KI REPORTS
KIReports.org
NEPHROLOGY ROUNDS

# Kidney Transplant Outcomes in 2 Adults With Down Syndrome



Kammi J. Henriksen[1], Anthony Chang[1] and George P. Bayliss[2]

[1]Department of Pathology, The University of Chicago, Chicago, Illinois, USA; and [2]Department of Medicine, Division of Kidney Disease and Hypertension, Brown University, Providence, Rhode Island, USA

**Correspondence:** George Bayliss, Department of Medicine, Division of Kidney Disease and Hypertension, Alpert Medical School, Brown University, Transplant Clinic, APC 9, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02903, USA. E-mail: gbayliss@lifespan.org

*Kidney Int Rep* (2018) **3,** 979–984; https://doi.org/10.1016/j.ekir.2018.02.006



## INTRODUCTION

Down syndrome (DS), or trisomy 21, is the most common chromosomal abnormality among live births in the United States, occurring in 1 of every 700 infants born.[1] The life expectancy for children born with this chromosomal abnormality has steadily increased in the developed world from 12 years in the late 1940s to nearly 60 years with proper health care.[2] In the United States in 2007, the mean and median life expectancies for persons with DS were 47.3 years and 53.0 years, respectively, up from 12 years in 1960.[3] With increasing survival, the spectrum of diseases reported in patients with DS is expanding and now includes kidney diseases. Population-wide studies have shown that people with DS are at higher risk for hypothyroidism, dementia, some forms of cancer, and respiratory infections.[4] DS is also associated with a higher risk of stroke, largely embolic, but a lower risk of coronary events in male individuals.[5] There is not a great deal of data on diabetes mellitus in persons with DS.[6] A few reports indicate an increased risk of type 1 diabetes in individuals with DS,[7,8] but there are few data on type 2 diabetes. There does not appear to be an increased risk of renal disease in people with DS, nor does there appear to be an increased risk of end-stage renal disease (ESRD) requiring renal replacement therapy.[9] There are very few data on dialysis outcomes in people with DS and ESRD, and even fewer data surrounding renal transplantation. The few reports of kidney transplantation in DS concern pediatric patients[10,11]; as far as we are aware, there is no literature regarding renal transplantation in adults with DS. Here we present 2 adults with DS and ESRD who underwent deceased donor kidney transplantation. We discuss their posttransplant course and review the literature on possible complications related to trisomy 21 that may have affected the outcomes.

## CASE PRESENTATION

### Case 1

Patient 1 is a 47-year-old man with insulin-dependent type 2 diabetes, hypothyroidism, and obesity, initiated on hemodialysis in 2010. He underwent kidney transplantation in April 2014 from a 52-year-old woman who died of a stroke. Warm ischemic time was 25 minutes, and cold ischemic time was 12 hours. Pretransplant biopsy showed 7% glomerular sclerosis and 1% interstitial fibrosis. Final cross-match was negative, and immunosuppression induction was with basiliximab 20 mg i.v. on postoperative day (POD) 0 and 4. He was placed on a standard steroid taper and started on mycophenolic acid and tacrolimus. The kidney appeared well perfused on the operating table after re-anastomosis and was making 12 to 20 ml per hour of urine at first postoperative check that evening.

The next morning, however, the patient appeared volume overloaded in respiratory distress and had serum potassium of 8.2 mg/dl. He required emergent dialysis on POD 1 and then 3 more sessions before his urine output picked up. Transplant allograft ultrasound showed elevated resistive indices, suggesting acute ischemic injury without evidence of thrombosis. Tacrolimus level on POD 2, the first time checked, was 4.3 ng/ml and remained low until POD 6, when it rose to 10.1 ng/ml. It subsequently fluctuated from 6.1 to 11.4 ng/ml. He remained dialysis dependent on discharge and returned to his outpatient dialysis unit.

