Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Caitlin Mertzlufft Date

Detecting Creutzfeldt-Jakob disease in the United States: An analysis of CDC surveillance data, 1994-2006

By

Caitlin Mertzlufft

Master of Public Health

Global Epidemiology

_____

Brad Pearce, PhD

Faculty Thesis Advisor

_____

Ryan Maddox, MPH

Thesis Field Advisor

Detecting Creutzfeldt-Jakob disease in the United States: An analysis of CDC surveillance data, 1994-2006

By

Caitlin Mertzlufft

Bachelor of Science, University of Georgia, 2008

Faculty Thesis Advisor: Brad Pearce, PhD

Thesis Field Advisor: Ryan Maddox, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2011

Abstract

Detecting Creutzfeldt-Jakob disease in the United States: An analysis of CDC surveillance data, 1994-2006

By Caitlin Mertzlufft

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive fatal neurodegenerative disease associated with infectious prions. The Centers for Disease Control and Prevention (CDC) have monitored potential variant Creutzfeldt-Jakob disease (vCJD) cases in the United States since 1996 in individuals diagnosed with prion-related disease who were less than age 55 at time of death, following the novel identification of this disease in the UK; two years of retrospective data were also collected from 1994 and 1995. Using data collected from this surveillance effort, this paper seeks to examine the clinical presentation and associated demographic characteristics of this < 55 cohort, especially in comparison with the typical clinical presentation of known CJD cases from around the world and a cohort of older (age $\geq$ 55) prion disease cases from the United States. World Health Organization (WHO) and CDC diagnostic criteria were used to sort the 309 individuals who fit study criteria into CJD subtype by clinical presentation, and a logistic regression model was used to evaluate the association of the typical electroencephalogram (EEG) signal seen in sporadic CJD patients with symptoms of interest. Typical EEG characteristic of sporadic CJD was found to be significantly associated with myoclonus and visual or cerebellar signs. The majority of cases were sporadic CJD at 70.55%, and no cases of variant CJD were identified. Analyses of clinical features of the CJD cases emphasize the importance of robust neuropathologic testing to confirm diagnoses.

Detecting Creutzfeldt-Jakob disease in the United States: An analysis of CDC surveillance data, 1994-2006

By

Caitlin Mertzlufft

Bachelor of Science, University of Georgia, 2008

Faculty Thesis Advisor: Brad Pearce, PhD

Thesis Field Advisor: Ryan Maddox, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2011

Acknowledgements

I am grateful to my advisors Brad Pearce and Ryan Maddox for their guidance throughout the many stages of this project. I also appreciate the support and aid of everyone in the Prion and Public Health Office, Centers for Disease Control and Prevention, without whom this paper would not be possible.

Table of Contents

Introduction

Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a group of rare human and animal neurodegenerative diseases (1). These diseases are invariably fatal, and are characterized by long incubation periods, often spanning many years, followed by rapidly progressive neurologic deterioration (1, 2).

Most prion diseases, both in humans and animals, only became apparent within the last century (1, 2). The exception is scrapie, a TSE which affects goats and sheep, which was first described in the United Kingdom in the early 1700s (2). Experiments done on this particular prion disease in the 1930s first demonstrated the transmissible nature of the etiologic agent, leading to a wide array of hypotheses as to this agent's exact nature (2, 3). For many years, the popular belief was that TSEs were caused by a "slow virus", though the possibility of a viroid was also considered; however, no virus could be isolated, nor disease-specific nucleic acid detected (1). Further confusing researchers, the agent was found to be resistant to standard sterilization and disinfectant techniques, including formaldehyde, ethanol, protease, nuclease and radiation (1, 4).

In 1967, Pattison and Jones suggested the possibility of a protein as the primary agent, or at the very least protein involvement in the disease transmissibility, sparking much controversy (5). This theory gained popularity, however, and in 1982 the phrase "prion" was coined by Dr. Stanley Prusiner to describe proteinaceous infectious particles (6). In this same year, both Prusiner et al. and Bolton et al. were able to purify the scrapie prion (1, 7, 8).

The prion is an abnormal form of a cellular protein, which is known as the prion protein and denoted PrP^{C} (2) . This protein is found in large quantity in mammals, particularly in neurons, though its function remains unclear (1). The abnormal form of the protein (denoted PrP^{TSE}) differs from PrP^{C} primarily in structure—PrP^{C} has high α-helix content, while prions are primarily composed of β-sheet; this structural difference may be one contributing factor to the prion's resistance to standard sterilization techniques (4). Laboratory tests are able to identify distinctive prions among TSEs of different species, and in some cases among different phenotypes of prion disease within the same species, suggesting the existence of multiple prion strains (1). Prion replication and neuronal destruction methods remain unknown (1).

Human prion diseases include Creutzfeldt–Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker syndrome (GSS), and kuru. Among animals, the most well-known are bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD), and scrapie, although other zoological TSEs have been identified in captive wild ruminants, in mink, and in felines (2, 4).

Human Prion Disease

CJD is the most common of human prion diseases, and was first recognized in Germany in the late 1920s (3). It occurs worldwide in three recognized forms: sporadic CJD (sCJD), familial CJD (fCJD), iatrogenic (iCJD) (3). A variant form of CJD was recognized in the mid-1990s. While sporadic and familial CJD occur naturally, both the iatrogenic and variant forms are acquired through exogenous sources of infection.

Around 85% of all CJD cases are sporadic (3). This form occurs worldwide with neither seasonal nor geographic clustering, nor any other recognizable transmission patterns, at an estimated rate of one case per one million per year (3, 4). Men and women are similarly affected, with an average age-of-onset of 60 years; 90% of patients are deceased within one year (3, 4).

Though the exact cause remains unclear, two theories have been put forward to explain sCJD occurrence. The first suggests a spontaneous mutation of PrP^{C} to PrP^{TSE} through a chance misfolding, leading to a domino-type effect in PrP^{TSE} generation (4). The second hypothesis suggests an age-related somatic mutation of the prion protein gene, which can randomly occur in a population at a rate very near that which is observed with sCJD (3).

The familial form of CJD comprises the majority of non-sporadic cases, accounting for 10-15% of cases overall. In these cases, genetic mutations of the prion gene (PRNP) are inherited in an autosomal dominant manner, and it is the prevailing belief that these mutations lead to a greater likelihood of PrP^{C} spontaneously mutating to PrP^{TSE} (9). Individuals with this form of CJD tend to be younger at age of onset and tend to have a longer duration of illness than those with sCJD (4). GSS is considered to be a variant form of fCJD, and another familial prion disease, FFI, is closely related, although common fCJD symptoms are accompanied with severe insomnia in these patients (3, 4).

The rarest forms of CJD are the acquired iatrogenic and variant type infections. Iatrogenic CJD first became apparent in 1974 when evidence mounted suggesting a corneal transplant operation as the cause of CJD transmission. The patient developed CJD eighteen months after receiving a corneal graft from a donor who had died of

pathologically confirmed CJD (10). In addition to corneal transplants, iCJD has been linked to human growth hormone injections and dura mater grafts from infected cadaver sources, as well as to contaminated neurosurgical tools (10). The incubation period for iCJD varies, depending heavily on the mode of infection (3). Variant CJD (vCJD) is associated with the zoonosis BSE, and will be addressed in greater depth further in this paper.

The final known human TSE is kuru, discovered in 1957, which is confined solely to the Fore population of Papua New Guinea. Its transmission is associated with ritual cannibalism undertaken in a bereavement ceremony in which families consume deceased relatives (4). Researchers found kuru to be the leading cause of death among women in the population for several subsequent years after its discovery, but it has now nearly disappeared due to cessation of cannibalism within the culture (3).

Animal Prion Disease

Scrapie, the first known TSE and the first to prove transmissible, is primarily a disease of sheep, but has shown to be transmissible to goats sharing a common pasture. No evidence suggests natural transmission to humans, despite centuries of exposure, though researchers have found in experimental settings that transmission of scrapie to rodents, primates and other species is possible through intracerebral injection of infected material (2, 4, 11). Scrapie generally occurs in sheep aged 2-5 years and is characterized by gradual neurological, behavioral, and dermatologic changes, leading to death 3-6 months after symptoms become apparent (2, 4).

CWD is a prion disease that affects deer, elk and moose. First detected in Colorado in captive mule deer in 1967, it was not recognized as a TSE until 1978 (1). CWD was first seen in wild cervids in 1981, also in Colorado, and has since been identified in 15 states as well as two provinces in Canada. While the first cases were initially thought to result directly from those originating in Colorado, some models suggest that some current high risk regions were endemic for CWD already, and that the recent increase in cases has resulted instead from increased surveillance (1, 2). Characteristics of CWD include behavioral changes, emaciation, unsteadiness, and excessive salivation (4). Many studies continue to monitor individuals exposed to infected cervids, but thus far no evidence has been found to support natural transmission to non-cervid species (4).

BSE, commonly referred to as “mad cow disease”, is the most recent of the prion-related epizootics and was first discovered in the United Kingdom in 1986 after a large number of cattle died of unknown cause (4). Symptoms of the infected cattle were similar to those of animals with scrapie and CWD, with the additional characteristic of marked aggression towards humans and other cows. The UK Ministry of Agriculture officially recognized this illness as a new TSE in 1987 (2).

The origin of the BSE epizootic is not entirely clear, but two popular theories exist. The predominant hypothesis suggests that scrapie prions crossed the species barrier when scrapie-infected sheep remains were introduced as protein supplements in cattle feed (1, 2, 4, 12). The other theory suggests the first episode of the disease was a sporadic case of BSE, much like sCJD in humans (1, 2, 4, 12). Regardless of the origin, it is widely accepted that the disease was perpetuated and amplified by the practice of

feeding cattle the rendered remains of BSE-infected cattle carcasses in the form of meat-and-bone meal (MBM) supplements (1, 2, 4, 12).

Once this method of perpetuation was suspected, legislation was rapidly enacted to end this practice. In 1988 the UK placed a temporary ban on the inclusion of ruminant-derived protein in MSM intended for ruminant consumption, and in 1989 this was extended indefinitely (12). However, due to an incubation period of BSE of 4-6 years, many cattle showed signs of illness after the bans were implemented, with peak incidence from late 1992 to early 1993 when more than 37,000 cases were confirmed among herds (1, 2, 4).

