Review

Creutzfeldt-Jakob disease: a systematic review of global incidence, prevalence, infectivity, and incubation

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Creutzfeldt-Jakob disease (CJD) is a fatal disease presenting with rapidly progressive dementia, and most patients die within a year of clinical onset. CJD poses a potential risk of iatrogenic transmission, as it can incubate asymptomatically in humans for decades before becoming clinically apparent. In this Review, we sought evidence to understand the current iatrogenic risk of CJD to public health by examining global evidence on all forms of CJD, including clinical incidence and prevalence of subclinical disease. We found that although CJD, particularly iatrogenic CJD, is rare, the incidence of sporadic CJD is increasing. Incubation periods as long as 40 years have been observed, and all genotypes have now been shown to be susceptible to CJD. Clinicians and surveillance programmes should maintain awareness of CJD to mitigate future incidences of its transmission. Awareness is particularly relevant for sporadic CJD, which occurs in older people in whom clinical presentation could resemble rapidly developing dementia.

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Introduction

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal neurodegenerative disease and is caused by misfolded, transmissible proteinaceous infections particles, or prions. The concentration of CJD prions varies throughout the body of an infected individual but is high in the brain and the posterior eye (retina and optic nerve),[1,2] resulting in neurological symptoms, including rapidly progressing dementia, cerebellar and extrapyramidal signs, and myoclonus and visual symptoms. Most people with clinically diagnosed CJD die within a year of symptom onset.[1]

There are three major groups of human prion disease: sporadic, genetic, and acquired. Sporadic CJD (sCJD) is most common, accounting for about 85% of CJD cases.[3] It generally occurs in late middle age; patients have a mean age of 67 years and short survival post-diagnosis of about 4 months. However, there are at least six different clinicopathological CJD subtypes with variable presentations.[4,5] Although there is evidence of a genetic predisposition to sCJD,[6] the precise cause of the disorder is unknown.

Genetic forms of CJD are associated with pathogenic mutations in the prion protein gene *PRNP* and include familial CJD, fatal familial insomnia, and Gerstmann-Schäussler-Scheinker syndrome. Together, genetic forms of CJD account for between 10–15% of prion diseases.

Acquired forms of CJD include Kuru (related to historical ritualistic cannibalism in Papua New Guinea), iatrogenic CJD (iCJD), and variant CJD (vCJD). Cases of vCJD were observed in the UK population after its exposure to bovine spongiform encephalopathy (BSE) during the late 1980s and early 1990s. The disease was presumably transmitted through consumption of BSE-infected beef. The vCJD epidemic peaked in 2000 with 28 deaths in the UK and has since declined with only two definite or probable deaths reported in the UK, three in France, one in Italy, and one in the USA since 2012. Compared with sCJD, vCJD occurs in a younger age group (mean age 26 years at onset) and has a longer clinical manifestation (median 14 months).[1] All people who contracted symptomatic vCJD have died. A key pathological finding in people with vCJD is extensive lymphoreticular deposition of prion protein that is not seen in other forms of CJD[7] and, notably, this deposition is present during the disease's preclinical phase (figure 1). Most iatrogenic CJD (iCJD) cases have been reported after procedures for dura mater grafts and growth hormone treatment, with a few cases resulting from electroencephalography (EEG), neurosurgery, or receipt of corneal grafts, gonadotrophin, or packed red blood cells.[8] Iatrogenic transmission could potentially occur during surgery when instruments are used in high-risk neurosurgical procedures in patients who have asymptomatic CJD but who are infectious because neural tissue has a high infectious load.[9]

More than 15 years have passed since the vCJD epidemic but iCJD is still a potential public health risk. The long asymptomatic incubation periods noted in some cases of CJD, the difficulties of neutralising prions from neurosurgical instruments,[10] the high infectious titres of brain tissue,[11] and a presumed subclinical underlying prevalence in the general population[12] mean that there is a

