Clinical Study

Iatrogenic Creutzfeldt-Jakob disease via surgical instruments

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A B S T R A C T

Creutzfeldt-Jakob disease (CJD) is a neurodegenerative prion disease that can spread via contaminated neurosurgical instruments previously used on an infected patient. We examine current guidelines on how to recognize, handle, and prevent instrument-related iatrogenic CJD. Despite only four reported patients worldwide implicating contaminated neurosurgical instruments, and none in the past 30 years, the public health consequences of potential instrument-related iatrogenic CJD can be far-reaching. Conventional sterilization and disinfection methods are inadequate in reducing prion infectivity of contaminated instruments, and World Health Organization recommendations for disinfection using bleach or sodium hydroxide are often impractical for routine decontamination. Recently, possible CJD exposure via infected surgical instruments was suspected at a large teaching hospital. Although CJD was later dis-proven, the intervening investigation exposed the difficulty in tracking infected surgical instruments and in protecting subsequent surgical patients from prion infection. To identify patients at risk for iatrogenic CJD, infectivity of instruments after this index patient is estimated using simple scenario modeling, assuming a certain log reduction of infectivity for each cleansing cycle. Scenario modeling predicts that after six cycles of instrument use with conventional cleansing following an index patient, other patients are highly unlikely to be at risk for iatrogenic CJD. Despite its rarity, the threat of iatrogenic CJD transmission via contaminated instruments poses tremendous challenges to neurosurgeons. Basic prevention strategies should be employed for patients with suspected CJD, including use of disposable instruments where possible and quarantining non-disposable instruments until the diagnosis is ascertained, or using special instrument reprocessing methods if CJD is suspected.

1. Introduction

Creutzfeldt-Jakob disease (CJD) is a uniformly fatal neurodegenerative disease thought to be caused by a prion—a transmissible and infectious protein agent. Clinically, it presents as rapidly progressive dementia, often with myoclonus, ataxia, and multifocal neurologic signs. Like other prion diseases, the pathologic hallmark is spongiform changes in the brain caused by intracellular vacuoles in neurons and glia. There are three forms of CJD: iatrogenic, familial, and sporadic. Although the sporadic form constitutes 85% to 90% of CJD, 1,2 the possibility of iatrogenic transmission offers tremendous challenges to the neurosurgical community. Of the iatrogenic patients reported globally, four were likely caused by transmission from contaminated neurosurgical instruments previously used on infected patients. 3 Although this reported number is low, animal studies have shown standard hospital instrument sterilization to inadequately prevent transmission of prion agents. 4 Because neural tissue carries the highest infectious burden in affected patients, neurosurgical procedures have the potential for high transmission rates of CJD. These facts, combined with the long incubation period and the need for tissue sampling for definitive diagnosis, create the theoretical possibility of uncontrolled CJD transmission through neurosurgical procedures. Neurosurgeons must gain familiarity with this disease and understand the threat of spread via contaminated instruments. They must be aware of the possibility of CJD in patients considered for surgery, ensure proper protocols are followed in procedures when it is suspected, and prevent further propagation by contaminated instruments. Current knowledge and theories of these facets of the disease will be reviewed here. The following patient illustrates how the threat of unsuspected instrument-related iatrogenic CJD can challenge even a large tertiary care center.

2. Case report

An 85-year-old woman presented with a 1 year history of progressive gait and short-term memory deficits, but no urinary incontinence. Brain CT scans (Fig. 1) and MRI revealed enlargement of the lateral and third ventricles, with an Evans ratio of 0.36. After
a large-volume lumbar puncture, she had temporary improvement in her gait so the decision was reached to place a ventriculo-peritoneal (V-P) shunt. In the operating room, a right frontal Codman programmable valve V-P system (Codman & Shurtleff, Raynham, MA, USA) with a Rickham-style reservoir was successfully placed. Postoperatively the patient noted initial improvement in her symptoms.