On POD 15 he underwent a transplant biopsy (Figure 1a and b), which showed features of acute rejection, including intimal arteritis with fibrinoid necrosis of arterial walls (Banff type III) and tubulointerstitial inflammation (Banff type IA). He also had glomerular and peritubular capillaritis suggestive of antibody-mediated rejection, despite negative C4d staining. Finally, there was evidence of acute

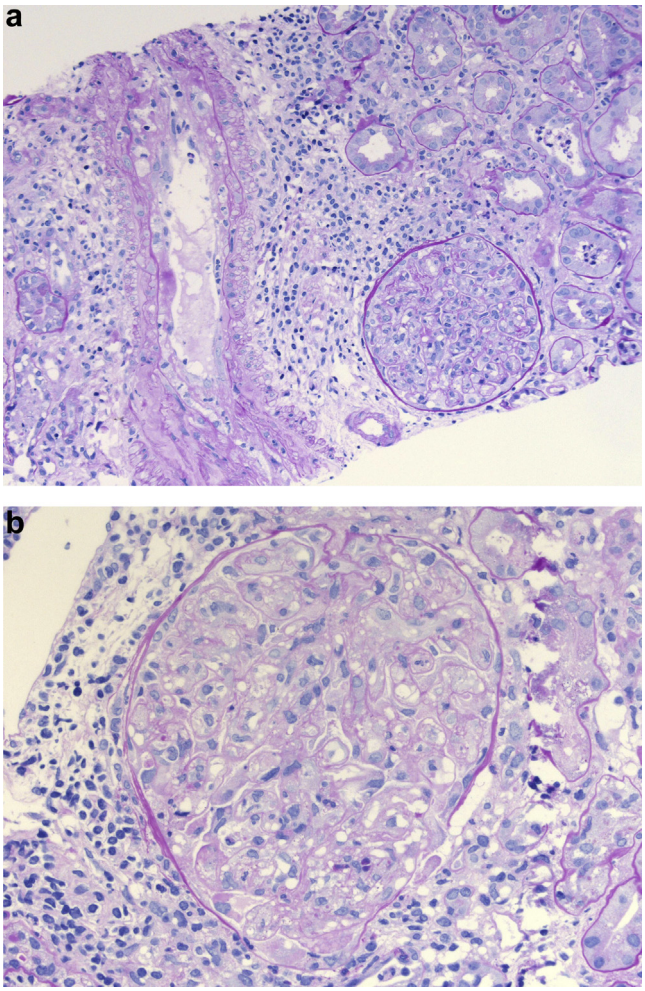


**Figure 1.** Patient 1 at posttransplant day 15. (a) Features of acute T-cell–mediated rejection, including intimal arteritis and interstitial inflammation with focal tubulitis (periodic acid–Schiff [PAS], original magnification ×200). (b) Transplant glomerulitis, consistent with acute antibody-mediated rejection (PAS, original magnification ×400). Not shown are biopsy findings of acute thrombotic microangiopathy, including glomerular capillaries occluded and distended by fibrin thrombi and an artery demonstrating mural fibrinoid necrosis and inflammation.

thrombotic microangiopathy involving the glomeruli and arterioles. He received 3 i.v. doses of methylprednisolone 500 mg, 3 doses of antithymocyte globulin 150 mg i.v., and underwent therapeutic apheresis. Testing for donor-specific antibodies was negative, and apheresis was stopped. Tacrolimus level at the time of the biopsy was 5.7 ng/dl. Given the possibility of thrombotic microangiopathy due to tacrolimus, calcineurin inhibition was switched to cyclosporine at approximately POD 25, with the tacrolimus level only 2.4 ng/ml at the time. Repeat allograft biopsy (POD 27, Figure 2) showed acute tubular injury with resolving interstitial inflammation, features of acute and chronic thrombotic microangiopathy, and mild interstitial fibrosis and tubular atrophy. A final biopsy at 2 months posttransplant (Figure 3) showed thrombotic

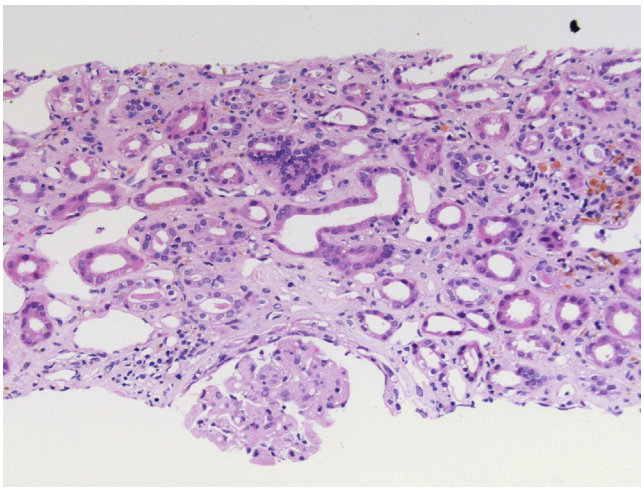

**Figure 2.** Patient 1 at posttransplant day 27. Acute tubular injury with attenuation of the proximal tubular epithelial cells and resolving interstitial inflammation (hematoxylin and eosin, original magnification ×200). Not shown are an artery with features of acute thrombotic microangiopathy, including mucoid intimal expansion and incorporation of fragmented red blood cells.

microangiopathy with chronic features, despite switching tacrolimus to cyclosporine. One month after transplantation, he had cyclosporine troughs of 291 to 452 ng/ml.

