ABSTRACT
This review provides the rationale and background for the development of diagnostic criteria for Creutzfeldt-Jakob Disease (CJD), which is recent outbreak including risk factors and neuropathological findings in human, epidemiology, and clinical characteristics, along with treatment, and future research directions. Overall, there is substantial research to suggest that the dementia that may co-occur with this CJD different from dementia of other neurodegenerative disorders. Future prospective for further research necessities to better define core symptoms, mode of transmission, efficacy of treatment in human are highlighted.

Key words: neurodegenerated disorder, abnormal prion protein, methionine/valine polymorphism, rapidly progressive dementia, bovine spongiform encephalopathy, magnetic resonance imaging.

INTRODUCTION
Recent attention on the “Mad Cow” scare in the US has reminded public health of the importance of timely, accurate, surveillance of Creutzfeldt-Jakob Disease (CJD) (brain wasting disease). It is a rare neurodegenerative disorder affecting approximately one in every million persons. It is one of several transmissible spongiform encephalopathies (TSE), which occur in varying forms in both humans and animal species. Statistics analysis says increased incidence of brain-wasting disease in Britain. A research letter published in the Lancet medical journal points to a possible increase in the rate of people dying from new variant...
Creutzfeldt-Jakob disease (nvCJD), a fatal brain-wasting disease also called Human BSE has scare the public\(^1\).

**DEFINITION: What is Creutzfeldt- Jakob Disease(CJD)**

CJD is a brain wasting disease, invariably fatal brain disorder characterised by symptoms meomory impairment, behavior change and ultimately dementia, similar to Alzheimer’s disease\(^2\). Typically, onset of symptoms occurs about age 60, and about 90 percent of individuals die within 1 year. In the early stages of disease, people may have failing memory, behavioral changes, lack of coordination and visual disturbances. As the illness progresses, mental deterioration becomes pronounced and involuntary movements, blindness, weakness of extremities, and coma may occur\(^4\).

There are four types of brain wasting disease: sporadic (spontaneous), familial (hereditary), iatrogenic (acquired) and variant.

**Sporadic CJD** - is the most common human prion disease and accounts for approximately 85-90% of CJD cases. The disease results from the spontaneous conversion of the normal brain protein into the disease -causing abnormal prion protein. The genotype at codon 129 of the prion protein gene, the site of a common methionine/valine polymorphism, results in two types of protease-resistant prion proteins that differed in size and glycosylation\(^3,30\).

**Familial CJD** - is an inherited form of CJD and occurs in people with a family history for the condition and who test positive for the genetic mutation in their prion. This affects younger people and accounts for 5-15% of cases. This mutation makes it more likely that the brain protein will convert to the abnormal disease causing form.

**Iatrogenic CJD** - is transmitted by direct exposure to abnormal prion proteins from an external source during a medical procedure. In rare situations, CJD has been spread by the re-use of contaminated surgical instruments or the transplantation of certain high-risk tissues from a CJD infected donor. There is no evidence that CJD is contagious through casual contact with a CJD patient.

**Variant CJD** (vCJD)- is linked to the consumption of meat from an animal infected with BSE or by blood transfusion from a donor infected with vCJD. Variant CJD is a separate disease and is caused by a different prion than the sporadic or familial forms of CJD\(^3\).
All these are caused by a transmissible infectious particle called PRION, a misshapened protein which alters the shape of other proteins, causing cavities in the brain. The disease is caused by an abnormal form of a brain protein, which self-replicates and accumulates in the brain causing damage and eventually death.

The typical Creutzfeldt-Jakob disease phenotype or myoclonic variant and the Heidenhain variant were linked to methionine homozygosity at codon 129 and to "type 1" protease-resistant prion protein. The atypical and rarer variants such as that with dementia of long duration, the ataxic variant, and the variant with kuru plaques were linked to different genotypes at codon 129 and shared the "type 2" protease-resistant prion protein. The methionine/valine polymorphism at codon 129 of the prion protein gene and two types of protease-resistant prion proteins are the major determinants of these variants. These findings suggest the existence of prion strains in humans and provide the molecular basis for a novel classification of sporadic Creutzfeldt-Jakob disease.

