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Review Article

Revisiting the risks involved in using homograft ossicles in otological surgery

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Abstract

Despite the fact that cartilage, cortical bone and corneal homograft tissue is still widely used in South Africa and that there has never been a reported case of human immunodeficiency virus or Creutzfeldt–Jakob disease infection transmission via this route, otolaryngologists are still reluctant to use homograft ossicles. In third world countries, such as South Africa, where ossicular prostheses are not always readily available due to financial constraints, the question arises as to whether we should be reconsidering the use of homograft ossicles. This review examines the risk of developing Creutzfeldt–Jakob disease or acquiring human immunodeficiency virus following the use of homograft ossicles during ossicular reconstruction, and discusses sterilization techniques that have proven effective in eradicating the human immunodeficiency virus and prions.

For decades, homograft ossicles have been used worldwide in otological surgery, especially in patients lacking suitable autograft ossicles. There has never been a reported case of transmission of the human immunodeficiency virus, and no cases of transmissible spongiform encephalopathy have been reported in the literature after otological surgery involving only the use of homograft ossicles. There have only been two documented otological cases of Creutzfeldt–Jakob disease; these involved the use of cadaveric dura mater and pericardium for tympanic membrane grafting. The human immunodeficiency virus is easily inactivated by simple sterilisation techniques, and there is a statistically insignificant risk of transmitting this virus if proper sterilisation protocols are followed.

Key words: Homologous Transplantation; Creutzfeldt-Jakob Syndrome; Auditory Ossicles; Otologic Surgical Procedures

Introduction

Hundreds of thousands of homograft ossicles have been used globally over a period of 40 years (since the early 1960s to the late 1990s) without any reported transmission of infection, and many otologists still consider the homograft ossicle superior to other prosthetic material. Chalat introduced the first otological allograft in 1964.[1] However, after the discovery of the first case of acquired immunodeficiency syndrome (AIDS), in 1981, surgeons became anxious about the safety of using homograft materials.

Creutzfeldt–Jakob disease (CJD) is one of the transmissible spongiform encephalopathies. The first case of iatrogenic transmission was documented in 1974, when a homograft cornea from a CJD-infected patient was transplanted into a non-infected recipient.[2]

Dural homografts derived from human cadavers have been used as graft material since the late 1950s. In 1987, the first case of iatrogenically transmitted CJD via dura mater was published.[3]

On reviewing cases involving CJD transmission during surgical procedures involving the use of cadaver-derived homografts, definite risk factors have been identified in all cases. In retrospect, transmission of CJD could have been avoided if the true nature of the disease and the infectivity potential had been known at the time and specific countermeasures undertaken to avoid such transmission.

The aims of this review are threefold. Firstly, specific cases of CJD transmission in otological surgery are reviewed. Secondly, the risk of CJD and HIV transmission during ossiculoplasty using homograft ossicles is assessed. Thirdly, sterilisation methods used for allograft products in centres around the world are compared and the safety of these methods in preventing disease transmission reviewed.

Material and method

An extensive literature search was performed (using the Pubmed and Medline databases), using the

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search term 'CJD transmission cases'. A total of 153 article abstracts was reviewed, giving special attention to those cases involving tympanoplasty surgery. A second literature search used the search term 'homograft ossicles', and a total of 111 article abstracts was obtained. Information on CJD was obtained from World Health Organization (WHO) statistics,[4] the CJD Surveillance Unit (Western General Hospital in Edinburgh, Scotland) and the National Tissue Bank (The National Tissue Bank of the University of Pretoria, Pretoria, South Africa). Information regarding current uses for human bone (allograft) products, and sterilisation techniques used to disinfect human bone products, were obtained from the National Tissue Bank of the University of Pretoria, South Africa.

Results

Up to 1999, more than 10 000 prepared, cadaveric, tympanic membrane homografts had been used worldwide, and hundreds of thousands of homograft ossicles had been transplanted during ossicular reconstructions.[13] To date, there has not been a single reported case of disease transmission between donor and recipient.[5]

The first documented otological case of CJD transmission dates back to 1987, when cadaveric dura mater was used in a 26-year-old woman during mastoid surgery for cholesteatoma.[6] She developed rapidly progressive dementia and died two years after the initial surgery. Brain biopsies showed spongiform changes characteristic of CJD.

