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EDITORIAL

LIVER TRANSPLANTATION: WHERE ARE WE?

Modern surgery was born in the second half of the 19th century, with the introduction of general anesthesia. Gradually, surgeons began to become more and more daring, performing operations that were not possible until then. In this context, at the beginning of the 20th century, the old dream of medicine was revived, that of completely replacing organs whose function was destroyed, with healthy ones.

The decisive step was taken by the great scientist Alexis Carrell, laureate of the Nobel Prize for medicine in 1912, who described the technique of vascular anastomoses (as it is easy to imagine, the new organ is connected to the receptor using such anastomoses).

From this moment begins a spectacular race that contributed to a huge extent to the progress of medicine in general, allowing not only the development of surgery at an unprecedented level, but also of other specialties such as anesthesia and intensive care, immunology, infectious diseases and not in lastly, internal medicine specialties such as nephrology, cardiology, hepatology, pneumology, etc.

The driving force of this race, which today is in full swing, were the surgeons, the ones who stubbornly demonstrated that the operations to replace irremediably compromised organs can be performed.

The operation was not the biggest problem in the case of the kidney, which was the first organ successfully transplanted in December 1954 at the Peter Bent Brigham Hospital in Boston by Joseph Murray and his team (the surgeon being rewarded with the Nobel Prize in 1991). Instead, at least at the beginning, it seemed that in the case of the liver, the technical problems are so great that there were opinions that the operation to replace this organ with the survival of the patient will never be possible.

At the beginning there were two great surgeons who tried to contradict these opinions: Thomas Starzl in Denver and Francis Moore in Boston (the same place where the first kidney transplant had been performed). Both surgeons performed the first liver transplant operations in the first half of 1963, but none of the transplanted patients survived. It seemed that the pessimists would be right! Nevertheless, Francis Moore was selected by Time magazine as the most important personality of that year and made the already famous cover.

Meanwhile, anesthesia and intensive care had made remarkable progress, which had considerably increased the chances of success of the operations.

On the other hand, advances in immunology allowed the identification of the phenomenon of "rejection", set up against the transplanted organ by the recipient's immune system which recognizes the new organ as "non-self".

The first therapeutic protocols for the control of rejection, based on cortisone and azathioprine (Imuran), had limited success and it was obvious that something more efficient would be necessary.

After four years in which none of the transplanted patients survived postoperatively, in 1967 Thomas Starzl obtained the great victory: the first liver transplantation with patient survival!

At the end of the 1960s, an ad hoc

Committee (including besides doctors and ethicists as well as a priest) from Harvard University sets up the criteria for declaring "brain death", which regulated organ donation from people whose brain was irreversibly destroyed.

The 60s saw moments of enthusiasm for xenotransplantation, the transplantation from an animal (chimpanzee or baboon) to a human, but the immunological barrier proved very strong and the method was abandoned until more effective immunosuppression protocols were found.

The real success of the liver transplant occurred only after 1980, the year in which Ciclosporin was introduced. This was a powerful and effective immunosuppressive drug discovered by chance in a sample of Norwegian soil by Jean Borel in the laboratories of the Sandoz company and tested in the clinic by the great surgeon and pioneer of liver transplantation in England, Roy Calne, at Cambridge University.

Also, in the 80s, the Belzer solution (or UW-University of Wisconsin solution) was discovered, which replaced the old Collins solution (with the later version Euro-Collins) and allowed the preservation of the liver outside the body for up to 12 hours.

Since 1983, liver transplantation has become an accepted therapeutic method. Pittsburgh, the city where Thomas Starzl had moved with his team, became the world capital of transplantation, a position it would remain until the early 1990s. In Europe, successful programs were built by Roy Calne at the University of Cambridge, Henri Bismuth at the Paul Brousse Hospital in Paris and Rudolf Pichlmayr at the Hanover University Hospital.

