AHPHP).¹ The program was suspended in mid 1985 in response to the recognition of a link between hGH therapy and the development of Creutzfeldt–Jakob disease (CJD) in a young hormone recipient in the United States.² CJD is an incurable and rapidly progressive neurodegenerative disorder and one of the transmissible spongiform encephalopathies. As of mid 2010, 25 years after the moratorium on the AHPHP, and 20 years since an Australian recipient developed CJD, we present a likely, and we hope, final assessment of the Australian experience of medically transmitted CJD from human-derived pituitary hormone therapy, and compare our experience here with that in other countries.

The Australian experience

In total, four Australians have had their deaths from CJD attributed to pituitary hormone therapy, with the most recent occurring in early 1991. Unique to Australia, these four deaths were related to treatment with hPG: three had CJD confirmed at autopsy and the fourth was classified as “probable CJD” after evaluation by the Australian National Creutzfeldt–Jakob Disease Registry (ANCDJR) using World Health Organization surveillance criteria.³

The death of an Australian hGH recipient in 1991 is considered unlikely to be the result of CJD, as this person had numerous confounding comorbidities. However, in the absence of relevant premortem investigations and an autopsy, this case was conservatively classified as “possible CJD” and, as such, is excluded from formal epidemiological analyses and incidence data.

The Box summarises the total number of hPG and hGH recipients in Australia and in selected, larger national human pituitary hormone programs in other countries. It also shows the number of deaths from CJD among these recipients, and the relative risk of developing CJD for recipients in each country. Each national pituitary hormone treatment program has only ever confirmed iatrogenic CJD in either hPG (Australia only) or hGH recipients, never in both. This is an empirical observation, the reasons for which are not understood; however, it spans many countries and thousands of recipients over a period of 25 years.

Abbreviations

AHPHP	= Australian Human Pituitary Hormone Program
ANCDJR	= Australian National Creutzfeldt–Jakob Disease Registry
CJD	= Creutzfeldt–Jakob disease
hGH	= human growth hormone
hPG	= human pituitary gonadotrophin
PRNP	= prion protein gene

ABSTRACT

- From 1967, the Australian Human Pituitary Hormone Program offered treatment for short stature and infertility using human cadaver-acquired pituitary hormones (human growth hormone [hGH] and human pituitary gonadotrophin [hPG]). The program was suspended in 1985 when a growth-hormone recipient in the United States developed Creutzfeldt–Jakob disease (CJD), an incurable and rapidly progressive neurodegenerative disorder.
- Since this time, recipients have lived with the significant anxiety that they have an elevated risk of developing CJD. Furthermore, additional CJD infection control measures are required when recipients undergo some types of surgery.
- As it is 20 years since the last Australian pituitary hormone recipient developed CJD, we evaluated the risk for Australian recipients of developing iatrogenic CJD, and compared Australian data with data from New Zealand and selected other countries who had pituitary hormone programs.
- Our evaluation indicates that pituitary hormone recipients in Australia have the lowest risk of developing iatrogenic CJD, and that Australia is the only country not to have experienced ongoing CJD-related deaths. Thus, we believe that:
 - in the Australian hGH recipient cohort, the risk of developing CJD is sufficiently low for this cohort to no longer require additional infection control measures in the health care setting; and
 - in the Australian hPG recipient cohort, if another 5 years elapses with no further occurrence of CJD in this group, the hPG recipient cohort could also be considered as not requiring additional infection control measures in the health care setting.
- These recommendations should not be misunderstood as implying that there is no ongoing risk, but that the risk is acceptably low and generally in keeping with guidelines that stratify the risk.

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The Australian figures are presented in two sets. The first gives the recipient numbers reported in the 1994 *Report of the inquiry into the use of pituitary derived hormones in Australia and Creutzfeldt–Jakob disease* (known as the Allars report),¹ and the second gives the recipient numbers published in 1999 by the Australian Government Department of Health and Ageing (DoHA).⁴ Both sets of recipient numbers are included for transparency. Discrepancies between the sets could be attributed to early audits of program lists providing the number of patients approved for treatments, and later figures representing only those recipients confirmed by DoHA as having received treatments.