The second otological case of CJD involved a 54-year-old man who developed spongiform encephalopathy after a tympanoplasty with homograft pericardium.[6]

Discussion

Four types of CJD are recognised. Sporadic cases account for 85–90 per cent of the total number; these are of unknown cause, and occur worldwide with an incidence of one per million people. Familial CJD accounts for 5–10 per cent of all cases and is due to a genetic mutation. Variant CJD was first described in 1996 and is strongly associated with the transmissible spongiform encephalopathy of cattle termed bovine spongiform encephalopathy (BSE). Iatrogenic CJD is a very rare form of CJD and accounts for less than 5 per cent of all cases.

Iatrogenic CJD results when cornea, dura mater or human-derived pituitary growth hormone are transplanted from a CJD-infected donor into a non-infected host. Contaminated surgical equipment, such as the electrodes used during neurosurgical procedures, can also transmit viral particles.

In 2001, the UK Department of Health advised that all tonsillectomy equipment should become disposable, because of the possible risk of iatrogenic variant CJD transmission. This led to huge costs being incurred by the UK National Health Service.[7] This practice was soon abandoned due to an alarming increase in post-operative complications. In Scotland, no tonsillectomies were performed in the first six months of 2001 due to fear of variant CJD transmission, and since July 2001 only disposable instruments have been used during tonsillectomies.[8]

On 21 July 1998, the European Group on Ethics in Science and New Technologies made a statement to the European Commission suggesting that the use of certain types of tissue for allografts should be banned or at least limited. These tissues included dura mater, auditory ossicles, and tympanic and petrosal tissue. The Group felt that the safety of these tissues could not be proven due to the absence of valid tests.[9] Despite this, homograft ossicle bone banks still exist, such as that at the Bio Implant Services Foundation in the Netherlands. In Belgium, homograft ossicles may still be used in ossiculoplasty surgery. In 2006, the Bio Implant Services Foundation only procured two homograft ossicles, due to poor demand from centres performing reconstructive procedures. This was a dramatic decrease from the 44 homograft ossicles supplied in 2005. Other homograft tissues, such as bone, cornea, aorta, heart valves and skin, are still regularly being harvested by the the Bio Implant Services Foundation.[10]

Epidemiological and clinical data

A total of 273 cases of iatrogenic CJD had been reported worldwide up to the year 2003. Transmission was due to gonadotrophin injection in four cases, growth hormone injection (prepared from corpses with at least one CJD patient in the donor pool) in 139, corneal transplants in three, stereotactic electroencephalography (EEG) leads in two, neurosurgical cases without dura mater grafting in five and dura mater grafting in 114.[11]

The CJD surveillance unit in Edinburgh, Scotland, UK, has reported 1228 deaths due to definite or probable CJD in the UK, up to 4 September 2007.[12] 920 deaths were due to the sporadic form, 54 were iatrogenic, 60 familial, 33 due to Gerstmann- Sträussler-Scheinker disease, 161 due to vCJD.

Investigation of CJD surveillance in other countries up to 1997 revealed the following numbers of iatrogenic cases: 21 cases due to corneal transplantation; two due to transmission via infected neurosurgical electrodes implanted into the cerebrum; and 70 patients who developed CJD after prolonged therapy with human growth hormone derived from a pool of autopsied pituitary glands.[13]

An excellent review of all published cases of iatrogenic CJD transmitted via dural and corneal transplants was published by Lang *et al.* in 1998.[14] A total of 71 cases of iatrogenic CJD transmission via dural transplant and four via corneal transplant were documented. Two of the corneal grafts were harvested from patients who had died of CJD. All but three of the dura mater grafts most likely to be responsible for CJD transmission were identified as being supplied by the B. Braun Melsungen AG company (Melsungen, Germany) (under the brand name 'Lyodura®') and being produced before May 1987.

In December 2003, a Japanese CJD surveillance group identified 97 cases of CJD occurring between 1979 and 2003 which had been due to infected

dural grafts. Eighty-nine per cent of these patients had received Lyodura grafts; the remainder of the grafts were of unknown brand.

