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Tympano-Ossicular Allografts and HIV Transmission

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Objective: To evaluate the potential risk of human immunodeficiency virus (HIV) transmission by tympano-ossicular allografts by studying the efficacy of standard preservation techniques to eliminate the presence of proviral HIV-1 DNA fragments in contaminated ossicles.
Study Design: Randomized single-blind prospective study on the ossicles of HIV-1 patients.
Material: Ossicles of five patients who had died of acquired immune deficiency syndrome (AIDS) (HIV-1 infection) were taken within 6 hours postmortem and allocated randomly to a treatment and nontreatment group. Liver and skin biopsies were taken as positive control specimens.
Processing: The treatment group was processed with standard techniques (formaldehyde) for tympano-ossicular allograft preservation and the nontreatment group was only washed, dried, and stored in sterile tubes at –70° without further processing.
Main Outcome Measure: Proviral HIV-1 DNA was detected using polymerase chain reaction amplification techniques.
Results: No proviral HIV-1 DNA was detected in any of the treated ossicles, whereas three of five sets of untreated ossicles were positive. The positive control specimens of all treated and nontreated sets were positive for proviral HIV-1 DNA.
Conclusions: These results suggest that the preservation technique for tympano-ossicular allografts is safe with regard to HIV-1 transmission. **Key Words:** HIV transmission—PCR—Tympano-ossicular allograft—Middle ear surgery—Reconstruction—Homograft.
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The development of tympano-ossicular allografts in the late 1960s was a major contribution to reconstructive middle ear surgery (1). Both functional and anatomic results have been reported to be good, and the tympano-ossicular allograft technique is valid for the reconstruction of tympanic membranes (e.g., in drum perforations), of isolated ossicles (e.g., in erosion of the incus), and of entire middle ears (e.g., in cholesteatoma) (1–5).

The potential risk of viral transmission from donor to receiver is considered to be a drawback of the technique. The recent evolutions regarding human immunodeficiency virus (HIV) infections (6) and prion-diseases (7,8) have increased our concern about the potential danger of the use of allografts (9–11).

Published data on the risk of HIV transmission with bone allografts and the safety of preservation procedures used for tissue banking are contradictory (10,12–14). However, it generally is believed that allografts are safe regarding HIV and Creutzfeld–Jakob disease transmission when the guidelines for selection and processing of tissue banking are respected (15–18), as is the case for Belgian banks, which are strictly regulated by legislation (Belgisch Staatsblad, June 13, 1996). The chance of having a donor who is carrying a transmissible disease is therefore extremely low. In addition, it is believed that in the event of an HIV infection, the HIV virus is too sensitive to survive the preservation technique. Still this remains to be proved for the particular situation of a tympano-ossicular allograft.

To answer this question of HIV transmission by tympano-ossicular allografts, one would like to find out whether the processing of a virus-infected ossicle is capable of eliminating the infectiousness. The way to detect HIV in tissue is to look for proviral DNA by means of polymerase chain reaction (PCR). The absence of such material in the tissue provides evidence of the absence of virus, active or even inactive.

The aim of this article is to study the efficacy of our standard preservation technique (including formaldehyde) to denature proviral HIV-1 DNA detected in ossicular allografts that were taken from HIV-infected donors.

MATERIALS AND METHODS

Middle ear ossicles were collected from five patients who had died recently of acquired immune deficiency syndrome (AIDS) at the Department of Tropical Diseases (Instituut Tropische Geneeskunde), Antwerp University Hospital. All pa-

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tients were white and were infected by HIV-1 virus. All patients were seropositive for many years (range, 1987–1994) and died of respiratory insufficiency due to pulmonary edema secondary to bronchopneumonia (*Pneumocystis carinii*, cytomegalovirus, *Enterobacter cloacae*), cerebral toxoplasmosis, and disseminated atypical mycobacteriosos (*Mycobacterium avium*). The seropositivity (enzyme-linked immunosorbent assay anti-HIV tests) was confirmed in all cases with Western blot on plasma samples. None of the patients were positive for HIV-2.

