Renal Transplantation in Familial Dysautonomia: Report of Two Cases and Review of the Literature

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Background and objectives: Chronic kidney disease (CKD) is an increasingly recognized complication of familial dysautonomia (FD), a neurodevelopmental disorder with protein systemic manifestations that are the result of sensory and autonomic dysfunction. Progressive renal dysfunction occurs due to chronic volume depletion and cardiovascular lability with supine hypertension and orthostatic hypotension. By age 25, nearly one-half of all patients with FD will have reached stage 3 CKD. Furthermore, dialysis for ESRD in FD patients is associated with multiple complications and poor outcomes.

Design, settings, participants, & measurements: We report two patients with FD who developed ESRD at ages 27 and 16, respectively, and underwent renal transplantation. Transplant was performed after 3 months on intermittent hemodialysis (HD) in the first case and after 1 month on twice-weekly continuous veno-venous hemodialysis (CVVHD) in the second case.

Results: Both patients tolerated surgery well and have maintained good graft function at 20 and 24 months posttransplantation, respectively. Symptomatic and functional improvements have included lower supine BP and increased sensitivity to antihypertensive agents.

Conclusions: As general supportive care improves the lifespan of FD patients, issues related to the management of ESRD will become more important. Renal transplantation provides a viable alternative to dialysis for FD patients with ESRD.

Kidney disease is a common complication of FD. A recent study of chronic kidney disease (CKD) in the FD population found that nearly 40% of those studied reached at least stage 3 CKD by age 20, and greater than 75% progressed to stage 3 CKD or beyond by age 35 (6). Moreover, 3.5% of patients in the database of 596 patients had reached end-stage renal disease (ESRD) requiring dialysis. Global ischemic-type glomerulosclerosis (GS) has been described as the primary histopathology in patients with FD (7). An interplay between chronic volume depletion, BP lability, and the inability to regulate renal hemodynamics due to sympathethic dysfunction likely underlies the development and progression of kidney disease in these patients. These factors also greatly increase the risk of complications with dialysis, which is associated with increased mortality in the FD population (6).

As survival improves and a greater proportion of FD patients are living into their 20s, measures aimed at the treatment of ESRD and at quality of life during ESRD are becoming more important. To our knowledge, there has been only one previously reported case of successful renal transplantation in a patient with FD. We present our experience with two additional patients, the first U.S. cases, who have undergone successful renal transplantation at our center and have continued to do well since transplantation.
Case One
Clinical History
At the time of transplantation, the patient was a 27-year-old Ashkenazi Jewish male with FD diagnosed at birth (1980). The patient’s FD had been characterized by the pathognomonic alacrima; recurrent aspiration pneumonia; gastroesophageal reflux requiring Nissen fundoplications (1986 and 1990) and gastrostomy tube placement; labile BP with orthostatic hypotension, supine hypertension, and several hypertensive crises per week; syncopal episodes necessitating pacemaker placement (1999); respiratory insufficiency requiring nightly BiPAP; severe anxiety; and CKD with progression to ESRD. Serum creatinine was 1.3 mg/dl in 2005, 1.5 mg/dl in 2007, and 4.0 mg/dl in 2008 when he presented with new-onset edema and 24-hour urine protein of 4 to 6 g/d. Renal biopsy, done out of clinical concern for a superimposed glomerular disease, showed 14 of 15 glomeruli globally sclerotic or approaching global sclerosis. There were features of chronic thrombotic microangiopathy, with widening of the subendothelial space of glomerular capillaries by electron-lucent material, mild mesangiolysis, irregular foot process effacement, and endothelial swelling without overt thrombosis in the few residual glomerular capillaries. This was felt to represent chronic hypertensive nephrosclerosis with periods of accelerated hypertension.