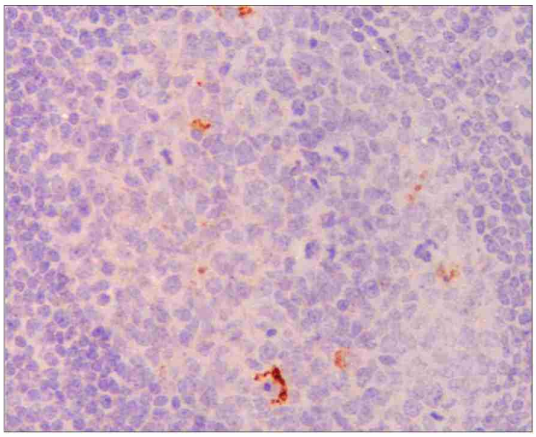

Figure 1: **Immunohistochemistry using an antibody to prion protein (brown staining) showing abnormal accumulation in an appendicectomy specimen taken from an individual 8 months before the onset of symptoms of variant Creutzfeldt-Jakob disease**
Magnification ×200.

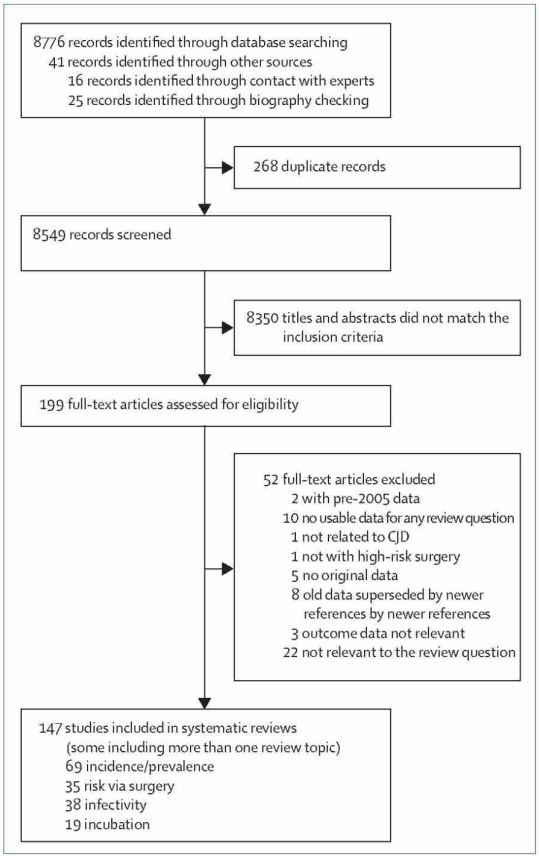

Figure 2: **PRISMA diagram of study inclusion**

	Period of estimation	CJD incidence or mortality per million people
Sporadic CJD		
Australia[16]	1993–2018	1·25
Austria[16]	1993–2018	1·52
Belgium[16]	1997–2018	1·17
Canada[16]	1994–2018	1·05
Czech Republic[16]	2000–2018	1·20
Cyprus[16]	1995–2017	1·04
Denmark[16]	1993–2018	1·47
Estonia[16]	2004–2018	0·32
Finland[16]	1997–2017	1·41
France[16]	1993–2018	1·60
Germany[16]	1993–2018	1·33
Greece[16]	1997–2008	0·62
Hungary[16]	1997–2018	1·07
Italy[16]	1993–2018	1·42
Netherlands[16]	1993–2018	1·23
Norway[16]	1995–2018	1·02
Slovakia[16]	1993–2018	0·86
Slovenia[16]	1993–2018	1·46
Spain[16]	1993–2018	1·28
Switzerland[16]	1993–2018	1·73
Taiwan[17]	1998–2007	0·55
UK[18]	1993–2018	1·24
Excluding vCJD		
Germany[16]	1993–2017	1·33
Hungary[16]	1997–2018	1·07
Netherlands[16]	1993–2018	1·23
Sweden[16]	1997–2017	1·42
USA[19]	2016	1·22
All CJD types		
Argentina[20]	2008	0·85
Japan[21]	1999–2015	1·3

CJD=Creutzfeldt-Jakob disease. vCJD=variant CJD.

