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New challenges to infectious safety in the implementation of medical activities related to organ and tissue donation for transplantation

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Changes in current scientific literature and regulatory documents related to the issues of infectious safety in organ and tissue donation have been analyzed. The suggestions have been given for changing the existing practices to meet new challenges. Data on threats to the safety of organ and tissue donation associated with the COVID-19 pandemic have been presented.

Keywords: organ donation, infectious safety, transmission of infectious diseases, HIV, hepatitis B, hepatitis C, COVID-19

AIDS, acquired immunodeficiency syndrome

HIV, human immunodeficiency virus

PCR, polymerase chain reaction

Introduction

The growing need for organ and tissue transplantation makes it necessary to maximize the use of donor resources. The deterioration of the epidemiological situation of vector-borne and respiratory infections increases the individual risks of infecting a donor organ and raises new questions, the search for answers to which is an important task [1].

The very essence of organ transplantation is the interconnection of the internal environment of the donor and the recipient bodies, in which not only the donor organ, but also all the potentially infectious agents present in the donor become asynchronously common for the two bodies. Recognizing that the entire spectrum of infectious agents, including viruses, prions, etc., remains unknown, we have to assume that any transplantation cannot be considered completely sterile and that the transmission of infectious agents can occur with every transplantation. At the same time, some of these agents are harmless to recipient's organism, some are conditionally pathogenic, and some may be life-threatening [2,

3]. Infectious safety of the transplantation process is a much broader task than providing aseptic and antiseptic measures, and is not a goal, but an ongoing process.

Current legislation

Infectious safety of organ and tissue transplantation in post-mortem donation is ensured in accordance with the Government of the Russian Federation Decree No.797 of June 22, 2019, "On the approval of the rules for the collection, storage, transportation and clinical use of donated blood and its components," the Decision No. 95 of the Chief State Sanitary Doctor of the Russian Federation, dated July 21, 2016, "On Amendments to SP 3.1.5.2826-10 "HIV Prevention", Resolution No.58 of the Chief State Sanitary Doctor of the Russian Federation, dated October 22, 2013, "On approving the sanitary and epidemiological regulations of SP 3.1.3112-13 "Prevention of viral hepatitis *C"*, Resolution No.14 of the Chief State Sanitary Doctor of the Russian Federation, dated February 28, 2008 "On approval of the sanitary and epidemiological rules of SP 3.1.1.2341-08 "Prevention of viral hepatitis B". In 2016, the All-Russian Public Organization of Transplantologists *"Russian Transplantology Society*" adopted the National Clinical Guidelines "Post-mortem organ donation", which also reflects the requirements for the examination of potential organ donors.

The requirements of the above documents have not completely been harmonized. For example, in National Clinical Guidelines, the necessary donor screening measures for vector-borne infections include the testing for antibodies against human immunodeficiency virus (anti-HIV antibodies), antibodies against hepatitis *C* virus (anti-HCV antibodies), the surface antigen to hepatitis *B* virus (HBsAg), antibodies against cardiolipin antigen (RPR screening test for syphilis diagnosis),

and testing for total antibodies against Treponema palladium antigens. Meanwhile, there is no mentioning of molecular genetic assays prescribed by applicable sanitary norms and regulations, which are mandatory in blood donation.

The lack of proper differentiation in the legislation between the regulation of blood transfusion and of organ transplantation, clear norms and instructions lead to numerous discrepancies and unresolved issues. The medical community has repeatedly raised the issue of acceptability of organ transplantation from donors who have previously had syphilis and recovered from this disease, but having the treponemal antibodies. The lack of a clear regulation does not allow the use of this donor resource. Another known problem is the prohibited organ transplantation from donors infected with hepatitis C virus to recipients infected with the same virus of the same genotype or to uninfected individuals, but provided the subsequent antiviral therapy is undertaken, which guarantees a cure. This fragment of the donor pool successfully used abroad, could have given an increase in the number of effective organ donors by 15–20% in some regions [4, 5].

Methods to study the medical history of potential donors

The requirements of sanitary norms and regulations determine the need for a thorough medical history taking during organ donation activities. This practice takes place in the United States, where a thorough medical history is taken among relatives or contacts of a potential post-mortem donor. It seems appropriate to pay special attention to the facts of injecting drug use by a potential donor, imprisonment, promiscuous sexual intercourse, the presence of tattoos, the facts of visiting manicure salons, gynecologist's offices, and dentist's offices for the previous 6 months [6].

According to the Decree No.667 of the Government of the Russian Federation, dated August 5, 2013, "On a unified database of donated blood and its components", the blood service institutions are daily provided with the information from blood dispensaries and medical organizations (anti-tuberculosis, dermatovenerologic, narcological, neuropsychiatric dispensaries; centres on prevention and control of AIDS (acquired immunodeficiency syndrome) and infectious diseases; hygiene and epidemiology centres of the Federal Service for the Supervision of Consumer Rights Protection, human health and well-being, as well as the centres of hygiene and epidemiology of the Federal Medical and Biological Agency) about people who have showed absolute contraindications to blood donation. The positive experience of accessing this database through an operational request to the Blood Service before carrying out organ donation activities allows us to recommend this action as an element in collecting anamnestic information about a potential organ donor. Corresponding entries should be made to the organ donor screening card [7, 8].

