Palliative care in Creutzfeldt-Jakob disease: looking back, thinking ahead

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative disease for which there is no cure. However, it is difficult to diagnose and is unique in that it is both a genetic and transmissible disease. The disease is characterised by symptoms of a rapidly progressive dementia. Palliation is the only treatment and early diagnosis is an important aspect in relation to gaining speedy access to palliative and end-of-life care services. People with CJD may be cared for in a diversity of settings including; general hospital wards, neurological units, hospices; care homes and in their own home. Management of physical and psychosocial symptoms and dealing with family bereavement is complex and challenging. Due to the complexity of the physical symptoms input from clinicians with palliative care expertise is an important consideration. Given transmission risk and the latent incidence of infection in the general population, following the emergence of variant CJD; plus the recent hypothesis of a potential relationship between immune responses to COVID-19 and the acceleration of preclinical or evident neurodegenerative disease, there is a need for renewed interest in research in this field. Over the past 20 years, many thousands of articles have been published on CJD. These have been predominately in the medical and science literature and very few publications have addressed the nursing care of persons and families dealing with CJD. There is a need for renewed interest in the management of the disease by supportive and palliative care services.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative disease first described in the 1920s. CJD belongs to a group of diseases known as transmissible spongiform encephalopathies (TSE) that are known to occur in both humans and animals. The progress of multifocal encephalopathies is aggressive and brain damage that occurs is characterised by the spongy appearance of brain tissue as seen under a microscope. It is also referred to as prion disease, an acronym for a proteinaceous infectious agent. The prion theory suggests that the infective agent of CJD is only composed of protein and does not contain nucleic acid, which would be necessary if the agent was a conventional virus. The transmittable agent is either genetic or an abnormal form of prion protein that causes aggregates of cellular protein to accumulate in the brain. The exact process that occurs that leads to brain damage from original inoculation/contamination is incompletely understood.[1] CJD is also described as a rapidly progressive dementia, which is a clinical syndrome that is not well defined and is little studied. However, CJD is considered to be one of the causes.[2] There is no cure for CJD. Palliation has been considered the only treatment with early diagnosis being an important aspect in relation to the management of the disease.

In this paper, we consider the emergence of latent infection within the community through the variant CJD crisis and the recent hypothesis of a potential relationship between immune responses to COVID-19 and the acceleration of preclinical or evident neurodegenerative disease, and what that may mean for future supportive and palliative care services.

LOOKING BACK

Types of CJD

Four types of CJD have been identified; iatrogenic, inherited, sporadic and variant CJD. Iatrogenic CJD refers to the cases of CJD that have been caused by medical treatment. These comprise a very small number of cases. The causes include; injections of infected human-derived growth hormone and human gonadotrophin;

tissue grafts, particularly corneal transplants and human dura mater grafts; and contamination from neurosurgical instruments and depth electrodes.[1–3] More recently iatrogenic CJD has occurred as a result of a CJD contaminated blood transfusion.[1 3–6]

Inherited CJD occurs where there is a mutation in the prion protein gene that makes conversion into the abnormal form more likely. Approximately 10%–15% of all cases of CJD are inherited and the most common of these are Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia and familial CJD. Sporadic CJD (also referred to as classical CJD) refers to cases of CJD that occur at random throughout the world. They are categorised as sporadic if they have no genetic mutation or any known iatrogenic infection. Sporadic CJD accounts for 85% of all cases of CJD and has a median age at death of 65 years.[3] Thirty cases of a more recently described form of sporadic prion disease,variably protease sensitive prionopathy, have been identified in the UK and are subject to ongoing monitoring.[7 8] Variably protease sensitive prionopathy is characterised by a unique biochemical profile when compared with other human prion diseases but has been shown to have restricted potential for human-to-human transmission.[8] In 1996, in the UK, a new variant of CJD was officially recognised[1 6 9–11] and is believed to be linked to the Bovine spongiform encephalopathy (BSE) outbreak during the 1980s.[6 11] It is widely accepted that the BSE epidemic that occurred in the mid-1980s originated from animals consuming feed that was contaminated with scrapie, a sheep prion disease.