Table 1: **Global estimations of CJD incidence by country from studies published in 2005 or after**

margin of uncertainty around detecting and quantifying the risk of CJD transmission. The work on this Review updated systematic reviews from 2005[13] and underlay a wider research project[14] that assessed the risk of surgical CJD transmission to inform the UK National Institute of Health and Care Excellence Interventional Procedures guidelines.[13] We addressed four topics: the incidence of CJD and the prevalence of CJD-related prions in humans, the risk of secondary transmission of prions from surgery, the infectiousness of CJD by disease subtype, and the incubation periods of CJD. Our topic reviews were informed by best practice guidelines[15] and prospectively registered on the PROSPERO database, CRD42017071807. We identified 8776 publications from database searches, 16 from clinical experts, and 25 from the bibliographies of relevant studies. We selected 147 studies that were relevant to our topics, with some papers relevant to more than one review question (figure 2). Full methods and search terms for our systematic review are shown in the appendix.

For the **NCJDRSU** see http://www.cjd.ed.ac.uk/

See Online for appendix

Incidence of CJD

Globally, CJD incidence data are gathered by the CJD International Surveillance Network EuroCJD;[16] however, this online resource was last updated in May, 2015. Data obtained through personal communication with EuroCJD were dated to 2018. UK referrals of suspected, definite, or probable CJD-related deaths are recorded by the National CJD Research and Surveillance Unit (NCJDRSU). This source estimates that since 1990 there have been 3873 UK referrals for investigation and 2541 deaths of definite or probable CJD (as of Jan 31, 2019). The global incidence of CJD is typically reported to be around 1–2 cases per million per year,[16] on the basis of surveillance studies published from 2005 onward (table 1). Reports of increased incidence might be more probable in areas with access to established surveillance units for referring suspected cases of prion disease. In the UK, since 1990, the NCJDRSU has been mandated to actively monitor and identify all CJD cases. By contrast, a Korean study

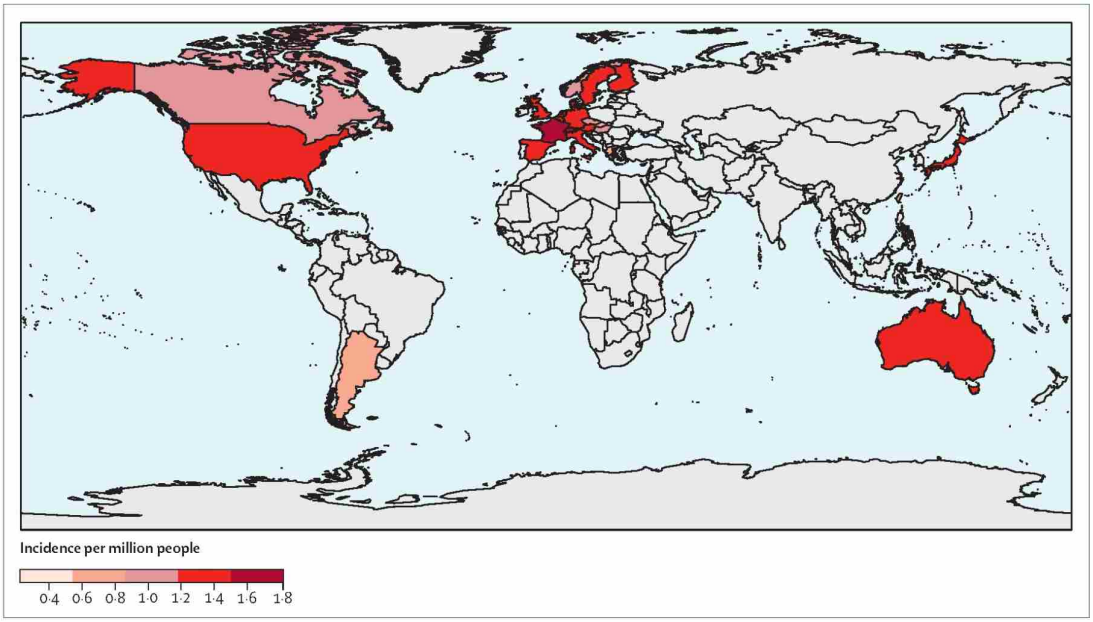

Figure 3: **Global reporting of sporadic Creutzfeldt-Jakob disease incidence per million people**

described that CJD surveillance did not begin in Korea until 2001, and iCJD was not studied in Korea before 2011.[22] Geographical variation in how CJD is detected and reported globally is shown in figure 3.