The ossicles were removed through a transmeatal approach within 6 hours after death. From each ear, two ossicles were taken, yielding two sets (right and left) of the ossicles per cadaver. In addition, samples of skin and liver (1 × 1 cm) were collected as control specimens. The specimens were stored in sterile, sealed, and dry tubes resistant to freezing (Multilab, Westmalle, Belgium).

The two sets of ossicles of each cadaver were randomly allocated to a treatment and nontreatment strategy. The treatment group was processed in our standard way, which means storage in a 4% pH 5.6 buffered formaldehyde solution at 4° C for at least 2 weeks, followed by storage in a 1:5,000 diluted aqueous solution of Cialit (Hoechst Pharmaceuticals, Somerville, NJ, U.S.A.) at 4° C for at least 2 more weeks. These treated ossicles then were put in dry tubes and stored at -70° C. The untreated ossicles were washed in saline, dried, and stored immediately at -70° C. All soft tissue samples were stored at -70° C immediately after collection. All collected material was coded and transported to the Virology Department of Leuven, where it was stored immediately at -70° C.

Each set of ossicles was pulverized separately between two sterile metal plates using a hammer, while the soft tissue samples were cut into small pieces under sterile conditions using scissors. Twenty-five milligrams of each set of ossicles and 20 mg of soft tissue were put into 1.5-ml micro-test tubes (Eppendorf, Hamburg, Germany). The remaining material was stored at -70° C. From the material in the micro-test tubes, DNA was extracted using the QIAamp Blood and Tissue Kit (Qiagen, Hilden, Germany). To the samples, 180-µl buffer ATL and 20-µl proteinase K solution 14.4 mg/ml (Boehringer, Mannheim, Germany) were added, mixed by vortexing, and incubated at 55° C for 7 hours. Samples were vortexed occasionally during incubation to disperse the sample to ensure efficient lysis. After incubation, 200-µl buffer AL was added, vortexed, and incubated for 10 minutes at 70° C. After addition of 210-µl 100% ethanol and vortexing, the samples were applied to the QIAamp spin columns in collection tubes. The precipitate that remained in the ossicular samples was not applied to the columns. The QIAamp spin columns in collection tubes were centrifugated at 3,200 relative centrifuge force (RCF) for 1 minute. During centrifugation, the sample passes through the QIAamp silica membrane in the column. Salt and pH conditions in the lysate ensure that DNA is absorbed onto the membrane and that protein and other contaminants, which may inhibit PCR, are not retained on the membrane. The collection tube was discarded and the membrane was washed twice with 500-µl buffer AW by placing the spin column in a fresh collection tube and centrifuging at 3,200 RCF for 1 minute the first time and at 6,600 RCF for 3 minutes the second time. The DNA was eluted from the membrane by placing the QIAamp spin column in a fresh 1.5-ml micro-test tube, applying 100 µl of preheated (70° C) 10-mmol Tris–HCl buffer pH 9.0 onto the membrane and centrifuging for 1 minute at 6,600 RCF. In this way, we got for every soft tissue sample and every set of ossicles 100 µl of DNA solution. The DNA solutions were denaturated at 95° C for 30 minutes.