Other rarer types of spongiform encephalopathies include ‘kuru’. Kuru is a TSE that was confined to the Fore social group or tribe, and among other groups who intermarried with the Fore group, in the Eastern highlands of Papua New Guinea. It was transmitted through an endocannibalistic ritual associated with mourning. Women and children comprised the majority of kuru victims.[12] Kuru is now very rarely found among this group due to the cessation of cannibalism in Papua New Guinea.[12]

Diagnosis of CJD

CJD is always fatal, is very difficult to diagnose and is unique in that it is both genetic and transmissible. Considering the rapid progression of dementia symptoms that often occur, early diagnosis is an important feature in relation to the management of the disease and supporting families. Diagnosis of all forms of CJD is made by clinical and neuropathological examination and conclusive diagnosis can only be made by microscopic examination of brain tissue.[1] The diagnosis of CJD has improved in recent years. This is due to enhanced brain imaging, development of specific CSF tests and the potential for diagnostic tests in plasma and urine for variant CJD.[13] The number of confirmed cases of CJD has risen steadily in recent years. It is believed that this may be due to more accurate diagnosis and an increased awareness of the disease, but also due to the emergence of variant CJD.[3] This latent incidence of infection in the general population of concern and the parallels between prion diseases and other protein misfolding disorders are an area of continuing research within the sciences; but research on palliation and symptom management of this group of patients and their families is less active.

Clinical progress of CJD

CJD is characterised by a rapidly progressive dementia (of less than 2 years), together with at least two of the following symptoms: myoclonus (muscle twitches or spasms and involuntary jerky type movements); visual or cerebellar problems; extrapyramidal or pyramidal signs and akinetic mutism.[3] Initial signs of illness may be non-specific with complaints of dizziness, headache, sleep disturbances, apathy, mood swings and depression. Neurological symptoms for sporadic and variant CJD develop and progress extremely quickly. Cognitive processes, such as memory, concentration and problem solving are affected and the person may become disoriented. Movement is affected, particularly balance and gait and the person may become apraxic (unable to perform complex sequential tasks) and experience a tremor and rigidity. Ataxia (not to be confused with apraxia) is a common neurological sign and consists of lack of voluntary coordination of muscle movements.

Speech becomes slurred and quiet (dysarthria), the person will have word finding difficulties as the content of language is reduced and reading and writing deteriorates. As the illness progresses swallowing difficulties and visual disturbances occur and at later stages there may be cortical blindness. The person may experience seizures in the final stages. A distinguishing feature of variant CJD is the presence of persistent painful sensory symptoms such as paraesthesia (pins and needles) and/or dysaesthesia (pain arising or persisting from innocuous touch).[9]

Iatrogenic CJD has a slightly different clinical progress where dementia is not a prominent feature.[3] The incubation period for iatrogenic CJD ranges from 5 to 42 years (mean 17 years) and unlike sporadic CJD, signs and symptoms almost never included dementia. If dementia symptoms do occur this is typically at an advanced stage of the clinical course. It is posited that the era of iatrogenic CJD is nearly over with only occasional cases that have had exceptionally long incubation periods, still being diagnosed.[14]

The emergent variant CJD was also distinguished from other types of CJD: by the age of onset; symptom profile; duration of symptoms; histopathology and mode of occurrence. The median duration of illness from onset of first symptoms to death is 13 months (range 6–36 months) for variant CJD, compared with a disease trajectory of 4 months (range 1–74 months)

for sporadic CJD.[5] Up to 2014, 177 cases of definite or probable variant CJD, who have since died, had been identified in the UK.[3] Scrutiny of variant CJD diagnoses and deaths suggests that a peak was passed, however, the occurrence of variant CJD may rise again, if different genetic subgroups with longer incubation periods are identified.[3] The average age of onset of variant CJD was 28 years (compared with 65 years for the median age at death for sporadic CJD) with a range of 12–74 years reported.[1 3] However, based on one case of variant CJD diagnosed in a 74 year old, some concerns have been expressed that variant CJD may be misdiagnosed as Alzheimer's disease in the older population.[15]

During the early stages of the illness people with CJD usually experience psychiatric symptoms; this is a particular manifestation of variant CJD.[5 16 17] These symptoms most commonly take the form of depression or, less often, a schizophrenia-like psychosis. A misdiagnosis may mean that the person is treated inappropriately with antidepressant or antipsychotic medications and people with CJD may be referred to psychiatric services in the early stages of the illness.[17–21] Referral to psychiatric services has been found to cause distress to family members[20] particularly if the person died while still in a psychiatric unit.[16]

THINKING AHEAD

Risk of infection from CJD

Some tissues pose a greater risk of infection than others and the highest risk is from contact with the brain (including dura mater), spinal cord and eye tissue; however, four cases of CJD in the UK have been identified through blood transfusion transmission.[5 22] These people received blood in 1999, or earlier, from donors who were later diagnosed with variant CJD.[23] Common challenges within studies on contamination and CJD include access to and content of past medical/dental treatment records for diseases with long incubation periods[1]; the management of the risk of transmission of prion diseases by blood and plasma products remains highly problematic.[6] Therefore, further research and continuing surveillance is required to assess the risk of transmission between patients, including risk through organ donation.[24] A prototype blood test for diagnosis of CJD in symptomatic patients has been developed which in the future could allow development of large-scale screening tests for asymptomatic variant CJD.[25]