**PREVALENCE**

CJD is transmissible neurological disorder, occurs worldwide with an incidence 1 to 2 cases per million population per year. In a year, 300 CJD cases were found which lead to rapid death in the elderly, according to the Centers for Disease Control. CJD has been increasing in frequency in the United States over the past two decades. The Centers for Disease Control and Prevention (CDC) monitors the trends and current incidence of CJD in the United States using several surveillance mechanisms, gives evidence of CJD occurs in US. In France during 1968–1982, 329 cases died. Paris was found to have a much higher case rate than the rest of France, according to Statistical analysis of clustering. Six cases of CJD have been reported in Canada this year, says the Public Health Agency of Canada. The Australian National Creutzfeldt-Jakob Disease Registry, 6 pathologically confirmed sporadic cases were recognized. In Switzerland and the rest of Europe essential to monitor the situation to see if this rise of CJD is sustained in Switzerland. New variant Creutzfeldt-Jakob disease (nvCJD) is a novel human transmissible spongiform encephalopathy which was first identified in 1996 in the United Kingdom (UK). nvCJD had been reported (49 cases in the UK, two cases in France and one case in the Republic of Ireland. There is no seasonal distribution. These cases appear to represent a new variant of CJD, which may be unique to the UK. Epidemiological studies of CJD using similar methodology to the UK study have been carried out in France, Germany, Italy, and the Netherlands between 1993 and 1995.
Similar cases have not been identified in other countries in the European surveillance system.\textsuperscript{16}

**SIGNS AND SYMPTOMS**

At UCSF (University of California San Francisco), CJD is sometimes called the "great mimicker" because it causes symptoms that occur in many other neurological diseases. First symptoms vary widely and may include the following:

- Behavioral and personality changes
- Confusion and memory problems
- Depression
- Insomnia
- Lack of coordination
- Strange physical sensations
- Vision problems

As the disease advances, patients may experience a rapidly progressive dementia and in most cases involuntary and irregular jerking movements called myoclonus. Patients also may appear startled and become rigid.\textsuperscript{6} Case study by the Florida Department of Health and CDC give evidence for this symptoms.\textsuperscript{13} CJD does not cause a fever or other flu-like symptoms.\textsuperscript{4}

In advanced stages of the disease, patients have difficulties with movement, swallowing and talking. In the final stage, patients lose all mental and physical function and may lapse into a coma. Many patients die from an infection such as pneumonia.\textsuperscript{6,19} The average duration of disease — from the onset of symptoms to death — is four to six months. Ninety percent of patients die within a year. Some cases progress very rapidly, lasting only a few weeks before the patient’s death, and others may last two or three years, especially if the disease occurs at an early age.\textsuperscript{6}

There are several known variants of CJD. These variants differ somewhat in the symptoms and course of the disease. For example, a variant form of the disease-called new variant or variant (nv-CJD, v-CJD), described in Great Britain and France-begins primarily with psychiatric symptoms, affects younger individuals than other types of CJD, and has a longer than usual duration from onset of symptoms to death. Another variant, called the panencephalopathic form, occurs primarily in Japan and has a relatively long course, with
symptoms often progressing for several years. Scientists are trying to learn what causes these variations in the symptoms and course of the disease. Some symptoms of CJD can be similar to symptoms of other progressive neurological disorders, such as Alzheimer’s or Huntington’s disease. However, CJD causes unique changes in brain tissue which can be seen at autopsy. It also tends to cause more rapid deterioration of a person’s abilities than Alzheimer’s disease or most other types of dementia. In nv-CJD first symptoms of case study patient were purely psychiatric and difficult to distinguish from common psychiatric disorders.

Uncommon clinical and morphological features also characterized in some cases. An evident atrophy syndrome, confirmed in morphological findings, developed soon after the CJD onset. The spongiform change also observed within the white matter of cerebral hemispheres allowed us to diagnose the ‘panencephalopathic’ form of CJD.