Acceptability of using rapid diagnostic tests for vector-borne infections

In the current instructions, the use of rapid diagnostic tests (test strips) for vector-borne infections when examining potential donors is not explicitly provided. Conducting such a test in one case was regarded by regulatory authorities as a violation of sanitary standards. However, the feasibility of conducting such tests for a rapid assessment and screening of obviously infected individuals is beyond doubt. We consider it possible to use rapid tests as an additional component in assessing the patient’s medical history, noting the fact of their use in the “medical history” section of the donor documentation. A preliminary examination

of a potential organ donor using simple/rapid tests to detect antibodies against HIV-1, 2, hepatitis B virus antigen HbsAg, hepatitis C virus antibodies, and antibodies against syphilis pathogen is performed in order to assess the epidemic situation [9].

The correct performance of laboratory testing

All potential organ donors are subject to mandatory screening for the presence of blood-borne infections (HIV, hepatitis *B* and *C*, syphilis) performed by immunological and molecular genetic methods.

According to the requirements of regulatory authorities in the United States, blood sampling for screening for vector-borne infections from a potential donor should ensure that he does not have hemodilution. The possible hemodilution is calculated as follows. To perform the calculation, it is necessary to calculate the following intermediate parameters: A, a total volume of blood products transfused during the previous 48 hours before the fact of death or blood sampling (depending on which happened earlier); B, a total volume of colloids transfused within 48 hours before the moment of death or blood sampling (which happened earlier); C, a total volume of crystalloids transfused within 1 hour before the moment of death or blood sampling (depending on which happened earlier); BV, the donor blood volume (mL) calculated by the formula:

BV = W/0.015 kg/mL or W·70 mL/kg,

where W is the donor's body weight in kg; PV, the donor plasma volume (mL) calculated by the formula:

PV = W/0.025 kg/mL or W·40mL/kg,

where W is the donor's body weight in kg. The presence of hemodilution is confirmed if at least one of the following criteria is met: [B + C> PV] or [A + B + C> BV]. Blood samples should be taken in the

amount of 3 at 10 mL each, into vacuum-containing (vacuum-forming) disposable tubes by the staff of the donor hospital in conditions that do not allow a sample replacement; they should be labelled with the full name (surname, name, patronymic) of the donor and the date of blood sampling. Regardless of the result of simple/rapid tests, a potential organ donor should be considered infectious until the immunological and molecular biological assays have been performed. The use of organs from these donors should not be allowed. The safety of donor organs is confirmed by the negative results of immunological and molecular biological assays of donor blood samples taken prior to surgical removal of donor organs for transplantation for the presence of pathogens of blood-borne infections [10].

In accordance with the legislation requirements and in accordance with Order No.1030 of the USSR Healthcare Ministry, dated 04.10.1980, the blood samples of possible and potential organ donors must be submitted to medical facilities for laboratory tests with the attached referral containing complete identifying information about the potential organ donor: surname, name, patronymic in full, name of the healthcare institution where the potential donor is located, year of birth, gender, date and time of blood sampling, specifying the test or assay and a specific method of investigation, the full name and signature of the employee responsible for sampling the material [11].

Molecular biological assays (polymer chain reaction, [PCR]; NAT) are performed in parallel with immunological studies (enzyme-linked immunosorbent assay, immunochemiluminescent assay) for the markers of HIV, hepatitis *B* virus, hepatitis *C* virus. Given the need for laboratory monitoring in case of controversial situations, it is advisable to organize a long-term storage of frozen samples of biological material from the

potential donors for the duration of the incubation period of blood-borne infectious pathogens [10, 11].

Negative test results for the presence of HIV, hepatitis *B* and *C* viruses, the syphilis pathogen obtained by testing blood samples of a potential organ donor using the immunological and molecular biological methods during the period of time preceding the surgical removal of donor organs are the basis for recommending the donor organs for transplantation to a potential recipient. Copies of the medical report on negative test results for HIV, hepatitis *B* and *C* viruses, and the syphilis pathogen obtained when testing blood samples of a possible or potential organ donor should be attached to the passport of the donor organ and be an integral part of it. The principle of copying (entering in a handwrite) the results to the passport contains the risk of potential mistakes, therefore it should be rejected [12].

Finally, the classic question remains about the volume of an enzyme-linked immunosorbent assay in potential donors for the presence of viral hepatitis *B.* Refraining from an anti-HBcor assay performance entails the risk of missing some potential hepatitis B virus-infected donors with the suppression of viremia.

Information on the positive blood test result for HIV of a potential donor should be mandatory transmitted to the territorial authority responsible for the state sanitary and epidemiological surveillance, the Federal Scientific and Methodological Centre for the Prevention and Control of AIDS, within 24 hours. If HIV infection is detected in the resident of another region of the Russian Federation, the information should be transmitted to the Territorial Centre for the Prevention and Control of AIDS at the place of permanent residential registration [13].