Presumed high-risk parts of cattle, selected based on knowledge of scrapie infectivity in sheep and goats, were banned from human consumption in 1989 and from all non-ruminant animal feed in 1990 (1, 2). However, even animals born after the bans were implemented began to show signs of infection. This occurrence was widely considered to be due to exposure to residual BSE-contaminated feed or cross-contamination of MSM intended for other animals; therefore, a complete ban on the use of mammalian MSM for farm animal feed or as fertilizer was enacted in the UK in 1996 (2).

Unfortunately, BSE continues to appear in cattle born after 1996 in both the UK and in other countries, albeit in very small numbers, through processes not clearly understood (2). One investigation found contaminated feed bins that were in use before 1996 and not adequately disinfected afterwards to be a probable cause (13). By 2007 BSE had been identified in cattle of 25 countries, including three cases in the United

States (two indigenous cows, one of Canadian origin); no new cases in the United States have been identified since 2006 (2).

BSE and vCJD

Initially, comfort was taken in the fact that scrapie had never been shown to be transmissible to humans, and while precautions were taken to minimize human exposure to this new TSE, the United Kingdom's ministry of health initially reassured the population that BSE posed no threat to humans (2). Despite this reassurance, CJD surveillance efforts were initiated in the UK in May 1990 to monitor any possible variation in cases that might indicate transmission of BSE across the species-barrier (2). The UK CJD Surveillance Unit obtained clinical details and any available information on risk factors on all suspected CJD cases, as well as neuropathological examinations where possible (14).

By 1995, the CJD Surveillance Unit had confirmed 207 cases of CJD throughout the UK based on neuropathology; ten of these cases presented with unusual findings (14). In 1996, Will and colleagues discussed their findings on these ten cases in the Lancet, and proposed the emergence of a new variant of CJD (14). The ten cases, comprised of six women and four men, presented with clinical and pathological symptoms that clearly distinguished them from other known forms of CJD. Compared with trends normally seen in sCJD patients, these individuals were remarkably young at age of onset (mean age 29 years) and had a relatively long duration of illness (over 6 months) (14, 15). The clinical course of these patients was also different than that which could be expected with

other forms of CJD, with high occurrence of psychiatric symptoms and a low occurrence of initial memory loss; none of the ten patients presented EEG features typically associated with CJD (14).

Neuropathological examination revealed widespread amyloid plaques throughout both cerebellum and cerebrum, as well as smaller plaques in the thalamus, basil ganglia and hypothalamus, similar to the plaques found in individuals with kuru (3, 14). The morphology of the plaques greatly resembled those found in animals with scrapie (3).

Many wondered about the possibility of a link between BSE and this new variant form of CJD, and in 1997 Bruce and colleagues found striking similarities in the pathology and incubation periods of mice exposed to each of the two diseases (16). Compelling evidence linking BSE causally to vCJD grew as studies using brain extracts found similar Western blot patterns in both diseases, and determined that the etiologic agents of both were molecularly and biologically indistinguishable, though different from those of other TSEs (4, 17). This theory was further supported by the similarities in geographical occurrence and through patterns observed in epidemiologic curves (17).

Present Day vCJD

Variant CJD is now recognized as a disease in its own right, and since its discovery in 1995 it has been identified in eleven countries, primarily in Western Europe (18). A total of 221 cases have been confirmed worldwide in the last fifteen years, three of which were detected in the United States (18). These three cases had illness onset in 2002, 2005 and 2006, and though they occurred in the United States among US residents,

exposure to the infectious agent is believed to have occurred elsewhere (19). Two cases were born in the United Kingdom and resided there at some length during the defined period of high risk exposure to BSE, which is 1980-1996 (19). The third patient originated from Saudi Arabia, and had no history of neurosurgery or visits to European countries (19).

The prevailing hypothesis as to the mode of acquiring vCJD through BSE is that transmission of BSE to humans occurs through consumption of contaminated beef, although no specific food product has ever been directly linked to vCJD occurrence (2). Studies that have researched cattle tissue infectivity have found the brain, spinal cord, retina and nictating membrane to be the most infective in a natural environment, although both the distal ileum and dorsal root ganglia have also shown to be infective in experimental settings (12).

In the fifteen years since its appearance, researchers have learned much about vCJD and medical practitioners now have clear guidelines to aid in recognition of the distinctive differences between vCJD symptoms and clinical presentation as compared to classic CJD. The median age at time of death continues to be much lower in vCJD patients than sCJD patients, at 28 years and 68 years respectively (1). Median illness duration is much longer, at 13-14 months in vCJD patients compared to 4-5 months in sporadic cases. The periodic short waves that are commonly found in the EEGs of sporadic cases are almost always absent in variant cases, although variant cases show a bilateral symmetrical pulvinar high signal on MRIs, while sCJD cases do not (20).

In clinical presentation, vCJD patients generally show marked psychiatric and behavioral symptoms, as well as sensory problems and delayed neurologic signs and

dementia. sCJD patients, in contrast, show early neurologic signs and early, rapidly progressive dementia (1, 21). vCJD is easily detected in the lymphoid tissue of patients, while sCJD is not (1).

Based on the vCJD cases observed so far, there appears to be an indication of increased risk for individuals who are homozygous for methionine at codon 129 of the prion protein gene (PRNP) (10). Humans may be homozygous at codon 129 with either two methionine (MM) alleles or two valine (VV) alleles, or may be heterozygous with one of each (MV). All the cases of confirmed vCJD observed so far have been homozygous for methionine (22). One possible, but uncertain, exception was a man who received a blood transfusion from a donor who subsequently developed vCJD. The blood recipient was heterozygous at codon129, and though he never developed clinical vCJD or PrP^{TSE} accumulation in the central nervous system, he was shown to be infected with the vCJD agent after dying of other causes (2, 17). This incident is currently considered an asymptomatic case, and whether it would or would not have developed into clinical vCJD is unknown. However, the existence of the case itself suggests the possibility of the susceptibility of a much larger percentage of the population than previously considered (2, 17). Alternatively, some research suggest that homozygosity for methionine only predisposes individuals to a shorter incubation period for vCJD, and that additional cases of individuals with VV or MV may develop after relatively longer periods of time (1, 22, 23).

Other noted risk factors for vCJD include young age and area of residence (17). As the UK was the origin of the BSE epizootic, individuals who spent significant amounts of time in this location, or in close proximity, during the 80s and early 90s are

thought to be at higher risk of past BSE exposure (10). It is not entirely clear why vCJD develops more often in younger individuals, though Will suggests that it could be related to biological factors, or possibly to increased consumption of the BSE agent through age-related propensities toward certain food products (10).

vCJD Surveillance in the United States

To date, only three confirmed cases of BSE infected cows have been detected in the United States, and epidemiologic data from each of the three cases of vCJD found in the US suggest that infection was likely to have occurred in each case's respective country of origin (19). Therefore, those considered at highest risk among US citizens continue to be those individuals who consumed UK beef products at a young age, between the years of 1980-1996 (19). Incident cases of both BSE and vCJD appear to be on the decline, but the possibility of new cases cropping up after long incubation periods is still a possibility. Exacerbating this concern is the inability of experts to definitively determine the total population of humans exposed to BSE or to determine a standard vCJD incubation period, due to the fact that there is no information on exact moment of BSE exposure and contamination in any of the described cases. The effects of genetic variation on incubation period must also be taken into account, as well as the possibilities of human-to-human and iatrogenic transmission of vCJD (1, 2, 13, 22).

An additional concern is the possibility that the known cases of vCJD are not attributable to the well-documented BSE outbreak, but from unrecognized BSE contamination that occurred years earlier (22). This would put the observed incubation

period of vCJD at anywhere from 12-22 years, and set the stage for a second wave of cases in the next decade (22). This is particularly alarming given that models have estimated that the consumption of as many as 3 million cattle with pre-clinical and sub-clinical BSE infections occurred before 1989 (13). Cooper and Bird studied cohorts of individuals with different levels of dietary exposure to BSE and have called a second wave of cases likely (24).

In contrast to the high degree of uncertainty in the incubation period associated with primary transmission, the incubation periods of four cases of highly probable secondary transmission due to blood transfusions have been well documented at five to nearly ten years (22, 25-27). One of these cases was the controversial heterozygous individual mentioned previously; all other cases were homozygous for methionine at codon 129 (22, 26). Most recently, vCJD infection was found in a hemophiliac who died of non-vCJD causes; transmission of the infectious agent through plasma was implicated as a likely cause (28). Concerns of transmission via a bloodborne route have led to blood donation bans in the US from individuals who have spent specified amounts of time in the UK or other high risk areas; organ and tissue restrictions have also been implemented (22, 25).

Additional concerns have risen due to the widespread distribution of PrP^{TSE} in the lymphatic system, as there is sufficient evidence to support infectivity of the tonsils, spleen, and appendix (22). Several studies have examined the prevalence of PrP^{TSE} in appendices removed in standard appendectomies in otherwise healthy individuals (29-31). One study extrapolated their results to estimate a vCJD prevalence of 237 per million population in the UK (30).

Due to these concerns, surveillance programs enacted in the 1990s remain vigilant around the globe (19, 25, 32). In the United States, the Centers for Disease Control and Prevention (CDC) began actively monitoring potential vCJD cases in 1996, after the first cases in the UK were reported. Two years of retrospective surveillance data were also collected from 1994 and 1995. The National Prion Disease Pathology Surveillance Center (NPDPSC), located at Case Western Reserve University, was established in a collaborative effort between the CDC and the American Association of Neuropathologists in 1997. The NPDPSC assists in monitoring the occurrence of vCJD and other human TSEs in the United States, regardless of clinical diagnosis or patient age, through free diagnostic services for diagnosed or suspected cases of human TSEs (3, 32).

The CDC's vCJD surveillance project is a subset of a broader CJD surveillance program, and focuses specifically on patients with a diagnosis of CJD who were less than the age of 55 at time of death. CJD is a rare disease, and prion disease cases occurring at a young age (<55 years) are rarer still, and may be an indication of an exogenous source of infection. These cases are located through several mechanisms, which include a periodic review of national mortality data, and reporting from the NPDPSC, state and local health departments, physicians, family members, and the media. Mortality data is considered an effective means of tracking CJD since the disease is invariably fatal and over 85% of cases die within one year (3, 32). Confirmation of CJD is dependent on analysis of brain tissue obtained through biopsy or autopsy.

Using data collected from this surveillance effort, this paper seeks to examine the clinical presentation and associated demographic characteristics of this young cohort,

especially in comparison with the typical clinical presentation of known CJD cases from around the world and a cohort of older (age $\geq$ 55) prion disease cases from the United States.

