Iatrogenic Creutzfeldt–Jakob disease

The waning of an era

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Abstract—The outbreaks of iatrogenic Creutzfeldt–Jakob disease (CJD) from cadaveric human growth hormone and dura mater are winding down and, like the only other environmentally acquired form of CJD (variant CJD due to infection with the agent of bovine spongiform encephalopathy), iatrogenic disease seems to have reached its high water mark during the 1990s. The total number of cases has reached 405, and the diminishing number of new cases is due to extremely long incubation periods from infections acquired before 1985 (up to 23 years for dura mater and 36 years for growth hormone). Although no cases associated with surgical or other invasive procedures have been identified during the past several decades, the recent discovery of three transfusion-associated variant CJD infections has provoked new concerns about the possibility of further secondary transmissions from operative procedures as well as blood and tissue donations. Therefore, at least in those countries in which variant CJD has occurred, precautionary measures must continue for the indefinite future.

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Five years have passed since the last review of iatrogenic Creutzfeldt–Jakob disease (CJD), and although the total number of cases has increased from 267 to 405 (table 1), the downward trend that was already beginning in 2000 has continued (figure). In particular, the outbreaks of disease due to contaminated human growth hormone (hGH) and dura mater grafts have largely subsided and, apart from variant CJD (vCJD) transfusion-associated disease, the new cases that occur each year are the result of longer and longer incubation periods following infections acquired during the 1980s.

These long incubation cases have significantly extended the maximum range and median values of incubation periods after infection by contaminated hGH or dura mater, but the clinical presentations have not changed (table 2). A homozygous genotype at PRNP codon 129 continues to be overrepresented in cases of iatrogenic disease (as in all other forms of CJD), but the duration of the incubation period remains uninfluenced by the genotype except in French hGH cases, where it is positively correlated with a heterozygous genotype. A further interesting observation is that florid plaques such as those found in vCJD have been seen in the brains of several dura mater–associated cases.

Apart from codon 129 homozygosity, risk factors seem to have differed in each of the three countries in which outbreaks of hGH-related CJD occurred (table 2). In the United States and United Kingdom, the risk of being infected was clearly much diminished when size exclusion chromatography replaced the original organic solvent extraction, but additional factors were duration of treatment in the United States, and age at onset of treatment (8 to 10 years) in the United Kingdom. In France, hormone was always extracted using ion exchange chromatography, and the fact that all cases shared a limited treatment period between December 1983 and June 1985 suggests that a major contamination event, or events, occurred at some time during this period, due to the presence of pituitary tissue from one or more CJD patients and cross-contamination of multiple batches of hormone. For dura mater graft recipients, the only risk factor was the use of Lyodura brand grafts processed before 1987, when an NaOH disinfection step was added to the processing protocol (only a very few cases were associated with non-Lyodura grafts).

There have been no new cases of iatrogenic disease (or at least none identified) due to corneal grafts or cross-contamination of instruments used for surgical or invasive medical procedures, although we are aware of several instances in which patients with unsuspected CJD underwent neurosurgery or donated ocular tissues. This is both

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Table 1 *Global distribution of cases of iatrogenic Creutzfeldt–Jakob disease*

	Surgical procedures				Hormone therapy		Blood transfusion
	Dura mater grafts	Surgical instruments	EEG needles	Corneal transplants*	Growth hormone†	Gonadotropin	Packed red cells‡
Argentina	1						
Australia	5				1	4	
Austria	2						
Brazil					1		
Canada	4						
Croatia	1						
France	13	1			107		
Germany	8			1			
Holland	2				1		
Ireland	1						
Italy	4						
Japan	123						
New Zealand	2				6		
Qatar					1		
South Africa	1						
Spain	10						
Switzerland	1		2				
Thailand	1						
United Kingdom	7	3			51		3
United States	3			1	26		
Totals	196	4	2	2	194	4	3

* Additional possible single cases after corneal transplant or keratoplasty (not included in the table) occurred in Japan, the United Kingdom, and the United States.

† Brazil and New Zealand human growth hormone (hGH) was prepared in the United States; Qatar hGH was prepared in France. Additional possible single cases due to hGH (not included in the table) occurred in The Netherlands, Scandinavia, and New Zealand.