The number of deaths between 1990 and 2018 that were attributed to definite or probable CJD are recorded in the UK by the NCJDRSU (data captured Jan 31, 2019; figure 4).[18] A steady increase in sCJD cases is apparent over the 28-year period, whereas cases of iatrogenic, genetic, and variant forms have remained low. Unpublished data from the EuroCJD network obtained through personal communication provides estimates for 12 other countries across three continents with data from the same time period of 1996–2018 (figure 5). A less pronounced, but relatively consistent increase in sporadic CJD cases can also be seen with the apparent reduction in cases from 2018, which can be attributed to a delay in obtaining definitive data for the most recent year.

Possible explanations for the increase in the detection of sCJD cases include: improved clinician awareness; an age-specific incidence increase in people aged 55 years and older; an ageing population; population increase; changes to the sporadic case definition; and improvements in diagnostic testing to include cerebrospinal fluid and MRI diagnostic tests. The gradual increase in the incidence of sCJD, but not that of genetic CJD supports the notion that it is a result of the globally ageing population. The increase in sCJD cases only could be taken as evidence that there is a real increase in sCJD.

Case ascertainment is likely to improve in areas where CJD surveillance is strong, where health professionals are increasingly aware of CJD, and where there are more neurologists. This notion is supported by studies in Australia indicating that the intensity of surveillance can impact the estimated incidence of this rare disease.[24,25] Moreover, in the UK, because of the potential for iatrogenic transmission of vCJD, there has been a focused collaborative effort to examine evidence of transmission through different exposures by investigating links to confirmed cases through retrospective studies.[26] The most detailed academic analyses appear to originate from and around countries that have experienced a CJD epidemic

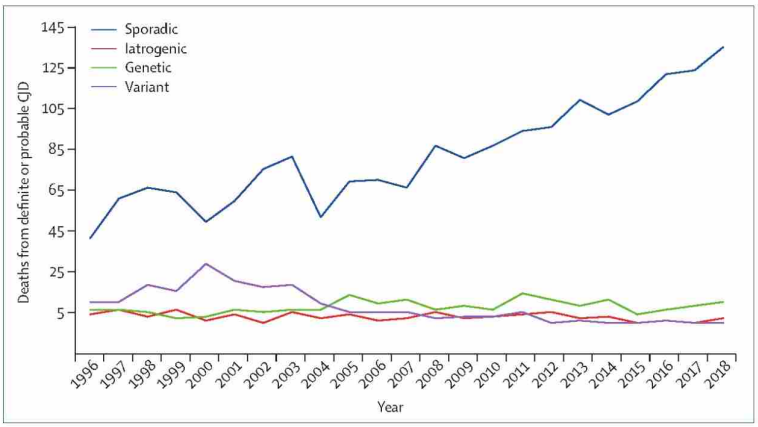

Figure 4: **Deaths from probable or definite Creutzfeldt-Jakob disease in the UK for 1996–2018**
Data were taken from the National Creutzfeldt-Jakob Disease Research and Surveillance Unit.[23]

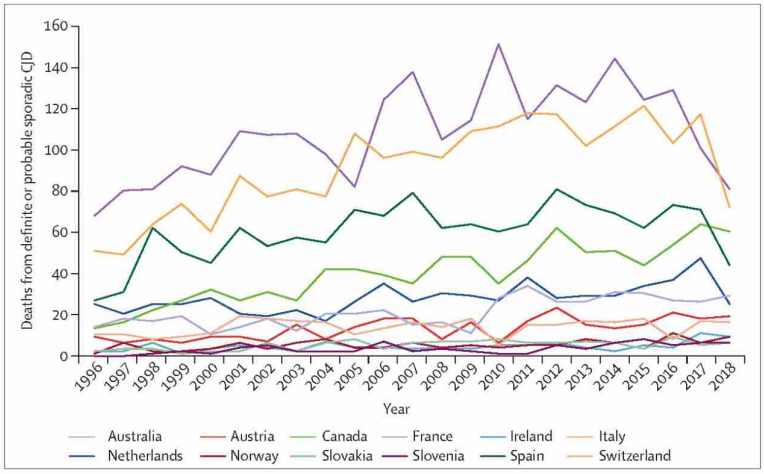

Figure 5: **Deaths from probable or definite sporadic Creutzfeldt-Jakob disease in countries with data for 1996–2018 reported by the EuroCJD network**

or incidences of iCJD (ie, UK, France, USA, and Japan). Published reports of increased incidence of sCJD were noted from other countries. In Finland, an increased incidence of sCJD was noted for the 1974–89 period of 0·6 per million to 1·36–1·44 per million in 2007–13.[27] Additionally, one study reported that sCJD incidence in Taiwan doubled between 2008 and 2015.[28]