Methods

In an effort to identify variant CJD in the United States, the CDC collects medical records of young CJD cases, as determined by national mortality data, on an annual basis. This process began in 1996, but data from 1994 and 1995 were collected retrospectively. Abstraction forms are utilized to pull relevant information from these records in order to assess CJD status. Two different abstraction forms were created and have been used by the CDC since the surveillance was initiated. The first of these forms is the shorter of the two, and has been used with every record detected from the surveillance (Appendix A). The primary purpose of this form is to determine vCJD status, and so consists of questions based on the current CDC diagnostic criteria for vCJD with the aim of ruling in or ruling out the disease. Demographic characteristics are also collected.

The longer form was only used consistently in records collected for years 1994-1998, though it exists in some records up to year 2000 (Appendix B). This form is broader in scope and collects information on symptoms and risk factors associated with sporadic, familial and iatrogenic CJD, in addition to demographic characteristics and symptoms associated with vCJD. Broadly, the information from this longer form fits into six categories: general/personal information, clinical information, neuropathological symptoms/signs, risk factors, clinical testing results, and case assessment.

This study analyzes all abstraction completed for cases who died between the years 1994-2006. Cases with incomplete forms were common, due to either the inherent variability of data included in patient medical records or a lack of access to an individual's full medical history. Incomplete forms were included in the analysis. Cases

initially collected but later determined exempt from this surveillance database due to postmortem diagnosis of non-prion related disease were not included. A total of 309 individuals with a corresponding 309 short forms and 116 long forms from years 1994-2006 were analyzed.

Data was initially checked for entry errors and for consistency between overlapping variables among individuals who had both short and long forms. Data consistency was checked to ensure corresponding short and long forms referred to the same individual, as variables from each were used concurrently for some analyses. Only identical variables of interest for this analysis were checked across forms. Overlapping variables that were not of interest were date of death, date of birth, date of initial illness, and duration of illness by month (this variable was redundant and the information utilized elsewhere). These variables were referenced in instances where variables race, sex, age at death, and state of residence were inconsistent across forms to ensure each form pertained to the same individual.

Sixteen identical variables, comprised of demographic characteristics and clinical presentation were checked for consistency. In the short form, possible answers to questions regarding the presence of clinical symptoms or risk factors are “yes”, “no”, or “unknown”. Answer options vary in the long form and are often more specific in regard to symptom onset. Ten of the overlapping sixteen variables had different answer options between the two forms and required a merging of the more numerous long form answers to conform to the short form answer scheme before comparisons could be made. Long form options for the timing of symptom presentation were “initial”, “presentation”, “early”, “late” and “yes, no onset”; these were all set to “yes” for symptom occurrence.

"Not mentioned" and "unknown" were options on this form as well, and were combined into an "unknown" category. "No" was an option on both forms and was not altered.

For individuals with inconsistent answers, the most recently abstracted or updated form was considered correct, as some cases had additional records or information become available after the initial abstraction. For the purposes of all analyses answers "not mentioned" or "unknown" were considered equivalent to "no", and so inconsistencies between these answers were not addressed across forms.

Demographic data was assessed to examine the distribution of sex, race, age at time of death, and state of residence. Ethnicity was not considered due to the high percentage of cases missing this information. Age was broken into three categories: < 34, 35-44, and 45-54. The cutoff at age 55 for variant CJD is widely accepted as > 98% of vCJD cases in the United Kingdom have been younger than age 55 at time of death (33). Prion disease cases in general younger than age 55 at time of death are rare, and those less than age 35 are even more so. The age breakdown used in this study allows us to highlight the rarest of the rare.

State of residence was used rather than location at time of death in all possible cases because it was considered to be the more stable of the two categories; it is possible that individuals crossed state lines seeking treatment as these variables were not constant for all cases. Eight individuals were lacking state of residence data and so state of death occurrence was substituted as a proxy. State data was merged into region in accordance with the classification scheme of the United States Census Bureau. Region categories used were South, Northeast, West, and Midwest. Prevalence ratios were assessed for all demographic variables.

Age, race and region variables were compared to a cohort of 3103 CJD cases in the United States equal to or older than age 55 at time of death. The National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC) identifies these cases by annually reviewing death certificate data and selecting decedents with CJD listed as a cause of death (19). Death records where CJD is the primary cause of death comprise the majority of this database, though records are occasionally added or ruled exempt due to prion surveillance effort findings (19). Prevalence ratios and corresponding 95% confidence intervals were assessed to compare the distribution of these three demographic variables between the two cohorts.

A definite diagnosis of CJD of any type is dependent on neuropathological confirmation via autopsy or biopsy, yet the occurrence of these tests is expected to vary widely based on the varying nature of disease progression by patient and the corresponding response by doctors. In order to determine whether any particular demographic characteristic is associated with presence of neuropathological confirmation, variables age at death, region of residence, sex and gender among cases who had autopsy or biopsy testing were compared to those who had not. Prevalence ratios were used to determine whether significant differences existed between groups on these four demographic characteristics.

The typical breakdown of CJD by type is well defined in the literature. Sporadic CJD accounts for nearly 85% of cases, while familial CJD accounts for the majority of the rest. Iatrogenic and variant cases are the rarest by far. Individuals from the CJD surveillance database were sorted into subgroups by CJD type in order to explore whether the observed breakdown among this less than 55 cohort is comparable to the breakdown

we could expect in the general population. WHO diagnostic criteria were used to sort each individual into CJD subtype; an unknown category was also generated for those who fit none of the subgroup criteria (Appendix D). Subgroups of interest that were explored were sporadic CJD (definite, probable, and possible), iatrogenic CJD, familial CJD, and possible variant CJD. Chi-squared tests were utilized to compare observed versus expected percentages.

The diagnostic criteria for the different subtypes of CJD are essentially a check-list of symptoms, but in all instances multiple combinations of key symptoms can lead to an identical categorization. In order to assess which symptoms occur most often and whether any element of the diagnostic criteria appears to be associated with another, probable and definite sporadic CJD cases were compared with possible sporadic CJD cases to determine the breakdown of patient symptoms between each of these categories. Diagnostic criteria differed slightly between these two categorizations, but there were four overlapping variables that were compared across the two subgroups—presence of myoclonus, presence of visual or cerebellar signs, presence of pyramidal or extrapyramidal signs, and presence of akinetic mutism. Each element of the diagnostic criteria was additionally compared against all other criteria within the possible or definite and probable sCJD groups to check for trends or frequent pairings of symptoms within each category.

A similar analysis was run on all 135 cases with autopsy or biopsy confirmation of non-vCJD prion disease using the diagnostic criteria for variant CJD (Appendix C). Prion disease at a young age, here designated less than 55 at time of death, is extremely rare and is the first flag for a potential vCJD case and sufficient for entry into this

database. Of those individuals initially flagged as possible vCJD patients but later confirmed exempt, it is of interest to examine the occurrence of other symptoms indicative of vCJD in their clinical presentation. Not all of the less than age 55 cases are autopsy or biopsy confirmed to not have vCJD, so by assessing the symptoms indicative of variant CJD of those that are, we can apply this knowledge to our assessment of cases lacking neuropathological confirmation.

The final analysis that was performed with these surveillance data was a logistic regression model used to determine the association between the typical electroencephalogram (EEG) signal seen in sporadic CJD patients with the symptoms of myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, and akinetic mutism. Two of these four symptoms are required to be present for a diagnosis of probable or possible sporadic CJD.

The model initially included all four symptoms of interest, the variables age, race, gender, and 18 additional terms to test the interaction of symptoms and demographic variables. Collinearity diagnostics were run using SAS 9.2 software and conditional indices of less than 30 were considered acceptable. The model was adjusted several times to reach this point, as the initial largest conditional index was 9849.39, indicating high levels of collinearity. To reduce the conditional indices the variable with the highest variance decomposition proportion (VDP) was dropped and collinearity was tested again. In every case the two highest VDPs were linked to a primary variable of interest and a higher level interaction terms; interaction terms were always dropped to maintain a hierarchically well formulated model. This process was continued until acceptable levels of conditional indices were reached.

After testing and adjusting for collinearity, the model was reduced to the symptoms and demographic characteristics of interest and seven interaction terms. Interaction terms were tested for significance using Wald chi-square tests; of these, only myoclonus*pyramidal/extrapyramidal symptoms showed significant interaction and was kept in the model. The model was further tested for confounding by comparing the odds ratio of the full model—all seven symptom and demographic variables of interest, plus the one significant interaction term—to those of reduced models with all possible subsets of the demographic variables. Odds ratios plus or minus 10% of the full model were acceptable, and confidence intervals around the odds ratio were used to determine degree of precision. The variable gender was ultimately dropped from the model as this resulted in an increased precision without compromising the odds ratio. Wald tests were used to determine the significance of association between EEG and the four symptoms of interest and the one interaction term. Likelihood ratio tests were used to determine the significance of the association between EEG and age and race variables, as dummy variables were used in the model for these ordinal categories.

This study does not meet the definition for human subject research and so institutional review board (IRB) submission was not necessary (Appendix E).

Results

There were a total of 469 individuals who were less than age 55 at time of death identified through the national CJD surveillance system to have died of a prion disease between 1994-2006. A total of 309 cases with completed abstraction forms were analyzed for this study.

The demographic characteristics of this subset of the <55 population are shown in Table 1. Patients were much more likely to fall within the two older age brackets, ages 45-54 (RR 52.46, CI 31.60 – 87.10) and 35-44 (RR 12.73, CI 7.37 – 21.98), than to be < 35 years old at time of death. They were also more likely to be white than African American (RR 12.73, CI 7.37-21.98); the vast majority (92.56%) of patients were white. African American, Asian and American Indian/Alaska Native individuals comprise the rest of this study population, though cases among these populations were few. There was no significant difference in gender, at 142 males and 167 females, or in region of residence.

This demographic breakdown was compared to the demographic characteristics of 3103 individuals who were diagnosed with CJD in the United States between the years 1994-2006 and were over the age of 54 at time of death (Table 2). There was no significant difference in the distributions of either population by sex, race or region, which implies that the older cohort follows the same distribution trends as the subset of the < 55 population. In particular, we again find the majority of the population to be white in this older cohort, at 94.36 %, while other races comprise only 5.64% of patients.

The distribution of both of these populations by year was compared for the period of interest (Figure 1). The breakdown by age group does not reveal any strong trends in incidence beyond highlighting the known fact that CJD is much less common in the < 55 age group than in the older population. This difference appears greater than it actually is, however, since approximately one-third of < 55 cases are not represented. Within this study period, we see that cases peaked in 1997 at 300 individuals (274 cases > 55 and 22 cases < 54), and were lowest in 2000 with 226 cases (206 cases > 55 and 22 cases < 54). The totally number of CJD cases did not vary dramatically over the study period.

