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Case Study

Paediatric renal failure - a lifelong battle requiring multiple transplantations

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Renal Transplantation, Transplant, Paediatric Transplantation, Renal Dysplasia.

Key learning points
Dr Georg Ebeling
The following were the most important takeaways from the case study:

1. Challenges faced by paediatric recipients of renal transplants.
2. Indications for paediatric kidney transplantation.
3. Factors that promote graft survival, such as HLA compatibility, sensitization, and living as opposed to deceased donation.
4. Long-term effects of kidney transplantation in children.

Introduction

Kidney transplants are the most common form of transplant surgery performed in the UK - both in adults and in children. In 2019-20, 3190 adult[1] and 112 paediatric[2] kidney transplants were carried out in the UK. Importantly, in paediatric renal transplantation, the recipient often outlives their graft and therefore require multiple transplantations throughout their lifetime. This report focuses on patient ZG, a 32-year-old female undergoing her third renal transplantation. Patient ZG had her first transplant, aged 16 months, following a diagnosis of bilateral dysplastic kidneys, a subsequent transplantation 18 years later and a third transplant in 2021. This report will describe the salient features of the case of ZG, and the issues raised such as:

(1) Indications for Paediatric Renal Transplantation
(2) Promoting graft survival
   a. HLA matching
   b. Sensitisation
   c. Living Vs deceased donor
(3) Long-term effects of Paediatric renal transplantation
(4) Balancing multiple Transplantations Vs Haemodialysis

The Case of Patient ZG

Patient ZG was born with bilateral dysplastic kidneys. This led to end stage renal failure and essential hypertension. In 1990, aged 16 months, patient ZG received an intra-abdominal deceased donor renal transplantation. However, the transplant underwent acute rejection, after 18 years, due to non-compliance. This led patient ZG to spend one year receiving haemodialysis. In 2011, she received a living related donor (LRD) kidney from her father.

In 2014, patient ZG tragically had a stillbirth pregnancy. She became pregnant again, very soon after, and delivered at 30 weeks. Patient ZG's renal function deteriorated after delivery and never fully recovered. Her serum creatinine was 430 µmol/L, with a haemoglobin of 106 and low Tacrolimus levels. Patient ZG had, once again, reached end-stage renal failure. This was accompanied by further haemodialysis.

In 2021, patient ZG underwent her third renal transplant. In this instance, the patient received a LRD kidney, from her mother. During the operation, an arterial and venous anastomosis was formed between the renal vasculature and the external iliac artery. The kidney was placed in the left iliac fossa region. Intra-operatively, patient ZG received Alemtuzumab (Campath), a monoclonal antibody which targets the CD52 antigen for antibody dependent cellular cytotoxicity (ADCC), leading to lymphocyte depletion. This antibody serves as an induction agent for solid organ transplantation as it reduces acute rejection in the first 6 months following transplantation[3]. There were no complications associated with the surgery.

Patient ZG recovered well from the operation, her creatinine levels began to fall, as shown in Figure 1, indicative of significantly improved renal function . Four days post-operation, patient ZG appeared well and comfortable at rest. ZG was afebrile with a HR of 83 and BP of 117/79. On abdominal examination, there were three scars. One fully healed Rutherford-Morrison scar located at the right iliac fossa following her transplantation in 2011; one Pfannenstiel incision at the hypogastric region due to a caesarean section; As well as a recent tender scar from her most recent transplantation in 2021 located at the left iliac fossa. The abdomen was soft and bowel sounds were present. As expected, there was tenderness over the site of incision.