Case of 77-year-old woman with CJD lasting 1 year, there was extensive degeneration of cerebral white matter in addition to severe loss of neurons and hypertrophic astrogliosis in cortex and striatum. The extent and severity of white matter lesions makes the case unusual.

ETIOLOGY/PATHOPHYSIOLOGY

CJD in humans is caused due to prion proteins, due to decreased neurotransmitter receptor expression. Prions replaces the normal PrP\(^c\) (prion protein) by a protease-resistant, isoforms (PrP\(^{CJD}\), PrP\(^{Sc}\), PrP\(^{BSE}\)) that are pathogenic. Classical CJD can be presented as sporadic, infectious or familial, whereas the new variant of CJD (nvCJD) is considered a BSE-derived human disease. Spongiform degeneration, glial proliferation, involving astrocytes and microglia, neuron loss and abnormal PrP deposition are the main neuropathological findings in most human and animal prion diseases. The characteristic feature is extensive degeneration of cerebral white matter not related to cortical damage in addition to the spongiform changes in the cortical gray matter. The case was diagnosed clinically and at post mortem marked neural loss, astrocytic macrogliosis, and degeneration of subcortical white matter were found. Senile plaques and neurofibrillary tangles were virtually absent. Degeneration of the white matter is uncommon in C-J disease, and when it occurs is usually mild, and limited in distribution. Various clinicopathologic features (including age of onset, disease duration, EEG) and pattern of histopathologic changes are obeserved in slide.
Fig. 1 This tissue slide shows sponge-like lesions in the brain tissue of a classic CJD patient. This lesion is typical of many prion diseases.22

Another neuropathological receptor based mechanism is decreased GluR2/3 and NMDAε1 expression correlated with prion protein deposition, neuron loss and spongiform degeneration in the cerebral cortex. Decreased GluR2/3 immunoreactivity in the frontal cortex, entorhinal cortex and Purkinje cells; reduced NMDAε1 immunoreactivity in the frontal cortex, entorhinal cortex, and molecular and granular cell layers of the cerebellum is hypothesized. 10 The new variant of Creutzfeldt-Jakob disease differs from sporadic, genetic and iatrogenic CJD. Creutzfeldt-Jakob disease is closely associated with an abnormal isoform PrPSc of a cell-surface glycoprotein, prion protein. Molecular analysis suggests that nvCJD is caused by the same prion strain as bovine spongiform encephalopathy (BSE).15

MODE OF TRANSMISSION
The mode of transmission of most cases is unknown, but consistent experimental transmission of infectivity has been possible with homogenates of brain, spinal cord and eye tissue.7 A variety of major surgical procedures constitute a risk factor for sCJD. Number of sCJD cases originate from health care-related accidental transmission.5 Transmission occurred in less than half of the attempts with preparations of lung, liver, kidney, spleen, lymph node and cerebrospinal fluid.7 Iatrogenic cases sources are contaminated growth hormone (226 cases) and dura mater grafts (228 cases) derived from human cadavers with undiagnosed CJD infections; a small number of additional cases are caused by neurosurgical instrument contamination, corneal grafts, gonadotrophic hormone, and secondary infection with variant CJD transmitted by transfusion of blood products.8

Variant CJD cases appear to have a relationship to consumption of cattle brain or spinal cord in sausage, hamburger and other processed meat from BSE infected cattle starting in the
As of early October 2002, a total of 138 vCJD cases were reported worldwide, including the case described in this report. Consistent with the conclusion that the agent of BSE is also the agent responsible for vCJD, most vCJD cases (n=128) were reported in the United Kingdom, where most BSE cases in cattle have occurred.¹³ And now thought to have ended because of changes in animal feeding and slaughtering practices.