Despite the falling number of clinical cases in the UK up to 90% of infected persons may sustain long-term preclinical or subclinical disease and these are in the 20–40 years age group which would suggest that there is a significant pool of potentially infectious blood donors.[6] In the years following the emergence of variant CJD prevalence studies have shown that up to 1 in 2000 people in the UK could have a subclinical variant CJD infection.[26] This prevalence data would suggest that future, and multiple, cases of variant CJD are likely.[22 26 27] It is also possible that the national surveillance system might be missing some variant CJD cases, particularly in older age groups, possibly because clinical presentation is atypical of variant CJD.[28] Surveillance data have shown that the greatest relative increase in the number of cases of sporadic CJD in the UK from 1970 to 1999 was in those over 70 years[3] with a continuing increase trend of CJD-related deaths each year in this age group.[15 28]

Furthermore, the authors have personal links with clinical practice where clinicians have described cases of sudden onset and accelerated dementia symptoms in older people, leading quickly to death. However, the reverse scenario has also been identified where, due to heightened awareness of CJD, there has been an increase in consideration of the differential diagnosis of patients with rapidly progressive dementia, leading to misdiagnosis of CJD in older people with Alzheimer's disease.[29]

More recently, a potential relationship between immune responses to the novel coronavirus (COVID-19) and the acceleration of preclinical or evident neurodegenerative disease has been made.[30] The researchers identified a link between the first manifestations of CJD occurring alongside the symptomatic onset of coronavirus disease suggesting that cascade of systemic inflammatory mediators, in response to the virus, augmented the pathogenesis of a patient with prion disease.

WHAT DOES THIS MEAN FOR PALLIATIVE CARE SERVICES?

Management of symptoms of CJD

There is no cure for CJD; palliation is the only treatment. Once the illness is diagnosed people with CJD may be cared for in a variety of settings. These include; general hospital wards; neurological units; hospices; care homes and in their own homes. Due to the complexity of the physical symptoms input from clinicians with palliative care expertise is an important consideration.[18 20 21 31]

People with CJD experience a myriad of symptoms as outlined above. The control of these is complex and requires careful assessment and expertise in symptom management (table 1).

Managing psychosocial impact of CJD

Stigma has been identified as a significant issue for people with CJD and may arise on a number of accounts. These can be associated with diagnostic labels that may be applied to neuropsychiatric illness in general and are related to the overt symptoms of CJD, particularly the earlier psychiatric manifestations and later severe and debilitating dementia symptoms.[20] In the initial days of variant CJD emergence some patients were referred to mental health services in the early stages of the illness.[16–18 20 21] CJD, in common

Table 1 Common symptoms and methods of management for CJD at end of life

Symptom	Management
Myoclonus	Minimal movement when touching, turning or repositioning the patient Maintaining a quiet environment Levetiracetam, sodium valproate and benzodiazepines such as, clonazepam
Spasticity	Baclofen, dantrolene and diazepam, although these are less effective in the presence of muscle rigidity
Ataxia	This is extremely difficult to treat and there are in most cases no effective medications
Visual hallucinations	Respond well to drugs used in Alzheimer's disease for example, donepezil, galantamine and rivastigmine
Aggression and agitation	Atypical antipsychotic drugs such as quetiapine, risperidone or olanzapine Diazepam can also sometimes help
Pain	Assessment of pain is difficult due to communication problems Potential for pain exists in the presence of spasticity, hyper-reflexia, mouth infections and bladder and bowel disturbance The analgesic ladder should be used in assessing and managing pain
Paraesthesia and/or dysesthesia	Gabapentin, pregabalin and amitriptyline are all useful for neuropathic pain of this type
Heightened startle reflex	Non-pharmacological approaches such as: communicating calmly and gently; using minimal and gentle touch; ensuring minimal sound; playing soft familiar music; using soft lighting
Swallowing difficulties (dysphagia)	Thickened fluids and puréed food Appropriate positioning to reduce the risk of aspiration Any decision to institute measures such as nasogastric tube feeding or nutrition via a gastrostomy need to be carefully considered and negotiated with family
Increased salivation as result of swallowing difficulties	Can be managed by drugs that reduce the amount of saliva such as atropine drops or hyoscine patches
Mouth infections for example, candida albicans	Mouth care is important in relation to preventing infection and maintaining comfort May be difficult to carry out in the presence of myoclonic jerking Administration of analgesia such as paracetamol may help facilitate mouth care
Urinary frequency	Urinary antispasmodics such as tolterodine
Urinary incontinence	Frequent, scheduled toileting Incontinent pads If skin breakdown is of concern or the end of life is approaching, urinary catheterisation will reduce the need for frequent touching and turning when changing continence pads or wet beds
Constipation	Occurs as a result of reduced fluid intake, immobility and the effects of neurological disturbance on the bowel Careful balance is required in the management of this between over-intervention and distress from unrelieved constipation