Beyond primary allograft dysfunction, the patient's posttransplant course was complicated by thrombocytopenia related to apheresis. He was admitted to the hospital several times after transplantation with pneumonia. His cyclosporine level 2 months after transplantation was 441 ng/ml, but the immunosuppression was thought to be a contributing factor to the pneumonia and was lowered and eventually weaned to prednisone alone because the kidney never functioned. The patient remains on dialysis, where he has done well, continuing to participate in Special Olympics. He is inactive on the waiting list, but eligible to regain his waiting time. His mother is reluctant to let him go through transplantation again. More recently he was thought to be having seizures while at dialysis and started on an antiepileptic medication, but has otherwise been stable.

## Case 2

Patient 2, 38 years old when he died in 2014, was diagnosed with type 1 diabetes in 1980 and subsequently developed ESRD secondary to diabetic nephropathy. He was initiated on hemodialysis in 2000 and was switched to peritoneal dialysis 6 months later. After discussion with the family, the transplant team opted for kidney transplantation followed by possible pancreas transplantation, rather than risk a combined kidney-pancreas transplant, to see first how he tolerated surgery and immunosuppression with the kidney

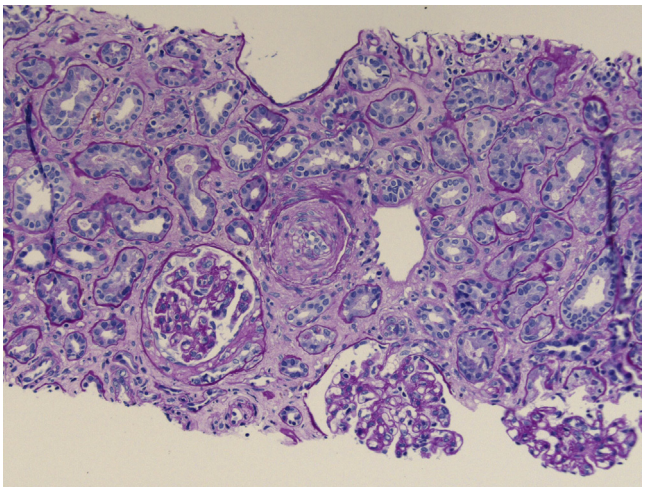

**Figure 3.** Patient 1 at 2 months posttransplantation. Features of chronic thrombotic microangiopathy, including an artery with concentric "onion-skin" fibrosis, ischemic glomerular changes, and progressive tubulointerstitial scarring (periodic acid–Schiff [PAS], original magnification ×200). Not shown are glomerular features of chronic thrombotic microangiopathy, including duplication of the glomerular basement membranes and mesangiolysis.

alone and assess later whether diabetes continued to limit his daily life. Patient 2 underwent deceased donor kidney transplantation in 2006 from a 5-year-old donor who underwent prolonged resuscitation efforts. The postoperative course was notable for delayed graft function, for which the patient received dialysis and thymoglobulin infusion. He was discharged with stable renal function after 2 weeks, at a tacrolimus trough of 4.5 ng/ml. Drug troughs remained therapeutic after 6 weeks at 8.1 ng/ml and after 7 months at 6.9 ng/ml. He enjoyed excellent renal function for 7.5 years on standard immunosuppression.

Patient 2 continued to have episodes of both hyperglycemia and hypoglycemia, which required close monitoring and insulin administration. He therefore underwent deceased donor pancreas transplantation in 2009. The operation and immediate postoperative course were uneventful, but on POD 3 his hemoglobin started to decrease. He required transfusion on POD 9 and also developed abdominal distention, intermediate-grade fever, and persistent leukocytosis. Computed tomography angiogram demonstrated thrombosis of the pancreatic transplanted vein and superior mesenteric vein. On POD 10 he underwent allograft pancreatectomy; operative findings were significant for a thrombosed pancreas with thrombus in the portal vein and splenic artery of the transplanted pancreas. He recovered from the second operation with a relatively uneventful postoperative course.