The quality of DNA was first checked by amplifying the specific one-copy human globin gene using a single primer set (PC03-KM38) (19). Only a globin positive sample is tested for HIV-1 PCR. The HIV-1 PCR was performed using three nested primer sets in three different genome regions of HIV-1 (pol: outer H1P4235-4538 and inner H1P4327-4481; LTR-gag: outer AV10-13 and inner AV11-12; env: outer AV18-21 and inner AV19-20) (20,21). Ten microliters of DNA solution was added to 40 µl of outer or single (human globin) PCR mix. For the nested reactions, 2 µl of the outer reactions was transferred into 48 µl of the inner reactions. The PCR mixes contained 10-mmol Tris–HCl pH 8.3, 50-mmol potassium chloride, 200-µm dNTPs, 1.25-U AmpliTag DNA polymerase (Perkin–Elmer), and the specific magnesium chloride concentration (Table 1). The primer concentration for each primer in the single PCR mix was 1 µM, in the outer PCR mixes was 0.2 µM, and in the inner PCR mixes was 0.5 µM. All amplifications were performed using the GeneAmp PVR System 9600 (Perkin–Elmer) with the specific temperature programs (Table 1). Amplification products from the single reaction (human globin) and the inner reactions—for the three nested protocols (HIV-1 pol, LTR-gag, and env)—were analyzed using polyacrylamide gel electrophoresis and visualized with EtBr staining.

TABLE 1. *Study results*

Patient no.	Code	Material	Human globin	HIV-1 pol	HIV-1 LTR-gag	HIV-1 env	Result	Treatment
1	1A[a]	Liver-skin	+	+	+	+	+	
	1B	Ossicle	+	+	+	+	+	Untreated
	1C	Ossicle	+	–	–	–	**Negative**	**Treated**
2	2A[a]	Liver-skin	+	+	+	+	+	
	2B	Ossicle	+	+	+	+	+	Untreated
	2C	Ossicle	+	–	–	–	**Negative**	**Treated**
3	3A[a]	Liver-skin	+	+	+	+	+	
	3B	Ossicle	+	+	+	+	+	Untreated
	3C	Ossicle	+	–	–	–	**Negative**	**Treated**
4	4A[a]	Liver-skin	+	–	+	+	+	
	4B	Ossicle	+	–	–	–	Negative	Untreated
	4C	Ossicle	+	–	–	–	Negative	Treated
5	5A[a]	Liver-skin	+	+	+	+	+	
	5B	Ossicle	+	–	–	–	Negative	Treated
	5C	Ossicle	+	–	–	–	Negative	Untreated

[a]All tubes containing skin and liver biopsies were coded A. The tubes with the ossicles were randomly coded and blinded.

A dilution series of ACH2 cells was always incorporated to control the detection limit: a failure to detect 10 HIV-1 copies is not acceptable. It is acceptable that one copy is not detected, because it is statistically possible that at this dilution, the tube contains no copy at all. Only results from reactions with properly performing positive and negative control specimens were accepted. Samples were reported negative if all three primer sets gave a negative result, and samples were reported positive if two or three primer sets are positive. A positive result with only one primer set might be because of PCR carryover contamination, the presence of a very divergent HIV-1 strain, or the presence of HIV-1 DNA in amounts that are close to the detection limit. Therefore, they should be classified as indeterminate.

During the whole procedure, rigorous laboratory practices were applied to avoid PCR carryover contaminations (19). In particular, three separate levels were established in three separate rooms: a pre-PCR laboratory, a nested PCR laboratory, and a post-PCR laboratory, each with its own equipment and materials.

RESULTS

The tissues of five patients with AIDS were collected on average 3h15 (range, 1h30–5h30) after death. Skin and liver samples were not treated and served as positive control specimens. The results are listed in Table 1.

All specimens were examined for the presence of HIV-1 pol, LTR-gag, and env-genes. All positive control specimens, taken from all five HIV-contaminated cadavers, were positive regarding these three different genome regions of HIV-1. All ossicles that underwent the standard processing were negative regarding the presence of proviral HIV-1 genes in all five cadavers, whereas the untreated ossicles did show presence of proviral DNA in three of five cadavers. The untreated ossicles of cadavers 4 and 5 did not show detectable traces of HIV-1 DNA despite positivity of their skin and liver tissue samples.

