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REVIEW ARTICLE

Creutzfeldt–Jakob disease and ENT

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Abstract

Objective: This review addresses Creutzfeldt–Jakob disease in the context of ENT, and aims to summarise the relevant history, pathophysiology and implications for contemporary practice.

Overview: Creutzfeldt–Jakob disease is a rare, fatal, neurodegenerative disorder. It is a prion disease with four different subtypes that can only be definitively diagnosed post-mortem. The main implications for the ENT surgeon lie in the risk of iatrogenic transmission. The three facets of assessing individual patient risk are: patient history; tissue infectivity; and procedure infectivity.

Conclusion: This is a controversial area in medicine, and ENT in particular. This review highlights a clinically applicable approach for everyday use.

Key words: Creutzfeldt-Jakob Disease; Transmissible Spongiform Encephalopathies; Prions; Otorhinolaryngology

Introduction

Creutzfeldt–Jakob disease (CJD) is a rare, fatal, neurodegenerative disorder. It is one of the transmissible spongiform encephalopathies that are found throughout the animal kingdom, and which produce vacuolisation of the cerebral cortex.[1] This disease has fluctuated in its prominence in the public eye, although it has always been of importance to the clinician; now, more than ever, it should be a constant concern.

This article aims to review the history and pathophysiology of CJD, and also to summarise the assessment of patient risk and the potential peri-operative impact for the ENT surgeon.

Prions

Scrapie has been recognised for hundreds of years as a disease in which affected sheep scrape the wool from their backs by constantly rubbing against posts. What we now know to be human prion disease was first diagnosed in 1920 by German neurologists Hans Gerhard Creutzfeldt and Alfons Jakob. They described a rare, spontaneously occurring encephalopathy of unknown aetiology.[2]

In the 1950s, a CJD-like disease called kuru, affecting alleged human cannibals in Papua New Guinea, reached epidemic proportions. Studies found characteristic spongiform changes in the brains of affected individuals, similar to those changes found in sheep with scrapie.[3,4] A subsequent ban on cannibalism led to a decline in the incidence of kuru, and further studies demonstrated transmission of kuru in chimpanzees inoculated intracerebrally with infected brain material.[5,6]

Pruisner first coined the term 'prion' in 1981 to describe novel proteinaceous, infectious particles that caused scrapie (one of the transmissible spongiform encephalopathies).[7] Prions are simple proteins with no associated nucleic acids. They are derived from physiological but non-essential glycoproteins found on the membranes of nearly all cells, and particularly those in the nervous and lymphoreticular systems. The normal prion protein undergoes a conformational change to a pathological isoform which makes it resistant to metabolic breakdown, leading to aggregation, accumulation and deposition in the brain tissue.[8–10] In advanced cases, the brain tissue is vacuolised and assumes the consistency of a sponge (hence the name spongiform encephalopathy).[11] Transmissible spongiform encephalopathies have an extended asymptomatic incubation period which can last for decades. Creutzfeldt–Jakob disease occurs in four clinical forms: sporadic CJD, genetic CJD, iatrogenic CJD and variant CJD.[12]

Creutzfeldt–Jakob disease subtypes

Sporadic CJD is the most common form of the disease, with an annual incidence worldwide of approximately 1 in 1 000 000. This type generally occurs in people aged 55–75 years and causes a rapidly progressive dementia with a fatal outcome within 6 months.[13]

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Genetic CJD is associated with point mutations or insertions in the cellular gene locus for the prion protein, located on the short arm of chromosome 20.[14] This form of the disease is very rare.

Variant CJD is considered to be a consequence of human exposure to bovine spongiform encephalopathy (BSE). This latter disease is recognised to have originated from the recycling of cattle cadavers into cattle feed. In 1982, the sterilisation procedures applied to cadaver meal had been replaced to reduce costs, enabling a rare animal prion strain to accumulate in British cattle herds.[11] Before the ban on this type of cattle meal was instituted, more than half a million infected cattle had entered the human food chain.

In 1995, the first case of transmission to a human was identified.[15] No case of variant CJD had been reported before this time. Patients presented younger, compared with sporadic CJD, initially with behavioural symptoms, often delaying the eventual diagnosis. Since 1995 in the UK, 176 people have been registered as having either probable or confirmed variant CJD, and 173 have died.[16] Variant CJD was initially perceived as a European or specifically UK problem; however, with subsequent evidence of BSE-infected animals in Canada, the USA and Asia, this disease is now a worldwide concern, with 222 cases reported worldwide up to October 2011.[16] The main clinical differences between sporadic and variant CJD are shown in Table I.