No CJD cases have been reported for patients receiving dural grafts after 1991, and the data suggest that the infected dura grafts were all processed before 1987. All infected patients died within 18 years of receiving their grafts.[15] Three of the four corneal transplant patients underwent transplantation before the risk of CJD transmission was known and before special precautionary measures were instituted to prevent such transmission.

There is no CJD surveillance unit in South Africa, and no statistics regarding CJD incidence. Africa's first known graft-associated case of CJD was reported in July 2006.[16] The patient had received a lyophilised, Lyodura dura mater graft 12 years previously during a neurosurgical procedure. There is no reason to believe that the South African incidence of the sporadic form of CJD should be higher than the quoted worldwide incidence of 0.5 to 1 per million population.

Creutzfeldt–Jakob disease infectivity

The brain has the highest CJD infectivity, followed by the dura mater and then the cornea. The spleen, lymph nodes, tonsils and cerebrospinal fluid are placed in category II, according to Nunery's 2001 classification, and have medium infectivity.[17] Category III structures, with low infectivity, comprise the peripheral nerves, nasal mucosa and bone marrow. Category IV tissues have no detectable infectivity, and include bone, skin and skeletal muscles; these tissues did not harbour infection in experimental models.[18]

There has never been a case of CJD transmission via blood transfusion, but variant CJD prions have been detected in tonsil tissue, appendix, spleen and lymph nodes. No prions have been detected in bone marrow tissue; however, some authorities (e.g. in Germany) remove all leukocytes from blood transfusion units in order to ensure prion-free blood products.

However, experimental studies on monkeys and sheep have proven that the animal form of variant CJD is transmissible via the haematogenous route.[19]

The British media published an article on 27 September 2004 suggesting two possible cases of variant CJD due to blood transfusions.[20] Britain has been importing all of its blood products from the United States since 1998 due to concerns about variant CJD transmission.

In South Africa, the only CJD risk comes from sporadic CJD, with a maximal incidence of one per million population. The risk can be reduced even further by eliminating the use of homografts from donors over the age of 55 years, as the age of onset of sporadic form CJD is 55 to 70 years (median age, 65 years).

Calculations have been performed to determine the risk of encountering CJD, variant CJD or an asymptomatic prion carrier in countries with a low BSE incidence, such as South Africa. The risk assessment performed for such a country estimated an incidence of one case of variant CJD for every 1000 such cases in the UK.[19]

Decontamination

The standard sterilisation and preservation methods for homograft ossicles once involved their immersion in 70 per cent alcohol, followed by freezing until such time as they were needed. Research has shown that this method is ineffective and that prion proteins are not inactivated by this process. Similarly, microwave irradiation, ultraviolet irradiation, and autoclaving after aldehyde or alcohol immersion do not inactivate prions.[21,22]

The only direct test for prions is based on an immunoblot technique that can only be used on postmortem brain tissue. *In vivo* markers and tests (i.e. 14-3-3, Tau, S100, NSE=neurone specific enolase, nuclear resonance scanning, EEG and PrP^{Sc}) are used in experimental animals to determine prion transmission.

The following disinfection methods have been evaluated using experimental animal models and shown to inactivate prions and to leave no detectable post-sterilisation infectivity: 1 or 2 M NaOH followed by autoclaving at 121°C; autoclaving at 121°C in 1 M NaOH; autoclaving for 18 minutes at 134–138°C; boiling in 1 M NaOH; autoclaving for 18 minutes at 134–138°C; bleaching with 2.5 per cent sodium hypochlorite for 1 hour; and exposure to sodium hypochlorite solution (16 500ppm available chlorine) for 30 minutes.[23]

Hotz *et al.* evaluated the mechanical and radiological properties of ossicles after disinfection with either 1 M NaOH or a mixture of 5 per cent formaldehyde and cialit (2-mercapto-5-benzoxazolecarboxylic acid), followed by autoclaving at 134°C.[24] They concluded that all disinfection methods caused some changes in the stiffness and strength of the ossicles, and that radiological density changes occurred in all except those treated with NaOH. They therefore felt that the NaOH sterilisation method was the most suitable. In 2005, this group published their results for the new NaOH autoclaving inactivation and preservation technique, using 22 homograft ossicles in ossicular reconstruction procedures. No extrusion, resorption or disease transmission was observed, and post-operative audiological results were comparable with those of other studies using homograft ossicles.[25]