To further assess CJD incidence by age group, the two populations were considered by five-year age bracket (Figure 2, 3). The youngest case of CJD was age 25 at time of death and the oldest was age 97. Among the subset of <55 cases, the majority were clustered near the 55 year threshold. Among the older population, there was a peak of cases among patients in their late 60s and early 70s.

To determine whether any demographic characteristic increases likelihood of autopsy or biopsy procedure—which is necessary to confirm CJD diagnosis—an analysis was run comparing those with and without these tests by gender, age, race and region among the less than 55 cohort; results are shown in Table 3. No significant differences were found in the distribution of diagnostic characteristics between those who had had an autopsy or biopsy and those who had not, suggesting that there is no strong demographic factor that predisposes an individual to receive this level of testing. In both categories we see a repetition of the distribution of cases we've seen in the prior analyses, specifically that the majority of patients are white and more likely to be near in age to the 55 threshold and are otherwise fairly evenly distributed across region and gender.

World Health Organization (WHO) diagnostic criteria were used to classify this less than 55 cohort according to CJD type (Table 4). The majority of the cases were sporadic CJD, at 70.55%. Among these, 135 were definite cases, confirmed through neuropathology, while the others were nearly evenly split between probable and possible sporadic CJD, at 41 and 42 cases respectively. The majority of the remaining cases were familial CJD (N = 41, 13.27%), though there were 14 instances of iatrogenic CJD (4.53%). Thirty-six individuals from the less than 55 cohort were classified as unknown CJD. These individuals presented with symptoms typical enough to produce a physician diagnosis indicative of CJD, but were lacking sufficient data recorded on the abstraction form to meet any of the case definitions. No patients were neuropathologically confirmed positive for variant CJD.

Using the WHO diagnostic criteria, it was of interest to determine which specific criteria were met in certain CJD classifications, as in many instances multiple combinations of symptoms were sufficient to categorize a patient as having a specific type of CJD. Percentages and raw numbers of cases that met specific diagnostic criteria were compared between patients with definite or probable sCJD (N=176) and those with possible sCJD (N=42) (Table 5). Visual or cerebellar signs were most common in both groups of CJD patients and are seen in 85.8% of patients with definite or probable sCJD and 95.24% of patients with possible sCJD. A higher percentage of possible sCJD patients showed presence of myoclonus and pyramidal or extrapyramidal signs as well, though both groups had a similarly low percentage of patients with akinetic mutism at only 20%.

Not only were diagnostic criteria compared between groups, but each diagnostic symptom was also compared with all other possible symptoms within the group. This assessment allowed us to determine whether any symptoms appear to be commonly associated with another. Within both definite and probable sCJD patients and possible sCJD patients the most commonly associated symptoms were visual or cerebellar signs and pyramidal or extrapyramidal signs. Within definite or probable sCJD cases both symptoms occurred in 116 patients, or 65.91% of the total group; within the possible sCJD cases both symptoms occurred in 36 of the 42 total individuals, or 85.71% of the group. Of the total number of patients who had pyramidal or extrapyramidal signs in each sCJD group, nearly 95% also had visual or cerebellar signs.

The second most common pairing of symptoms within the probable or possible sCJD cases occurred between myoclonus and visual or cerebellar signs (N=102). Individuals with both of these symptoms accounted for 57.94% of the total group, and 91.89% of those with myoclonus also had visual or cerebellar signs. Among patients with possible sCJD, both combinations of myoclonus and visual or cerebellar signs and myoclonus and pyramidal or extrapyramidal signs accounted for 71.43% of the total group (N=30). Among patients with myoclonus alone, 93.75% also had visual or cerebellar signs and pyramidal or extrapyramidal signs.

While the same association between myoclonus and visual or cerebellar signs is reflected in the cases with definite or probable CJD, a much smaller percentage had both myoclonus and pyramidal or extrapyramidal signs, at only 49.43%. Akinetic mutism is the least common symptom in each sCJD subgroup and is therefore the least commonly associated with other symptoms. However, among the total number of individuals with

akinetic mutism among definite or probable sCJD cases (N=39, 22.16%) only 10 of these also have a positive 14-3-3 assay and clinical duration of symptoms under two years, making this paring exceedingly rare at 0.06% of this subpopulation.

A similar assessment of symptom breakdown was evaluated for symptoms associated with variant CJD among patients neuropathologically confirmed to have sporadic CJD. Although no cases were identified with definite or probable variant CJD during the study period, it is of interest to determine the regularity of occurrence of symptoms associated with vCJD among more common CJD cases, especially in a population < 55 years of age as this is often the first major flag for a potential vCJD case. Among those with definite sCJD (N=135), 70.37% had a normal or abnormal EEG not associated with the diagnostic EEG changes expected in sporadic CJD. A total of 57 (42.44%) had a duration of illness over six months, rather than the more expected shorter illness duration. Only 7.41% of confirmed sCJD patients had dementia and a greater than or equal to 4-month delay in the appearance of two of five key neurologic signs—poor coordination, myoclonus, chorea, hyperreflexia, and visual signs—but 18.52% had psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (N=25). One patient was neuropathologically confirmed to have sporadic CJD but also had an alternate non-CJD diagnosis of central pontine myelinolysis. Two cases met all diagnostic criteria for vCJD, but were confirmed to have sporadic CJD by autopsy or biopsy.

A final assessment was conducted using a logistic regression model to determine the association between a set of key symptoms and typical diagnostic EEG changes associated with sporadic CJD, controlling for age and race. Among symptoms both

myoclonus (p-value = 0.0368) and visual or cerebellar signs (p-value = 0.0369) were found to be significantly associated with this type of EEG result, while akinetic mutism was strongly non-significant (p-value = 0.7214). Patient age was also found to be associated with a typical EEG output (p-value = 0.0469), though race was not.

Discussion

The 309 patients analyzed in this study are a subset of the 469 individuals identified through CDC's national surveillance to have died of a prion disease at an age less than 55 years between 1994-2006. The 160 individuals not assessed were not included in this work due to a lack of patient medical record information or other combinations of key variables and information integral to the analyses of interest. Given the exclusion of these 160 individuals, it is possible that the breakdown of demographic characteristics for the 309 less than 55 CJD cases found in this paper do not reflect this cohort as a whole. However, due to the objective nature of the surveillance methods utilized to identify suspected patients and equal efforts to secure patient record information across individuals, this population of 309 is believed to be a randomly sampled subset of the larger < 55 CJD case population, and thus likely representative of the group.

The demographic breakdown of this < 55 cohort illustrates significant links between likelihood of CJD and variables age and race. In particular, older individuals and white individuals appear to present with CJD in greater numbers than their respective comparison groups, and this trend has been well documented in the literature and verified across CJD cases of all ages (19, 33). Race is known to be associated with the relative frequency of codon 129 alleles in the global population, which have further been linked to the development of CJD, and it is possible that this factor influences the racial distribution noted in this study (34). The analysis of this small cohort suggest that likelihood of CJD increases dramatically as the threshold age of 55 is neared, and more

inclusive studies which focus on broader age ranges show that this likelihood continues to increase significantly with increased age (19). Such studies have also shown region and gender to significantly increase likelihood of this disease in less specific populations, though neither variable was found to be a significant factors among this < 55 cohort.

The classification of this young cohort into subtypes of CJD based on diagnostic criteria produces a distribution of cases similar to that which is expected based on known overall percentages in the broader population. The majority of cases of CJD are sporadic in the general population, at nearly 85%, followed by familial at 10-15%; iatrogenic cases are rare, and variant cases even more so. Although it is rare to find sporadic CJD cases in individuals less than age 55, these cases make up the majority of the < 55 cohort of interest, highlighting the fact that although atypical cases of sporadic CJD are rare, they are still far more common than the variant counterpart.

Among these sporadic CJD cases, it was of interest to examine which symptoms appeared regularly and perhaps might be of most use as warning signs of atypically young cases. However, visual or cerebellar signs and pyramidal or extrapyramidal signs were found to be the most commonly met criteria, which is not entirely surprising as any one of 8 and 9 symptoms respectively fulfills each criteria; the other sCJD diagnostic criteria are much more specific by comparison. It would be of more use to further break down each of these diagnostic criteria to see which signs within each category occurred most often. This information was available only for a subset of the 218 sCJD, however, and comparisons of the broader range of symptoms would have held little meaning in this small population.

Akinetic mutism was found to be the least commonly reported symptom among the cohort of sCJD patients. This is a rare symptom in general, and is characterized by absence of movement or speech in a patient who otherwise seems alert (35). This is primarily an end-stage symptom in neurological disease, and it is possible that many patients in this cohort did not live long enough to progress to this stage (36). It is also possible that this symptom occurred, but was not indicated in the medical records made available to the CDC.

Due to the high number of sporadic cases presenting at a young age, a characteristic flag for vCJD, it was of interest to determine the prevalence of other symptoms associated with vCJD within this group of individuals. This is of particular interest to a county like the United States where risk of vCJD is low and atypical presentation of sporadic CJD in unexpectedly young individuals may be of more relevance to physicians. A high percentage of the sCJD patients expressed some symptoms characteristic of variant CJD, especially a longer than expected duration of illness and an EEG other than that commonly associated with the sporadic form. However, it is not entirely uncommon for sporadic CJD patients to exhibit vCJD symptoms. While this phenomenon has not previously been studied in a cohort of CJD patients, this occurrence has been documented in the literature among a handful of patients presenting with atypical symptoms, both young in age and at ages more typical for sCJD (37, 38). Patients who present with all clinical and epidemiologic signs of vCJD but are proven to have sporadic CJD by pathology are more rare, but are also known to occur (37). Many of the symptoms associated with variant CJD have been observed in less common variants of sporadic CJD, and key symptoms such as age at

onset, testing results and survival time have been shown to differ by sCJD phenotype (39).

The breakdown of vCJD symptoms among sCJD patients was only conducted among those with definite sCJD confirmed through autopsy or biopsy, as this was the only subset of CJD type where accuracy of diagnosis could be confirmed. Restrictions in study design and data abstraction limited the certainty to which patients could be assigned to all other groups. During the data abstraction phase, it was difficult in many cases to distinguish whether a particular symptom had not occurred or was just not mentioned. For this reason, symptoms were considered to definitively not have occurred only when specifically mentioned as such within the medical records; any symptom not mentioned at all was classified as unknown. This presented an interesting problem when classifying cases into CJD subtypes based on diagnostic criteria, as most of the criteria require a binary "yes" or "no" answer format; all "unknown" answers were classified as "no". Cases with a large amount of missing information were categorized in an unknown CJD category, as they had presented with enough symptoms to be indicative of CJD, but were still lacking sufficient information to fall into a particular category.