The number of deaths from variant CJD is not an accurate reflection of the prevalence of infected individuals, due to the occurrence of asymptomatic carriers. Hilton *et al.* studied 12 674 appendicectomy and tonsillectomy specimens, and found abnormal prion levels in three appendix and no tonsillectomy samples.[17] This discovery led to estimation that the UK prevalence of variant CJD was 1 in 4 000. However, testing of 63 007 tonsillectomy samples (32 661 of which were from a population exposed to BSE, or from a birth cohort in which most variant CJD cases had arisen) revealed no positive samples.[18]

Iatrogenic CJD is acquired during medical or surgical treatment. Worldwide data for 2012 showed there had been 469 cases of iatrogenic CJD.[19] The National Creutzfeldt–Jakob Research and Surveillance Unit reported 67 cases of definite or probable iatrogenic CJD in the UK between 1990 and October 2011.[16]

TABLE II
REPORTED CASES OF IATROGENIC CJD[19]

Source or group	Cases (*n*)
Dura mater recipients	228
Human cadaveric pituitary hormone recipients	230
Corneal transplant recipients	2
Neurosurgical procedure patients	6
Blood product recipients	3

CJD = Creutzfeldt–Jakob disease

The majority of iatrogenic CJD has resulted from the use of human cadaveric pituitary-derived hormones (specifically growth hormone and gonadotrophin). Dura mater homograft recipients represent the next most common group (see Table II).[11] This issue is of considerable clinical concern for the surgeon.

How is CJD diagnosed?

The clinical presentation, progressive nature of the disease, and failure to establish any other diagnosis are characteristic of prion disease. Clinical diagnostic criteria have been specified, and combined with results for magnetic resonance imaging scans, cerebrospinal fluid tests, tonsil biopsy and electroencephalography findings, to define cases as 'possible' or 'probable'.[20] A definitive diagnosis can only be made from brain tissue. Brain biopsy can be performed to rule out a treatable cause for the patient's condition, but it is important to remember that it will not necessarily obtain tissue from the part of the brain affected by prion disease. As such, post-mortem diagnosis remains the only way to confirm the diagnosis.[20]

Risk factors for iatrogenic Creutzfeldt–Jakob disease

Understanding the risk factors for iatrogenic CJD and applying this knowledge clinically present several challenges. We need to identify patients for whom special precautions should apply, and also recognise the specific infectivity of different human tissues. We also need to understand possible routes of exposure, the potential risk of different surgical procedures and instruments, and the implications for decontamination.

TABLE I
DIFFERENCES BETWEEN VARIANT AND SPORADIC CJD

Parameter	Variant CJD	Sporadic CJD
Age of onset (mean; years)	27	65
Duration (mean; months)	13	4
Presentation	Behavioural & psychiatric symptoms	Rapidly progressive dementia, ataxia
Electroencephalography	Normal or non-specific	Typical periodic discharges
Cerebrospinal fluid	14-3-3 CSF protein positive in <50%	14-3-3 CSF protein positive in most
Prion protein type	Type 4	Type 1 or 2
Tonsil biopsy	Positive	Negative

CJD = Creutzfeldt–Jakob disease; CSF = cerebrospinal fluid

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TABLE III
WHO CLASSIFICATION OF TSE TISSUE INFECTIVITY[21]

Tissue infectivity	Tissues
High	Brain, spinal cord, retina, optic nerve, dura mater, spinal ganglia, trigeminal ganglia, pituitary gland
Lower	Peripheral nerves, tonsil, spleen, lymph nodes, GI tract, lung, liver, kidney, adrenal gland, bone marrow, skeletal muscle, tongue, blood vessels, nasal mucosa, salivary glands, cornea, CSF, blood
None	Thyroid, skin, gingiva, adipose tissue, mammary gland, testis, prostate, semen, ovary, uterus, fetus, bone, heart, tendon, saliva, sweat, mucus, bile, urine, faeces

WHO = World Health Organization; TSE = transmissible spongiform encephalopathy; GI = gastrointestinal; CSF = cerebrospinal fluid

Tissue infectivity

For the purposes of CJD prevention, tissues have been classified by the World Health Organization as high infectivity, lower infectivity and no detected infectivity (see Table III).[21] This classification has been based on observations of naturally occurring disease or primary experimental infection (although bile has never been studied).

Categories of infectivity do not equate to categories of risk, as the latter also requires consideration of the quantity of tissue to which a person is exposed and the transmission route. For instance, in blood transfusion a large quantity of low infectivity material is administered directly into the circulation, which may pose a greater risk to an individual than eating high infectivity tissue as food.