The human immunodeficiency virus is found mainly in cells of the lymphoid and monocytic lineage. There is therefore very little viral load in the ossicles, which consist mainly of compact bone. Studies have been done in which minced homograft ossicles from HIV-infected patients have been cultured in a very sensitive culture medium with PHA (phytohaemagglutinin)-stimulated lymphoblasts. No virus was detected within the lymphoblasts.[26] Numerous studies have concluded that autoclaving does not alter ossicular bone matrix and that it removes all viable cells within and on the surface of the ossicles.[27]

Prevention of human immunodeficiency virus and prion infection

Homograft ossicles should be harvested from serologically screened donors whose medical histories are known. The risk of HIV transmission via bone grafts is already negligible, and if the donor is

serologically tested and the correct decontamination procedures followed, the risk becomes infinitesimal. Patients with mental disorders should be excluded as donors. Since the CJD prion is concentrated in brain tissue and cerebrospinal fluid, the ossicles must be harvested using techniques that prevent any contamination by these tissues. The homograft ossicles should then be decontaminated using the techniques described above.

Recommendations

Many centres still use allografts during orthopaedic and neurosurgical procedures. Spinal grafts consisting of cancellous bone blocks, femoral rings (i.e. cortical bone rings procured from the femoral shaft) and even full femur shafts have been utilised in reconstructive procedures.[28] These human bone products have been used for many years by orthopaedic surgeons and neurosurgeons, with no resulting cases of CJD or HIV transmission reported in the literature. Despite this, otolaryngologists worldwide are reluctant to use homograft ossicles, which are a thousand times smaller than a femur shaft.

Cortical bone has proven to be a useful and reliable alternative when no artificial prosthesis or homograft ossicle is available. Studies have shown good long term outcome, little risk of extrusion, and hearing results compatible with those for reconstruction with autograft ossicles.[10,29]

Some centres have continued using homograft human bone, with no reported transmission of CJD or HIV.[10,28,30] The incidence of CJD worldwide is 0.5 to 1 per million,[5] but it could be much lower in certain countries. In Africa, the first graft-associated case of CJD was only reported in July 2006.[16] In South Africa, neurosurgical, spinal and orthopaedic bone grafts are still frequently used, and homograft ossicles can be found in bone banks in some academic centres.

Serious reconsideration needs to be given to maintaining ossicular replacement bone banks, especially in developing countries where the high cost of ossicular prostheses precludes reconstructive surgery at times. Although the possibility of infection transmission can never be said to be zero, it must surely be almost infinitesimal.

The following 1999 guidelines have been suggested by Minatogawa and Kumoi, and have proven effective in preventing disease transmission since the inception of ear bank facilities in the early 1980s.[13] Firstly, all donors should be serologically screened for HIV 1 and 2, and donors with any history of dementia, Alzheimer's disease or mental disorder should be excluded. Secondly, ossicles should be harvested in a way that prevents any contact with dura mater or cerebrospinal fluid; transcanal harvesting versus en bloc temporal bone resection would ensure that no contamination occurred.

In 2003, Hotz and Häusler suggested their 'SHIP' protocol for selection, harvesting, inactivation and preservation, and their methods have been tested and proven safe over the years.[31] They suggested the following inactivation procedure, which we would recommend as a third protocol step: complete ossicle immersion in 1 M NaOH for 60 minutes at room temperature; ossicle rinsing in 1000 ml 0.9 per cent sterile NaCl solution overnight at room temperature; and then ossicle autoclaving for 8 minutes at 134°C.[31,32] Ossicles should then be stored under sterile conditions, as for any other sterilised product or instrument.

The only graft materials that have ever been implicated in CJD transmission are dura mater (specifically the Lyodura brand), corneal grafts and pericardial grafts. It is therefore inappropriate to continue to deny patients in developing countries reconstructive surgery using ossicular homografts.

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