Nearly 2 months after surgery, the patient presented to the emergency room with a 12 hour history of disorientation, a moderate expressive aphasia, mild weakness of bilateral upper and lower extremities, twitching of her upper extremities, and a temperature of 37.9 °C. CT scans and MRI showed no evidence of shunt malfunction or acute intracranial process. Lumbar puncture and shunt tap revealed only mild pleocytosis consistent with the presence of her V-P shunt hardware. All cultures, including cerebrospinal fluid (CSF), remained sterile. Over the next 3 days after admission, her mental status continued to decline. Repeat electroencephalograms (EEG) showed disorganized activity and triphasic waves but no definite periodic sharp wave complexes, and 14-3-3 protein immunosassay testing of her CSF was moderately positive. Although the patient’s clinical picture, including fever, sudden deterioration, and lack of MRI findings, did not suggest prion disease because of these positive tests and the lack of other probable causes, CJD was considered the probable diagnosis by the consulting neurology service. Eighteen days after admission, the patient’s suspected prion disease and poor prognosis was discussed with her family, service. The ethics committee deliberated on whether actual risk to subsequent patients was sufficiently high to justify disclosing to families the possibility of exposure. At the height of this response, the patient expired in hospice 2 weeks after discharge from the hospital. An autopsy of the brain was performed at the USA National Prion Disease Pathology Surveillance Center. One month after instrument quarantine, pathology from the final autopsy report showed lymphocytic vasculitis, with no evidence of CJD.

3. Discussion

3.1. Epidemiology and pathophysiology

CJD is the most common of the prion diseases, which also include variant CJD (vCJD), Gerstmann-Straussler-Scheinker syndrome, Fatal Familial Insomnia, and kuru. Eighty-five percent of patients die within 12 months of diagnosis, with a mean survival from symptom onset of 7.3 months. The annual age-adjusted incidence in the United States is approximately one case per 1,000,000 population and the median age at death is 68 years. The incubation period for iatrogenic CJD is highly variable, but appears to average 18 months.2

The transmissible agent in CJD – the prion – is exceptionally stable and inherently less susceptible to standard methods of sterilization. The prion is thought to be PrPSc, a protease-resistant and conformationally different form of a normal cellular protein, PrP. Homozygosity for a polymorphism at codon 129 in the gene encoding the prion protein (PRNP gene) is associated with sporadic or iatrogenic CJD, and especially with vCJD.

3.2. Diagnosis of CJD

At the present time, definitive diagnosis of CJD can only be made by brain biopsy or autopsy, but immunocytochemical analysis and Western blot to detect PrPSc can also aid in attaining definitive diagnosis. In the absence of a tissue sample, clinical signs combined with ancillary tests are used to arrive at a probable diagnosis of CJD. The World Health Organization (WHO) has published clinical diagnostic criteria for CJD that includes progressive dementia and at least two other neurologic signs (Table 1). Ancillary tests that can suggest the presence of CJD include MRI, EEG, and CSF testing. MRI can show cerebral atrophy, bilateral hyperintense signal in the caudate and putamen and/or cortical ribbon hyperintensity, and MRI sensitivity and specificity for CJD has been reported as high as 92% and 93%, respectively (Fig. 2). Bi- and tri-phasic waves and/or periodic sharp-wave complexes on EEG are other typical findings. Using strict objective diagnostic EEG criteria, one study reported a sensitivity of 61% and a specificity of 93%. CSF testing for the 14-3-3 protein is useful only in the correct clinical setting. According to published results, the sensitivity is 93% and the specificity 84%. However, the incidence of CJD is so low that the utility of this test is limited to patients who meet the clinical diagnostic criteria for CJD. In unselected patients with dementia, its positive predictive value is only 14.3%.

Fig. 1. Preoperative CT scan of brain without contrast showing enlargement of lateral and third ventricles with some sulcal prominence in a patient with suspected Creutzfeldt-Jacob disease.
Table 1
World Health Organization’s clinical diagnostic criteria for probable Creutzfeldt-Jakob disease

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<th>Progressive dementia</th>
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<td>At least 2 out of the following 4 clinical features:</td>
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<td>- Myoclonus</td>
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<td>- Visual or cerebellar disturbance</td>
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<td>- Pyramidal/extrapyramidal dysfunction</td>
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<tr>
<td>- Akinesia</td>
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Typical electroencephalogram during an illness of any duration and/or:
- Positive 14-3-3 cerebrospinal fluid assay, in the appropriate clinical setting, and a clinical duration to death <2 years
- Routine investigations should not suggest an alternative diagnosis

Electroencephalogram interpretation:
- Strictly periodic activity (variations in inter-complex intervals are no higher than 500 ms; periodic activity is continuous for at least one 10 second period).
- Bi- or tri-phasic morphology of periodic complexes.
- Duration of majority of complexes 100–600 ms.
- Periodic complexes may be generalized or lateralized but not regional or asynchronous.