Given the large number of "unknown" responses and their subsequent classification in this analysis, the accuracy of the breakdown of cases by CJD subtype is not known; it is possible that symptoms occurred and went unnoticed by physicians or unmentioned in the medical records in such a manner that another CJD classification would be more appropriate. Additionally, the variable nature of illness presentation among patients and the inherent differences between doctors likely leads to differences which may also influence the known symptoms per patient, and thus the classification by

CJD type. Many of the symptoms considered for diagnosis also involve a time element, usually early or late presentation, which is highly dependent on the duration of illness; for example, occurrence of psychiatric symptoms at five months may be early presentation for one patient and late-stage for another. Differences between patient records may also occur based on the individual's stage in illness at first treatment.

The final analysis in this study addressed the association of four common CJD symptoms to the typical EEG reading characteristic of sporadic CJD. While every effort was made to test and control for confounding factors, several potentially confounding elements were outside of this study's control, particularly where the EEG outcome itself was concerned. There is no way, for example, to measure the quality of testing or control for the inherent variability among the individuals responsible for preforming these tests, nor a way to control for changes in technology or radiologist training that may have occurred over the study period. This study also lacked information on the frequency and timing of EEG testing in relation to illness duration, which is particularly important as EEG outcome may change dramatically over the course of illness and can play a key role in ruling out rarer forms of CJD (38).

Of symptoms tested, myoclonus and visual or cerebellar signs were found to be significantly associated with the characteristic EEG found in sporadic CJD. Both the typical EEG signal and these two symptoms are highly specific to sporadic CJD diagnosis, especially when they occur concurrently (40, 41). The other symptoms, particularly pyramidal and extrapyramidal signs, are much more general. Age was also shown to be significant.

Conclusion

This study analyzed a cohort of individuals aged less than 55 at time of death from the Centers for Disease Control and Prevention's (CDC) national Creutzfeldt-Jakob disease surveillance system database for the years 1994-2006. Though this age group is typically associated with variant CJD, there was no evidence of variant CJD cases among these individuals. Variant CJD remains a disease of concern worldwide, and while vigilant surveillance continues to be of importance within the United States, the risk of this illness within this country appears to be low.

The majority of cases within this cohort were in fact atypically young sporadic CJD cases. Because some of these cases exhibited symptoms that could be considered to be indicative of variant CJD, the importance robust neuropathologic testing to confirm diagnoses is emphasized.

References

1. Belay ED, Schonberger LB. The public health impact of prion diseases. Annu Rev Public Health 2005;26:191-212.

2. Sejvar JJ, Schonberger LB, Belay ED. Transmissible spongiform encephalopathies. J Am Vet Med Assoc 2008;233(11):1705-12.

3. Belay ED. Transmissible spongiform encephalopathies in humans. Annu Rev Microbiol 1999;53:283-314.

4. Johnson RT. Prion diseases. Lancet Neurol 2005;4(10):635-42.

5. Pattison IH, Jones KM. The possible nature of the transmissible agent of scrapie. Vet Rec 1967;80(1):2-9.

6. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science 1982;216(4542):136-44.

7. Bolton DC, McKinley MP, Prusiner SB. Identification of a protein that purifies with the scrapie prion. Science 1982;218(4579):1309-11.

8. Prusiner SB, Bolton DC, Groth DF, Bowman KA, Cochran SP, McKinley MP. Further purification and characterization of scrapie prions. Biochemistry 1982;21(26):6942-50.

9. Gambetti P, Parchi P, Chen SG. Hereditary Creutzfeldt-Jakob disease and fatal familial insomnia. Clin Lab Med 2003;23(1):43-64.

10. Will RG. Acquired prion disease: iatrogenic CJD, variant CJD, kuru. Br Med Bull 2003;66:255-65.

11. Baker HF, Ridley RM, Wells GA. Experimental transmission of BSE and scrapie to the common marmoset. Vet Rec 1993;132(16):403-6.

12. Collee JG, Bradley R. BSE: a decade on--Part I. Lancet 1997;349(9052):636-41.

13. Bradley R, Collee JG, Liberski PP. Variant CJD (vCJD) and bovine spongiform encephalopathy (BSE): 10 and 20 years on: part 1. Folia Neuropathol 2006;44(2):93-101.

14. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996;347(9006):921-5.

15. Will R. New variant Creutzfeldt-Jakob disease. Biomed Pharmacother 1999;53(1):9-13.

16. Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, et al. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 1997;389(6650):498-501.

17. Collee JG, Bradley R. BSE: a decade on--Part 2. Lancet 1997;349(9053):715-21.

18. (EUROCJD/NEUROCJD) EaACSGoC. Figures for the number of vCJD cases worldwide. In: The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU); 2010.

19. Holman RC, Belay ED, Christensen KY, Maddox RA, Minino AM, Folkema AM, et al. Human prion diseases in the United States. PLoS One;5(1):e8521.

20. Ingrosso L, Vetrugno V, Cardone F, Pocchiari M. Molecular diagnostics of transmissible spongiform encephalopathies. Trends Mol Med 2002;8(6):273-80.

21. Zerr I, Poser S. Clinical diagnosis and differential diagnosis of CJD and vCJD. With special emphasis on laboratory tests. APMIS 2002;110(1):88-98.

22. Collee JG, Bradley R, Liberski PP. Variant CJD (vCJD) and bovine spongiform encephalopathy (BSE): 10 and 20 years on: part 2. Folia Neuropathol 2006;44(2):102-10.

23. Bishop MT, Hart P, Aitchison L, Baybutt HN, Plinston C, Thomson V, et al. Predicting susceptibility and incubation time of human-to-human transmission of vCJD. Lancet Neurol 2006;5(5):393-8.

24. Cooper JD, Bird SM. Predicting incidence of variant Creutzfeldt-Jakob disease from UK dietary exposure to bovine spongiform encephalopathy for the 1940 to 1969 and post-1969 birth cohorts. Int J Epidemiol 2003;32(5):784-91.

25. Belay ED, Holman RC, Schonberger LB. Creutzfeldt-Jakob disease surveillance and diagnosis. Clin Infect Dis 2005;41(6):834-6.

26. Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. Transfus Med Rev 2008;22(1):58-69.

27. Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari Et, et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009;49(5):977-84.

28. Peden A, McCardle L, Head MW, Love S, Ward HJ, Cousens SN, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia;16(2):296-304.

29. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Penney M, et al. Accumulation of prion protein in tonsil and appendix: review of tissue samples. BMJ 2002;325(7365):633-4.

30. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, et al. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. J Pathol 2004;203(3):733-9.

31. Ironside JW, Hilton DA, Ghani A, Johnston NJ, Conyers L, McCardle LM, et al. Retrospective study of prion-protein accumulation in tonsil and appendix tissues. Lancet 2000;355(9216):1693-4.

32. Belay ED, Maddox RA, Gambetti P, Schonberger LB. Monitoring the occurrence of emerging forms of Creutzfeldt-Jakob disease in the United States. Neurology 2003;60(2):176-81.

33. Louie JK, Gavali SS, Belay ED, Trevejo R, Hammond LH, Schonberger LB, et al. Barriers to Creutzfeldt-Jakob disease autopsies, California. Emerg Infect Dis 2004;10(9):1677-80.

34. Soldevila M, Calafell F, Andres AM, Yague J, Helgason A, Stefansson K, et al. Prion susceptibility and protective alleles exhibit marked geographic differences. Hum Mutat 2003;22(1):104-5.

35. Spiegel DR, Casella DP, Callender DM, Dhadwal N. Treatment of akinetic mutism with intramuscular olanzapine: a case series. J Neuropsychiatry Clin Neurosci 2008;20(1):93-5.

36. Larner AJ. A Dictionary of Neurological Signs. Second ed: Springer; 2006.

37. Rossetti AO, Bogousslavsky J, Glatzel M, Aguzzi A. Mimicry of variant Creutzfeldt-Jakob disease by sporadic Creutzfeldt-Jakob disease: importance of the pulvinar sign. Arch Neurol 2004;61(3):445-6.

38. Martindale J, Geschwind MD, De Armond S, Young G, Dillon WP, Henry R, et al. Sporadic Creutzfeldt-Jakob disease mimicking variant Creutzfeldt-Jakob disease. Arch Neurol 2003;60(5):767-70.

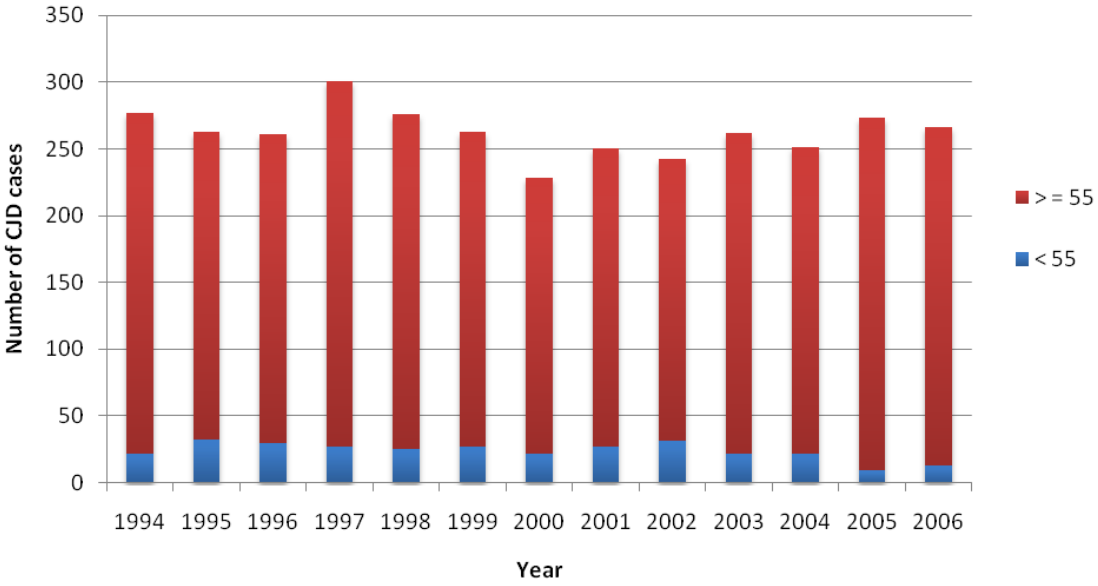
39. Appleby BS, Appleby KK, Crain BJ, Onyike CU, Wallin MT, Rabins PV. Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. Arch Neurol 2009;66(2):208-15.