Post-operatively, ZG was prescribed mycophenolate mofetil and tacrolimus, two immunosuppressive anti-

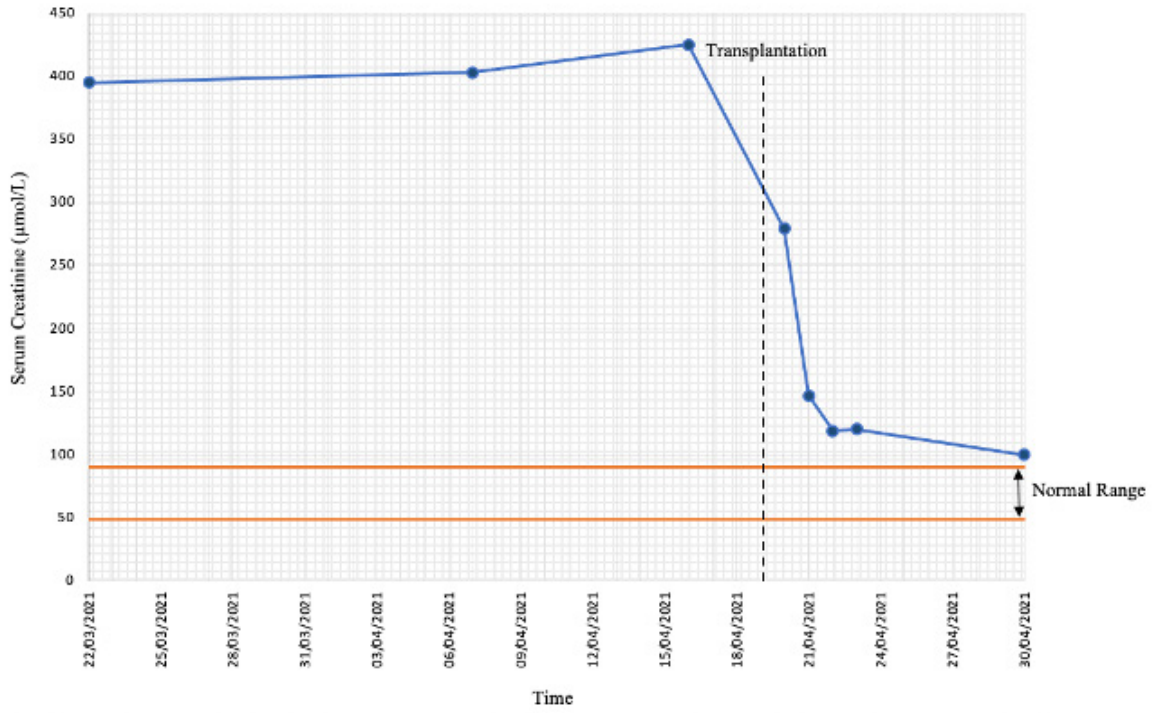

Figure 1: Serum creatinine levels pre- and post-transplant for patient ZG.

rejection drugs. She was also started on valganciclovir for CMV prophylaxis and co-trimoxazole for PCP prophylaxis . Four days post-operation, ZG was able to return home. Moreover, 9 months following the operation, patient ZG remained well with no long-term complications.

Paediatric End-stage Renal Disease

It is estimated that there are 5-10 cases of paediatric end-stage renal disease (ESRD) per million of the age-related population[4]. This is 20-fold less than that of adults. Importantly, the causes of ESRD differs between children and adults. In children, the most common causes of ESRD include congenital abnormalities of the kidney and urinary tract, hereditary nephropathies, glomerulonephritis, and cystic kidney disease. In adults, the most common causes are Diabetes Mellitus, hypertension and glomerulonephritis[4].

Renal dysplasia is a major cause of childhood ESRD[5]. Patient ZG was diagnosed with bilateral renal dysplasia in utero. Renal dysplasia refers to a collection of conditions in which the internal structure of one or both of a foetus' kidneys do not develop normally while in the womb[6]. During normal development, ureters grow into the kidney and branch out to form a network of tubules. In dysplasia, the tubules fail to branch out completely. Urine, that would normally flow through the tubules, collects inside the affected kidney and forms cysts which replace the normal kidney tissue[7] . Ultimately, less urine is unable to be excreted from the kidney - this is known as renal oligohydramnios (ROH)[8]. Neonates with bilateral kidney dysplasia generally do not survive birth - this is due renal dysfunction and pulmonary hypoplasia associated with ROH[9]. For those who do survive, renal transplant or dialysis are the only treatment options[10].