3.4. Iatrogenic transmission from contaminated instruments

All proven or probable cases of iatrogenic CJD have arisen from exposure to infected brain, pituitary, dura mater, or eye tissue, unlike its cousin disease, vCJD, in which a wider variety of tissues have proven infectivity. Most (95%) involved dura mater grafts and human growth hormone (HGH), with virtually all of these cases occurring before the advent of improved screening of dural grafts and the use of recombinant HGH in the 1980s. There have been only four reported patients implicating contaminated neurosurgical instruments as the cause of iatrogenic CJD. The original report describes the admission of three cases of CJD in patients 18 to 24 months after they had undergone invasive neurosurgical procedures concurrently with several other patients with CJD, and a fourth patient was reported in France. Unfortunately, details of the instrument sterilization process used were not published. Contaminated neurosurgical implants, such as depth and multi-contact electrodes, have also been implicated.

In the past several decades, no known cases of CJD transmitted by contaminated medical instruments have occurred. This may reflect inefficient transmission, the effectiveness of conventional instrument sterilization and cleaning, and improved precautions after recognition of the disease. However, despite these few reported patients, many laboratories have examined prion infectivity after disinfection methods and have found high infectivity of contaminated instruments and poor inactivation of PrP, the infective agent.

3.5. Infectivity of tissues

Experimental studies have demonstrated that the infectious agent may be present in many body tissues. Based on the rates of successful experimental transmission, the risk of infection from different tissue types are categorized as high, low, or none. Brain, spinal cord, and eye tissue offer a high risk of infection, as successful experimental transmission using these tissues has been achieved in greater than 50% of attempts. CSF, liver, lymph node, kidney, lung, and spleen are considered low risk because of poor success with experimental transmission and no epidemiologic evidence of infection. Tissues in the no-risk category have not produced a single successful experimental inoculation to our knowledge. The infectious burden of tissue is often measured in infectious units per gram, where 1 infectious unit is the amount that will produce a successful transmission of the disease 50% of the time (the ID$_{50}$). Infectivity within the central nervous system (CNS) is low in the early incubation stage but increases as the disease develops.

3.6. Decontamination methods

Disinfectant and sterilization procedures for CJD have been thoroughly studied in the laboratory, and practical methods to achieve sufficient log-reductions in infectivity titers have been sought but are sorely lacking. However, none of these studies accurately reflect the reprocessing procedures employed in clinical settings. Importantly, these studies do not combine disinfection with the cleaning process, which in the case of microbes, account for a significant 4- to 6-log reduction in contaminant burden. Moreover, several studies now show that the use of alkaline and enzymatic detergents effectively eliminate the infectivity of prions.

The most effective but certainly not the least expensive solution to difficulty with sterilization is to use disposable instruments. If contaminated instruments need to be reprocessed, the CDC recommends that the most stringent WHO procedures should be considered. The methods outlined in Annex III of the WHO guidelines are summarized in Table 2. The guidelines generally recommend disinfection with bleach (NaOCl) or 1 M sodium hydroxide (NaOH), either alone or with autoclave. Unfortunately, these treatments are damaging to instruments and not practical for routine decontamination. The USA Food and Drug Administration investigators
found that bleach agent especially caused severe damage to some instruments, though mostly cosmetic.\textsuperscript{33} Rutala and Weber\textsuperscript{30} recently published special prion instrument reprocessing guidelines after reviewing experimental studies for both safety and efficacy. After cleaning, medical devices that have contacted high-risk tissues should be sterilized in one of four ways:

- **Option 1.** Autoclave at 134 °C for 18 minutes in a pre-vacuum sterilizer.
- **Option 2.** Autoclave at 132 °C for 1 hour in a gravity displacement sterilizer.
- **Option 3.** Immerse in 1 M NaOH for 1 hour; remove and rinse in water, then transfer to an open pan and autoclave (121 °C gravity displacement sterilizer or 134 °C porous or pre-vacuum sterilizer) for 1 hour.
- **Option 4.** Immerse in 1 M NaOH for 1 hour and heat in a gravity displacement sterilizer at 121 °C for 30 minutes, then clean and subject to routine sterilization.