A renal allograft biopsy at the time of pancreas transplantation showed focal segmental glomerular sclerosis and mild scarring but no evidence of rejection (Figure 4). Kidney allograft function was stable with serum creatinine 1.1 mg/dl, but sub-nephrotic proteinuria. In 2014, the patient was admitted from an outside hospital with small bowel obstruction and sepsis, and subsequently died.

## DISCUSSION

As far as we are aware, this small case series is the first to examine kidney transplant outcomes in adult patients with DS. What is known about renal disease and transplant outcomes in patients with DS comes largely from the pediatric literature.[10,11] More broadly, research has focused on risk factors for cardiovascular disease and infection in patients with DS, as well as seizures and dementia related to aging.

It is unclear from the literature whether persons with DS are at an increased risk for renal disease and/or ESRD as a direct result of trisomy 21, nor does it seem from autopsy studies that patients with DS are more prone to one renal disease over another. Ariel and colleagues[12] examined 97 autopsy cases of patients with DS (ages 1 day to 25 years), and found glomerular microcysts in 23 cases and renal hypoplasia (defined as kidney weight less than two-thirds expected) in 18 cases. There were no controls, leading other authors to question the generalizability of the findings. Lo and colleagues[13] performed a follow-up autopsy study comparing 43 autopsy cases in patients with DS with findings in 57 age-matched controls. Glomerular diseases reported with similar frequencies in DS and control groups included acute glomerulonephritis, minimal change disease, and membranous

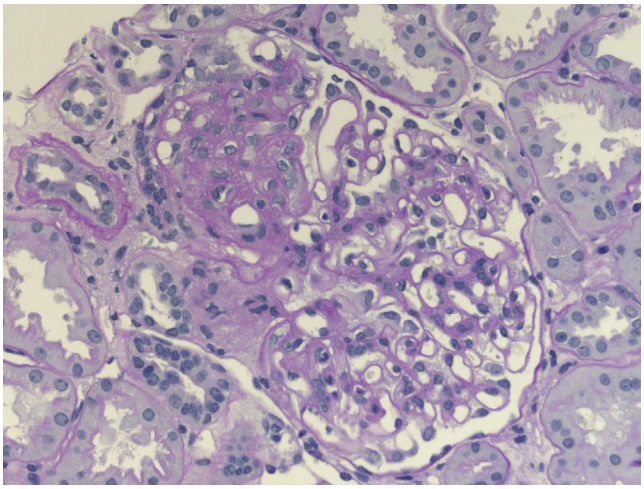

**Figure 4.** Patient 2 at 3 years posttransplantation. Focal segmental glomerular sclerosis with segmental matrix accumulation and solidification in a perihilar distribution (periodic acid–Schiff [PAS], original magnification ×400). Not shown are normal-appearing glomerulus, tubules, and an interstitium without evidence of rejection (PAS, original magnification ×200).

nephropathy. Only glomerular microcysts were found more frequently in the DS cases than in the controls. The findings were nonspecific, and the authors could not say whether they had any significance in DS.[13]

More recently, Said *et al*.[14] reviewed kidney biopsies from 17 persons with DS for causes including elevated creatinine, hematuria, and proteinuria. They found a wide spectrum of glomerular lesions in this patient group (ages 6–45 years), including IgA nephropathy (5 cases), focal segmental glomerular sclerosis (4), membranoproliferative glomerulonephritis (2), post-infectious glomerulonephritis (2), pauci-immune glomerulonephritis (2), membranous nephropathy (1), and lupus nephritis (1). These researchers were able to follow 16 of the 17 subjects for a mean of 47 months. Six of the 16 subjects progressed to ESRD, and 4 of these (ages 28 to 44) died on dialysis. One patient remained alive on dialysis, and 1 patient underwent renal transplantation at age 13 and enjoyed normal allograft function 9 years later. There has been 1 additional small series documenting membranoproliferative glomerulonephritis in 4 patients with DS and progressive renal disease, with no apparent underlying etiology.[15]

The literature on renal replacement therapy in persons with DS focuses on dialysis, with case reports indicating that either hemodialysis[16] or peritoneal dialysis can be done without difficulty.[17] Patient 1 has been successfully dialyzed in our outpatient unit since 2010 through an arteriovenous fistula, enjoying good clearance but only fair compliance with diet and fluid restrictions.

