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**Creutzfeldt-Jakob disease: A review of current available
evidence and the implications for pre-hospital emergency
care**

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Review

Creutzfeldt-Jakob disease: A review of current available evidence and the implications for pre-hospital emergency care

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Abstract

Introduction

Creutzfeldt-Jakob disease affects one in 1 million people worldwide each year. It is an invariable fatal neurodegenerative disease belonging to the group of transmissible spongiform encephalopathies. This review aims to examine the current clinical evidence surrounding the disease, present management techniques to assist in minimising the effect of symptoms, and highlight the important role that paramedics play in reducing associated mortality and morbidity.

Methods

An electronic search was conducted using MEDLINE (Via EBSCOHost), CINAHL and the Cochrane Database of Systematic Reviews.

Results

The search resulted in 265 articles. Articles unavailable as full text, those not available in English, those articles not peer reviewed, and review articles were excluded from analysis. The remaining 16 articles met the search criteria and are included in this report.

Conclusion

Scientific advancements are resulting in encouraging clinical trials, however, further research needs to be conducted. Training and education programs should be made available to pre-hospital workers to prevent further spread of infection.

Keywords:

Creutzfeldt-Jakob disease, CJD, transmissible spongiform encephalopathies, prion disease

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Introduction

Creutzfeldt-Jakob disease (CJD) belongs to the group of transmissible spongiform encephalopathies (TSE), and is also known as Prion disease. It affects the central nervous system, is incurable and invariably fatal. Creutzfeldt-Jakob disease is named after the physicians Creutzfeldt and Jakob, who carried out extensive research into the disease in Germany in the 1920s (1). There are four subtypes with different causes, onset ages and incubation periods. Although there is no cure for the disease, there are different treatment and management options available to sufferers, with scientific research being carried out in search of a possible cure for all variants of CJD.

Creutzfeldt-Jakob disease is a neurodegenerative disorder that results in spongiosis of the brain, neural death, astrogliosis and production of abnormal prion proteins. The cause of CJD is not entirely understood, however it is believed that the degradation of neural tissue in CJD is due to a naturally occurring prion protein that has folded abnormally after the translation phase of protein synthesis (2). This abnormal prion protein is immune to protease and therefore unable to be degraded before it causes cerebral harm. In 1996, research discovered the neural protein 14-3-3, and specifically proteins 130 and 131, are found in abundance in the cerebrospinal fluid of infected patients. Although it is still unclear the role these proteins play in CJD, it has recently been discovered that it is feasible in certain instances to use protein 14-3-3 as a pre-mortem immunoassay. However, this is only an indication that the patient may be suffering

from CJD and a postmortem brain biopsy is needed for confirmation of diagnosis (2).

Spongiosis, small vacuole-like structures, occur in the neuropil of the cerebral cortex, basal ganglia and thalamus, resulting in large cavities throughout the brain. Due to the destruction of the neurons, astrogliosis, excessive production of astrocytes, occurs. Astrocytes are glial cells found in the central nervous system that, in the healthy person, provide stable foundations for neurons.

This review aims to examine the current clinical evidence surrounding CJD, present management techniques to assist in minimising the effect of symptoms, and highlight the important role paramedics play in reducing associated mortality and morbidity.

Methods

A search was conducted using the electronic databases MEDLINE (via EBSCOHost), CINAHL and the Cochrane Database of Systematic Reviews, and included the keywords 'Creutzfeldt-Jakob disease', 'CJD', 'transmissible spongiform encephalopathies' and 'prion disease'. Articles unavailable as full text, those not available in English, those articles not peer reviewed, and review articles were excluded from analysis.

Results

The search identified 16 articles, which were included for analysis. The results are detailed in Figure 1.

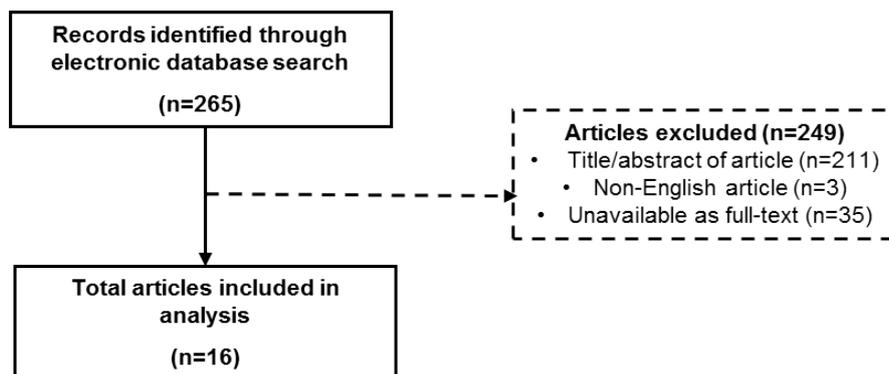


Figure 1. Search results

Discussion

The aetiology of CJD can be described within four distinct variants.

