Renal transplantation and rare diseases

Vukić, Tea

Master's thesis / Diplomski rad

2018

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:280989

Rights / Prava: In copyright

Download date / Datum preuzimanja: 2020-10-08

Repository / Repozitorij:

Dr Med - University of Zagreb School of Medicine Repository
Tea Vukić

Renal transplantation and rare diseases

GRADUATE THESIS

Zagreb, 2018.
This graduation paper was completed at the Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation at University Hospital Centre Zagreb, under the guidance of Doc.dr.sc. Nikolina Bašić Jukić and it was submitted for evaluation in the academic year of 2017/2018.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>aHUS</td>
<td>Atypical haemolytic-uremic syndrome</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>DWM</td>
<td>Dandy-Walker malformation</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>FD</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HD</td>
<td>Haemodialysis</td>
</tr>
<tr>
<td>HRNBF</td>
<td>Hrvatski registar za nadomještanj bubrežne funkcije</td>
</tr>
<tr>
<td></td>
<td>Croatian registry of renal replacement therapy</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney disease: Improving global outcomes</td>
</tr>
<tr>
<td>PD</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>PH</td>
<td>Primary hyperoxaluria</td>
</tr>
<tr>
<td>pmp</td>
<td>per million population</td>
</tr>
<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>TS</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberous sclerosis complex</td>
</tr>
</tbody>
</table>
## Contents

Summary...................................................................................................................................... I
Sažetak....................................................................................................................................... II

1. Preface .................................................................................................................................. 1

1.1. Chronic kidney disease ................................................................................................. 1

1.2. Renal replacement therapy ............................................................................................. 4

1.2.1. Haemodialysis ........................................................................................................ 5

1.2.2. Peritoneal dialysis .................................................................................................. 6

1.2.3. Hemofiltration ......................................................................................................... 7

1.2.4. Renal transplantation ............................................................................................. 8

2. Hypothesis ......................................................................................................................... 10

3. Objectives ......................................................................................................................... 10

4. Patients and Methods ....................................................................................................... 11

5. Results ............................................................................................................................... 12

5.1. Primary hyperoxaluria type I ....................................................................................... 12

5.1.1. Case presentation of a patient with PH1 ............................................................... 14

5.2. Fabry disease.................................................................................................................. 16

5.2.1. Case presentation of a patient with FD ................................................................ 18

5.3. Atypical haemolytic-uremic syndrome ......................................................................... 20

5.3.1. Case presentation of a patient with aHUS ............................................................ 22

5.4. Tuberous sclerosis complex .......................................................................................... 24

5.4.1. Case presentation of a patient with TSC (I) .......................................................... 26

5.4.2. Case presentation of a patient with TSC (II) ......................................................... 28

5.5. Turner syndrome .......................................................................................................... 29

5.5.1. Case presentation of a patient with TS ................................................................ 31

5.6. Dandy-Walker syndrome ............................................................................................. 33

5.6.1. Case presentation of a patient with DWM ............................................................ 34

6. Discussion ......................................................................................................................... 35

7. Conclusion ........................................................................................................................ 40

8. Acknowledgements .......................................................................................................... 41

9. References ........................................................................................................................ 42

10. Biography ......................................................................................................................... 48
Summary

Renal transplantation and rare diseases

Tea Vukić

End-stage renal failure requires replacement of kidney function by different methods, the best of them being renal transplantation owing to significant survival advantage and better quality of life compared to the other renal replacement therapy methods. This is a case-series study that was done at the Department of Nephrology, Arterial Hypertension, Dialysis and Renal Transplantation at University Hospital Centre Zagreb where we tried to demonstrate correlation between renal transplantation and influence of rare diseases on post-transplantation period. In this study, seven patients with rare diseases were included, all of them being transplanted and treated for primary disease. Rare diseases and their effects on kidney function that are discussed in this study are Primary hyperoxaluria type I, Fabry disease, Atypical haemolytic-uremic syndrome, Tuberous Sclerosis Complex, Turner syndrome and Dandy-Walker syndrome. Four percent of people on renal replacement therapy in Croatia have idiopathic chronic kidney disease, and high proportion is administered under the diagnosis of chronic glomerulonephritis, diabetic nephropathy and nephroangiosclerosis. It is probable that some of these patients have rare diseases that are not diagnosed and are responsible for graft failure in post-transplantation period due to untreated primary disease. Screening for rare diseases in pre-transplantation period would improve overall outcome of transplantation in these patients. This study emphasizes the importance of early diagnosis and treatment of rare disease and their effect on post-transplantation period.