Graft Survival in Paediatric Patients

As aforementioned, paediatric patients with end-stage renal failure will require multiple transplantations throughout their lifetime . The average half-life of a kidney transplant in a paediatric patient is 10 years; Given a median age of transplantation at 13 years, 50% of all current paediatric kidney recipients will need a second graft before the age of 25[11]. To maximise the longevity of each transplanted kidney, understanding the factors which influence graft survival is of paramount importance. There are three main factors which influence graft survival: a) immune activity against the graft, b) sensitisation , referring to the presence of recipient antibodies against the donor organ, and c) quality of the donor organ.

HLA Matching

The major histocompatibility complex (MHC) is made up of 3.6 million base pair genomic regions located on chromosome 6[12]. MHC is a family of genes that encodes HLAs - these are expressed on the surface of cells and are responsible for identifying foreign antigens[13]. Importantly, the polymorphism of the MHC makes it a unique barcode for each individual - the only exception being identical twins.

The most important cause of late graft failure in paediatric renal transplant patients is chronic renal allograft injury - including T-cell mediated rejection[4]. The risk of rejection can be reduced by carefully matching the donor and recipient to maximise compatibility prior to the transplantation - this is based on a combination of factors such as ABO blood group, tissue typing to assess human leukocyte antigen (HLA) compatibility and cross matching to look for donor-specific antibodies (DSA)[15]. DSA target specific epitopes the polymorphic regions of HLA antigens - this includes the polymorphic a-chain of HLA class 1 and the beta-chain of DQ HLA class 2.

There are three predominant mechanisms by which graft rejection occurs. Firstly, there is direct presentation. In this scenario, a resident population of antigen-presenting cells (APC) from the donor are carried over in the transplantation process. These 'stowaway' APCs present MHC molecules, bound with endogenous peptide

Level	HLA Mismatch Summary	HLA Mismatch Combinations included
1	000	000
2	[0 DR and 0/1 B] or [1 DR and 0B]	100, 010, 110, 200, 210, 210, 001, 101, 201
3	[0 DR and 2 B] or [1 DR and 1 B]	020, 120, 220, 011, 111, 211
4	[1 DR and 2 B] or [2 DR]	021, 121,221, 002, 102, 202, 012, 112, 212, 022, 122, 222

Table 1: HLA mismatch levels for HLA-A, B and DR, sourced from reference[20].

from the host, to trigger a polyclonal T cell response by the recipient. In addition, there is an indirect pathway. In this pathway, donor-derived antigens are acquired by recipient APCs that process and present these peptides to the host. Lastly, a semi-direct pathway exists in which the donor membrane components are fused with recipient APCs and thus intact donor MHC molecules are presented to the host[14].

The degree of similarity between the HLA genes of the donor and the recipient is known as histocompatibility. There are three general groups of human leukocyte antigens (HLA) molecules. These are HLA-A, HLA-B and HLA-DR[16]. The more genetically compatible the donor and the recipient, the smaller the degree of the immune response against the graft will be.

Data from the Collaborative Transplant Study showed that with or without cyclosporine use, the renal transplant success rate was 20% higher when there was no mismatch of HLA-B and -DR than where there was mismatch[17]. In addition, Wissing et al. (2008) demonstrated, in a retrospective single centre study of live and deceased renal transplants, that HLA-mismatches remained an important determinant of immune rejection in patients receiving quadruple immunosuppression. In this study, increasing the number of HLA mismatches was an independent predictor of acute rejection, with HLA-DR locus mismatches being associated with the highest risk of rejection[18,19].

HLA mismatch level is assessed between the donor and the recipient, generating an overall score. This algorithm takes into account the differing immunological effect of mismatches at different loci[20]. The HLA mismatch between patient ZG and her mother was 1-1-0, representing mild degree of mismatch (Table 1).