CJD, Creutzfeldt-Jakob disease.

with other neurological diseases such as Parkinson's disease and epilepsy, affect people of all ages and are stigmatising, unpredictable and disabling illnesses.[32] However, little is written on the subject of stigma in relation to many neurological disorders including CJD.

A diagnosis of CJD leaves family members and significant others in a state of shock and confusion and has a profound impact on the bereavement reactions of family members.[16 20 21 33–35] Bereavement experiences and responses are highly influenced by the manner in which people come to know of their illness and how the time was spent between diagnosis and death. The opportunity for family and friends to be able to spend quality time with their terminally ill relative and to be able to say their good-byes has a significant impact on their ability to cope with the loss when it does occur.[36] This is complicated by the variable and unpredictable disease trajectory for CJD as the period from diagnosis to death may be very short (1 month) or prolonged over a number of years with no means of prognostication of time of death. The profound neurological damage that occurs leads to inability to communicate which can be particularly frustrating, distressing and isolating for the person with CJD, their family members and professional caregivers. Also, witnessing cognitive and physical deterioration over a prolonged period of time, for example in Alzheimer's disease, has been shown to lead to depression, strain, and burden for caregivers.[37] The National Prion Clinic has established a counselling service for people with CJD which provide information, advocacy and support from diagnosis through bereavement for people with this diagnosis and their families.[33] Furthermore, guidelines for social workers and other social care professionals who work with people with CJD and their families been put in place.[34] These guidelines focus on the importance of responding without delay, due to the rapid decline and complexity if CJD.[35] In cases where there is a family history of CJD genetic counselling should be considered, however genetic counselling may also be especially challenging due to the emotional impact of these diseases on the patient and family members.[38]

Thousands of articles have been published on CJD over the past 20 years. These have been predominately in the medical and science literature and very few publications have addressed the nursing care of persons and families dealing with CJD.[31] Using Kolb's experiential learning model, a workshop, for nurses and other healthcare providers, was developed to provide training to improve the quality of care given

to CJD patients and their families.[39] Evaluation of the workshops indicated that participants had limited knowledge about CJD and often felt poorly prepared and were uncomfortable in providing care to this patient group.

In summary, the complexity of CJD presents a number of challenges to the delivery of comprehensive and compassionate end-of-life care. The rapid progression of CJD requires timely and specialist diagnosis,[1] which is further complicated by early indications of illness that are common to other conditions, such as changes to sleep and mood. During the current COVID-19 pandemic, it is likely that such symptoms may be misattributed or not thoroughly investigated as CJD. This potential for misdiagnosis[15] can lead to inappropriate referrals to psychiatric services,[16] further exacerbating the sense of stigma and shock experienced by those living with CJD and their families.[20] When the disease trajectory can be as short as 4 months,[5] it is imperative that patients receive the right care and support as soon as possible. In other end-of-life contexts, the practice of advance care planning (ACP) helps to identify individual's wishes and needs ahead of time, helping to ensure that their final days are as comfortable and peaceful as possible. Producing an ACP for a person with CJD is a challenge, for all of the reasons listed here. It may be that the current COVID-19 context offers an opportunity for patients with CJD to receive an ACP, as these conversations are becoming more widespread among healthcare professionals.

CONCLUSION

CJD is a unique condition in that it can be both genetic and transmissible. Transmission risk and the latent incidence of infection in the general population, plus the recent hypothesis of a potential relationship between immune responses to COVID-19 and the acceleration of preclinical or evident neurodegenerative disease, has caused a renewed interest in research in this field. Family members may be faced with a range of issues such as: general lack of information and awareness at a clinical level; delays in diagnosis; insensitive information provision and breaking bad news by healthcare professionals; insensitive approaches by healthcare professionals regarding autopsy procedures; delays in autopsy results; delays in genetic testing; and delayed access to appropriate healthcare services. Nursing care for a person with CJD and their family at the end of life is complex. It requires sound knowledge about the specific symptoms of the diseases, awareness of the type of stresses that may be experienced by family members and also a general awareness and knowledge of issues and challenges in caring for any person with a dementia syndrome at the end of life.

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