Cases of CJD have been reported in adolescents and one of these was iatrogenically transmitted, while another was familial. Epidemiologic investigation of the present case excluded a familial component, and provided no evidence for iatrogenic or natural case-to-case transmission, or of other environmental sources of viral contamination.²¹

**DIAGNOSIS**

CJD, especially in its early stages, is an extremely challenging disease to diagnose. The clinical symptoms are relatively nonspecific and overlap with other dementia disorders. The characteristic EEG findings are seen in only 66% of patients and have a reported specificity of 74%.²⁶ A series of tests (including specific brain scans) are done to diagnosis CJD. The correct diagnosis is possible only after the death when postmortem is performed.² The common diagnostic feature is increase in nuclear DNA vulnerability leading to augmented numbers of cells bearing nuclear DNA fragments in the brains of humans affected by prion diseases examined at post-mortem, but also in archival biopsy samples processed with the method of in situ end-labeling of nuclear DNA fragmentation.⁹ Examination of immunohistochemistry in the cerebral cortex (frontal cortex) entorhinal cortex, hippocampus and cerebellar cortex in nine patients with sporadic Creutzfeldt-Jakob disease (CJD) and eight age-matched controls obtained 3–8 h after death. All patients with CJD showed methionine/methionine in codon 129 of the prion protein gene.¹⁰,¹⁴

**CLINICAL AND PATHOLOGICAL CHARACTERISTICS DISTINGUISHING CLASSIC AND VARIANT CJD**²²

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Presence of agent in lymphoid tissue | Not readily detected | Readily detected
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Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein | Not reported | Marked accumulation of protease-resistance prion protein


- An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery sequences on brain magnetic resonance imaging (MRI); in the appropriate clinical context, this signal is highly specific for vCJD.

Repeat EEG demonstrated bihemispheric triphasic wave complexes. Cerebrospinal fluid cytology and cultures were normal, but cerebrospinal fluid protein 14-3-3 was abnormally elevated. Magnetic resonance imaging (MRI) of the brain revealed areas of diffusion restriction in the right cerebral cortex and right basal ganglia.²⁵ (figure 2)

![Figure 2](image-url)

In inherited CJD diagnosis depends on analysing symptoms and genetic testing. Iatrogenic CJD is based on symptoms developed in humans on exposure to hormones. Diagnosis of variant CJD is very difficult but brain scanning, using magnetic resonance imaging (MRI) and tonsil biopsy are used.² Computed tomography scans of the brain may show either nonspecific atrophy or no abnormality at all. Brain biopsy can be conclusive, but the elevated risk of disease transmission makes this a rarely plausible option. Given this diagnostic dilemma, MRI of the brain is an increasingly useful tool in the evaluation of patients with suspected CJD. Most importantly, MRI is helpful in excluding other possibly treatable causes of encephalopathy.²⁵ The biochemical characteristics and the intracerebral distribution of
protease-resistant prion protein are studied with Western blot and immunohistochemistry in some cases of sporadic Creutzfeldt-Jakob disease.²⁹

TREATMENT
There is no other treatment beyond treating symptoms like spasm, seizures. Drugs that control symptoms and make patient comfortable are valproate, clonazepam for jerky movements.² Current treatment for CJD is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relieve pain if it occurs, and the drugs clonazepam and sodium valproate may help relieve myoclonus. During later stages of the disease, changing the person's position frequently can keep him or her comfortable and helps prevent bedsores. A catheter can be used to drain urine if the patient cannot control bladder function, and intravenous fluids and artificial feeding also may be used.²³

Potential treatments for Creutzfeldt-Jakob Disease (CJD)
Creutzfeldt-Jakob disease and other human prion diseases are invariably fatal and there is currently no proven treatment for the underlying process. There are however a number of potential treatments in development or under consideration. It must be stressed that, to date, no treatment has been shown conclusively to slow or halt the disease process in humans with any form of CJD. There has been media coverage of two potential treatments in particular: Quinacrine and Pentosan Polysulphate and Flupirtine.²⁴,²⁷ There is an MRC-funded trial (PRION-1) that is currently studying the possible effects of Quinacrine.