Sensitisation

Sensitisation refers to the presence of antibodies (DSA) with specificity towards donor HLA. These antibodies recognise the antigenic epitopes displayed by the HLA molecule on the transplanted allograft and cause damage, thereby decreasing graft survival[21]. Development of HLA antibodies may occur prior to or after transplantation - this is termed pre- and post-transplant HLA sensitisation, respectively[22]. Exposure to non-self HLA can cause the production of HLA-directed antibodies[23].

The most common causes of HLA-sensitising events include exposure to blood transfusions, prior transplants and pregnancy[23]. Prior to her third transplant, Patient ZG was noted to have DSA, with a calculated reaction frequency (cRF) of 100%. cRF is a measure of the recipient HLA sensitisation, calculated as the percentage of 10,000 recent donors to which the recipient has pre-formed HLA antibodies[24]. Thus, patient ZG was highly sensitised prior to the transplantation - this was, most likely, due to her previous pregnancies and transplantations. Moreover, the development of donor specific antibodies can also be caused by insufficient immunosuppression, either due to insufficient prescription or non-compliance to medication[4]- this is especially the case in adolescent patients, including patient ZG whose first transplant is quoted to have failed due to 'non-compliance'.

Matching for second and subsequent renal transplantations becomes more challenging in the presence of DSA. There is an increased risk of acute rejection and the pool of donors is decreased leading to longer waiting times for an organ[25]. More HLA mismatching at the time of the first renal transplantation is associated with higher degrees of sensitisation, lower rates and longer times to re-transplantation and worse graft outcomes in children who are re-transplanted. Therefore, ideally, paediatric renal transplant programmes should use highly matched HLA donors[26].

Living Donor versus Deceased Donor

Transplantation can occur between living related donors, unrelated living donors, deceased after cardiovascular death or decreased after brain stem death donors. The success of a transplant is intrinsically linked to the donor organ. Roodnat et al. (2003), performed a retrospective cohort study looking at 1,124 patients who had undergone kidney transplantation in the space of 19 years. The incidence of graft failure was significantly