Confirmation of CJD from autopsy or brain biopsy is required to obtain a definitive sCJD diagnosis. However, autopsy is not routinely done on patients with sCJD. Only about 50% of all deceased patients in the UK referred to the NCJDRSU are autopsied[1] and this rate is potentially decreasing.[4] The most recent UK case of vCJD appeared, on clinical presentation and neuroimaging, to be sCJD, but as the age of the patient was atypically young (36 years), a neuropathological examination after their death in February, 2016, confirmed vCJD despite the fact that the patient did not exhibit clinical and epidemiological diagnostic signs for probable or possible vCJD.[29] On the basis of this vCJD case, pathological examination of every sCJD case would be necessary to know the true numbers of patients with autopsy-proven sCJD and vCJD. Given this scenario, an alternative possible explanation for the increasing number of sCJD cases in the UK over the past 20 years could be that the altered incubation and clinical presentation of acquired CJD (vCJD or iCJD) appear to mimic sCJD or another neurological condition, as has been shown in murine models.[30] Global differences in pursuing autopsy to confirm any CJD diagnosis and subtype also probably exist, depending on national CJD surveillance protocols and differences in practice and approach.[31–33]

Because the onset of sCJD symptoms occur in people with an older mean age (67 years) than other forms of CJD, it is possible that sCJD cases might be concealed among cases of more commonly encountered but similarly rapidly progressing neurological conditions that affect older people. Numerous reports were noted of sCJD mimicking other conditions including stroke,[34,35] acute neuropathy,[36] hyperparathyroidism,[37] general dementia,[33,38–41] dementia with Lewy bodies,[33] encephalitis,[33] aphasia,[42] Alzheimer's disease,[33,40] psychiatric decompensation,[32] and movement disorder.[33] The potential for CJD cases to be misdiagnosed was first shown in a 1995 study, in which only about 60% of cases of prion disease were identified clinically during life after an analysis of tissue samples from patients who had died from dementia.[44] Therefore, the reported incidence of any type of CJD could still be an underestimate of the actual incidence of deaths due to CJD, in the absence of definitive pathological examination of all cases. It is also plausible that numerous cases of sCJD that occur late in life, particularly in settings where access to clinicians with experience of diagnosing CJD is inadequate, are being misclassified as other neurodegenerative disorders.

The annual number of confirmed cases of clinical vCJD has declined globally since 2005. As of 2016, the NCJDRSU recorded 178 cases of vCJD in the UK. A further 53 cases have been reported from other countries, bringing the global total of clinical vCJD cases to 231.[18] Between 2005 and 2014, 68 vCJD cases were reported from 11 countries.[16] Three of the 178 UK cases that occurred up to 2016 are considered to have resulted from blood transfusion.[4] In the fourth case of vCJD transmission through blood transfusion, vCJD was identified in the spleen of an individual (heterozygous at codon 129), who died of a non-CJD-related cause and was considered to have had preclinical vCJD.[45]

The most common causes of iCJD are injections of human growth hormones (hGH) and dura mater grafts obtained from human cadavers. A review of worldwide iCJD cases in 2012 identified 469 cases from dura mater grafts (n=228), hGH injections (n=226), gonadotropin injections (n=4), contaminated surgical instruments (n=4), contaminated EEG needles (n=2), packed red blood cells (n=3), and corneal transplants (n=2).[8] A more recent review by the NCJDRSU of 85 UK iCJD cases between 1970 and 2016 found eight from dura mater grafts, 76 from hGH injections, and one from a human gonadotrophin injection.[18] All of these patients have died at a mean age of 35 years (range 20–51) for those injected with hormones and 47 years (range 27–78) for those receiving dura matter grafts.