The limited reports of transplantation in patients with DS are largely in the pediatric literature. An early report in 1995 described a successful living related kidney transplant to a 14-year-old girl from her mother in Philadelphia.[10] The report prompted a response from a German pediatrician who said that over the course of 20 years his group had not seen a patient with DS who required renal replacement therapy. The pediatrician called on others to publish their reports. But he concluded by saying "I see no reason why a patient with Down syndrome and end stage renal failure should not be offered RRT [renal replacement therapy] if the patient and the parents are prepared to cooperate."[18]

Subsequently, researchers in the United States published a report on 14 children with DS who received renal transplants between January 1987 and November 1995.[11] Eight patients received kidneys from deceased donors; 6 received kidneys from living donors. One had previously received a kidney. Ten of the patients were on dialysis at the time of transplantation, and 4 underwent preemptive transplantation. All were maintained on prednisone, cyclosporine, and azathioprine, standard immunosuppression at the time. As of early 1998, the authors wrote that 9 grafts were still functioning and 2 failed due to acute rejection. Three patients died with functioning allografts. They concluded that "renal transplantation is a perfectly reasonable option for renal replacement therapy in patients with Down syndrome."

Immunologically there does not appear to be any contraindication to transplantation in patients with DS, although persons with DS may be predisposed to autoimmune disorders, including celiac disease, and have higher levels of rheumatoid factor.[19] Other investigators have reported a reduced inhibitory capacity of regulatory T cells in persons with DS that may explain the increased risk of autoimmune diseases.[20] There appears to be an increased prevalence of type 1 diabetes in persons with DS.[7,8] The authors who described the series of pediatric transplants suggested that the immune dysregulation of DS may mean that patients require less immunosuppression, and that more immunosuppression increases the risk of infection. They recommended against antibody-depleting induction therapy.[11] Patient 1 in our report was induced with basiliximab and started on standard immunosuppression. Nevertheless, he had evidence of both rejection and increased pulmonary infections in the first postoperative year. He remains on a low dose of prednisone.

A larger concern in transplanting adults with DS surrounds life expectancy and comorbid conditions. Researchers in Scandinavia reviewed the records of 4872 individuals with a hospital discharge of DS by linking to national cancer and vital statistics registries in Denmark and Sweden. They were found to be at increased risk of acute lymphocytic and non-lymphocytic leukemia. Mortality was also increased due to dementia of the Alzheimer's type, epilepsy, ischemic heart disease, cerebrovascular disease, infectious diseases, and congenital anomalies.[21] Incidence of obesity and sleep apnea may be greater in persons with DS, but rates of type 2 diabetes seem to be less.[6] Advances in the genetics of DS mean that the way in which the genes on chromosome 21 are expressed in the phenotype of DS is better understood and opens the possibility of regulating the function of those genes.[22]

Finally, the literature has also considered ethical questions about transplantation in patients with DS, and more generally in patients with intellectual disabilities in the equitable distribution of scarce societal resources. Patient 1's mother was initially reluctant for him to go through with transplantation because he seemed to be doing so well on dialysis. Although they hoped for a living donor, a family friend considering whether to undergo evaluation did not progress

through the workup. A major challenge for the patient while he waited for the transplant was weight gain, as he put on 30 pounds in one 6-month period. He has never had issues with attending dialysis, but has found compliance with fluid restrictions and diet difficult. After his experience, his mother is reluctant to allow him to be reactivated on the list, but gave her consent for his case to be discussed in the hope it would help other families facing similar decisions.

Patient 2 underwent careful review by the transplant team over several years. He lived with his aging mother, who suffered from Alzheimer dementia and was wheelchair-bound, and spent much of his time caring for her. The swings in his blood sugars prevented him from being placed in a group home or receiving vocational training. His brothers and sisters lived in the area and helped facilitate his care. During his years on dialysis, he had difficulty with vascular access and had to be switched to peritoneal dialysis, which he did quite well. The transplant team in its review thought that a kidney and possible pancreas transplant would dramatically change his quality of life, allow him to pursue vocational training, and aid in future placement in a facility that could better care for him. Posttransplant follow-up was intermittent.

In summary, we report the outcomes of 2 adults with DS who underwent renal transplantation for ESRD secondary to diabetes. In 1 case, the patient experienced primary allograft dysfunction and remains on hemodialysis, where he continues to do well. He is eligible to regain all of his waiting time, but remains temporarily unavailable because his mother is reluctant to reactivate him and subject him to another surgery. In the other case, the patient enjoyed 7 years of a functioning allograft but died from an unrelated condition (sepsis). As far as we are aware, these are the only cases in the literature documenting the experience of adults with DS undergoing renal transplantation. Although the number of cases is small, we think they illustrate that adults with DS must be evaluated on a case-by-case basis to assess their suitability for kidney transplant, just as with children. Both of our patients had family support, were compliant with dialysis, and also appeared very functional. We suggest that these would be important criteria to consider in the selection process of adults with DS for kidney transplantation.