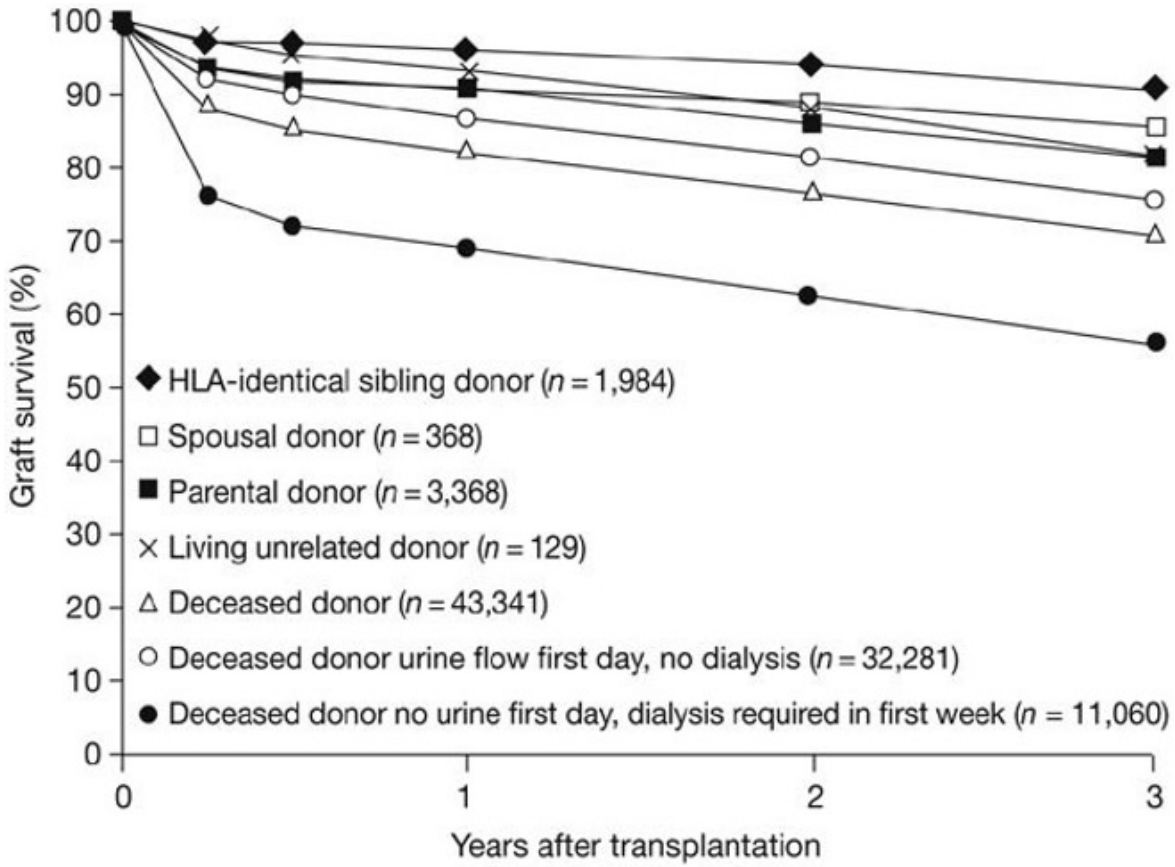

Figure 2: The survival rates of first kidney grafts. Sourced from ref 30.

greater in the deceased donor recipients in comparison to the living donor recipients[27] Delayed graft function is defined as the failure of the renal transplant to function immediately, with the need for dialysis in the first post-transplantation risk[28]; it is a known risk factor for renal graft loss. This is a complication that occurs in ~50% of deceased after cardiovascular death donors[29]. Cold ischaemia time (CIT), defined as the period of elapsed after the cessation of circulation until the beginning of vascular anastomosis in the renal graft recipient, is increased in deceased donors. This contributes to ischaemia-reperfusion injury, leading to delayed graft function. Moreover, data indicate that outcomes of LRD transplants between genetically unrelated donors and recipients are superior to those using deceased organs with a closer HLA matching (Figure 2)[30]. This can be explained by the damage suffered by the kidneys due to CIT and donor organ quality.

Living-donor kidney transplantation is encouraged for children with ESRD due to superior long-term graft survival compared with a deceased donor. This is supported by the work of Arendonk et al. (2014) who analysed first and second graft survival among 14,799 paediatric renal recipients. Living-donor grafts had a longer survival compared with deceased-donor grafts for both the first and second transplant[31]. Interestingly, it was shown that the cumulative graft life of two transplants was the same, regardless of the order of deceased-donor and living-donor transplantations. This implies that deceased-donor renal transplants in paediatric recipients followed by living-donor re-transplantation does not negatively impact the living-donor graft survival and provides a similar overall graft life in comparison with living-donor followed by deceased donor[31].

Long Term Effects of Paediatric Renal Transplantation

The adverse effects of immunosuppressive medication and reduced graft function may hamper long-term health. Complications include metabolic complications - such as post-transplantation diabetes mellitus, hyperlipidaemia, and metabolic syndrome; as well as increased risk of malignancies - namely, colorectal cancer, melanoma, kidney, ureter malignancies and lymphomas[4]. Paediatric renal transplant recipients may also experience cardiovascular complications - for example 312 deaths were reported in renal recipients under the age of 30 between the years 1990-1996. 10% of these deaths were cardiac in origin. However, it must be noted that the rate of cardiac deaths was 10-15 times higher in dialysis patients[32]. Moreover, paediatric renal transplant recipients may also experience issues in growth and pregnancy - as was the case in patient ZG.