No direct cases of surgically acquired CJD have been noted since 2005.[8] Four historic cases between 1952 and 1974 (three in the UK and one in France) occurred before the vCJD epidemic and when methods for cleaning surgical instruments were less rigorous than current decontamination standards. Consequently, the risk of transmission of all types directly apportioned to surgery appears currently to be low. As sCJD is idiopathic, its aetiological basis is presumed to be spontaneous, but the validity of this assumption is uncertain.[46] 12 publications between 2005 and 2017 implicate a potential relationship

between past neurosurgery and sCJD incidence. These include four case reports,[47–51] a surveillance study,[52] and six case-control studies.[53–60] Case-control studies are a frequently encountered design in estimating possible and plausible risk factors for sCJD. Some concerns have been expressed about potential biases affecting CJD case-control studies and their validity[61] that could be undermined by: selection of control cases, assessing exposure in lifetime periods of different duration, disregarding at-risk periods for exposure in control patients, asymmetry in case and control data, and confounding by concomitant blood transfusion or surgery at the time of clinical onset.

Prevalence of subclinical vCJD

In vCJD, prions appear to replicate extensively in lymphoid tissue early in the disease process and, therefore, the tonsils and appendix are some of the earliest sites that can be used to assess abnormal prion accumulation. Such abnormal accumulation before the onset of clinical symptoms is regarded as subclinical vCJD and is thought to represent a potential background, albeit low, level of infection in the population.[62] The infectious load of prions is known to be increased in certain tissues, such as the CNS in the symptomatic phase of disease,[63] and therefore the risk of infectivity from peripheral tissue has been questioned.[64–67]

The hypothesis of zoonotic transmission through dietary exposure from the BSE outbreak is largely upheld as the most plausible route of vCJD infection in humans and transmission has been replicated in wild-type mice.[68] An analysis of excised peripheral tissues from the Appendix II general population study done by Gill and colleagues[69] found subclinical prion accumulation in patient cohorts born in 1941–60 and 1961–85.[69] Detection of abnormal prion accumulation in appendix samples from these two cohorts resulted in a central estimation of 493 cases per million people (95% CI 282–801) for populations exposed to the BSE epidemic. The subsequent Appendix III study using immunohistochemical staining of appendices from two birth cohorts (table 2)[70,71] estimated a central prevalence of asymptomatic carriers of vCJD in the UK population (who had been presumed to be unexposed to BSE) of approximately 240 per million (95% CI 16–492).[56]

The presence of stained appendices positive for abnormal prion accumulation in the 1941–60 and 1961–85 cohorts of people who were not considered to have had exposure to BSE suggests that there is either low background staining of abnormal prion protein in human lymphoid tissue that might not represent subclinical vCJD and would be unlikely to progress to vCJD, or that the BSE epidemic was longer than previously thought.[70] Moreover, planned statistical analysis found no significant difference between the prevalence observed in the cohort considered to be most at risk to the BSE epidemic, as described as by Gill and colleagues,[69] and the prevalence observed in the Appendix III study.[70]

	Immunohistochemistry results	Central estimate
Appendices removed between 1970–79 and before the BSE epidemic	Two positive samples from 14 692 appendices	One in 7000
Appendices removed from patients born after Jan 1, 1996, and after measures to remove BSE were in place	Five positive samples from 14 824 appendices	One in 3000

BSE=bovine spongiform encephalopathy.

Table 2: **Results of the Appendix III study[69]**

Infectivity of CJD

Methionine homozygosity at *PRNP* codon 129 is considered to be the most susceptible genotype for developing CJD, with sCJD and vCJD occurring mostly in such individuals. In sCJD, both methionine and valine homozygotes at codon 129 are at increased risk of the disease.[72] In northern Europe, the methionine homozygous genotype represents 38% of the general population, whereas 11% of people carry the valine homozygosity genotype and 51% are heterozygous for methionine and valine at codon 129.[73]