‡ Donors had variant CJD.

gratifying and surprising, in view of the fact that standard hospital decontamination procedures are suboptimal for sterilization of the infectious agent of CJD. Although it is possible that this unblemished record might be tainted by a failure to report such cases, it seems more likely that it reflects a level of donor screening and/or decontamination that even if suboptimal is adequate to prevent disease transmission. Additional protection is afforded by comparatively inefficient peripheral routes of infection in general surgery and medical instrumentation.

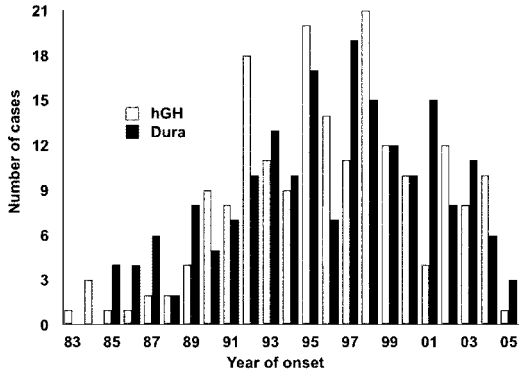

Figure. Symptomatic onset of iatrogenic Creutzfeldt–Jakob disease in patients infected by contaminated human growth hormone (hGH) or dura mater grafts, as of January 2006. The earliest dura mater case (not shown) occurred in the United States in 1978. Some additional growth hormone and dura mater cases with onsets after long incubation periods are likely to be diagnosed in 2006 (and beyond).

However, the recent appearance of three transfusion-associated vCJD transmissions after incubation periods of 6 to 8 years indicates that in this form of disease, the IV route is efficient (primary vCJD infections have an estimated average incubation period of 10 to 13 years). Also, one of the disease-transmitting donations was made more than 3 years before the donor became symptomatic, raising concerns about further secondary vCJD cases via blood or tissue donations and surgical instrument contamination from a possibly large number of "silently infected" (and thus currently undetectable) individuals.

With respect to iatrogenic disease as a whole, it can be said that the diminishing number of cases is the result of a quarter century of improvement in the diagnosis of CJD, which has minimized donor risk, and a better understanding of the ways by which contamination from patients who do escape detection can be thwarted by a rigorous application of disinfecting procedures. Our earlier obituary of iatrogenic CJD was premature; now, finally, the casket is nearly closed.

Table 2 *Clinical features of iatrogenic Creutzfeldt–Jakob disease according to the mode and route of infection*

Mode of infection	Agent entry into brain	Mean incubation period (range)	Clinical presentation
Corneal transplant	Optic nerve	18 and 320 mo	Dementia/cerebellar
Stereotactic EEG	Intracerebral	16 and 20 mo	Dementia/cerebellar
Neurosurgery	Intracerebral	17 mo (12–28 mo)	Visual/dementia/cerebellar
Dura mater graft	Cerebral surface	11 y (16 mo–23 y)	Cerebellar (visual/dementia)
Growth hormone	Hematogenous (?)	15 y (4–36 y)*	Cerebellar
Gonadotrophin	Hematogenous (?)	13 y (12–16 y)	Cerebellar
Blood transfusion	Hematogenous (?)	6.5 and 8 y†	Psychiatric

* Median and range were 12 (4 to 22) years in France; 17 (8 to 27) years in the United Kingdom; and 21 (10 to 28) years in the United States. The case with the longest incubation period (36 years) occurred in a New Zealand patient (hormone prepared in the United States).

† The incubation period of a third case is unknown, as the transmission was discovered only by detection of the pathognomonic misfolded protein in spleen and lymph node at autopsy in a patient with neither neurologic symptoms nor brain pathology, who died from an unrelated disease 5 years after having received contaminated blood (i.e., in a preclinical or subclinical stage of Creutzfeldt–Jakob disease).

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Citations are organized chronologically according to the category of iatrogenic disease and include nearly all published references known to the authors for definite, probable, and possible cases (a few repetitive superseded articles have not been listed, and many dura mater and growth hormone cases identified in ongoing Creutzfeldt–Jakob disease surveillance programs remain unpublished).

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