40. Borg M. Symptomatic myoclonus. Neurophysiol Clin 2006;36(5-6):309-18.

41. Gozke E, Erdal N, Unal M. Creutzfeldt-Jacob Disease: a case report. Cases J 2008;1(1):146.

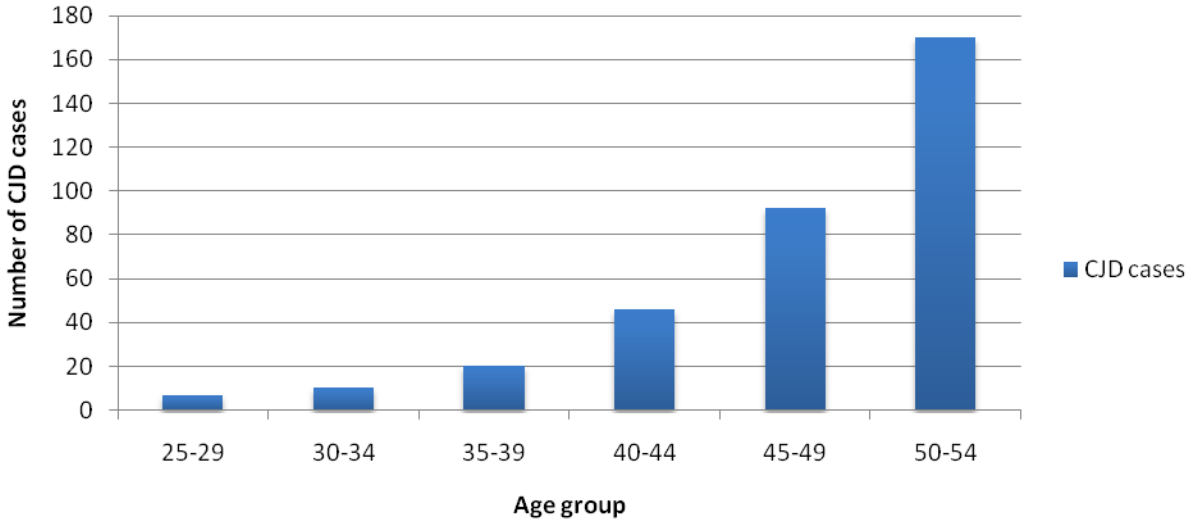
Tables and Figures

Figure 1. Distribution of Creutzfeldt-Jakob disease cases by year among those individuals<55* and > = 55 identified through the national Creutzfeldt-Jakob disease surveillance system‡, 1994-2006



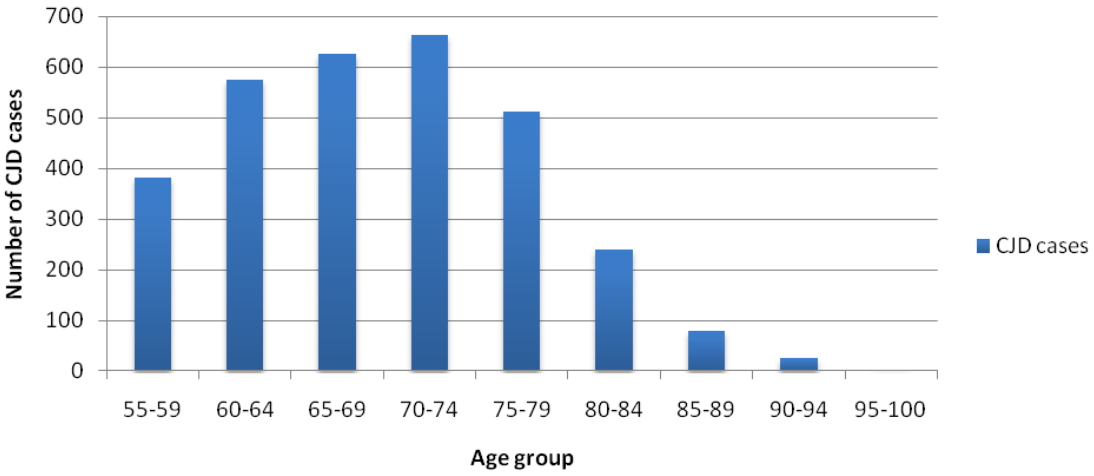
* Less than 55 cases depicted here are the 309 cases with completed abstraction forms. These cases are a subset of the total 469 cases aged less than 55 identified by the national CJD surveillance system 1994-2006.
‡ Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

Figure 2. Distribution of CJD cases by age among those idividuals < 55 identified through the national Creutzfelt-Jakob disease surveillance system‡, 1994-2006



‡ Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

Figure 3. Distribution of CJD cases by age among those individuals > 54 identified through the national Creutzfelt-Jakob disease surveillance system‡, 1994-2006



‡ Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

Table 1. Demographic characteristics of individuals aged < 55 at time of death identified through the national Creutzfeldt-Jakob disease surveillance system†, 1994-2006

		total N = 309		*2000 Census Population*	*risk ratio[1] (95% Confidence Interval)*
		N	*%*		
Sex					
	Male	142	46.95	138,053,563	reference
	Female	167	54.05	143,368,343	1.13 (0.91-1.42)
	missing	0			
Age					
	< 35	16	5.18	139,328,990	reference
	35-44	66	21.36	45,148,527	**12.73 (7.37 - 21.98)**
	45-54	227	73.46	37,677,952	**52.46 (31.60 - 87.10)**
	missing	0			
Race					
	White	286	92.56	161,001,999	**3.49 (2.08 - 5.86)**
	African American	15	4.85	29,465,130	reference
	Asian	6	1.94	8,665,659	1.36 (0.53 - 3.51)
	American Indian/ Alaska Native	1	0.32	2,179,797	0.90 (0.12 - 6.82)
	missing	1			
Region[2]					
	West	75	24.27	51,198,655	0.99 (0.71 - 1.39)
	Midwest	74	23.95	50,586,284	0.99 (0.71 - 1.39)
	Northeast	61	19.74	41,414,725	reference
	South	99	32.04	78,955,805	0.85 (0.62 - 1.17)
	missing	0			

† Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

[1] Risk expressed per 100,000 persons in the corresponding group. RR and corresponding 95% confidence intervals in bold are significant at $\alpha = 0.05$.

[2] Follows the US Census breakdown of US states into region

Table 2. Comparison of demographic characteristics between individuals < 55 years of age and ≥ 55 years of age at time of death identified through the national Creutzfeldt-Jakob disease surveillance system, United States†, 1994-2006

	< 55 *N = 309*	*≥ 55* *N = 3103*		
	N (%)	*N (%)*	*PR[1]*	*(95% CI)[2]*
Sex				
Male	142 (45.95)	1510 (48.66)	reference	—
Female	167 (54.05)	1593 (51.34)	1.10	(0.89 - 1.37)
missing	0	0		
Race				
White	286 (92.56)	2928 (94.36)	0.75	(0.46 - 1.22)
African American	15 (4.85)	111 (3.58)	reference	—
Other	7 (2.26)	64 (2.06)	0.83	(0.35 - 1.94)
missing	1	0		
Region[3]				
West	75 (24.27)	667 (21.50)	1.27	(0.92 - 1.75)
Midwest	74 (23.95)	749 (24.15)	1.13	(0.82 - 1.56)
Northeast	61 (19.74)	705 (22.73)	reference	—
South	99 (32.04)	981 (31.62)	1.15	(0.85 - 1.56)
missing	0	1		

† Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

[1] Prevalence ratio

[2] 95% confidence interval

[3] Follows the US Census breakdown of US states into region

Table 3. A comparison of demographic characteristics between individuals < 55 years of age who had an autopsy or biopsy performed and those who did not among those identified through the national Creutzfeldt-Jakob disease surveillance system† 1994-2006

	testing performed *total N = 178*	*testing not performed* *total N = 131*		
	N (%)	*N (%)*	*PR[1]*	*(95% CI)[2]*
Sex				
Male	82 (46.07)	60 (45.80)	reference	—
Female	96 (53.93)	71 (54.20)	1.00	(0.82 - 1.21)
missing	0	0		
Age				
< 35	11 (6.18)	5 (3.82)	reference	—
35-44	37 (20.79)	29 (22.14)	0.82	(0.55 - 1.21)
45-54	130 (73.03)	97 (74.05)	0.83	(0.59 -1.18)
missing	0	0		
Race				
White	162 (91.01)	124 (95.28)	0.77	(0.56 - 1.07)
African American	11 (6.18)	4 (3.15)	reference	—
Other	5 (2.81)	2 (1.52)	0.97	(0.56 - 1.70)
missing	0	1		
Region[3]				
West	49 (27.53)	26 (19.85)	1.14	(0.87 - 1.49)
Midwest	39 (21.91)	35 (26.72)	0.92	(0.68 - 1.25)
Northeast	35 (19.66)	26 (19.85)	reference	—
South	55 (30.90)	44 (33.59)	0.97	(0.73 - 1.50)
missing	0	0		

† This surveillance system is conducted by the Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

[1] Prevalence ratio

[2] 95% confidence interval

[3] Follows the US Census breakdown of US states into region

Table 4. Classification by CJD type[1] among individuals < 55 years of age identified through the national Creutzfeldt-Jakob disease surveillance system†, 1994-2006

	N ***(total N = 309)***	***%***
sporadic CJD	**218**	**70.55**
definite CJD[2]	135	43.69
probable CJD	41	13.27
possible CJD	42	13.59
iatrogenic CJD	**14**	**4.53**
familial CJD	**41**	**13.27**
unknown‡	36	11.65

† Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).
[1] CJD type, based on WHO diagnostic criteria.
[2] Definite CJD must be confirmed through autopsy or biopsy.
‡ Physician reports were indicative of CJD, but these cases were lacking sufficient data to meet the WHO case definitions.