Clinical Course
In June 2008, the patient was evaluated at the Renal Transplant Program of New York-Presbyterian Hospital/Columbia University Medical Center. Home medications included clonidine 0.1 mg daily, amlodipine 10 mg daily, and clonidine patch 0.2 mg. Physical examination revealed BP 118/74 mmHg (supine) and pulse 60 beats/min. Laboratory values were significant for blood urea nitrogen of 124 mg/dl and serum creatinine of 8.6 mg/dl. Hemodialysis (HD) was initiated shortly thereafter.

The patient underwent living-related renal transplant (LRRT) in August 2008, with his mother as the donor. He was admitted to the hospital the evening before transplant for preanesthetic evaluation in anticipation of issues in perioperative BP management. Admission examination revealed: weight 35 kg, height 170 cm, temperature 36.5°C, BP 158/104 mmHg (semirecumbant), pulse 72 beats/min. Neurologic exam was notable for impaired pain and temperature appreciation, positive Romberg, dysmetria on finger-nose-finger, absent deep tendon reflexes, and wide-based gait.

The patient was anesthetized with propofol, succinylcholine, midazolam, and fentanyl, with sevoflurane and dexmedetomidine for maintenance. The intraoperative course was uneventful with systolic BPs ranging from 110 to 210 mmHg. The BP of 210/130 mmHg responded to sodium nitroprusside at 0.2 µg/kg/min, stabilizing at 150s/100s mmHg. He was transferred to the intensive care unit (ICU) in stable condition, with BP of 120/80 (supine), oxygen saturation 91% to 94% on 2 L/min O2 via nasal cannula, and urine output of 500 cc/h. Ultrasound examination demonstrated a right lower quadrant (RLQ) allograft without hydronephrosis or perinephric collection, normal resistive indices, and good perfusion.

Transplant induction therapy consisted of thymoglobulin for 4 days and tapered intravenous methylprednisolone for 5 days. Chronic immunosuppression therapy was begun with mycophenolic acid 720 mg twice daily and tacrolimus 1 mg twice daily. BP was controlled with clonidine 0.2 mg twice daily, clonidine patch 0.2 mg, and propranolol 20 mg twice daily. The patient tolerated feeds via his gastrostomy but was kept NPO (nothing by mouth) due to aspiration risk. Creatinine reached a nadir of 0.8 mg/dl on day 4 posttransplantation.

The postoperative course was complicated by mucous plugging of the left bronchus on day 4 posttransplantation, requiring intubation for 1 day. The remainder of the hospital course was notable for labile BPs with supine hypertension to 190s/110s and orthostatic hypotension to 80s/40s; fludrocortisone 0.1 mg daily and midodrine 2.5 mg daily were begun. The patient was discharged home on day 14 posttransplantation on mycophenolate mofetil (MMF) 500 mg twice daily and tacrolimus 6 mg twice daily.

The patient has done well since transplant. He continues to exhibit BP lability with orthostatic changes and episodes of hypertensive crisis. His baseline pressures, however, have trended lower than pretransplant values, and his sensitivity to antihypertensive agents has increased so that doses were reduced accordingly. Fludrocortisone 0.1 mg daily has been continued for orthostatic hypotension. In the first 9 months posttransplantation, serum creatinine generally remained stable between 0.9 to 1.1 mg/dl with transient rises to 1.3 to 1.4 mg/dl that were felt to be due to volume depletion. A period of frequent dysautonomic crises was accompanied by a rise in creatinine to 1.9 mg/dl. Urinalysis consistently showed only trace proteinuria. At present, his serum creatinine is 1.4 mg/dl.

Case Two
Clinical History
At the time of transplantation, the patient was a 16-year-old boy with FD diagnosed as a newborn (1991). The patient’s father had undergone renal transplant for medullary cystic disease. The patient’s FD had been characterized by alacrima, supine hypertension, orthostatic hypotension, oropharyngeal incoordination requiring Nissen fundoplication with gastrostomy tube placement at age 4 months, and CKD in the context of labile BP and moderate proteinuria but unremarkable renal ultrasounds. Renal biopsy was not performed. The patient progressed to ESRD in April 2008. Due to concern for BP-related intolerance of HD, he was maintained on continuous venovenous hemodialysis (CVVHD), with twice-weekly 20-hour treatments for 1 month. The home BP regimen included clonidine 0.1 mg daily, clonidine patch 0.2 mg, amlodipine 2.5 mg daily, and hydralazine 12.5 mg daily for supine hypertension, and fludrocortisone 0.1 mg daily for postural hypotension.

