

Creutzfeldt-Jakob Disease Is A Rare Fatal Disease With No Treatment

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Abstract

Creutzfeldt-Jakob disease (CJD) is a rare, degenerative, invariably fatal brain disorder caused by prions. The patient is usually mute and immobile in the terminal stages and in most cases, death occurs within a few months of onset of symptoms. Electroencephalogram, Cerebrospinal fluid 14-3-3 analysis and Magnetic resonance imaging might provide support for a diagnosis of CJD.

There is no cure for CJD and the search for viable treatments continues. Prions are not destroyed by standard sterilization methods.

Researchers are examining whether the transmissible agent is, in fact, a prion and trying to discover factors that influence prion infectivity.

Need for further research into the molecular properties of the CJD agent that could lead to potential disease modifying compounds.

Efforts should also be made to identify pre-symptomatic diagnostic tests, and to enable any future therapy to be used as early as possible in the disease course.

INTRODUCTION

Transmissible Spongiform Encephalopathy (TSE) or prion diseases are caused by prions. Prion diseases include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) and kuru in humans, as well as bovine spongiform encephalopathy (BSE) commonly known as mad cow disease, chronic wasting disease (CWD), and scrapie in sheep (1).

CJD is a rare, degenerative, invariably fatal brain disorder (2). Among the types of TSEs, it is the most common (1), has a worldwide death rate of about 1 case per million people each year, and typically affects people between 55 and 75 years of age (3). It is classified as a transmissible spongiform encephalopathy because of characteristic spongy degeneration of the brain and its ability to be transmitted to laboratory animals (4). There are three major categories of CJD: sporadic CJD, hereditary CJD, and acquired CJD (2). Classic CJD has been recognized since the early 1920s. The most common form of classic CJD is believed to occur sporadically (5).

New variant Creutzfeldt-Jakob disease (vCJD) is an infectious form of CJD. vCJD is a new disease that was first identified in 1996 in the United Kingdom. Most people who have developed vCJD have lived in the UK. In contrast to the traditional forms of CJD, vCJD accounts for less than 1% of cases, affected younger patients (average age 29 years, as opposed to 65 years), has a relatively longer duration of illness (median of 14 months as opposed to 4.5 months) and is strongly linked to exposure, probably through food, to a TSE of cattle called Bovine Spongiform Encephalopathy (6, 7).

SYMPTOMS

The first symptom of CJD is rapid development of delirium or dementia, followed by personality changes, hallucinations, muscle stiffness, nervous, changes in gait, lack of coordination, speech impairment, sleepiness, memory loss, anxiety, stress, and tension (6).

The patient is usually mute and immobile in the terminal stages and in most cases, death occurs within a few months of onset of symptoms (3).

DIAGNOSIS

An absolutely definitive diagnosis of any form of CJD requires neuropathological examination of brain tissue. This would usually be undertaken at post mortem examination. Rarely, a brain biopsy may be taken but this is not usually necessary in the investigation of cases of possible CJD.

When a diagnosis of CJD is suspected, investigations are undertaken for two broadly separate reasons. Firstly, investigations are used to exclude other possible diagnoses. Secondly, there are certain investigations which are supportive of the diagnosis of CJD. These supportive investigations are discussed below. It is important to note that some of these investigations (such as the MRI scan and the cerebrospinal fluid examination) may be undertaken for both reasons (8).

There are three investigations which might provide support for a diagnosis of CJD. These are:

1. THE EEG

The EEG (electroencephalogram) becomes abnormal in CJD, causing a characteristic pattern in 60-80% of cases. Although it may be present in several other conditions, it is helpful in making a diagnosis for a 'probable' case. Prior to the CSF 14-3-3 test, the EEG was the most useful test (8, 9).

2. CEREBROSPINAL FLUID 14-3-3 ANALYSIS

Raised CSF levels of a specific brain protein called 14-3-3 are helpful in supporting a clinical diagnosis. Elevation of the 14-3-3 protein in the CSF is a marker for rapid neuronal death. This marker may also be raised in other conditions associated with rapid cell death (e.g., intracerebral hemorrhages and encephalitis) (10), and 14-3-3 analysis cannot be used as a general screening test for CJD.

However, it is usually a straightforward clinical matter to exclude the other possible illnesses which may give rise to an elevated 14-3-3 level. Therefore, in an appropriate clinical context, a positive test is strongly supportive of a diagnosis of CJD and a negative test is unusual (8, 9).

3. MAGNETIC RESONANCE IMAGING

Brain scans to rule out other possible illnesses. CT scans (X-ray scans) are usual but MR (magnetic resonance) scans may show an abnormality in two parts of the brain called the caudate and putamen nuclei. While this is not always present and is not absolutely specific to CJD, it is helpful in making a diagnosis in a suspect case (9).

The following criteria proposed for probable CJD diagnosis (11):

Progressive dementia; and

At least two out of the following four clinical features:

- Myoclonus, ?Visual or cerebellar disturbance, Pyramidal/extrapyramidal dysfunction, 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 <2 years;
- Routine investigations should not suggest an alternative diagnosis.

Clinical and Pathologic Characteristics of Classic CJD as compared to variant CJD are presented in the table below (5).