In 1989, Christoph Broelsch initiates the first successful program in Chicago with a liver fragment from an adult (usually one of the parents) to a child. After 1990, Asian surgeons (Masatoshi Makuuchi and Kyoichi Tanaka in Japan, ST Fan in Hong Kong) introduced liver transplantation from adult to adult, usually using the right hemified (whose volume represents about 65% of the liver volume).

At the beginning of the 1990s, Thomas Starzl successfully tests Tacrolimus, an immunosuppressant more effective than Ciclosporin. Using the new medicine, in 1992 he performed two xenotransplants from baboon to man, but the two patients did not survive and the method was again abandoned for a while. The main conclusion was that the two calcineurin inhibitors (Cyclosporin and Tacrolimus) effectively control acute rejection (mediated by T lymphocytes), but do not control hyperacute rejection (mediated by antibodies).

Liver transplantation was making remarkable progress based on the two types of donors: those who are "brain dead" and "living" donors (parents or relatives).

Transplantation with a fragment of liver solves pediatric patients to a great extent, especially after, thanks to Rudolf Pichlmayr and Henri Bismuth, it is proven that a fragment of liver can also be obtained by dividing the entire liver from a brain-dead donor (in which case segments 2 and 3 are transplanted to a child, and the rest of the liver, i.e. segments 1,4,5, 6, 7 and 8, to an adult). Together, the living donor (mother or father) and the split liver, covered completely most waiting lists in pediatric programs.

The living donor liver transplantation was more difficult to implement in adults, due to the risks to the donor (right hepatectomy being an operation that registered an estimated mortality of 1-1.5% in the 90s).

That's why it succeeded primarily in Asia and less so in Europe and the USA, where the legal problems in the case of donor death even led to the closure of some

transplant programs. Among the Asian programs for liver transplantation from a living donor, the greatest success was SG Lee's program from Seoul (University Center "Asan"), where the so-called dual transplantation was also introduced: when a single fragment of liver was not enough (this fragment must represent between 0.8 and 1% of the recipient's body weight), two donors were used, from which two liver fragments were taken and implanted into a single recipient.

As the experience of the transplant teams increased, the indications of liver transplantation were better defined:

- In children: biliary atresia and metabolic diseases
- In adults: Cirrhosis in terminal stages (after infection with virus B or C, alcoholic, biliary, autoimmune and, more recently, through the evolution of hepatic steatosis), acute liver failure (poisoning with poisonous mushrooms or with drugs such as paracetamol), cancer (hepatocarcinoma in the first place) and metabolic diseases (Wilson's disease, amyloidosis)

At the end of the 1990s, a new category of donors was introduced, those in so-called "circulatory death", i.e. donors with cardiac arrest who did not respond to resuscitation maneuvers but from whom, if the harvesting is done very quickly, the organs can be used for transplantation.

In Romania, liver transplantation was introduced at the "Fundeni" Clinical Institute. The first four operations (performed between 1997-1999) did not result in the survival of the patients. The first two liver transplants with survival took place in 2000 (April 15th for patient Gheorghe Penea and, respectively, May 5th for patient Gheorghe Badea), with a liver from a brain-dead donor. Currently both are alive and in very good health, 24 years after the transplant.

A very short time later, the liver transplant from a living donor was introduced (with a fragment of liver from the mother to little Timeea Balogh, aged one year at the time of the transplant). Currently, Timeea is a university graduate and mother of a 2-year-old boy.

Later, liver transplantation from a living donor to an adult was introduced, with the help of the team from the University of Essen (Christoph Broelsch, Massimo Malago).

Although the number of donors was initially reduced, the number of operations increased from year to year, reaching a maximum in 2013, with 122 liver transplant operations. It was also the year in which Professor Vladimir Hotineanu's team, partially trained at the "Fundeni" Clinical Institute, inaugurated the transplant program from the Republic of Moldova at the Republican Hospital in Chisinau. In 2014, the second transplant program was inaugurated in Bucharest, at the "Sf. Maria" Clinical Hospital in Iasi, and in 2016, the liver transplant program started at the "Sf. Spiridon" Clinical Hospital in Iasi. Finally, in 2021, the first transplants from a living donor were performed at the "Sanador" Hospital in Bucharest and the pediatric transplant program at the "Grigore Alexandrescu" Children's Hospital started (joint program with the one at the "Fundeni" Clinical Institute, where both the harvesting from the living adult donor and the splitting of the liver, in the case of split liver transplantation, are performed).