DISCUSSION

Retroviruses

Retroviruses (Retroviridae) are RNA viruses with a unique replication mechanism with formation of DNA (provirus) as an essential step in the replication sequence. This DNA is integrated into a host chromosome. The HIV-1 virus is genetically different from HIV-2 and is responsible for AIDS in Central Africa, Europe, the United States, and the worldwide pandemic. The HIV-2 virus was isolated from West African patients and rarely is encountered in Western countries (22). All patients treated in this article had HIV-1 infections, none of whom had HIV-2 positive infections.

Allograft and risk of human immunodeficiency virus transmission

Chemically preserved allografts bear a potential risk of HIV transmission. Reports exist of HIV transmission with nonvital allografts such as fresh frozen orthopedic bone allografts (17,23,24). However, despite >30 years of experience, no transmission of HIV has ever been reported with tympano-ossicular allografts. Whatever chemicals or sterilization methods are used, it is clear that stringent selection criteria have a large contribution in the prevention of viral transmission through allografts. A strict regulation on human tissue banks, as in Belgium, where tissue banks are nonprofit organizations, constitutes another important way to prevent transmission. The quality standards are regularly subject to external audits and follow international tissue banking recommendations (25,26). Donor selection takes place at different levels, namely hospital patient records, specific donor files with additional questionnaires, and postmortem blood bacteriologic cultures and serologic examination (HIV 1, HIV 2, hepatitis B surface antigen, anti-hepatitis B core, hepatitis C virus, syphilis), which are performed routinely. For each donor, every single step of the procedure is documented and a detailed file is kept in the registered Temporal Bone Bank. The current exclusion criteria are summarized in Table 2.

Despite all these efforts, selection still can fail and one has to consider the possibility of HIV-infected ossicles being prelevated and further processed for donation. Therefore, the processing should be able to eliminate the infectiousness in these incidental cases.

Much has been written about the efficacy of different preservation chemicals and other procedures (such as irradiation and dry freezing) (23,27–29). In the processing of tympano-ossicular allografts, two chemicals are used routinely: a 4% buffered (pH 5.6) formaldehyde solution and Cialit (Hoechst Pharmaceuticals), an organomercuric compound. Cialit (2-ethylmercurithiobenzoxazol-5-carboxylic acid) repeatedly has been shown to be inadequate for reducing infectiousness of allografts (30,31). Formaldehyde, on the contrary, seems to provide better protection (13,15,16,32).

It is not obvious to prove infectiousness or absence of infectiousness of HIV-infected ossicles. One has to bear in mind that HIV transmission, through allografts, can take place in two ways. The first way is transmission of free virions. These have been proved to be infectious, although fragile and sensitive to almost any type of sterilization, especially to detergents because of their lipid-membrane envelope (6,22). The second way

TABLE 2. *Exclusion criteria of tympano-ossicular tissue bank*

Death by unknown etiology
Sepsis
Infectious diseases: syphilis, hepatitis B, hepatitis C, AIDS (including high risk groups), CJD
Neurologic diseases (including Alzheimer) of viral or unknown etiology
Treatment with pituitary-derived human growth hormone
Oncology in the hematopoietic system
Collagen diseases or therapies causing degeneration of collagen tissue
Ear irradiation
Local temporal pathology
Primary and secondary temporal oncology
Eardrum pathology

CJD, Creutzfeldt-Jakob disease.

TABLE 3. *Optimized conditions for the different polymerase chain reaction techniques*

Primers	$MgCl_2$ concentration (mM)	Cycling conditions	No. of cycles and final step	Detection limit
PCO3-KM38(single)	2	30 s 94°C 15 s 50°C 45 s 72°C	35 cycles + 10 min 72°C	10–100 human cells
H1P4235–4538(outer)	2	30 s 94°C 15 s 50°C 45 s 72°C	35 cycles + 10 min 72°C	1–5 HIV-1 DNA copies
H1P4327–4481(inner)	2	30 s 94°C 15 s 50°C 30 s 72°C	25 cycles + 10 min 72°C	1–5 HIV-1 DNA copies
AV10–13(outer)	2	30 s 94°C 30 s 65°C	35 cycles + 10 min 72°C	1–5 HIV-1 DNA copies
AV11–12(inner)	2	30 s 94°C 15 s 45°C 15 s 72°C	25 cycles + 10 min 72°C	1–5 HIV-1 DNA copies
AV18–21(outer)	3	30 s 94°C 30 s 65°C	35 cycles + 10 min 72°C	1–5 HIV-1 DNA copies
AV19–20(inner)	2	30 s 94°C 15 s 45°C 15 s 72°C	25 cycles + 10 min 72°C	1–5 HIV-1 DNA copies

