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The World's Youngest Cadaveric Kidney Transplant: Medical, Surgical and Ethical Issues

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Background. We report here the first successful transplant from a preterm cadaveric donor. This was performed in November 1994. The donor, who had been born at about 33 weeks of gestation, was diagnosed as having agenesis of the corpus callosum. The transplant was carried out 10 days after the donor's birth. The recipient was a 17-month-old boy with a diagnosis of Denys-Drash syndrome (WT1 mutation). **Method.** We describe and analyze the ethical, social, cultural, medical and surgical issues encountered and how these were addressed. The major issue of determining death in a beating heart, very young donor was dealt with in the absence of worldwide experience and guidelines. **Results.** The transplanted recipient has lived with the grafted pair of kidneys for more then 22 years. He has led a relatively normal life. **Conclusions.** It is possible for immature preterm deceased donor kidneys to be transplanted into a 17-month-old recipient and for the grafted kidneys to grow with the recipient and function for 22 years. There were challenges in ethically determining the death of the donor, in surgical techniques to obviate potential surgical complications, and in postoperative care of the recipient, but these were managed successfully.

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This is the first formal report documenting an unusual set of circumstances that, about 22 years ago, led to the performance of the youngest ever deceased donor kidney transplant.

In November 1994 we were faced with a unique challenge and opportunity: the mother of a baby boy approached us to consider using her baby's kidneys for transplantation. The mother was a healthy expatriate European living with her husband in Oman. After repeated failures to conceive over a 10-year period she had succeeded in becoming pregnant through an in vitro fertilization procedure. At 33 weeks gestation, this primigravid had gone into labour and delivered a baby boy at Sultan Qaboos University Hospital (SQUH) in Muscat, Sultanate of Oman. The preterm infant exhibited marked hypotonia and struggled to breathe. There were no external dysmorphic features. The baby was soon placed on a ventilator in the pediatric intensive care unit (PICU), and was put on gentamicin, although blood cultures were negative. Electron microscopy of a biopsy from the left quadratus muscle showed no pathological features.

No specific cause was established for the severe hypotonia and failure to breathe, but computed tomography scan of the brain showed agenesis of corpus callosum (ACC), a finding that was confirmed by radiologists in the family's own country of origin. The chief of the PICU informed the parents that the baby was not likely to survive.

The parents of the potential donor demonstrated a truly altruistic attitude. We communicated mainly with the mother, who said that the family wanted some good to come from this tragic situation and urged us strongly to consider transplanting her baby's kidneys, ideally into an Omani baby who needed them.

We identified a potential recipient: a 17-month-old baby, A.A., whom we had recently diagnosed as having Denys-Drash syndrome[1,2] based on clinical features and the histological findings of mesangial sclerosis on kidney biopsy.[3] That diagnosis was later confirmed when genetic testing showed that A.A. did indeed have a mutation in the WT1 gene.[4] A.A. had developed end-stage renal failure early, and he was started on maintenance haemodialysis. Several of his vascular access sites had thrombosed. and he was initiated on intermittent peritoneal dialysis but developed repeated episodes of peritonitis. He was thus approaching the stage where he could no longer be adequately dialysed using any

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A.S.D. directed the transplant surgery team, performed the transplant, and addressed the ethical issues involved. He shared responsibility for care of the recipient. N.M.A. cared for the recipient before and after the transplant and provided long-term follow up.

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technique, a situation that severely limited the chances of his long-term survival.

DONOR DETAILS AND RISK-BENEFIT ANALYSIS

The potential donor was continued on ventilatory support while the issues surrounding the transplant were being discussed. The baby did not trigger the ventilator and repeated attempts at discontinuing artificial support failed.

At day 7 after birth, the medical records noted that "the overall picture is gloomy." Peripheral blood leucocytes showed toxic granulation; cloxacillin and cefotaxime were added to the gentamicin he was already on.

The hypotonia increased. Expert neurological opinion was that this was central hypotonia because of the presence of exaggerated reflexes, jitteriness of the baby, and a computed tomography scan that showed ACC. Myasthaenia gravis was excluded by a Tensilon test, and both the child and the mother had normal electromyograms. The baby had some hyperbilirubinemia, which was treated with phototherapy. On November 5, 1994, when the baby was 9 days old, the medical records noted that "The parents have already decided to terminate (ventilatory) support pending arrangements for organ transplantation." The notes also state that the PICU had "received a report from (a European country) that the brain is badly damaged."