The main liver transplant program remains the one at the "Fundeni" Clinical Institute, where the range of types of operations gradually diversified, being carried out in addition to whole liver transplantation from a brain-dead donor other procedure like split liver transplantation (for an adult

and a child or for two adults), transplant from living donor to child and adult, with one or even two liver fragments (dual transplant), domino transplant.

Since 2016, the perfusion of the liver outside the body using the Liver Assist infusion machine has been introduced. The main indication of this method remains the liver from marginal donors (elderly donors, with resuscitated cardiac arrest, staying in intensive care for many days, requiring high doses of vasopressors or with a significant degree of steatosis, etc.) in which there is a risk of not function in the recipient's body ("primary non-function", a situation that requires urgent retransplantation).

Nowadays in such cases the marginal liver is installed on the machine and perfused for at least two hours, during which the aspect of the organ is monitored, the perfusion pressures in the portal vein and in the hepatic artery are evaluated and the transaminases in the perfusion liquid are measured.

After the introduction of this method, the percentage of non-primary liver functions was practically reduced to zero.

Another advance of modern surgery introduced in the program at the "Fundeni" Clinical Institute was the laparoscopic surgery for the harvesting of the liver fragment from the adult in the pediatric transplant. This first step can continue with the use of the method for the harvesting of the right hemi liver in the case of transplantation from an adult donor, an operation that is already performed in the US and Western Europe (where robotic surgery is increasingly used as an alternative to laparoscopic surgery).

The beginning of 2024 saw a revival of xenotransplantation at the international level. If in the past "donors" were chosen from primate species (chimpanzee, baboon), considered to be the closest to humans from a genetic point of view (and therefore the least exposed to rejection), nowadays there is a different approach. Advances in genetic engineering have led to the possibility of modifying the genome of animals in those places responsible for the synthesis of the blood components involved in hyperacute rejection (those that make up "the complement system"). Through the method called CRISPR (clustered regularly interspaced short palindromic repeats) - Cas9 (a protein that allows binding to the targeted DNA sequence) certain genes can be "cut out" and removed or, if necessary, replaced with others, depending on what you need. This method was considered as potentially capable of creating transgenic animals whose organs could be transplanted into humans

The animal on which the research is now focused is the pig, because its organs are very close in anatomy and function to human ones; in addition, the pig grows quickly and multiplies at a rate that allows obtaining as many organs as needed (unlike primates which, if they had proven to be suitable as organ donors for humans, would have risked disappearing very quickly as species).

The suppressed gene ("knock-out") is N-galactosyl transferase, which is involved in the synthesis of the complement system.

The American company eGenesis has managed to produce genetically modified transgenic pigs on an industrial scale so that their organs can be transplanted into humans. Starting from 2021, and especially at the beginning of 2024, several kidney, heart and liver transplants were performed in different centers in the United States. Although the initial evolution was favorable and no case of hyperacute rejection was registered, the transplanted patients did not survive in the long term, dying at intervals of weeks or months after the transplant.

Research does not stop here, however. It is hoped that, in the not too distant future, genetic engineering will obtain the "ideal" animal, whose organs can be successfully transplanted into humans. When this objective is reached, the biggest problem of organ transplantation will be solved: the insufficient number of donors compared to the large number of patients registered on the waiting lists! At that moment, each patient will be able to receive the organ he needs at the right time.

Moreover, if we are allowed to dream, this organ could be genetically modified in such a way that it is recognized as SELF by the body of the recipient. In this situation, the rejection reaction will no longer be triggered and, therefore, there will be no need for postoperative immunosuppression (which is now necessary for the rest of life in transplanted patients). It will be the moment when the golden dream of all transplantologists, IMMUNE TOLERANCE, will become reality!

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