High infectivity tissues comprise those that attain a high titre of infectivity in the later stages of transmissible spongiform encephalopathy, together with certain tissues anatomically associated with the central nervous system. Lower infectivity tissues are peripheral tissues that have tested positive for abnormal prion proteins in at least one form of transmissible spongiform encephalopathy.[21]

In the field of ENT, there have been two reported cases of CJD transmission due to otological surgery. These involved the use of cadaveric dura mater during cholesteatoma surgery, and pericardium as a tympanic membrane homograft.[22,23] Concerns have been raised over the use of homograft ossicles. Though not widespread practice in the UK, other countries do still have ear bank facilities, and, indeed, Lubbe *et al.* argue that homografts are essential in developing countries where access to prosthetic ossicles is limited.[24]

Minatogawa and Kumoi have published safety guidelines for otological allografts. Firstly, they suggest screening for and exclusion of potential donors with human immunodeficiency virus infection or any history of dementia, Alzheimer's disease or mental disorder. Secondly, the ossicles should be harvested without any contact with dura mater or cerebrospinal fluid.[25] Hotz and Hausler have reported their inactivation procedure for homograft ossicles, which involves immersion in NaOH followed by rinsing in NaCl and autoclaving.[26] Certainly, no reported cases of CJD transmission secondary to homograft ossicles have been reported.

Procedure and instrument infectivity

Guidance from the National Institute of Health and Clinical Excellence has classified interventional procedures as high risk, medium risk and low risk.

High-risk procedures involve handling of tissue considered to pose a high risk for CJD transmission. These procedures comprise intradural neurosurgical operations on the brain (excluding those on the spine and peripheral nerves), neuroendoscopy, and posterior eye procedures that involve the retina or optic nerve.[27]

Medium-risk procedures include all those involving the tonsils, spleen, lymphoid tissue, spinal cord, anterior eye and peripheral nerves.

Low-risk procedures comprise all other procedures.[25]

Surgical instruments themselves pose a range of challenges. In order for an instrument to act as a potential vector of prion transmission, it must come into contact with infective tissue, retain that infectivity, and have contact with new tissue in the recipient.[28] There are many sterilisation techniques in use but most fail to inactivate clinically important numbers of prions.[29] Chemical techniques using chlorine and NaOH, and high-temperature, prolonged autoclaving, have been shown to provide the most consistent prion inactivation, but these techniques are corrosive and unsuitable for devices such as endoscopes.[29] New low-temperature techniques that are less corrosive are currently being developed.

These limitations have particular implications for flexible endoscopy. In gastrointestinal endoscopy, the risk of iatrogenic CJD is based on the working channel of the endoscope becoming contaminated by submucosal lymphoid tissue as the result of taking a biopsy or performing some other invasive procedure (see Table IV).[30,31] Therefore, when performing invasive endoscopic procedures in patients who are at risk of variant CJD, endoscopes need to be quarantined (if they are not single-use models) pending establishment of the definitive CJD status of the patient.[31]

Olfactory epithelium has also been shown to harbour abnormal prions in sporadic CJD cases.[32] This issue has been raised in the context of guidance on the decontamination of endoscopes, and similarly in gastrointestinal endoscopy. If an endoscope is contaminated with olfactory epithelium from a patient deemed to be at risk, the endoscope needs to be quarantined at least until the patient's CJD status has been defined.[31]

A major issue in adenotonsillar surgery has been the introduction of single-use instruments. In 2001, the Department of Health recommended that all

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TABLE IV
CLASSIFICATION OF ENDOSCOPIC PROCEDURE INVASIVENESS*

Classification	Procedure
Invasive†	Endoscopy + biopsy
	Endoscopy + any use of diathermy
	Endoscopy + dilatation
	Endoscopy + argon plasma coagulation or heater or gold probing
	Endoscopy + ultrasound-guided therapy
Non-invasive	Endoscopy without biopsy
	Endoscopy + brush cytology
	Endoscopy then bougie dilatation of stricture
	Endoscopy + balloon dilatation

*British Society of Gastroenterology.[31] †Expected to potentially contaminate instruments with lymphoid tissue.

reusable instruments for adenotonsillectomy should be discarded, with the aim of making single-use instruments universal by the end of 2001.[33] However, due to numerous concerns regarding quality and haemorrhagic complication rates, reusable instruments were reintroduced on the basis of patient safety, later the same year.[34,35]

Welsh National Tonsillectomy Audit results indicated that single-use instruments were initially associated with increased bleeding rates, with a doubling in the prevalence of primary haemorrhage.[36] These rates returned to baseline when action was taken to ensure that consistently high quality instruments were provided. A more recent, multi-centre audit of single-use instruments found no increased risk of post-operative haemorrhage, suggesting that newer single-use instruments may be safer and of higher quality, as well as cost-effective.[37]

Scott *et al.* investigated the potential risk of CJD transmission via bone dust produced during temporal bone dissection. Even when dura and the facial nerve were avoided, neural tissue was detected in the bone dust in two out of three specimens.[38] This raises the possibility of potential prion transmission in an aerosolised form; however, this research needs to be extended as regards sample numbers and evaluation of whether prions are actually present in the sample material. Even so, such research could potentially call into question the use of reusable drill burrs.