Addendum: The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. The results presented in this paper have not been published previously in whole or part, except in abstract format.

## DISCLOSURE

All the authors declared no competing interests.

## REFERENCES


1. Centers for Disease Control and Prevention. Birth defects: Down Syndrome: data and statistics. Available at: http://www.cdc.gov/ncbddd/birthdefects/downsyndrome. Accessed December 20, 2017.
2. Bittles AH, Gleason EJ. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Dev Med Child Neurol*. 2004;46:282–286.
3. Presson AP, Partyka BS, Jensen KM, et al. Current estimate of Down syndrome population prevalence in the United States. *J Pediatr*. 2013;163:1163–1168.
4. Uppal H, Chandran S, Potluri R. Risk factors for mortality in Down syndrome. *J Intellect Disabil Res*. 2015;59:873–881.
5. Sobey CG, Judkins CP, Sundararajan V, et al. Risk of major cardiovascular events in people with Down syndrome. *PLoS One*. 2015;10:e0137093.
6. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. *Int Rev Res Ment Retard*. 2010;39:107–126.
7. Anwar AJ, Walker JD, Frier BM. Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. *Diabet Med*. 1998;15:160–163.
8. Bergholdt R, Eising S, Nerup J, et al. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: a nationwide population-based study. *Diabetologia*. 2006;49:1179–1182.
9. Malaga S, Pardo R, Malaga I, et al. Renal involvement in Down Syndrome. *Pediatr Nephrol*. 2005;20:614–617.
10. Edvardsson VO, Kaiser BA, Polinsky MS, Baluarte HJ. Successful living-related renal transplantation in an adolescent with Down syndrome. *Pediatr Nephrol*. 1995;9:398–399.
11. Baqi N, Tejani A, Sullivan EK. Renal transplantation in Down syndrome: a report of the North American Renal Transplant Cooperative Study. *Pediatr Transplant*. 1998;2:211–215.
12. Ariel I, Wells TR, Landing BH, Singer DB. The urinary system in Down syndrome: a study of 124 autopsy cases. *Pediatr Pathol*. 1991;11:879–888.
13. Lo A, Brown HG, Fivush BA, et al. Renal disease in Down syndrome: autopsy study with emphasis on glomerular lesions. *Am J Kidney Dis*. 1998;31:329–335.
14. Said SM, Cornell LD, Sethi S, et al. Acquired glomerular lesions in patients with Down syndrome. *Hum Pathol*. 2012;43:81–88.
15. Gupta SK, Venkataseshan VS, Churg J. Mesangiocapillary glomerulonephritis in Down's syndrome. *Am J Nephrol*. 1991;11:112–117.
16. Kosmadakis G, Smirloglou D, Gobou A, et al. Hemodialysis treatment on an adult patient with Down syndrome associated with ectopic right kidney and chronic obstructive nephropathy and secondary amyloidosis. *Saudi J Kidney Dis Transplant*. 2013;24:322–325.
17. Yavascan O, Kara OD, Anil M, et al. Chronic peritoneal dialysis treatment in a pediatric patient with Down syndrome. *Perit Dial Int*. 2008;28:558–559.

18. Ehrich JHH. What is known about renal replacement therapy in a child with Down's syndrome? *Pediatr Nephrol*. 1995;3:400.

19. Ramos da Rosa Utiyama S, Nisihara RM, Nass FR, et al. Autoantibodies in patients with Down syndrome: early senescence of the immune system or precocious markers for immunologic diseases? *J Paediatr Child Health*. 2008;44: 182–186.

20. Pellegrini FP, Marioni M, Frangione V, et al. Down syndrome, autoimmunity and T regulatory cells. *Clin Exp Immunol*. 2012;169:238–243.

21. Hill DA, Gridley G, Cnattingius S, et al. Mortality and cancer incidence among individuals with Down syndrome. *Arch Intern Med*. 2003;163:705–711.

22. Einfeld SL, Brown R. Down syndrome—new prospects for an ancient disorder. *JAMA*. 2010;303:2525–2526.