Key words: renal transplantation, rare disease, renal replacement therapy, post-transplantation period
Sažetak

Transplantacija bubrega i rijetke bolesti

Tea Vukić

Završni stadij kronične bubrežne bolesti zahtijeva liječenje nadomještanjem bubrežne funkcije različitim metodama, od kojih je najbolja transplantacija bubrega zbog značajno više stope preživljavanja i kvalitete života u usporedbi s drugim metodama nadomještanja bubrežne funkcije. Ovo istraživanje kliničkih slučajeva je provedeno na Zavodu za nefrologiju, arterijsku hipertenziju, dijalizu i transplantaciju bubrega Kliničkog bolničkog centra Zagreb u kojem pokazujemo povezanost između transplantacije bubrega i utjecaja rijetkih bolesti na period poslije transplantacije. U ovo istraživanje je uključeno sedam bolesnika s rijetkim bolestima nakon transplantacije. Rijetke bolesti i njihov utjecaj na bubreg koje se ovdje spominju su primarna hiperoksalurija tip I, Fabryjeva bolest, atipični hemolitičko uremijski sindrom, tuberozna skleroza, Turnerov sindrom i Dandy-Walkerov sindrom. Četiri posto bolesnika liječenih nadomjesanjem bubrežne funkcije u Hrvatskoj ima idiopatsku kroničnu bolest bubrega, a visoki udio se vodi pod dijagnozom kroničnog glomerulonefritisa bez biopsije, dijabetičke nefropatije i nefroangioskleroze. Vjerojatno je da neki od ovih bolesnika imaju rijetke bolesti koje nisu diagnosticirane, a odgovorne su za bubrežno zatajenje u periodu nakon transplantacije. Testovi probira na rijetke bolesti u predtransplantacijskom periodu bi poboljšali cjelokupni ishod transplantacije kod ovih bolesnika. Ovo istraživanje naglašava važnost ranog otkrića rijetke bolesti, liječenja i utjecaja te bolesti na posttransplantacijski period.

**Ključne riječi:** transplantacija bubrega, rijetke bolesti, nadomjesno bubrežno liječenje, posttransplantacijski period
1. Preface

1.1. Chronic kidney disease

Chronic kidney disease (CKD) refers to longstanding progressive impairment in renal function. According to KDIGO (Kidney disease; Improving Global Outcome) Clinical Practice Guideline, it is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. CKD is classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (1).

CKD is classified into five stages according to the values of GFR where the first stage is GFR≥90mL/min/1.73m² with other evidences of kidney damage such as proteinuria or haematuria. A second stage has a slight decrease in GFR (60-89mL/min/1.73m²) with other evidences of kidney damage. The third stage is divided into stage A and B, where stage A is marked by GFR of 45-59 mL/min/1.73m², and stage B by GFR 30-44 mL/min/1.73m² with or without other kidney disease traits. Most of elderly aged ≥65 are in CKD stage 3, but this may not progress much or impinge on their health status. Severe decrease in GFR below 29 mL/min/1.73m² is considered as stage 4 CKD. Symptoms usually occur once this stage is reached and are associated with accumulation of numerous metabolites. End-stage renal disease (ESRD) is established when GFR drops below 15mL/min/1.73m² and there is a need for renal replacement therapy (RRT) (2).