Summary of the number of recipients of cadaver-acquired human pituitary gonadotrophin (hPG) and human growth hormone (hGH) in five countries; the number of related deaths from Creutzfeldt–Jakob disease (CJD); and the relative risk of recipients in each country developing CJD using total national recipient numbers — data to December 2008

Country	No. of hPG-related deaths	No. of hPG recipients	hPG risk (%)	No. of hGH-related deaths	No. of hGH recipients	hGH risk (%)	Total risk (%) (hGH and hPG)	Year of last recipient death
Australia*	4 [†]	1589 ¹	0.25%	1 [‡]	906 ¹	0.11% [‡]	0.16%	1991
		1363 ⁴	0.29%		608 ⁴	0.16% [‡]	0.20%	
France	0	0	0	115	1700	6.76%	6.76%	2008
New Zealand	0	154 [§]	0	6 ^{¶5}	159 ^{**7}	3.77%	1.92%	2004
United States	0	0	0	28	~ 7700	0.36%	0.36%	2007
United Kingdom	1 [†]	~ 300 ^{††}	0	57 ⁶	1849 ⁸	3.08%	2.65%	2008

* The two recipient totals for Australia are derived from two different reports,^{1,4} and most likely represent the difference between patients approved for treatments (larger number) and those confirmed as having received treatments. Two corresponding risk calculations are given.

† One Australian hPG recipient is reported by both Australia and the UK; treatment took place in Australia, but disease onset and death occurred in the UK. This case is not included in Australian incidence figures, but for the purpose of this risk assessment, this recipient is analysed with the Australian hPG recipients only.

‡ This "possible CJD" case does not appear in Australian CJD incidence figures, and calculations of total risk exclude this case.

§ This total comprises nine hPG recipients with hormone source unknown; 37 recipients of Australian hPG; 29 recipients of US hPG; and 67 recipients of NZ hPG. A further four recipients received Australian and NZ hPG, three received Australian and US hPG, and four received US and NZ hPG. One recipient received hPG from all three sources (Medicines and Medical Devices Safety Authority [Medsafe], Ministry of Health, NZ, February 2009).

¶ These NZ recipients received US-sourced hGH (Medsafe, Ministry of Health, NZ, January 2010).

** This total comprises 34 recipients of US hGH, 15 recipients of US and Australian hGH, 94 recipients of NZ hGH, 12 recipients of Australian and NZ hGH, and four recipients of Australian- and/or Swedish-sourced hGH (Medsafe, Ministry of Health, NZ, February 2009).

†† Professor R G Will, The National CJD Surveillance Unit, Edinburgh, UK, personal communication, February 2009.



The four Australian hPG recipients who developed CJD all had disease onset in the period 1987–1990, which is consistent with a single, discrete contamination event and, most likely, effective removal of prions through routine pituitary processing methods. The now 20-year interval since an Australian recipient developed CJD offers some reassurance to recipients, who have, since 1985, lived with the anxiety that they have an elevated risk of developing CJD. It is considered unlikely that national surveillance has missed identifying a further CJD illness in an Australian hGH or hPG recipient, especially given the heightened awareness of this possibility among AHPHP recipients and their families, and the significant improvements in premortem diagnostic tests since 1993, when CJD surveillance commenced in Australia. Annual incidence rates of CJD reported by the ANCDJR have increased over time,⁹ in line with anticipated improvements in case ascertainment afforded by a dedicated national surveillance unit and better diagnostic tools.^{10,11} Families of all patients with CJD ascertained by ANCDJR are also routinely asked for details of any past medical history, and in particular hormone-related treatments.