Growth

Attainment of normal growth and maturation is a major challenge. Children with ESRD present with disproportionate stunting. Although post-transplant, there is an increase in height, very few patients reach their target adult height. Holmberg et al. demonstrated that, in the final height of patients transplanted between 1990 and 2007 was -1.2 standard deviations below the mean height for boys and -1.7 for girls . Poor graft function is correlated with poor pubertal height gain. In addition, immunosuppressive medication has a marked impact on growth in paediatric renal transplant patients. It has been noted that steroid avoidance and withdrawal, as well as alternating days on which steroids are given, is associated with improved growth.

Patient ZG is of short stature . When compared against UK growth charts, she is of the average height of a 13-year old girl, despite being 32-years of age[33]. Although her final height may be related to genetic and socio-economic factors, it is important to consider the long-term impact of multiple renal transplants and lifelong immunosuppression on overall growth.

Fertility and Pregnancy

Data relating to the fertility of young men and women who underwent renal transplantations are scarce. However, it has been noted that women who received renal transplants during their childhood, complications in pregnancy are common. The National Transplantation Pregnancy Registry, compiled data from 1356 pregnancies among 857 North American kidney transplant recipients. Overall, the registry data showed that kidney transplant recipients are at a higher risk of complications than the general population[34]. Premature birth (<37 weeks) and low birth weight (<2500 g) were among the most common neonatal complications and affected nearly half of all new-borns[35] . Transplant patients frequently required treatment for pre-eclampsia (28–31%) and hypertension (52–68%)[35]. According to Pezeshki et al. conceiving within 2 years of transplantation led to an increased risk of these maternal complications compared with those who delayed pregnancy. Therefore, it is advised that patients should be counselled to wait for a confirmation of graft stability before conceiving[34].

Patient ZG experienced significant complications with her first pregnancy, leading to a stillbirth. However, it is difficult to ascertain whether patient ZG's pregnancy complications were due to her transplant history or other factors - especially given that she subsequently delivered a healthy child.

Multiple Transplantations Vs Dialysis

Given the long-term complications of transplantation, as well as the physical and emotional toll of repeated transplantation, it is not unreasonable to question the benefits of multiple surgeries against haemodialysis.

However, it is important to note that young people undergoing transplantation have an optimised physical and psychosocial growth and well-being[25]. Importantly, kidney transplantation offers a significant survival advantage and reduction in co-morbidities in comparison to haemodialysis. Patients on dialysis have a higher rate of ischaemic heart disease, cerebrovascular disease and arrythmias as well as a higher risk of death and lower life expectancy[36,37].

In addition, third and fourth kidney transplants remain a viable and reasonable therapeutic option. Izquierdo et al. (2010) analysed graft and patient survival as well as surgical complications of third and fourth transplantations between the years of 1985-2008. Among 2,738 cases 74 third and 8 fourth transplantations were performed. Results revealed that third and fourth transplantations constitute a valid therapeutic option: Patient survivals at 5 years were 90.6%, for third and 85.7% for the fourth transplantation. The third and fourth transplantations showed a 5-year graft survival of 76.4% and 42.9%, respectively[38].

Ultimately, the choice between multiple transplantations versus dialysis falls to the patient - the role of the doctor is to assist the patient in making a fully informed decision regarding their options. Furthermore, not all young ESRD patients may be given the option of multiple transplants.

Conclusion

In summary, this case report has focused on patient ZG - a young woman undergoing a successful renal transplantation. Patient ZG developed ESRD as a neonate, resulting in multiple transplant surgeries and a lifetime of immunosuppression. The case of patient ZG brings to light considerations in young transplant recipients. For example, factors affecting graft longevity such as HLA matching and the quality of the donor graft and sensitisation. In addition, it is important to appreciate the long-term complications which paediatric renal transplant recipients experience throughout their life. Despite these complications and associated risks, transplantation has been shown to offer a reduction in mortality and morbidity in comparison to dialysis.

Declarations

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Consent

The patient has consented to the publication of this case study.

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