Ensuring infectious safety while transporting donor organs

It is necessary to prohibit the acceptance of donor organs from other regions of the Russian Federation for transplantation without attached documents confirming the fact of their testing for the presence of pathogens of blood-borne infections by immunological and molecular biological methods. It is necessary to provide copies of licenses for the activities of laboratories in which those tests have been performed. Meanwhile, the regional donor centre that provides a donor organ is responsible for the completeness of the medical history collection, including a request to the Blood Service and performance of simple/rapid tests, for the quality of the test performance, and for the reliability of the submitted information [10, 12].

When transporting donor organs and tissues by air, one must be guided by the requirements of the USSR Domestic Air Cargo Handling Manual and the IATA Guidelines “Airport Handling Manual” (AHM 346). The packaging is marked in conformity with its IATA LHO criteria. In accordance with paragraph 60 of Order No.104 of the Ministry of Transport of Russia dated July 25, 2007, "On Approval of the Rules of the pre-flight and post-flight inspections", the human organs and tissues, blood and its components, and samples of human biological materials designated for medical, therapeutic and diagnostic purposes, including for blood transfusion or transplantation (hereinafter, biological materials) are permitted for transportation in the aircraft passenger cabin. Inspection of biological materials shall be carried out without opening the package, by visually checking the documents envisaged by the International Agreements of the Russian Federation, including the Acts constituting the Law of the Eurasian Economic Union, and(or) the legislation of the Russian Federation establishing the procedure for the transportation of biological materials; and if there are suspicions indicating to find in them

any objects prohibited for transportation, by inspecting them using manual (contact) method without opening the package [13].

The donor organ or the tissue sample should have an attached package of accompanying documents: the employee's identity document, a copy of the license for transportation of human organs and(or) tissues, the passport of donor organ and(or) human tissue, its integral components being the data on their testing, declaration of the transported goods safety, the donor organ or tissue acceptance act. Taking into account the need to ensure a possible reference examination of the donor, immunological examination of the donor, and selection of the donor-recipient pair, the removed human donor organ and(or) tissue should be accompanied by the following biological material: 2 blood samples (4 mL each) in test tubes with K2-EDTA preservative, 1 blood sample (10 mL) in a test tube without preservative, a spleen fragment [11].

Persisting risk of infecting a recipient

Despite significant advances of current medicine, it is impossible to give an absolute guarantee of the infectious safety of donor organs. A potential recipient of a donor organ must be notified in writing before donor organ transplantation that, despite all existing sanitary and epidemiological measures taken to minimize the risk of a blood-borne infection transmission (including human immunodeficiency virus, hepatitis *B* and *C* viruses) through the donor organ, it is impossible to guarantee an absolute safety from such an infection. Green M., Covington S., Taranto S. reported a 0.16% incidence of one or another donor-derived infection among donor organ recipients in the United States, despite a proper donor organ testing [2].

New challenges

The pandemic caused by the SARS-CoV-2 virus proved to be a challenge that the health services of many world countries, including organ donation services, were not prepared for. The epidemiological situation is complicated by the fact that among patients with COVID-19, there are a large number of people with an asymptomatic course of the disease, during which the patient can be infectious. Cases have been described where PCR for SARS-CoV-2 remained negative for several days with already existing clinical manifestations. In this regard, the Transplantation Society notes that there are no tools for screening potential donors for coronavirus. Perhaps, the accumulation of the experience in the sensitivity and specificity of existing test systems for SARS-CoV-2 will make the screening of potential donors possible [14]. According to a number of authors, contacts with potentially infected SARS-CoV-2 individuals and visits to endemic territories for 14 days before and the reconvalescence state for 28 days after COVID-19 mandate an unambiguous rejection from organ donation [14]. In the epidemiological history description of potential donors during a pandemic, it is advisable to indicate the presence or absence of fever, cough, shortness of breath, lower respiratory tract infection, the fact of visiting endemic areas over the previous 14 days, or close contacts with a person who can actually or presumably be infected with SARS-CoV-2 [14]. The most logical and acceptable position is the one of Organización Nacional de Trasplantes (Spain), which uses a more differentiated tactics. Donation is undertaken only after screening tests for SARS-CoV-2 (yielding clear negative results) in the following cases: the presence of patients with COVID-19 in any department of the same hospital, donor's staying in or visiting endemic areas in the previous 21 days, donation of lungs or a small intestine fragment. A strict contraindication to donation

is a potential donor having a confirmed case of COVID-19 at least 21 days before recovery. In other cases, the donation process is carried out without restrictions [17].

Conclusion

Infectious safety of transplantation is not a set of prohibitions and rules, which blind implementation ensures an absolute absence of problems, sinecura. It is a process of continuous analysis of emerging risks and flexible response to them. Undoubtedly, the current situation in Russia with infectious screening of donor organs and tissues needs to be revised, supplemented and corrected, taking into account the latest scientific data and challenges. On the one hand, this can and should lead to the expansion of the donor pool due to a clear understanding of the acceptable use of certain donor organ contingents. On the other hand, it is necessary to streamline the control over and logistics of screening the potential donors to minimize the risk of transmission of infectious agents with a transplant.

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