CKD is classified into three stages according to albumin excretion rate (AER) and albumin to creatinine ratio (ACR). The first stage is characterized by AER <30 mg/24h and ACR <3 mg/mmol. Moderately increased albuminuria is considered when AER is 30-300 mg/24h and ACR is 3-30 mg/mmol. The third stage has severely increased AER of over 300 mg/24h and ACR of over 30 mg/mmol (1).
Aetiology of chronic kidney disease varies in different geographical areas, developmental status of the country and age (3). Most common causes of CKD worldwide are hypertension, diabetes mellitus and atherosclerosis (4). According to HRNBF (Croatian registry of renal replacement therapy) from 2014, most common aetiology requiring renal replacement therapy in Croatia is diabetic nephropathy (33% of all people with RRT), followed by vascular kidney disease (24%, with hypertensive nephroangiosclerosis being the most common), glomerulonephritis (11%) and pyelonephritis (10%). Other causes of ESRF and need for RRT are polycystic kidney disease (6%), interstitial nephritis (1%), endemic nephropathy (1%) and other. In Croatia, 4% of people undergoing RRT have idiopathic CKD (5). Some of these patients may have rare diseases that are underdiagnosed and that can lead to failure of renal transplantation due to the relapse of the primary disease.

Reduced renal excretion plays a decisive role for the course of the disease. The loss of nephrons increases the filtration and size in the remaining glomeruli. These mechanisms are compensatory and in a long-term lead to glomerular and interstitial sclerosis (6, 7). The GFR drop leads to inversely proportional rise in the plasma level of creatinine. After most of the nephrons have been destroyed, uric acid starts to accumulate and electrolyte, fluid and acid base balance disturbances develop (8). It has been implicated in a number of metabolic, endocrine and excretory kidney functions (3). Symptoms are common when the serum urea concentration exceeds 40 mmol/L, but many patients may develop uremic symptoms at lower levels (2). Symptoms associated with hyperurecemia are malaise, loss of energy, loss of appetite, insomnia, nausea, vomiting and diarrhea. Increased urea levels lead to hyperlipidemia. It can be decreased by dietary protein restriction. Degradation of urea yields ammonia, which contributes to derangements of gastrointestinal function (8). Very often, patients come to the office in later stages of a disease and that affects the outcome of the treatment of CKD.

Life expectancy in patients with CKD remains severely reduced compared with the normal population owing to a greatly increased incidence of cardiovascular disease,
particularly myocardial infarction, cardiac failure, sudden cardiac death and stroke (2). Diabetes Mellitus (DM) is the commonest cause of CKD and DM itself is a risk for cardiovascular disease. Dyslipidemia is universal in uremic patients and hypertension is a frequent complication of CKD. Smoking is common and places patients at even greater risk (9). Another risk factor is ventricular hypertrophy (2).

Many patients with CKD have anaemia caused by the impaired renal production of erythropoietin. That leads to activation of the sympathetic nerve tone and hypertension (10). The hypertension contributes to further kidney injury. Other causes of anaemia are decreased lifespan of erythrocytes due to the retention of toxins in bone marrow and increased red blood cell destruction, and increased blood loss during haemodialysis (2).

Renal osteodystrophy is present in many patients with moderate CKD and in almost all patients with ESKD. Phosphate retention owing to reduced renal excretion occurs in the early stages of CKD. Compensatory effects of released fibroblast growth factor 23 (FGF 23), the strongest independent predictor of mortality in patients with CKD, are overwhelmed after some time and secondary hyperparathyroidism develops. PTH promotes reabsorption of calcium from bone, increases proximal renal tubular reabsorption, increases osteoclastic activity, cyst formation and bone marrow fibrosis. This bone mineral disorder embraces the various forms of bone disease that may develop alone or in combination in CKD – hyperparathyroid bone disease, osetomalacia, osteoporosis and adynamic bone disease (2).