Sporadic

The sporadic variant is the first type discovered in 1921. It accounts for 85% of CJD cases, with the cause still unknown. The average age of onset is 66 years, with death occurring rapidly, usually within 4-6 months of diagnosis (a proxy for onset). The most common symptom is dementia with ataxia, myoclonus and visual disturbances. Patients suffering from sporadic type have abnormal magnetic resonance imaging and 14-3-3 protein marker is present in the cerebrospinal fluid in 99% of cases (3).

Familial

This variant is the second most common and affects 5-10% of CJD cases. The cause is an autosomal dominant mutation within the prion protein gene on the chromosome 20p. People diagnosed with this strain either have an immediate family member with CJD, or they suffer from a neuropsychiatric disorder and a mutation of the prion protein gene specific to CJD (3).

Iatrogenic

Iatrogenic infections of CJD are acquired from medical treatment that uses human body products from either a living donor or a cadaver. The procedures with the highest risk of infection are posterior eye surgery, neuroendoscopy and intradural neurosurgery. Patients present with sporadic CJD symptoms: dementia with ataxia, myoclonus and visual disturbances (3).

Variant (vCJD)

This particular strain was identified in 1996 and is the human manifestation of bovine spongiform encephalopathy (BSE), also known as 'mad cow disease'. Up until 2004 its only known cause was consuming animal products from BSE-infected animals. Since 2004 there have been four cases of patients who contracted CJD by accepting blood/plasma transfusions from infected humans (4,5). By March 2012, it was reported that since it was identified in 1996, 225 cases were reported worldwide, but due to procedures to prevent the spread of infection the incidence of vCJD has been steadily declining since 2002 (4). This strain tends to affect the younger population, with the average onset of age 27 years. However, it does not cause rapid declines, with death resulting on average 14 months after onset of symptoms. Symptoms are typically of a psychiatric nature with persistent painful sensory disorders progressing to movement disorders and dementia in the later stages (3).

Management of CJD

After nearly a century of research into CJD, there is still no known cure. There are few successful symptom management techniques available to sufferers, with some drugs found by researchers to slow or halt the disease process, though there is insufficient evidence enabling their recommendation as a standard of therapy (6). The pathophysiology of the disease process is uniform across all four variants. Treatments are either symptom based or focused on treating the disease process itself. Drugs found to have an effect on CJD belong to the classes: analgesic, anti-depressant, anti-psychotic, anti-microbial, corticoids and anti-coagulant. The three drugs studied most in-depth are flupirtine, intraventricular pentosan polysulphate and amantadine. These drugs focus on the inhibition of the prion protein with hopes of inhibiting progression of the disease and extending survival rates. Most trials are still in the observation stages, with a limited amount of controlled therapeutic human trials (7). Other worthwhile studies are being conducted on drugs that manage CJD symptoms, such as rivastigmine and levetiracetam. Researchers have also been studying fetal neural stem cell therapy, which may potentially repair damaged tissue.

Pentosan polysulphate (PPS) is currently being trialed in the United Kingdom and Japan. It is a glycosaminoglycan with mild anticoagulant effects. Data collected in-vitro indicates it affects the production, replication process and cell toxicity of prion proteins. However, PPS does not cross the blood brain barrier, so it must be administered via intraventricular means, making for a difficult study as complications can arise from the administration process (8). Pentosan polysulphate must be administered prophylactically around the time the patient contracts CJD (7), which would make its use impractical. According to Tsuboi et al. (9) PPS demonstrated no clinical improvement in human studies; however Bone et al. reported conflicting findings (10). The mean survival duration was reported longer than average for untreated patients with prion diseases in the United Kingdom, however Newman et al. found that PPS prolonged the survival duration significantly in four out of five patients treated with PPS (11). Postmortem examinations found no reduction in severity of brain degradation, and reported that intraventricular PPS was not a cure for Creutzfeldt-Jakob disease, but rather improved duration and quality of life through affecting the underlying disease process.

Doxycycline is a class of antibiotic and it has a similar mode of action to PPS. Animal experiments and cell culture research has revealed doxycycline may bind to the prion protein in CJD, preventing further damage (7). In a trial, doxycycline was administered to hamsters with survival time prolonged, even when doxycycline was administered in the late stages of CJD.

Due to these promising findings, this study was advanced to human trials. Patients were trialed with a daily 100 mg dose of doxycycline, substantial increased survival rates were noted, historical data showed an average survival time of 167 days, patients taking the doxycycline had an average survival time of 292 days. However, conclusions are limited as results are compared to historical statistics of CJD fatalities instead of comparing with a control group. It has been suggested that doxycycline may be useful as prophylactic treatment in patients without symptoms, however more research needs to be conducted into long term side effects and risks (12).