International comparisons

Incubation period

In Australia, there has been a 20-year interval since a pituitary hormone recipient developed CJD. This contrasts with the ongoing occurrence of CJD in hGH recipients in other countries, where, with the exception of New Zealand, hGH-related CJD cases have continued to be diagnosed and deaths reported (Box). The most recent death from CJD of an NZ recipient occurred in 2004 after an incubation period of 37 years (the incubation period is calculated from the mid-treatment point to the onset of

symptoms). The most recent death from CJD of a US recipient occurred in 2007 (reported in 2008), with 30 years elapsing before the onset of symptoms — the longest US incubation period to date. In both the United Kingdom and France, there were deaths of recipients in 2008, and these cases represent the longest incubation periods reported for each country, 32 and 24 years, respectively (Professor R G Will, The National CJD Surveillance Unit, Edinburgh, UK, personal communication, February 2009). Overall, the longest incubation period is currently believed to be 38 years, occurring in a recipient in the Netherlands who received several doses of hGH for diagnostic purposes.¹² By comparison, the longest incubation period reported in an Australian recipient is 15.3 years, with incubation periods in Australia ranging from 12 to 15.3 years.

Risk in relation to pituitary hormone source country

Both the total risk (hPG and hGH) and the hGH-only risk of pituitary hormone-related CJD in NZ and the UK are similar (Box), although the hGH product used in NZ until the late 1970s was predominantly manufactured in a laboratory in the south-eastern US. Earlier reports recorded 46 of a total of 184 hGH recipients in NZ¹³ as receiving hormone product processed in the US before 1977, the year when the hormone extraction method in the US was changed.¹³ The total number of hGH recipients on the NZ CJD Registry (159 individuals)⁷ was recently confirmed by the Medicines and Medical Devices Safety Authority (Medsafe), Ministry of Health, NZ, in February 2009. Up to the end of 2008, the six NZ hGH recipients who subsequently died of CJD all received US-sourced hormone product. The risk rate of CJD for the NZ recipients of US-sourced hGH (6/49) is 12.2%.

The explanation for the striking difference between US and NZ hGH risk rates — less than 0.5% compared with close to 4% — is

not entirely clear;¹³ however, the US hormone product received by NZ patients is not thought to be identical to that received by US patients.¹⁴ Potential differences include the final post-purification processing steps performed in the two countries; that is, the final pooling and filtering of material to eliminate bacterial contamination before placing the hormone product in sterile ampoules (Dr A Parlow, Director, National Hormone and Peptide Program, Harbor-UCLA Medical Center, Torrance, Calif, USA, personal communication, February 2009). For example, these final post-purification steps were performed manually in NZ on much smaller volumes than those used in the US.

As in Australia, in NZ, hPG was administered for infertility. There were a total of 154 NZ recipients of hPG Medsafe, Ministry of Health, NZ, January 2010). The risk analysis for these recipients can be differentiated into four groups, based on the source of the hormone administered: Australia only (37 recipients), the US only (29), NZ only (67 — from 1978),¹ and mixed sources (12). The risk for nine NZ recipients is unknown, as the hPG source was not recorded.

Recalculating the risk of developing CJD after adding the number of NZ recipients of any Australian-processed hPG to the total number of Australian hPG recipients results in no significant change in Australian risk rates; the risk of CJD in recipients of hPG processed in Australia is 0.24%–0.28%, a negligible shift of 0.01% (Box).

The risk for NZ recipients of US- and NZ-sourced hPG can be considered zero, as no CJD-related deaths have occurred in either recipient group. In contrast, combining the number of recipients of US-processed hGH in the US and NZ (7749) with the total number of CJD deaths in those countries (34) increases the US risk rate for iatrogenic CJD to 0.44%.