We evaluated all potential risk factors in the donor that might argue against proceeding with the transplant. These included:

(1) *The poor international experience of transplants from paediatric deceased donors* in general and especially of those younger than 4 years.[5-7] We were aware that there had been a very small number of neonatal donor transplants, some from anencephalic donors, where the failures had been due to technical reasons, including twisting or kinking of the transplant vessels postoperatively, leading to severe ischemia or even necrosis of the graft. One small 1980s clinical series had reported transplants successfully performed using paediatric donors,[8] but none of the donors had been preterm or even full term neonates. Additionally, up to 1994, at the time of the transplant reported here, there existed no widely accepted neurological brain death criteria applicable to such a young potential donor. Indeed, until April 2015, in the United Kingdom, beating heart donation from children younger than 2 months was not permitted.[9]

(2) *The international experience was also poor for young recipients*, especially those younger than 5 years and receiving deceased donor grafts.[10,11]

(3) *The amount of renal mass.*

Foetal kidneys do not develop fully until about 38 weeks of gestation. The donor was born at 33 weeks of gestation, and his kidneys were harvested 10 days after birth. Studies show that at about 35 weeks of gestation, foetal kidneys measure about 3 to 3.5 cm in length[12]; we found this to be the case in our donor. Although these small kidneys were able to support the life of our potential donor, who had normal renal function as assessed by serum creatinine, they were likely to become damaged during the transplant surgical process, especially considering the longer than normal warm ischemia time (WIT) that we were contemplating to adhere to the dead donor rule (see below). Additionally, the donor under consideration here had already been exposed to a potentially nephrotoxic antibiotic, gentamicin.

(4) *The local transplant experience.*

Understanding the context in which this transplant was performed is important. Generally, in the mid-1990s most countries in the developing world had no transplant programs, and in the Middle East, these were still early days even for those countries that had established dedicated programs. Oman had established an adult living donor kidney transplantation program beginning slowly in 1989,[13] with only the occasional cadaveric kidney transplant being performed. We had no experience of transplanting children. However, Oman at that time was one of the few countries in the region that had a full transplant service, including a fully functioning local immunology and tissue typing service, and an imminent bone marrow transplant program.[14]

(5) *Potential congenital abnormalities:* With a working diagnosis of ACC we were faced with a situation where there might be concomitant congenital abnormalities in the donor that might or might not manifest in the transplanted kidneys in the future.

RECIPIENT DETAILS AND RISK-BENEFIT ANALYSIS

The potential recipient AA was born into a caring, loving family environment. The familial support at home was exemplary despite the mother being grand multiparous with 9 children. A.A.'s mother was actively involved in the discussions about the possible transplant. She understood that there was a high likelihood of failure if we proceeded with the surgery, but was also aware of the desperate situation likely to result in her son's death in the absence of a transplant.

Although A.A. had been on intermittent haemodialysis and attempted peritoneal dialysis, he was by this time in poor general condition, largely as a result of vascular access problems and recurrent sepsis. He was also hypertensive, requiring drug therapy. We estimated that he would not be able to survive beyond 6 months without a transplant. In addition, with his Denys-Drash syndrome, he would almost certainly go on to develop malignant tumours in his own native kidneys, and his hypospadias would increase the likelihood of postoperative urinary tract infections.[15,16] Yet if the transplant was to succeed, he could have his native kidneys removed at a later date, and his hypospadias could be surgically corrected.

ETHICAL ISSUES TAKEN INTO ACCOUNT

(1) *The likelihood of success was low*, particularly considering the potential donor's age and the size of his kidneys: this would be a technical surgical challenge, reflected by the paucity of the international experience. Indeed, until today, the discard rate of kidneys from donors under 10 kg weight is still very high.[17] Our donor had weighed only 2.5 kg at birth and was 2.2 kg at the time of his becoming a donor 10 days later