The research of management and treatment of CJD previously mentioned focus on inhibiting the prion protein from replicating and producing more damage. This next theory focuses on the possibility of not only halting the process, but also reversing the damage. Research into the use of stem cells as treatment for neurodegenerative disorders, including CJD, is leading to important discoveries. This interesting strategy explores the possibility of using fetal neural stem cells (NSC) to replace damaged neurons and subsequently prolong survival. Once administered into a host's brain, NSC have the ability to replicate into oligodendrocytes, astrocytes and neurons, all of which are vital for brain function. Mice were administered an intracranial dose of a similar strain of TSE and stereotaxic grafting of fetal neural stem cells into the hippocampus and lateral ventricle, this procedure was carried out into two groups of mice. Mice that were given neural stem cells 100 days after inoculation of the TSE, and those at 120 days. The first group of mice that were given stem cells at 100 days showed substantially increased incubation and survival period, the incubation period increased from 120 days to 140 days, and the survival period increased from 150 days to 175 days. The second group of mice that were administered stem cells 120 days post inoculation showed little to no improvement (6).

A symptom that patients complain of is vivid hallucinations. Rivastigmine is a cholinergic inhibitor that can prevent hallucinations. A woman, 79 years of age, was wrongfully diagnosed with Lewy body dementia and was prescribed rivastigmine for hallucinations. A few months later she was diagnosed with CJD and, as rivastigmine was controlling the hallucinations, it continued to be prescribed. It wasn't until the patient began to experience diarrhoea, an adverse effect of rivastigmine, that the drug was ceased and the hallucinations returned (13). Another symptom that occurs early in the disease process is myoclonus, an involuntary twitching of the muscles that can be severe and distressing to both the patient and family members. Levetiracetam is a relatively new anti-epileptic drug used to control partial seizures and it has proved to markedly decrease myoclonus in CJD patients (14).

Relevance to paramedic care

Creutzfeldt-Jakob disease rarely presents with emergency symptoms. However, due to the progressive nature of the disease patients may require paramedic care. The opportunity for paramedics to develop competency in recognising and managing symptoms of CJD is unlikely to arise. The most relevant issue for paramedics when managing CJD patients is to ensure proper aseptic practices are in place. Universal precautions are only adequate in preventing the spread of disease if followed correctly. The prion protein in CJD is transmissible via direct and indirect contact. Prions have an unusual high resistance to traditional methods of cleaning and sterilising that involve heat therapy, chemicals and irradiation (15). Prions have been found to survive without a host for 29 months and infect new hosts when contact was made (16). Use of personal protective equipment is paramount, as is cleaning all equipment thoroughly and effectively. The use of single-use items and plastic barriers over equipment is favorable due to the high resistance of the prion protein to cleaning and sterilising methods. For these reasons, paramedics should be trained in sterilisation, and an autoclave should be provided at each branch to sterilise equipment that cannot be discarded or protected with plastic barriers. Unfortunately the cost and time involved in implementing such steps could hinder an organisation's decision to do so.

The moods of patients suffering from CJD can change quickly without reason or warning, therefore paramedics must be attentive to the patient's state of mind, and be aware of any warning signs that a patient's attitude is altering. It may be necessary to change treatment and transport techniques if the patient has been known to be emotionally unstable, the use of chemical and/or mechanical restraints may be needed while ensuring clinical practice guidelines are adhered to. Taking a thorough medical history from patients, patient family members and/or health care workers can prove to be important for this reason, as medical problems that are secondary to CJD may be given on questioning, while CJD itself can be overlooked; for example, a patient suffering from CJD may also suffer dementia secondary to CJD (17), but may only mention dementia to paramedics seeking a medical history.

Ongoing training and education for paramedics has always been important and will continue to be. As researchers develop a greater understanding of CJD, and potentiate the development of better therapies or even potential cure for CJD, the paramedic profession needs to ensure strategies that provide for these evolutions are in place, as these will likely impact current pre-hospital treatment and management.

Conclusion

To help prevent the spread of CJD, pre-hospital emergency care providers must, within their education programs, highlight the single use of medical items where possible and adequate cleaning and the disinfection of all non-disposable equipment and surfaces to mitigate infection risk with CJD patients.

While there have been many medical advances towards a cure for CJD, no definitive drug or therapy has been identified. Results from current trials are encouraging, though the development of an ultimate treatment in the near future does not seem likely. As the search for a cure continues, it is clear that this important research needs to be supported and enhanced in order to reduce the mortality and morbidity of this disease.

Conflict of interest

The author has completed the ICJME conflict of interest statement and declares she has no competing interests.

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