is transmission of infected host cells presenting latent proviral DNA. This type of transmission is less sensitive to sterilization. To be efficient, a sterilization technique, therefore, has to eliminate proviral DNA from the ossicles if present. The presence of proviral HIV-1 DNA in ossicles of HIV-contaminated donors already has been shown by Leguillette and Buffet–Janvresse (33). The ability of formaldehyde to denature this proviral DNA has not yet been shown in typano-ossicular allografts.

Our study shows that proviral DNA can be detected in ossicles of patients with AIDS. After treatment, DNA detection becomes negative for the provirus. The authors conclude that the actual processing technique of tympano-ossicular allografts is safe and annihilates the risk of HIV transmission. One additional consideration has to be made regarding the DNA from the globin gene, which still is detected after the processing, indicating the possibility that intact cellular DNA remains after treatment. The chemical inactivation may thus only be a partial phenomenon sufficient to inactivate low copy numbers. Our patients died of AIDS and therefore represent a "worst case" with high viral loads. Still, it was not possible to detect the virus in two of these patients, and the proviral level dropped under the detection limit after treatment in the other patients. We, therefore, are confident that even if the stringent selection procedure would fail and if an occasional HIV-infected ossicle would be prelevated, the infectiousness would be annihilated by the processing technique. These findings constitute an important element that can be added to an already long list of arguments confirming the safety of tympano-ossicular allografts with respect to HIV transmission.

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COMMENTS

The authors have addressed an important issue in otology. After the identification of the virus responsible for the acquired immune deficiency syndrome (AIDS) in the mid-1980s, the possible transmission of this disease using homograft materials has been a constant concern of all surgeons who use homograft materials. Reports have documented the transmission of Creutzfeld–Jakob disease after the implantation of homograft dura. Others have described human immunodeficiency virus (HIV) transmission after the orthopedic use of bone transplantation.

This article examines whether current preservation techniques for homograft middle ear tissue adequately destroy the ability to transmit HIV infection from donor to recipient. The underlying hypothesis and methodology used in this article are sound. Although the reader should be reassured by the authors' results supporting the safety of these implants, the statistical power of the study is insufficient to confidently ensure the safety of current preservation techniques for tympano-ossicular allografts. A much larger series of specimens must be evaluated and found incapable of transmitting viable HIV genetic material before such assurances can be made unambiguously.

Although this study fails to present conclusive scientific assurances that these materials are *absolutely* safe, several factors should be weighed carefully when homograft middle ear prosthetics are being considered:

1. No documented cases of HIV transmission have been reported after the use of middle ear homografts.
2. Most early reports of viral transmission after homograft implantation occurred in a setting of poor donor screening. Current standards in the United States as well as internationally require that tissue banks adhere to strict donor selection criteria and fastidious record-keeping to help prevent transmission of blood-borne pathogens. Homograft implantation material should be obtained only from facilities that comply with these strict screening and selection criteria.
3. Even though this study cannot completely exclude the possibility of viable viral transmission after routine preservation, the data do provide compelling evidence that these modern preservation techniques reduce the chances of transmission significantly.

As with any medical procedure, risks must always be weighed against the potential clinical effectiveness of a particular technique. When tympano-ossicular homografts are deemed superior for a specific clinical otologic situation, the patient should be included in a discussion of the safety issues surrounding his or her use, including the risk of transmission of blood-borne pathogens.

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