(2) *The calculation of the risk-benefit ratio was really challenging*, considering the complexities in both the donor and recipient medical conditions, and the lack of experience on the part of both the surgical and paediatric nephrology teams in dealing with such young donors and recipients. There was little literature available to guide the surgeons, nephrologists, anaesthetists, intensivists, nurses, and others in preoperative

and postoperative care, including managing immunosuppression in a 17-month-old baby recipient. The transplanted kidneys would be placed in an abdomen with adhesions from past peritonitis, and would thus be difficult to biopsy in case renal function remained poor or deteriorated posttransplant.
(3) *Absence of experience with proclaiming brain death* in the ventilated, heart-beating potential donor. This was not just a local issue: internationally, in 1994, there were no clearly established neurological brain death criteria for such young donors; certainly, there were none that had been validated by being used in large cohorts of potential donors.
(4) *Obtaining consent in the face of uncertainty.* The mother of the potential donor was very keen that we proceed with the transplant. There was no doubt that she had a genuine desire to do good, to help a potential recipient, and to salvage a desperate, tragic situation. Thus, consent to remove the kidneys of the baby, and finally to be able to grieve, was offered willingly and enthusiastically—indeed she would have been devastated if the transplant did not go ahead. The mother of the potential recipient AA, knowing of the poor prognosis for her child, was also very keen to provide consent, even knowing the high risk of failure and the potentially life-threatening postoperative complications and lifelong follow-up.
(5) *Unclear legal situation.* Oman is a largely Muslim country. In 1994, there was no specific enabling legislation to undertake organ transplants, there had been no public engagement or discussion about organ transplantation per se, and there was no specific legal framework enabling the use of neurological brain death criteria to diagnose established death for any age group. Nevertheless, the successes of previous local adult transplants (mostly from living related donors) were widely publicized in the media, and Muslim legal experts in the Middle East, in consultation with medical experts, had accepted the concept of brain death in adults as constituting death of the individual person. Thus, the use of brain death criteria in adults, while remaining rather controversial, had been generally, but not universally, accepted in Muslim majority countries, both for purposes of organ transplantation and for switching off ventilation in intensive care units to release beds.[18,19]
(6) *The dead donor rule,* which at that time guided deceased donor organ transplantation and which we wanted to adhere to, required careful attention to ethical and technical details (see below).

THE TRANSPLANT PROCEDURE

The recipient was dialyzed as well as was possible with the limited vascular access and transferred from the Royal Hospital, where he was under the care of Nabil Mohsin al Lawati, to SQUH under the care of Abdallah S. Daar. Facilities were established at SQUH for final preoperative and postoperative dialysis in case the transplanted kidneys did not, as expected, immediately produce high quality urine to support the recipient's life.

The donor was brought to the operating theaters on the morning of November 7, 1994, and prepared in the standard way for bilateral nephrectomy. All personnel involved, in the PICU, among the surgical, nephrology, anesthetic and nursing teams, were informed about the procedures to be undertaken, and the issue of how death was to be established before donor nephrectomy was discussed in detail with all those directly involved. The hospital administrators were made aware of the plan to undertake the transplant operation, and they were supportive.

We had already concluded that applying any neurological brain death criteria in our situation would not objectively satisfy the dead donor rule, which essentially held that organs can only be removed from a donor whose death had been established, and conversely, that the removal of organs do not materially contribute to the demise of the potential donor. Instead we opted to apply what would now be called "Controlled donation after cardiac death, Maastricht Category III,"[20] and simply accept that the WIT would be longer than for transplants where neurological brain death criteria are applied.

At an agreed time, the anaesthetist switched off the ventilator in theater, and we waited until the donor's heart had completely stopped. After cardiac arrest, we waited a full 5 minutes but even then did not proceed. A.S.D. asked that attempts be made to resuscitate the baby, and only when these completely and repeatedly failed did we proceed to performing bilateral nephrectomy. This attempt at resuscitation, although technically unnecessary and futile and would further prolong the WIT, was done to demonstrate to all the staff and students present in the theatre, most of whom had never previously been part of, or observed, a cadaveric donation, that the donor was indeed now dead.

The kidneys, each having a single artery coming off the aorta, were removed en block (attached to a length of the aorta and vena cava), perfused with Eurocollins solution and taken to an adjoining theater for transplantation. Using magnifying loops the donor vessels were anastomosed to the iliac vessels of the recipient. The total WIT was about 70 minutes. On releasing the vascular clamps, the kidneys pinked up well: one produced no urine at all, whereas the second produced a tiny amount of watery urine. We were expecting to encounter tubular necrosis or even some cortical necrosis but a frozen section biopsy showed only immature tubules and glomeruli but no evidence of necrosis. The ureters were individually anastomosed to the dome of the bladder using standard technique.