Figure 1

| Characteristic | Classic CJD | Variant CJD |
|---|----------------------------------|---|
| Clinical signs and symptoms | Dementia; early neurologic signs | Prominent psychiatric/behavioral symptoms; painful dyesthesia; delayed neurologic signs |
| Periodic sharp waves on electroencephalogram | Often present | Often absent |
| *Pulvinar sign* on MRI* | Not reported | Present in >75% of cases |
| Presence of "florid plaques" on neuropathology | Rare or absent | Present in large numbers |
| Immunohistochemical analysis of brain tissue | Variable accumulation | Marked accumulation of protease-resistance prion protein |
| Presence of agent in lymphoid tissue | Not readily detected | Readily detected |
| Increased glycoform ratio on Western blot analysis of protease-resistance prion protein | Not reported | Marked accumulation of protease-resistance prion protein |
| Source: Adapted from Belay E., Schonberger L. Variant Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy. Clin Lab Med 2002;22:849-62. | | |
| * 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. | | |

TREATMENT

As of December 2006, there is no cure for CJD and the search for viable treatments continues. An experimental treatment was given to a Northern Irish teenager, beginning in January 2003 (12). The medication, called pentosan polysulphate (PPS), that does not seem to stop the disease from progressing. Both brain function and tissue continue to be lost. However, the treatment may have contributed to the

longer than expected survival of the seven patients that were studied (13).

Custodial care may be required early in the course of the disease. Medications may be needed to control aggressive behaviors. These include sedatives, antipsychotics, and others. The need to provide a safe environment, control aggressive or agitated behavior, and meet physiologic needs may require monitoring and assistance in the home or in an institutionalized setting. Legal advice may be appropriate early in the course of the disorder, to form advance directives (6).

TRANSMISSION

Transmission of CJD from case to case has occurred by a number of routes involving accidental inoculation with human prions as a result of medical procedures. Such iatrogenic routes include the use of inadequately sterilised neurosurgical instruments, dura mater and corneal grafting, and use of human cadaveric pituitary derived growth hormone or gonadotrophin (14). Cadaver-derived growth hormone has been replaced by synthetically manufactured growth hormone, so this source of contagion is no longer a problem (6).

In hereditary form, a mutation occurs in the gene for PrP (prion protein), PRNP. 10 to 15 percent of CJD cases are inherited; or it may appear for the first time in the patient (sporadic form) (1).

DECONTAMINATION

The matter of transmission of CJD is a worrisome one for hospitals: Prions stick on to re-usable appliances and are not destroyed by standard sterilization methods including heat, radiation, alcohol, benzene and formaldehyde (15, 16).

Copper-hydrogen peroxide has been recommended as a possible method of decontamination, but this work is at a very preliminary stage (17).

The following recommendations (3) are based on the best available evidence at this time and may require revision if new data become available.

The safest and most unambiguous method for ensuring that there is no risk of residual infectivity of CJD on contaminated instruments, materials and wastes is to discard and destroy them by incineration.

For heat-resistant reusable instruments immerse in 1N NaOH or sodium hypochlorite (20, 000 ppm available

chlorine) for 1 hr; transfer instruments to water; heat in a gravity displacement autoclave at 121°C for 1 hr; clean and subject to routine sterilization.

Moreover, hot alkaline hydrolysis reduces biological macromolecules to their constituent sub-units, thereby cleaning as well as inactivating.

Complex and expensive instruments cannot be decontaminated by the harsh procedures. Contaminated parts of the device should be subjected to the most effective decontaminating procedure that can be tolerated by the instrument.

Removable parts that would not be damaged by autoclaving, NaOH, or bleach

should be dismantled and treated with these agents.

Because TSE infectivity persists for long periods on work surfaces, whenever possible it is important to use disposable cover sheets, even though transmission to humans has never been recognized to have occurred from environmental exposure.

Surfaces and heat sensitive instruments can be disinfected by flooding or soaking, for one hour, with 2N NaOH or undiluted sodium hypochlorite, mop up and rinse with water.

Liquids used for cleaning should be decontaminated in situ by addition of NaOH or hypochlorite and may then be disposed of as routine hospital waste.

Persons involved in the disinfection and decontamination of instruments or surfaces should wear single-use protective clothing, gloves, mask and visor or goggles.

PREVENTION

Risk of transfer of the organism on equipment or tissue is minimized by the health care provider. Treatment equipment is sterilized to kill organisms that may cause the disease.

Medical histories of potential cornea donors that indicate a history of diagnosed or possible Creutzfeldt-Jakob disease rule out the use of those corneas for transplantation.

Most countries now have strict guidelines for management of infected cows and strict restrictions regarding what they are fed, to avoid the potential for transmission of CJD to humans (6).

FURTHER RESEARCH

Researchers are examining whether the transmissible agent

is, in fact, a prion or a product of the infection, and trying to discover factors that influence prion infectivity and how the disorder damages the brain. Using rodent models of the disease and brain tissue from autopsies, they are also trying to identify factors that influence the susceptibility to the disease and that govern when in life the disease appears (2).

Need for further research into the molecular properties of the TSE agent that could lead to potential disease modifying compounds.

Efforts should also be made to identify pre-symptomatic diagnostic tests, and to enable any future therapy to be used as early as possible in the disease course.

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