Table 5. Occurrence of symptoms associated with sporadic Creutzfeldt-Jakob disease* among individuals† < 55 years of age classified as having definite or probable sporadic Creutzfeldt-Jakob disease (N=176) and possible sCJD (N=42)

	Definite or probable sCJD		*Possible sCJD*	
	N	**%**	**N**	**%**
Myoclonus[1]	**111**	**63.07**	**32**	**76.19**
Visual or cerebellar signs	102	91.89	30	93.75
Pyramidal/extrapyramidal signs	87	78.38	30	93.75
Akinetic mutism	28	25.23	6	18.75
typical EEG	52	46.85	—	—
14-3-3 CSF assay and clinical duration < 2 years	34	30.63	—	—
no EEG or atypical EEG and clinical duration < 2 years	—	—	32	100.00
Visual or cerebellar signs[1]	**151**	**85.80**	**40**	**95.24**
Myoclonus	102	67.55	30	75.00
Pyramidal/extrapyramidal signs	116	76.82	36	90.00
Akinetic mutism	34	22.52	8	20.00
typical EEG	60	39.74	—	—
14-3-3 CSF assay and clinical duration < 2 years	44	29.14	—	—
no EEG or atypical EEG and clinical duration < 2 years	—	—	40	100.00
Pyramidal/extrapyramidal signs[1]	**123**	**69.89**	**38**	**90.48**
Myoclonus	87	70.73	30	78.95
Visual or cerebellar signs	116	94.31	36	94.73
Akinetic mutism	31	25.20	7	18.42
typical EEG	55	44.72	—	—
14-3-3 CSF assay and clinical duration < 2 years	37	30.08	—	—
no EEG or atypical EEG and clinical duration < 2 years	—	—	38	100.00

Akinetic mutism[1]	**39**	**22.16**	**9**	**21.43**
Myoclonus	28	71.79	6	66.67
Visual or cerebellar signs	34	87.18	8	88.89
Pyramidal/extrapyramidal signs	31	79.49	7	77.78
typical EEG	18	46.15	–	–
14-3-3 CSF assay and clinical duration < 2 years	10	25.64	–	–
no EEG or atypical EEG and clinical duration < 2 years	—	–	9	100.00
Typical EEG[2]	**69**	**39.2**	–	–
Myoclonus	52	75.36	–	–
Visual or cerebellar signs	60	86.96	–	–
Pyramidal/extrapyramidal signs	55	79.71	–	–
Akinetic mutism	18	26.09	–	–
14-3-3 CSF assay and clinical duration < 2 years	18	26.09	–	–
14-3-3 CSF assay and clinical duration < 2 years	**49**	**27.84**	–	–
Myoclonus	34	69.39	–	–
Visual or cerebellar signs	44	89.80	–	–
Pyramidal/extrapyramidal signs	37	75.51	–	–
Akinetic mutism	10	20.41	–	–
Typical EEG	18	36.73	–	–
No EEG or atypical EEG[2] and clinical duration < 2 years	–	–	**42**	**100.00**
Myoclonus	–	–	32	76.19
Visual or cerebellar signs	–	–	40	95.24
Pyramidal/extrapyramidal signs	–	–	38	90.48
Akinetic mutism	–	–	9	21.43

† Individuals identified through the national Creutzfeldt-Jakob disease surveillance system, years 1994-2006. This surveillance system is conducted by the Prion and Public Health Office, Centers for Disease Control and Prevention (CDC)

* Probable CJD type, based on WHO diagnostic criteria. Progressive dementia is required for a diagnosis of sporadic CJD and so was not included in this table (i.e. occurrence = 100%)

[1] At least two of these symptoms are required for a diagnosis of sCJD

[2] Typical EEG was defined as the diagnostic EEG changes commonly seen in classic CJD. Atypical EEG was defined as the absence of this distinctive EEG. Individuals lacking mention of EEG testing in their medical records were considered not to have had an EEG performed.

Table 6. Occurrence of variant CJD diagnostic criteria† among decedents < 55 years of age at time of death with neuropathologic confirmation of sporadic CJD[1], 1994-2006 (N=135)*

	N	*%*
Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms	25	18.52
Dementia and 2 of 5 neurologic signs[2]	10	7.41
A normal or abnormal EEG[3]	95	70.37
Duration of illness > 6 months	57	42.22
No alternative non-CJD diagnosis	134	99.26
Individuals who meet all 5 criteria above‡	2	1.48

* Individuals identified through the national Creutzfeldt-Jakob disease surveillance system, years 1994-2006. This surveillance system is conducted by the Prion and Public Health Office, Centers for Disease Control and Prevention (CDC), and focuses on individuals < 55 years of age at time of death.

† An age of less than 55 at time of death is required for a diagnosis of suspected variant CJD and was not included in this table as the entire cohort is less than 55. Also, no risk factors for iCJD or fCJD and no prion gene mutation are criteria for both suspected vCJD and definite sCJD, and are not included (occurrence=100%).

[1] Variant CJD diagnostic criteria used by the Centers for Disease Control and Prevention. Definite sCJD based on neuropathology.

[2] Dementia, and development of at least two of the following five neurologic signs 4 or more months after illness onset: poor coordination, myoclonus, chorea, hyperreflexia, or visual signs. (If persistent painful sensory symptoms exist, the 4 or more month time delay is not required.)

[3] But not the diagnostic EEG changes often seen in sporadic CJD

‡ To be considered a suspected case of variant CJD, an individual should meet all 5 criteria. These cases were confirmed by neuropathology to not have variant CJD.

Table 7. Logistic regression model to determine the association between typical electroencephalogram (EEG)[1] and symptoms of interest among CJD patients < 55 years of age identified through the national Creutzfeldt-Jakob disease surveillance system†, 1994-2006

Effect	*DF*	*Chi-square*[2]	*p-value*[2]
Myoclonus	1	**4.3615**	**0.0368**
Visual or Cerebellar signs	1	**4.3558**	**0.0369**
Pyramidal/Extrapyramidal signs	1	1.6199	0.2031
Akinetic Mutism	1	0.1272	0.7214
Age	2	**6.119**	**0.0469**
Race	2	5.38	0.0678
Myoclonus*Pyramidal/Extrapyramidal signs	1	1.2038	0.2726

† Prion and Public Health Office, Centers for Disease Control and Prevention (CDC).

[1] Typical EEG was defined as the diagnostic EEG changes commonly seen in classic CJD.

[2] Chi square values and corresponding p-values in bold are statistically significant at $\alpha = 0.05$

Appendix A – Short abstraction form

FORM FOR INVESTIGATING
CREUTZFELDT-JAKOB DISEASE CASES AGED <55 YEARS

Form Approved
OMB 0920-009

CDC No__ __ __ __ __ __ __

I. General Information

Patient's code number: __ __ __ __ __ __ __ Date form filled out: _ _/ _ _/_ _ _ _ (mm/dd/yyyy)
State of death occurrence: _____County of death occurrence: _____
State of residence: _____ County of residence: _____
Date of birth: _ _/_ _/_ _ _ _ (mm/dd/yyyy) Age at death: __ __ years Sex: 1 Male 2 Female
Ethnicity: 1 Hispanic or Latino 2 Not Hispanic or Latino
Race (mark one or more): 1 White 2 Black or African American 3 Asian
4 Native Hawaiian/Other pacific islander 5 American Indian/Alaska Native 6 Unknown
Month and year of initial symptoms:_ _/_ _ _ _ (mm/yyyy) Date of death: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

II. Patient's Clinical Data	**Yes**	**No**	**Unknown**
Did the patient have a progressive neuropsychiatric disorder?	1	2	9
Did the patient have early psychiatric symptom/s (anxiety, apathy, delusions, depression, and/or withdrawal)?	1	2	9
Did the patient have the psychiatric symptom/s at illness onset?	1	2	9
Did the patient have persistent painful sensory symptom/s (frank pain and/or dysesthesia)?	1	2	9
Did the patient have dementia?	1	2	9
Did the patient have poor coordination/ataxia?	1	2	9
Did the patient have myoclonus?	1	2	9
Did the patient have chorea?	1	2	9
Did the patient have dystonia?	1	2	9
Did the patient have hyperreflexia?	1	2	9
Did the patient have visual signs?	1	2	9
Did the patient have dementia as well as development at least 4 months after illness onset of at least two of the following five neurologic signs: poor coordination, myoclonus, chorea, hyperreflexia, or visual signs?	1	2	9
Was the duration of illness over 6 months?	1	2	9
Is there a history of receipt of human pituitary growth hormone, a dura mater graft, or a corneal graft?	1	2	9
If yes, please specify:_____			
Is there a history of CJD in a first degree relative?	1	2	9
Is there a prion protein gene mutation in the patient?	1	2	9

CDC No__ __ __ __ __ __ __

	Yes	No	Unknown
Did a radiologist or an attending physician report that the patient's EEG was indicative of a CJD diagnosis?	1	2	9
According to the radiologist or an attending physician, did the MRI scan show bilateral pulvinar high signal?	1	2	9
Did routine investigation of the patient indicate an alternative, non-CJD diagnosis?	1	2	9
III. Neuropathology Information			
Is a neuropathology report available on this patient?	1	2	9
Was a brain biopsy performed on this patient?	1	2	9
Was a brain autopsy performed on this patient?	1	2	9
If a biopsy or an autopsy was performed, was brain tissue sent to the National Prion Disease Pathology Surveillance Center at Case Western Reserve University, Cleveland, Ohio?	1	2	9
According to the pathologist's report, was the neuropathology indicative of a CJD diagnosis?	1	2	9
Are there numerous widespread kuru-type amyloid plaques surrounded by vacuoles (florid plaques) in both the cerebellum and cerebrum?	1	2	9
Is there spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum?	1	2	9
IV. Case Assessment			
Does the patient have clinical findings similar to that of the variant CJD?	1	2	9
Does the patient have neuropathologic findings confirming a variant CJD diagnosis?	1	2	9

IMPORTANT: Please attach the patient's neuropathology report, if available.