The first indication that valine homozygotes are also susceptible to vCJD infection came from a re-analysis of appendices[74] from the cohort of 12 674 appendix and tonsil samples analysed by Hilton and colleagues.[12] Of this cohort, only three appendix samples were positive for disease-associated prion protein (PrPd), and that two of the three samples were valine homozygotes. Although heterozygosity at *PRNP* codon 129 was previously believed to confer complete resistance to both sporadic and acquired prion disease,[75] the most recent case of clinical vCJD in 2016 was heterozygous.[29] Another earlier possible vCJD case in 2008 was also heterozygous,[76] but diagnosis was not confirmed by autopsy. Case reports have also found subclinical iCJD in heterozygous individuals,[45,77] highlighting their susceptibility, albeit at a lower level than homozygotes. A study in mice supports the notion that transmission efficiency of vCJD is greatest in methionine homozygotes, but indicated that all three genotypes are susceptible, with the heterozygous and valine homozygous genotypes conferring apparent reduced transmission efficiency and longer asymptomatic incubation periods than the methionine homozygous genotype.[78]

Knowing whether and when asymptomatic carriers of CJD become infectious is important in understanding the potential risks of iatrogenic transmission. Bougard and colleagues[79] describe an assay that detected prions in plasma samples from two blood donors who developed vCJD 1·3 and 2·6 years before clinical onset.[79] The authors report that the assay is able to identify presymptomatic (n=2) and symptomatic (n=18) vCJD positives in a masked cohort of 256 plasma samples comprising sCJD, Alzheimer's disease, Parkinson's disease, other neurological diseases, and healthy controls, demonstrating the possibility of detecting incubating or silent carriage of vCJD prions in blood and highlighting the potential risk of transmission via blood products.

Search strategy and selection criteria

We searched MEDLINE (Ovid), EMBASE: (Ovid), Science Citation Index (SCI-E), Conference Proceedings Citation Index (CPCI), and Web of Science for articles published between Jan 1, 2005, and Dec 31, 2017 with the terms "incidence", "prevalence", "incubation", and "infectivity" plus their synonyms were combined with "CJD" population terms. However, the goal of our Review was to include the most recent available data (published and unpublished); therefore, surveillance data retrieved after the date of the searches were also included from national surveillance registries and papers retrieved from contact with experts. Searches were not limited by language. The UK National Institute of Health and Care Excellence Interventional Procedures committee were also consulted as topic experts for potentially relevant papers. Included papers were subject to bibliography checking and our search strategy was revised in response to relevant studies not captured by the original searches. Eligible studies were of humans with Creutzfeldt-Jakob disease (CJD) or related prions in tissue, including in-vivo or in-vitro studies, observational studies, retrospective reviews, case series and reports, national surveillance reports, unpublished registry data, and pathological surveys. Ineligible studies were of laboratory parameters only, animal data without implications to humans, discussions or guidance without empirical data, superseded data, treatment or care of patients with CJD, filtering blood for transfusion or other blood products, and prion diseases without specific mention of CJD. Articles were imported into the reference management software EndNote (version 8) and duplicates were removed. Titles and abstracts of retrieved records were examined by LU and non-relevant citations excluded. 10% of randomly selected excluded citations were double-checked by CC and any disagreements were resolved by discussion between reviewers. Data from all countries were included.

The ability to detect prion accumulation depends on the sensitivity of the CJD assay.[80] For example, the heterozygous patient with clinical vCJD identified in 2016 tested negative for 14-3-3 protein and for misfolded PrP as detected by real time quaking-induced conversion (RT-QuIC) and the vCJD-focused direct detection assay, but immunoblotting of brain homogenate at autopsy confirmed the presence of vCJD prions.[29] Moreover, immunostaining of this patient's tissues for abnormal prion-protein-labelled amyloid plaques highlighted a relative lack of peripheral tissue involvement, with only minute amounts detected in the spleen and no detection in the appendix or mesenteric lymph nodes. However, Douet and colleagues[81] used a highly sensitive protein misfolding cyclic amplification assay to assess abnormal prion accumulation in an 82-year-old heterozygous patient with subclinical vCJD.[81] Previous investigations had not detected abnormal prion protein accumulation in the brain or infectivity of brain tissue at the time of death,[45,65] but using this assay, Douet and colleagues found vCJD prions in all lymphoid organs and many other tissues, including the salivary glands, lungs, and liver. The identification of extensive vCJD involvement in the peripheral tissues of a patient with subclinical disease provides further evidence of the potential for iatrogenic transmission of CJD through surgical procedures.