Clinical Course
The patient underwent LRRT in April 2008, with his maternal aunt as donor. He was admitted on the evening before transplant for intravenous hydration and preanesthetic evaluation. Admission examination revealed: weight 35 kg, height 153 cm,
temperature 38.4°C, pulse 111 beats/min, BP 153/101 mmHg (standing). On the morning of the procedure, nifedipine was given for a BP of 213/146 mmHg. Anesthesia was achieved with midazolam, remifentanil, etomidate, and rocuronium, with dexmedetomidine, remifentanil, cisatracurium, and sevoflurane for maintenance. Intraoperatively, he was hemodynamically stable with systolic BPs 150s to 170s mmHg. Postoperatively, sodium nitroprusside was begun at 1 μg/kg/min for systolic BPs above 200 mmHg. The patient was transferred to the ICU in stable condition on minimal oxygen support.

Transplant induction therapy consisted of intravenous basiliximab 20 mg (dosed twice, on the day of transplantation and on day 4 posttransplantation) and tapered intravenous methylprednisolone for 5 days. Chronic immunosuppression therapy consisted of MMF 500 mg twice daily and tacrolimus 2 mg twice daily. Sodium nitroprusside was titrated to systolic BPs of 160 to 200 mmHg. This was continued until day 2 posttransplantation, by which point all home antihypertensive medica
tions had been restarted. Despite this, supine hypertension to 190s/130s mmHg and orthostatic hypotension to 110s/40s mmHg persisted.

Urine output postoperatively was excellent. Creatinine reached a nadir of 0.7 mg/dl on day 3 posttransplantation. Ultrasound examination revealed a RLQ allograft with three small peritransplant collections, no hydronephrosis, and patent vessels with normal resistive indices. The patient’s home diet of soft solids orally with liquids through the gastrostomy was restarted on day 2 posttransplantation. The remainder of the hospital course was notable for intermittent fevers beginning on day 4 posttransplantation; vancomycin, piperacillin/tazobactam, and fluconazole were started empirically. Cultures of blood and urine remained negative, and ultrasound of the transplant kidney showed no evidence of anastomotic leak. The patient subsequently defervesced and was discharged home on day 7 posttransplantation on MMF 500 mg twice daily and tacrolimus 4 mg twice daily.

Two years posttransplant, the patient is doing well. He has gained 2.5 kg in weight and 5 cm in height. Elevations in supine BP have been less pronounced, especially upon awakening. BP have been less labile, with fewer episodes of dizziness upon standing. The current antihypertensive regimen consists of clonidine 0.1 mg at bedtime. Due to persistent orthostatic hypotension, fludrocortisone has been increased to 0.1 mg twice daily, and midodrine has been added at 3.75 mg each morning and 2.5 mg at noontime. Creatinine has remained stable at 1.5 mg/dl, and urinalysis has shown trace protein. Overall, he maintains good functional status and is doing well as a senior in high school.

Discussion

CKD in the FD population appears early, and its prevalence far exceeds that of the general population. In a group of 47 patients, average age 24 years, the mean measured creatinine clearance (CrCl) was 69 ml/min per 1.73 m² (8). In a subsequent retrospective analysis of 596 patients, significant impairment in kidney function was noted as early as age 15, the youngest group studied (6). By age 20, 39% had progressed to stage 3 CKD or beyond. This rose to 50% by age 25, and by age 35, 76% of the FD population had attained at least stage 3 CKD. Moreover, as of 2006, 21 patients (3.5%) had developed ESRD requiring dialysis. Of the 106 patients alive at age 25 years, 20 patients (19%) eventually required dialysis, with an average age of 33.6 years at the start of dialysis therapy (6).