Risk in relation to pituitary hormone purification processes

As described by Huillard d'Aignaux¹⁵ et al and Brown et al,¹³ higher-risk periods apparently exist for recipients of hGH in France and the US. Acknowledging the unusual biophysical properties of prions, including their resistance to conventional sterilisation measures,^{16,17} these higher-risk periods are considered to relate to differences in extraction and purification methods of human-derived pituitary hormones altering the infectivity of contaminated preparations.^{18–20} As a potential example, through to the end of 2008, all hGH recipients who developed CJD in the US received their hGH treatment before 1977, the year a column chromatography purification processing step was introduced; this step was considered to have significantly reduced, but not necessarily eliminated, contaminating prions.²¹ The risk estimate for US recipients treated before 1977 is 1%.¹³ The progressively lengthening intervals of absence of iatrogenic CJD cases in US hGH recipients treated after 1977 suggest that, as in Australia, this recipient group may have a considerably lower, perhaps a negligible, risk of developing iatrogenic CJD.

The overall risk of human pituitary hormone-related CJD in France is calculated at 6.8%. The higher-risk period for French hGH recipients occurred between 1982 and mid 1985; all iatrogenic CJD cases occurred in hGH recipients treated in that period. As in the US, processing changes were implemented from mid 1985, especially universal urea-inactivation of hGH, which is believed to have significantly lowered the prion transmission risk. In this higher-risk period, Huillard d'Aignaux et al¹⁵

reported that 1361 people were treated with hGH in France between January 1982 and July 1985, with an 8.4% risk of developing CJD, while Brown et al¹³ reported 1260 individuals receiving hGH in France between January 1983 and July 1985, with a 9.1% risk.

Limitations to further refinement of the risks for Australian recipients

The information available for UK hGH recipients⁸ and Australian hPG and hGH recipients does not clearly identify higher-risk periods. The UK has reported deaths from CJD in recipients treated over the entire program period — without temporal clustering. Unfortunately, the information available about the treatments administered to Australian pituitary hormone recipients is incomplete: batch numbers of hormones and the number of treatments from each batch administered are not available for all recipients. The absence of complete treatment details for all AHPHP recipients precludes further refinement of the risk for Australian recipients. In addition, the polymorphic codon 129 status of the prion protein gene (*PRNP*) is generally considered a risk factor for hGH-related iatrogenic CJD.²² However, *PRNP* genotyping of the four Australian hPG recipients who developed CJD showed no clear association: two were homozygous for methionine, one for valine, and the fourth was heterozygous.²³ This mixed result reduces the utility of codon 129 assessment for determining the risk of developing CJD in other Australian hPG recipients. Notwithstanding such limitations, the combined total risk of iatrogenic CJD for AHPHP recipients is relatively low at 0.16%–0.20%.

Time to re-evaluate the need for infection control measures for Australian recipients?

Our assessment shows that the Australian recipient community has the lowest risk of developing iatrogenic CJD of all the countries studied, and Australia is the only country not to have experienced ongoing CJD-related deaths. This is positive news for the AHPHP recipient community. Beyond any emotional or psychological benefits stemming from the confirmed, low absolute number and low relative risks of pituitary hormone-related CJD in Australia, as well as the absence of further occurrences of CJD among the treated cohort over the past 20 years, we believe these data prompt reconsideration of the current infection control measures for the Australian recipient community.

For Australian hGH recipients: given the absence of confirmed iatrogenic CJD in hGH recipients in Australia, and the freedom from any instances of pituitary hormone-related CJD over the past 20 years, we believe that the risk of developing CJD for members of the Australian hGH recipient cohort is sufficiently low for them to no longer require additional infection control precautions in the health care setting.²⁴

For Australian hPG recipients: a revision of infection control measures is less clear-cut and more contentious, principally due to the long incubation periods reported among hGH treatment cohorts in other countries where there is an established risk. Nevertheless, if another 5 years elapses²⁵ with no further occurrence of CJD in this Australian recipient group, we believe that an absence of iatrogenic CJD over a 25-year period would suggest that the residual risk is acceptably low, and that the Australian

hPG recipient cohort could also be considered as not requiring additional infection control measures in the health care setting.

These recommendations should not be misunderstood as implying that there is no ongoing risk, but that the risk is acceptably low and generally in keeping with guidelines that stratify the risk.²⁶

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Competing interests

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