### 3.7. Estimating infectivity of contaminated instruments and identifying at-risk individuals

The CJD Incidents Panel and the WHO recommend that while an index patient awaits a definitive CJD diagnosis, possibly contaminated instruments should be quarantined indefinitely. However, as in our patient, if the diagnosis of CJD was not entertained prior to the procedure, subsequent patients who were operated on who are “at-risk” for iatrogenic CJD need to be identified. Facing a similar but larger scale challenge in 2001 with the vCJD scare, the Economics and Operational Division of the Department of Health in the UK prepared a sequential operations model to estimate how many secondary infections could be expected to result from one operation on an infected patient by tracking infective material through the clinical system.\textsuperscript{34} It uses a simple sequential algebraic approach to estimate the amount of infectious unit transfer after each cycle of cleaning. The model assumes an average of 10 mg of infected material on each instrument, as suggested by the Advisory Committee on Dangerous Pathogens and Spongiform Encephalopathy working group, with 20 instruments used per operation and each contacting the same type of tissue as the index case. Each instrument may stay in the same set or may move to another set. The first decontamination cycle was assumed to result in a 10\textsuperscript{5}-fold infectious burden reduction, with each subsequent cycle resulting in a 10-fold reduction. These conservative estimates were based on studies of removal of protein soils from medical devices\textsuperscript{35} and autoclave inactivation of prions.\textsuperscript{6}

Applying this model, the CJD Incidents Panel constructed four scenarios with different levels of tissue infectivity and rates of tissue transfer to estimate the risk of transmission of CJD from contaminated surgical instruments after an index patient and typical instrument processing.\textsuperscript{36} In the pessimistic scenario of tissue infectivity of 10\textsuperscript{10} ID\textsubscript{50}/g, a 10\% transfer rate per instrument, and a 10\textsuperscript{5}-fold reduction in infectious burden with the first decontamination cycle and subsequent 10-fold reduction with each additional cycle.

### Table 2

Recommended methods of instrument sterilization, from Annex III, World Health Organization infection control guidelines for transmissible spongiform encephalopathies\textsuperscript{40}

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<th>Stringency</th>
<th>Cleaning method</th>
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<td>Most severe</td>
<td>Immerse in NaOH and heat in a gravity displacement autoclave at 121 °C for 30 minutes; clean; rinse in water and subject to routine sterilization</td>
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<tr>
<td>Least severe</td>
<td>Immerse in NaOH or sodium hypochlorite (20,000 ppm available chlorine) for 1 hour; transfer instruments to water; heat in a gravity displacement autoclave at 121 °C for 1 hour; clean; subject to routine sterilization</td>
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NaOH = sodium hydroxide.
the CJD Incidents Panel of the UK constructed a graph (Fig. 3) of the likelihood of a transmitted infection based on the cleaning cycle number, using this same tissue infectivity and transfer rate. On this basis, the panel safely concluded that instruments that have undergone a total of 10 cycles are unlikely to pose a significant risk.

This model produces a worst-case scenario to allow planning for and identification of “at-risk” individuals. It certainly does not reproduce the epidemiology of patients with CJD from contaminated instruments. Criteria for “contactable” patients are summarized in Table 3. Those individuals who underwent a “high risk” procedure involving the CNS, eye or dura mater within six decontamination cycles were considered contactable. At our institution, we determined that neurosurgical instruments would have undergone six cycles within 2 months, so all patients who had undergone high-risk neurosurgical procedures within 2 months following the index patient were considered contactable. At our institution, whether to inform these contactable patients was a matter of considerable debate. Given the uncertainty of the diagnosis of an index case and the very few cases of iatrogenic transmission, notifying these patients that they may have acquired a uniformly fatal disease may cause undue stress and harm. On the other hand, anything other than full disclosure may be considered disingenuous.