The increasing incidence and recognition of CKD in FD patients reflects improving survival rates for the FD population as a whole. More patients are now reaching adulthood, and recent statistics indicate that a newborn with FD has a 50% chance of surviving to 40 years of age. Functional status and quality of life continue to improve as well, and increasing numbers of patients are achieving independent function (9).

Kidney dysfunction in FD patients can likely be attributed to several features of the disorder. One factor is compromised intravascular volume due to both dysphagia impeding optimal fluid intake and acute episodes of dehydration during dysautonomic vomiting crises, which are often accompanied by increased insensible losses from excessive diaphoresis and hypersecretion (6). A second factor is BP lability. Patients exhibit orthostatic hypotension, without appropriate compensatory tachycardia (10). Supine hypertension occurs, as does episodic hypertension as an isolated response to anxiety or visceral pain, or as part of the dysautonomic crisis (8,11). Orthostatic changes are consistent with an attenuated sympathetic response; supine plasma levels of norepinephrine (NE) are normal or elevated but fail to increase appropriately upon standing (10,12). Supine episodic hypertension may reflect denervation hypersensitivity; in the context of reduced sympathetic innervation of peripheral blood vessels, there is exaggerated vasoconstriction in response to small increases in NE (13,14).

In this setting, renal perfusion is compromised, leading to progressive kidney dysfunction. A study of 10 autopsies and three biopsies from FD patients identified excess GS in 10 patients (7). GS was present in patients as young as 1 year, and the degree of sclerosis increased with age. GS was global, and findings of glomerular capillary basement membrane thickening and wrinkling suggested ischemic-type injury. The patient with the most marked supine hypertension had vessels showing severe intimal hyalinization and fibrosis with medial hypertrophy. The same series demonstrated an absence of sympathetic innervation of the renal vasculature (7). It was postulated that deficiency of sympathetic vasomotor tone might impair the ability to regulate intraglomerular pressure, resulting in ischemic damage to glomeruli during periods of orthostatic hypotension with further damage during periods of hypertension (6). Consistent with this, Doppler flow studies of the renal vasculature have shown that while vascular resistance is normal at baseline, there is reduced overall flow with markedly decreased end-diastolic flow upon standing and with exercise (8). The observation that proteinuria is initially absent but worsens as renal function declines is also consistent with global, ischemic-type secondary GS (6).

Treatment remains primarily supportive, with increasing emphasis on prevention and quality of life improvements. Medications include diazepam and clonidine during dysautonomic crises and for hypertension, and fludrocortisone (a min-
eralocorticoid) and midodrine (a peripheral alpha1-agonist) for orthostatic hypotension (15). Surgical interventions include Nissen fundoplication and gastrostomy tube placement to ensure adequate hydration and caloric intake, prevent aspiration, and decrease the frequency of overt vomiting (16). These targeted treatments are also likely to be important in addressing the development and/or progression of kidney disease, as both cardiovascular instability and chronic volume depletion increase the risk of severe CKD. Both the degree of orthostatic hypotension and the age at gastrostomy tube placement have been shown to correlate with progression to more advanced CKD (6). In our cases, the BP regimen included clonidine, fludrocortisone, and midodrine in case one, and clonidine, diazepam, fludrocortisone, and midodrine in case two. Gastrostomy tube placement occurred at age 6 years in case one, and at age 4 months in case two. Interestingly, angiotensin-converting enzyme (ACE) inhibition may not play a role despite the presence of proteinuria, since it appears that proteinuria in FD-related CKD is a late finding, developing as a secondary manifestation of GS. Initiation of ACE inhibitor therapy in early-stage CKD does merit consideration. However, it may be hypothesized that for FD patients, who have a defect in sympathetic activity and may indeed rely upon residual angiotensin II activity, ACE inhibition is not an optimal choice from the standpoint of BP control.