Quinacrine
'Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease' (Korth et al.). This article provided evidence of inhibition of the formation of the disease associated form of prion protein in scrapie infected neuroblastoma cells by a number of compounds, with quinacrine and chlorpromazine exhibiting the greatest potency. The article concludes "Because quinacrine and chlorpromazine have been used in humans for many years as anti-malarial and anti-psychotic drugs respectively, and are known to pass the blood brain barrier, we suggest that they are immediate candidates for the treatment of Creutzfeldt-Jakob disease and other prion diseases".²⁷

Pentosan polysulphate
Pentosan polysulphate (PPS) is derived from beechwood and has anti-thrombotic and anti-inflammatory properties. It has been used in routine clinical practice for some time in the
treatment of thrombotic disorders and interstitial cystitis. There is no scientific rationale to suggest that drugs like PPS will cause or aid any recovery to previously damaged neurones. The use of treatments like PPS in the incubation period of human CJD (prior to any symptoms) is not presently feasible; such an approach would require definitive demonstration of safety and efficacy in humans and a validated pre-symptomatic test (that does not, currently, exist). Therefore, it is important that patients seeking treatment with PPS be given it as early as possible.  

Researchers have tested many drugs, including amantadine, steroids, interferon, acyclovir, antiviral agents, and antibiotics. Studies of a variety of other drugs are now in progress. However, so far none of these treatments has shown any consistent benefit in humans. 

**PREVENTIVE MEASURES**

The National Prion Disease Pathology Surveillance Center (NPDPSC) was organized at Case Western Reserve University in Ohio. They provide free analysis of cerebral spinal fluid, blood, and brain tissue (obtained either at biopsy or autopsy) in order to confirm and identify the precise type of prion disease in a patient. Diagnostic services provided by this center are an essential component of public health’s ability to monitor any possible occurrences of vCJD or changes in the epidemiology of sporadic CJD in the United States. 

To reduce the already very low risk of CJD transmission from one person to another, people should never donate blood, tissues, or organs if they have suspected or confirmed CJD, or if they are at increased risk because of a family history of the disease, a dura mater graft, or other factor.

Normal sterilization procedures such as cooking, washing, and boiling do not destroy prions. Caregivers, health care workers, and undertakers should take the following precautions when they are working with a person with CJD:

- Wash hands and exposed skin before eating, drinking, or smoking.
- Cover cuts and abrasions with waterproof dressings.
- Wear surgical gloves when handling a patient's tissues and fluids or dressing the patient's wounds.
- Avoid cutting or sticking themselves with instruments contaminated by the patient's blood or other tissues.
To prevent possible contamination medical instruments should always be sterilized and disposed of properly.\textsuperscript{2}

Use face protection if there is a risk of splashing contaminated material such as blood or cerebrospinal fluid.

Soak instruments that have come in contact with the patient in undiluted chlorine bleach for an hour or more, then use an autoclave (pressure cooker) to sterilize them in distilled water for at least one hour at 132 - 134 degrees Centigrade.\textsuperscript{23}

Continued surveillance of both BSE and CJD is required in the UK and in other countries, to ensure that the scale of this potential epidemic is adequately monitored and that all possible steps are taken to prevent further human exposure to the BSE agent.\textsuperscript{14}

To reduce any risk of acquiring vCJD from food, travelers to Europe or other areas with indigenous cases of BSE may consider either avoiding beef and beef products altogether or selecting beef or beef products, such as solid pieces of muscle meat (rather than brains or beef products like burgers and sausages), that might have a reduced opportunity for contamination with tissues that may harbor the BSE agent. Milk and milk products from cows are not believed to pose any risk for transmitting the BSE agent.\textsuperscript{12}

FUTURE PROSPECTIVES

Yet new observations have shown cleaved (active) caspase-3 (17 kDa), a main executioner of apoptosis, expressed in scattered cells in the brains of mice with experimental scrapie and in the cerebellum of patients with sporadic CJD. Together, these data suggest activation of the caspase pathway of apoptosis in human and animal prion diseases.\textsuperscript{9} A number of different approaches are currently underway, although the difficulties of developing a method of sufficient sensitivity and specific are formidable. Continuing surveillance for vCJD is required in order to assess more fully the risks to these patients and to obtain more information about the prevalence of this disorder, particularly in relation to PRNP genotypes in which definite cases of vCJD have not yet been identified.\textsuperscript{28}

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