In the right side of the abdomen, we carefully dissected out adhesions caused by prior episodes of dialysis-related peritonitis. Then, to reduce the likelihood of vascular twisting or kinking of the renal vessels, we extended the vascular pedicle into the right upper abdomen and hitched the capsules of the two tiny kidneys, whose own capsules and some fatty tissue had already been stitched together, to the outer layer of the undersurface of the gall bladder. We then performed an appendicectomy to reduce the chances of complications should the child develop appendicitis in the future. The recipient was then taken back to the ward at SQUH for early postoperative joint care by the surgery/nephrology teams. He required intermittent dialysis, particularly to manage potassium levels. Cyclosporine, azathioprine and corticosteroids were initially given intravenously before switching to oral administration after a few days. The recipient did not receive induction therapy with polyclonal or monoclonal antibodies.

The blood vessels did not twist of kink postoperatively, probably as a result of the surgical precautions we had used. After about a week, the transplanted kidneys began to produce urine of increasing concentration and the recipient was taken off dialysis completely. By then, he was back at the Royal Hospital.

LONG-TERM POSTTRANSPLANT COURSE

There were very few complications over the following years.

As often happens posttransplant, A.A. continued to have moderate hypertension requiring treatment. There were no unexpected complications associated with immunosuppression.

In June 1995, about 7 months after the transplant, we removed A.A.'s native kidneys. Fortunately, they had not yet developed any nephroblastomas (Wilms tumor) or any other tumors.[21] The hypospadias was successfully repaired when A.A. was 7 years old. In 1997, he was switched to tacrolimus and mycophenolate mofetil while continuing on small doses of steroids.

Ultrasound and magnetic resonance imaging over the years showed that the kidneys were growing as A.A. grew and as more metabolic demand was placed on the transplanted kidneys. Although one of the kidneys was smaller than the other, suggesting possible hypoperfusion, we chose to adopt a conservative approach because of the continuing good overall renal function. We resisted the urge to biopsy the transplanted kidneys situated in the upper abdomen or to interfere with the kidneys and their blood vessels in intrusive ways.

A.A. had a relatively normal childhood, went to an ordinary school, graduated from high school, and led an uneventful life for the next 22 years. His serum creatinine for 21 years remained just above the normal range, as often is the case in patients who have undergone transplantation and are on immunosuppressive and other medication. In the past 1 year, the serum creatinine has begun to creep up. At the time of writing, he is still in robust health and not requiring any dialysis.

DISCUSSION

We adhered to the best of our ability to the ethical strictures of the time and satisfied the dead donor rule as was understood then. Over the next few years, the 1987 guidelines[22] for the determination of death in children were updated. However, even the newer 2011 guidelines[23] noted that because of insufficient data in the literature, recommendations for preterm infants younger than 37 weeks of gestational age were not included.

Thus, in 1994, there was nothing in the literature that would have allowed us fully to apply neurological brain death criteria in our 33 weeks plus 10 days donor. The procedures we used allowed us to retrieve the deceased donor's kidneys in a state that went on to support the life of the recipient for at least 22 years.

We still remain unsure of what caused the donor to have such severe hypotonia and to be unable to breathe. We were only recently able to find additional information about the baby's brain. It had been sent to Europe for postmortem examination. This revealed that the corpus callosum was not totally absent, but it was thinner than normal. The report also suggested that there might have been some thrombosis of veins draining the brain, which might have suggested some birth trauma, but the shipped specimen did not have these veins attached.

In 1995, the year after the transplant, the donor's mother sought genetics advice because she was contemplating further pregnancies and wanted to be sure there was no genetic contribution from her that might have caused the death of her first child. She was told that genetic factors in her case were unlikely. One genetic condition that apparently *might* have been a factor, myotonic dystrophy, caused by a mutation that a mother might carry and in which a child might have symptoms that the mother has not yet manifest, was excluded by that genetic testing. With this good news, the mother went on to have further in vitro fertilization treatment and subsequently delivered triplets who are now grown up and healthy.

This transplant entered the world transplant records maintained by the Paul Terasaki Laboratories at the University of California, Los Angeles.[24] It was, and continues to be, a record of the youngest cadaveric donor kidney transplant, and the second youngest cadaveric transplant recipient. We are not aware that the circumstances described above, wherein a baby born at about 33 weeks of gestation and became a kidney donor 10 days later, have been replicated by other teams.

Although the recipient, A.A., currently continues in good health, his serum creatinine has begun to rise, and there is a possibility that in time his transplanted kidneys will reach end-stage failure. We think he will likely then get a living related kidney from 1 of his 8 siblings.

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