Incubation periods

Reported incubation periods of iCJD in humans range from 1 to 42 years.[8,77,82–88] The shortest durations occurred in surgically transmitted CJD and the longest occurred in Kuru or iCJD via hGH injection. Diagnosis of definite or probable iCJD depends on correct identification of the probable source of contamination to which patients have been exposed.

Different incubation times might occur because of the resistance of different genotypes. Evidence from Kuru studies[82,89] indicates that incubation times are shorter, and mortality risk is significantly greater in homozygous individuals than heterozygotes, as older survivors are more likely to be heterozygous.[85,86] However, data from hGH studies suggest longer incubation times for methionine homozygote patients and shorter times for valine homozygotes. Where proportions of heterozygotes and homozygotes are similar across countries or groups, but incubation times are different, it has been proposed that differences in incubation times might be due to infection with different strains or subtypes of the CJD prion.[84,88] For example, most cases of iCJD caused by hGH in France were in methionine homozygotes, whereas in the UK, the valine homozygous and the heterozygous genotypes predominate. Infections that appear to affect people with certain genotypes in a specific setting might reflect an absence of genotypic resistance to a particular strain, resulting in shorter incubation times.[88] Hence, it is possible that the methionine homozygous genotype in the UK hGH-iCJD cohort had the longest incubation times because the infectious strain was of the valine homozygous or the heterozygous genotype. Other possible factors that could influence the duration of the incubation period include increased infectious doses or differences in the way in which the incubation period was recorded and reported in the studies. For example, in cases in which the precise date of contamination is known, incubation times appear to be shorter.[8]

Discussion

The prevalence of subclinical vCJD from pathological surveys suggests a constant underlying rate of abnormal prion accumulation in lymphoreticular tissue in the UK population, which might or might not represent disease that will progress to clinical vCJD. Surgical procedures (other than high-risk procedures) that could be regarded as risky for iatrogenic transmission include appendectomy or tonsillectomy. However, no direct evidence currently exits to show that there is risk of transmission from surgical procedures involving tissues that are not high-risk.

When opportunities for CJD transmission occur, a range of factors probably influence how the disease will manifest itself in terms of clinical phenotype, neuropathological pattern, incubation period, and duration. These factors include an interaction between the genotype at *PRNP* codon 129, the infecting prion strain, the route of transmission, and the location of prion protein conversion. Moreover, the method of detection and analysis of CJD is crucial to obtaining detailed and

accurate neuropathological confirmation of CJD type for the most plausible explanations for acquisition of iCJD. Global variations in the detection of this rare disease are expected, given the different surveillance programmes and detection assays used.

Our Review provides an updated, comprehensive, and interdisciplinary profile on the nature and occurrence of CJD globally. The methods aimed to include any relevant study design, from any source or discipline, that was relevant to our review questions. Although narrative reviews focusing on one type of CJD have been published previously,[8,46] our Review provides a complete overview of the trends in all types of CJD from current evidence. Input from clinical experts was sought to ensure that the reviews were objective, rigorous, and applicable.

A limitation to our Review is that we did not include studies published before 2005 but we did include data from retrieved sources with information before 2005. We used the context of knowledge available from the previous reviews and, as detection and reporting of CJD has improved, we consider our focus on the most recent evidence to be appropriate. The reliance on case-control studies and the problems of retrospective, observational designs were discussed. As a result, the analysis is restricted to a narrative, as formal statistical aggregation of data was not possible given the scarce presentation of CJD. However, we believe that the comprehensive and flexible design of this Review was appropriate to provide a clinical overview on this rare but highly infectious disease.

Clinical trials in patients with CJD have been attempted[80] but are not a feasible recommendation for understanding the epidemiological patterns of CJD in humans. Prospective national surveillance that follows referrals of possible or probable cases of CJD through to confirmed cases of CJD and international agreement on standard analytics for CJD detection could improve reporting in countries that have allocated resources for surveillance.

Contributors

LU designed the study and wrote the draft manuscript. LU and CC did the systematic reviews. RW searched the literature. CC, MS, and DAH provided comments on the manuscript. All authors critically reviewed the methods and results and contributed to writing the report.

Declaration of interests

We declare no competing interests.

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