Patient risk factors

In general, patients who are a potential CJD transmission risk can be classified as 'symptomatic' or 'asymptomatic'. Symptomatic patients can be divided into those with a probable or definite diagnosis, and those with a possible or unclear diagnosis. Asymptomatic patients comprise those at risk of iatrogenic or genetic forms of CJD.

Obviously, patients with confirmed or suspected CJD pose the highest risk. However, the concept of 'persons at risk of CJD' is important in terms of infection control. Healthy 'at risk' people are asymptomatic individuals, and consist of tissue recipients and those with a familial risk of genetic CJD.

The UK CJD incidents panel has identified a number of individuals and groups at increased risk of CJD (see Table V).[12] When an individual is notified that they are at increased risk of CJD, they are asked to take certain precautions, including: not donating tissue or organs; informing the relevant health care staff if they need to undergo a medical, surgical or dental procedure; and informing a family member or someone close to them in case they need emergency surgery.[12]

Assessing patients' Creutzfeldt–Jakob disease risk

Ideally, all patients scheduled to undergo any elective or emergency surgical or endoscopic procedure should be screened. This could be done by asking the question, 'Have you ever been notified that you are at increased risk of CJD or variant CJD for public health purposes?'[12]

If the answer is no, then normal infection control precautions should be observed. If the answer is yes, then special precautions should be taken regardless of whether the procedure involves contact with high or lower infectivity tissues.

Patients undergoing elective or emergency surgical or endoscopic procedures likely to involve high infectivity tissues should also be asked the following questions: (1) 'Have you a history of CJD or other prion disease in your family?'; (2) 'Have you ever received growth hormone or gonadotrophin?'; (3) 'Have you ever had surgery on your brain or spinal cord?'; and (4) 'Have you received more than 50 units of blood or blood components, or have you received blood or blood components on more than 20 occasions?'

TABLE V
PATIENTS AT INCREASED RISK OF IATROGENIC OR VARIANT CJD[12]

Source of risk	Patient group
Blood transfusions	Recipients of blood or blood components from ≥80 donors
	Recipients of blood or blood components from someone who went on to develop CJD
Surgery	Pts undergoing surgery using instruments used on someone who developed CJD
	Pts undergoing an intradural neurosurgical or intradural spinal procedure before August 1992
	Recipients of an organ or tissue from a donor infected with CJD or at increased risk of CJD
Other medical care	Pts treated with certain UK-sourced plasma products between 1980 and 2001
	Pts treated with growth hormone sourced from humans (before 1985)
	Pts treated with gonadotrophin sourced from humans (before 1973)
	Pts told by a specialist they are at risk of developing genetic CJD

CJD = Creutzfeldt–Jakob disease

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TABLE VI
SAMPLE CLINICAL CASE SCENARIO

A 25-year-old man presents acutely with a meat bolus obstruction that fails to respond to conservative measures. It is decided that rigid oesophagoscopy to remove the bolus would be appropriate. During routine pre-operative questioning, he reveals his father died of CJD. He does not remember what type of CJD, although he had apparently been told. His GP records are currently in transit as he has just moved house. Can this procedure take place, and if so what precautions should be taken?
Having been alerted to the potential for increased risk of CJD, it would be appropriate to ask the patient's family (with his permission) and his GP if they know more. Failing this, the oesophagoscopy would be able to go ahead but all equipment would need to be quarantined until his risk could be clarified. In this case, the patient's father died of sporadic CJD, so this patient has no increased risk of the disease. The oesophagoscope can therefore be sterilised as normal and re-used.

CJD = Creutzfeldt–Jakob disease; GP = general practitioner

If the answer is yes to questions 1, 2 or 3, then further investigations should be made to determine whether the patient is at increased risk of CJD; if they are, they should be offered referral to a specialist centre via their general practitioner. If no clear answers are possible pre-operatively, then the procedure should go ahead and the surgical instruments should be quarantined until details can be confirmed with the patient, family or general practitioner (see Table VI).

Conclusion

Prion disease continues to be an area of controversy in medicine. In the field of otolaryngology, poorly thought-out precautions have been introduced and subsequently withdrawn. The difficulty in making a definitive CJD diagnosis emphasises the importance of addressing this issue using an evidence-based approach. Using this review as a clinical tool, ENT surgeons should find it easy to insert simple precautions into everyday practice, including pre-operative assessment clinics.

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