Comments:

Appendix B – Long abstraction form

PRION DISEASE

CASE INVESTIGATION FORM

Patient's code number: __ __ __ __ __ __ __ __

Date form filled out: _ _/ _ _/_ _ _ _ (mm/dd/yyyy)

Person filling out form: _____

Personal Information

State of occurrence: _____

County of occurrence: _____

City of occurrence: _____

Occupation: _____

Sex: 1 Male 2 Female

Age: __ __ years

Date of birth: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Race: 1 White 2 Black 3 Asian/pacific islander

4 American Indian/Alaska native 5 Other 9 Unknown

Ethnicity: 1 Spanish 2 Not Spanish 9 Unknown

Source of information:-

Chart review:	1 Yes	2 No	9 Unknown
Neurologist:	1 Yes	2 No	9 Unknown
Death certificate:	1 Yes	2 No	9 Unknown
Neuropathologist:	1 Yes	2 No	9 Unknown
Relatives:	1 Yes	2 No	9 Unknown

Other: _____

Date of initial symptoms; _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Date of death: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Duration of illness: __ __ month

Is the duration < 2 years: 1 Yes 2 No 9 Unknown

Neurologic Symptoms or Signs

No	Initial Presentation	Early	Late	Yes, no onset	Not mentioned	Unknown
Akinetic mutism						
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**
Confusion						
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**
Dementia						
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**

Progressive: 1 Yes 2 No 9 Not mentioned

Dizziness							
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**
Dysesthesia/parasthesia in limbs/face							
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**
Myoclonus							
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**
Visual disturbances							
0	**1**	**2**	**3**	**4**	**5**	**6**	**9**

Specify: _____

No	Initial Presentation	Early	Late	Yes, no onset	Not mentioned	Unknown
Cerebellar disturbances:						
Ataxia						
0	1	2	3	4	5	6	9
Dysarthria						
0	1	2	3	4	5	6	9
Dysmetria						
0	1	2	3	4	5	6	9
Gait disturbances						
0	1	2	3	4	5	6	9
Hypertonia						
0	1	2	3	4	5	6	9
Hypotonia						
0	1	2	3	4	5	6	9
Nystagmus						
0	1	2	3	4	5	6	9
Pyramidal dysfunction:						
Extensor plantar reflexes						
0	1	2	3	4	5	6	9
Hyperreflexia						
0	1	2	3	4	5	6	9
Hyporeflexia						
0	1	2	3	4	5	6	9
Spasticity						
0	1	2	3	4	5	6	9

No	Initial Presentation	Early	Late	Yes, no onset	Not mentioned	Unknown
Extrapyramidal dysfunction:						
Athetosis						
0	1	2	3	4	5	6	9
Chorea						
0	1	2	3	4	5	6	9
Dystonia						

0 1 2 3 4 5 6 9

Rigidity

0 1 2 3 4 5 6 9

Tremor

0 1 2 3 4 5 6 9

Other neurologic symptoms/signs:

_____

Behavioral Change Symptoms

Agitation

0 1 2 3 4 5 6 9

Aggression

0 1 2 3 4 5 6 9

Anxiety

0 1 2 3 4 5 6 9

Apathy

0 1 2 3 4 5 6 9

Depression

0 1 2 3 4 5 6 9

Emotional lability

0 1 2 3 4 5 6 9

Poor concentration

0 1 2 3 4 5 6 9

Paranoid delusion

0 1 2 3 4 5 6 9

Recklessness

0 1 2 3 4 5 6 9

Sleep disorder

0 1 2 3 4 5 6 9

Withdrawal

0 1 2 3 4 5 6 9

Other behavioral

changes:_____

Were behavioral change symptoms or dysesthesia/parasthesia the predominant symptoms at the time of clinical presentation?

1 Yes 2 No 6 Not mentioned 9 Unknown

Was there a delay in the appearance of overt neurologic signs?

1 Yes, delayed by ____ months 2 No, neurologic signs appeared at the time of clinical presentation

6 Not mentioned 9 Unknown

Risk Factors

Did the patient receive a dura mater allograft?

1 Yes 2 No 6 Not mentioned 9 Unknown

If yes, please state reason for dural allograft:

_____

Date dural allograft received: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Did the patient receive a corneal allograft?

1 Yes 2 No 6 Not mentioned 9 Unknown

Date corneal allograft received: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Did the patient receive a pituitary hormone derived from cadavers?

1 Yes 2 No 6 Not mentioned 9 Unknown

If yes, please specify type of hormone: _____

Years pituitary hormone received: 19____ to 19____

Has the patient ever received a blood component or blood derivative?

1 Yes 2 No 6 Not mentioned 9 Unknown

If yes, please specify type of blood product received: _____

Indication/s for receiving blood component or derivative/s:_____

Date blood product received: __/__/_____(mm/dd/yyyy)

Is there history of a definite or probable case of CJD in a blood relative?

1 Yes 2 No 6 Not mentioned 9 Unknown

Is there history of other neurodegenerative or neuropsychiatric illness in a blood relative?

1 Yes 2 No 6 Not mentioned 9 Unknown

Is there any other possible risk factor identified?

1 Yes 2 No 6 Not mentioned 9 Unknown

If yes, please specify: _____

Date of exposure: _ _/_ _/_ _ _ _ (mm/dd/yyyy)

Clinical Tests

EEG findings: 1 Normal 2 Abnormal, classical 3 Abnormal, not classical
4 Not done 6 Not mentioned 9 Unknown

CSF 14-3-3 1 Not present 2 Present 3 Done, result unknown
4 Not done 6 Not mentioned 9 Unknown

Neuropathologic Findings

Neuropathology report available: 1 Yes 2 No 9 Unknown

Biopsy performed: 1 Yes 2 No 9 Unknown

Autopsy performed: 1 Yes 2 No 9 Unknown

Areas of brain samples taken:

_____

Is spongiform change associated with neuronal loss and gliosis present in:	Yes	No	Not mentioned	Unknown
Cerebral cortex	1	2	6	9
Frontal	1	2	6	9
Parietal	1	2	6	9
Temporal	1	2	6	9
Occipital	1	2	6	9
Caudate-Putamen	1	2	6	9
Thalamus	1	2	6	9
Cerebellum	1	2	6	9
Brain stem	1	2	6	9
Spinal cord	1	2	6	9

Other areas of the brain:_____

Is there proteinase-K resistant prion protein immunoreactivity?

1 Yes 2 No 6 Not mentioned 9 Unknown

Is the spongiform change most evident in the basal ganglia and thalamus and with sparse distribution throughout cerebral cortex? (This includes neuronal loss and astrocytosis focally).

1 Yes 2 No 6 Not mentioned 9 Unknown

Are there numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both cerebellum and cerebrum?

1 Yes 2 No 6 Not mentioned 9 Unknown

Is there prion protein accumulation in high density shown by immunocytochemistry, particularly in the cerebellum and cerebrum?

1 Yes 2 No 6 Not mentioned 9 Unknown

Western blot testing: 1 Type I 2 Type II 3 Others, please specify: _____

4 Not done 6 Not mentioned 9 Unknown

Polymorphism at codon 129 of PrP gene: 1 Met/Met 2 Met/Val

3 Val/Val 4 Not done 6 Not mentioned 9 Unknown

Point PrP gene mutations: 1 Absent 2 Present 3 Not done

6 Not mentioned 9 Unknown

If PrP gene mutations are present, please specify type:_____

Case Classification (For CDC use only)

Using the clinical diagnostic criteria for CJD, check for one or a combination of the following descriptions.

1 Definite CJD 2 Probable CJD 3 Possible CJD 4 Iatrogenic CJD

5 Familial CJD (Includes GSS and FFI) 6 Not CJD 9 Unknown

Similarity with the new variant of CJD reported in the United Kingdom:

1 Yes 2 No 9 Unknown

If yes, based on: 1 Clinical grounds alone 2 Neuropathology alone

3 Both clinical and neuropathologic findings

If no, based on: 1 Clinical grounds alone 2 Neuropathology alone

3 Both clinical and neuropathologic findings

Appendix C – CDC Diagnostic Criteria for variant CJD

Diagnostic Criteria for Variant Creutzfeldt-Jakob Disease in the United States

I. Definite Variant CJD: Neuropathologic examination of brain tissue is required to confirm a diagnosis of variant CJD. The following confirmatory features should be present.

a. Numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum - florid plaques.

b. Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.

II. Suspected Variant CJD

a. Current age or age at death <55 years (a brain autopsy is recommended, however, for all physician-diagnosed CJD cases).

b. Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (frank pain and/or dysesthesia).

c. Dementia, and development $4 months after illness onset of at least two of the following five neurologic signs: poor coordination, myoclonus, chorea, hyperreflexia, or visual signs. (If persistent painful sensory symptoms exist, $4 months delay in the development of the neurologic signs is not required).

d. A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.

e. Duration of illness of over 6 months.

f. Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis.

g. No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft.

h. No history of CJD in a first degree relative or prion protein gene mutation in the patient.

NOTE

1. If a patient has the typical bilateral pulvinar high signal on MRI scan, a suspected diagnosis of variant CJD requires the presence of a progressive neuropsychiatric disorder, d, e, f and g of the above criteria, and four of the following five criteria: 1) early psychiatric symptoms (anxiety, apathy, delusions, depression, withdrawal); 2) persistent painful sensory symptoms (frank pain and/or dysesthesia); 3) ataxia; 4) myoclonus or chorea or dystonia; and 5) dementia.

2. A history of possible exposure to bovine spongiform encephalopathy (BSE) such as residence or travel to a BSE-affected country after 1980 increases the index of suspicion for a variant CJD diagnosis.

Appendix D – WHO Diagnostic Criteria for CJD

Diagnostic Criteria for Creutzfeldt-Jakob Disease (CJD)

(Global Surveillance, Diagnosis, and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation, February 9-11, 1998, Geneva, Switzerland)

1. Sporadic CJD

Definite:
Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils.

Probable:
Progressive dementia; and at least two out of the following four clinical features:
- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

and
- A typical EEG during an illness of any duration; and/or a positive 14-3-3 CSF assay and a clinical duration to death of <2 years
- Routine investigations should not suggest an alternative diagnosis

Possible:
Progressive dementia; and at least two out of the following four clinical features:
- Myoclonus
- Visual or cerebellar signs
- Pyramidal/extrapyramidal signs
- Akinetic mutism

and
- No EEG or atypical EEG and duration <2 years

2. Iatrogenic CJD:
Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or Sporadic CJD with a recognized exposure risk, e.g. antecedent neurosurgery with dura mater implantation.

3. Familial CJD
Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or Neuropsychiatric disorder plus disease-specific PrP gene mutation.

Appendix E – IRB clearance

EMORY UNIVERSITY

Institutional Review Board

February 14, 2011

Caitlin Mertzlufft
Prion and Public Health Office
Centers for Disease Control and Prevention

RE: Determination: No IRB Review Required
Cruetzfelt-Jakob Disease Surveillance Database
PI: Caitlin Mertzlufft

Dear Ms. Mertzlufft,

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of research involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules.

Specifically, in this project, you will be using abstracted medical information on deceased individuals. As 45 CFR 56.102(f) specifically defines a human subject as a "living individual," research using deceased subjects is not subject to IRB oversight. Other regulations and ethics reviews may still apply.

This determination could be affected by substantive changes in the study design. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Sean Kiskel
Research Protocol Analyst
Emory University IRB

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu
An equal opportunity, affirmative action university