3.8 Preventative strategies

There are several important institutional measures that should be taken to prevent the reuse of possibly contaminated instruments. At our hospital, it is the responsibility of the neurosurgery service to consider the possibility of CJD in all adult patients, especially those receiving a diagnostic brain biopsy. All patients scheduled for brain biopsy without a mass lesion or CSF abnormalities are automatically considered to have “suspected CJD”. The Department of Infection Control and Epidemiology keeps a registry of all adult brain biopsies, indicating whether or not they involved a patient with suspected CJD and whether CJD precautions were fully observed. Single-use instruments are used whenever possible. When a reusable instrument must be used, it is placed in quarantine until the diagnosis of CJD is ruled out. If the diagnosis is confirmed, the instrument is placed in full-strength bleach and then discarded. The same precautions are extended to asymptomatic patients at high risk for CJD, such as recipients of HGH or dura mater grafts before 1980 or those with a family history of CJD. An alternative to quarantine is to use one of the four special reprocessing options outlined in the recent Society for Healthcare Epidemiology of America guidelines; the methods described in the WHO guidelines involving full-strength bleach tend to be too corrosive for instrument reuse. Of note, there is no evidence of occupational transmission of CJD to healthcare workers, who should employ standard precautions when caring for patients with suspected or confirmed CJD.

In a similar scenario, a system of individually tracking operating room instruments can be invaluable. It would allow only the actual instruments used on infective tissue in an index patient to be quarantined or discarded, rather than eliminating entire sets of instruments. It would also allow identification of the actual subsequent patients who were possibly exposed to the contaminated instruments. Whether the considerable financial commitment for a

![Fig. 3. Scenario modeling of the decreasing risk of infection with successive instrument re-uses. Tissue infectivity $10^{10} \text{ID}_{50}/\text{g}$ (for example, central nervous system tissue in patients with symptoms of Creutzfeldt-Jakob disease).](image)

<table>
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<tr>
<th>Clinical procedure performed on index patient</th>
<th>‘Contactable’ group</th>
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<tr>
<td><strong>High risk procedures</strong></td>
<td></td>
</tr>
<tr>
<td>CNS, retina, optic nerve procedures in patients with symptoms of any type of CJD, or develop symptoms within 1 year of procedure (and within 8 years).</td>
<td>First 6 patients</td>
</tr>
<tr>
<td>CNS, retina, optic nerve procedures in patients who develop symptoms of any type of CJD more than 1 year after procedure and within 8 years.</td>
<td>First 4 patients</td>
</tr>
<tr>
<td><strong>Medium risk procedures</strong></td>
<td></td>
</tr>
<tr>
<td>Other eye tissue procedures, or procedures that might result in contamination of olfactory epithelium</td>
<td>First 2 patients</td>
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CJD = Creutzfeldt-Jakob disease, CNS = central nervous system.
tracking system would not be spent elsewhere is a matter of debate. Nevertheless, many institutions appear to be moving toward more accurate and detailed operating room instrument tracking.

3.9. Future directions

Noninvasive diagnostic modalities such as MRI have shown promise in improving detection of CJD. Combined with the appropriate clinical picture, this may obviate the need for an invasive procedure to obtain a pathology specimen. Currently, peripheral markers of CJD that allow less invasive but accurate diagnosis are lacking. However, the use of olfactory biopsy to diagnose CJD has shown some promise, similar to the use of tonsil biopsy for vCJD. Improved assays to detect infectivity are being developed. In vitro assays exploiting the cell-based amplification of the PrP protein are displaying sensitivity similar to that of bioassays but are much faster and less expensive. New protocols for cleaning, using limited concentrations of alkali or stabilized bleach and shorter exposure times, may produce similar efficacy in removing prions with greater practicality, as compared with the WHO recommended methods. Integrating enzymatic or detergent agents in mechanical washers followed by steam sterilization has shown promise in eliminating prions from metal surfaces. New drying systems using vaporized hydrogen peroxide under vacuum may be more effective in deactivating prions than conventional steam autoclaves. Further validation of these new procedures is needed, however, before special prion instrument reproprocessing can be retired.

4. Conclusions

Clearly, vigorous efforts to study the transmissibility of the spongiform encephalopathies should be continued. Nevertheless, instrument contamination remains a frightening and costly possibility. Despite the low incidence rate of CJD, possible occurrences confront hospitals all too commonly. Institutional responses have been wide-ranging, as hospitals must negotiate science, ethics, public relations, and risk management. A standardized protocol that balances all of these important facets should be developed and adopted by all hospitals.

References