Despite the above medical and surgical interventions, both patients progressed to ESRD, at ages 27 and 16 (Table 1). In the case of other FD patients who have undergone dialysis, labile BP and the potential risk for intradialytic hypotension have raised concern regarding how best to offer renal replacement therapy. In fact, 18 of the 21 patients in the 2006 study were treated with peritoneal dialysis rather than HD to minimize intradialytic hypertension. Nonetheless, outcomes remain poor, and the course is often a catastrophic one. For the 13 patients who died after initiation of dialysis, the average time spent on dialysis was only 9 months (6). Thus, the clinician is often left without any acceptable renal replacement therapy to offer the FD patient with advanced CKD. The patient in case one underwent intermittent HD for less than 3 months before transplant. The patient in case two was placed on CVVHD for 1 month due to concern for BP-related intolerance of intermittent HD.

To our knowledge, there has been only one previously reported case of successful renal transplantation in a patient with FD, a 30-year-old woman with FD-related ESRD who underwent LRRT at Hadassah Medical Center in Israel (17). A variety of other surgical procedures have been performed in FD patients; the potential perioperative complications are numerous and often unique to this disorder. They include abnormal ventilatory responses to hypoxia; hypotension during anesthetic induction related to hypovolemia and/or bradycardia; supine hypertension; dysautonomic crises precipitated by the stress of surgery and/or postoperative visceral pain; and postoperative fever due to infection, atelectasis, and/or primary temperature dysregulation (18). Supportive measures such as preoperative admission for intravenous hydration and advances in anesthesia, combined with more clinical experience with the disease, have contributed to improved morbidity and mortality (19). In our cases, intraoperative issues related to BP control were manageable; this has been described in detail from the anesthetic perspective (20,21). Perioperative challenges included respiratory failure (case 1), supine hypertension (both cases), and postoperative fever (case 2). Nonetheless, since transplant, neither patient has experienced major complications. In fact, both describe decreased BP lability, symptomatic improvement, and overall improved functional status. Whether this relates to improved supportive care and close follow-up posttransplantation or other factors is unknown. In the Israeli case, severe respiratory complications necessitated month-long ICU-level care, but since transplant, as in our cases, the patient’s overall health and functional status have in fact improved (17).

All three transplants in patients with FD have in common the use of a living donor. Indeed, living-donor transplantation is preferable to deceased-donor, particularly in this population. Potential benefits include more opportunity for pretransplant management, as well as decreased wait times and better long-term graft survival, as these patients develop advanced CKD early and may not be candidates for a second transplant in the future.

There is clear potential for interventions such as renal transplantation to improve survival and quality of life in FD-related ESRD. In light of the young age of FD patients with CKD and the increased mortality on dialysis, transplantation may provide a better alternative. Early nephrology referral would likely be beneficial both in slowing the disease process through optimal BP control, and in allowing timely preparation for renal replacement therapy, preferably via transplant. After taking into consideration the patient’s functional status on an individual basis, it is likely that in most cases transplant should be offered to the patient, particularly if they are nearing or already undergoing dialysis. Although the overall impact on patient survival remains to be seen, the success of renal transplantation

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<tr>
<th>Table 1. Patient characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>Age at transplantation (years)</td>
<td>27</td>
<td>16</td>
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<tr>
<td>Time to ESRD (years)</td>
<td>&lt;3</td>
<td>&lt;2</td>
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<tr>
<td>Time on dialysis (months)</td>
<td>3 (intermittent HD)</td>
<td>1 (twice-weekly CVVHD)</td>
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<tr>
<td>Type of transplant (donor)</td>
<td>Living-related (mother)</td>
<td>Living-related (aunt)</td>
</tr>
<tr>
<td>Time since transplant (months)</td>
<td>20</td>
<td>24</td>
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represents a major breakthrough in the care of FD patients and offers hope to those with advanced CKD.

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Disclosures

None.

References