Before establishing irreversible kidney damage, we must exclude conditions such as urinary tract obstruction and immunosuppressive therapy for certain vasculitides that damages the kidney and can be reversed. In irreversible CKD further deterioration can be slowed by adequate treatment (4).
1.2. Renal replacement therapy

The aim of RRT is to mimic the excretory functions of the normal kidney which include excretion of nitrogenous compounds, maintenance of normal electrolyte levels and extracellular fluid volume. The goal is to maintain well-being of patients with ESRD. Optimal time to start RRT is when GFR reaches 15mL/min. Replacement of kidney function can be done in several different ways, such as haemodialysis, peritoneal dialysis, haemodialfiltration, haemofiltration or kidney transplantation. The appearance of symptoms such as persistent nausea, vomiting, mental deterioration or coma constitutes a prime indication for dialysis (2). Another important indication for starting the dialysis is hyperkalemia refractory to infusions of glucose, insulin and calcium. Severe metabolic acidosis, fluid retention and electrolyte imbalance are other indications (1). Hemodialysis is most often used method of RRT. Hemofiltration is reserved for patients that are in hemodynamic instability (5).

According to Croatian register from 2014, prevalence of RRT in Croatia at the end of that year was 957/per million population (pmp). That is 4102 people, of which 2051 (50%) were treated with haemodialysis, 1934 (48,2%) received a transplant and 117 (2,8%) were treated with peritoneal dialysis. 62.58% of people on RRT were males and 37,64% were females. A decrease of 4.3% of patients on RRT was recorded in 2014. Since year 2007, the number of people on haemodialysis drops constantly. Number of people on peritoneal dialysis has been dropping since 2009. Number of transplanted patients in 2014 has increased for 5.2% compared to the 2013. In the span from 19 to 94 years of age; most of the patients were over 60. Median age of both men and women on RRT was 67 (5).

Average length of RRT in Croatia is 3 years. 49 people are treated for 25 years and the longest therapy with RRT was 30 years. Mortality rate in people treated with RRT is 11%. Compared to the other European countries this is considered a good result (5).
1.2.1. Haemodialysis

Haemodialysis (HD) is a process in which patient’s blood is pumped through a semipermeable membrane (the dialyser) where it comes in close contact with dialysate, flowing countercurrent to the blood. The plasma biochemistry changes towards that of the dialysate owing to diffusion of molecules down their concentration gradient. The efficiency of dialysis depends on blood and dialysate flow and the surface area of the dialysis membrane (3). The most reliable long-term way of achieving adequate blood flow is surgical construction of an arteriovenous fistula (11). This is done by using the radial or brachial artery and cephalic vein and results in distension of the vein and thickening so that large-bore needles may be inserted. In patients with poor quality veins or arterial disease, polytetrafluoroethylene (PTFE) grafts are used. Patients are weighed at the start of each dialysis session and transmembrane pressure adjusted to achieve fluid removal equal to the amount by which they exceed their dry weight. The dialysate buffer is usually acetate or bicarbonate and we must carefully monitor sodium and calcium concentrations (2). All patients are anticoagulated during treatment as contact with foreign substances activates the clotting mechanism. Patients usually receive 4-5 hours treatment three times a week in the hospital (7).

Major complication during dialysis is hypotension due to an excessive removal of extracellular fluid and inadequate refilling of the blood compartment from the interstitial compartment during fluid removal. AV grafts have a very high incidence of thrombosis. Another common complication is infection and can easily be acquired through needles (2). Hypertension is a common finding in patients with long-term haemodialysis (12).
1.2.2. Peritoneal dialysis

Peritoneal dialysis (PD) utilizes the peritoneal membrane as semipermeable membrane, avoiding the need for extracorporeal circulation of blood and can be done at home after proper education of a patient (4). A soft catheter is inserted into the peritoneal cavity with a tip in the pelvis and an exit through the peritoneal cavity in the midline and lying in a skin tunnel with an exit site in the lateral abdominal wall. Dialysate is run into the peritoneal cavity under the influence of gravity and urea, creatinine, phosphate and other uremic toxins pass into it down their concentration gradient (2). Water is attracted into the peritoneal cavity by osmosis and this is determined by the glucose content of the dialysate (3).

There are few forms of PD such as Continuous ambulatory peritoneal dialysis (CAPD), Nightly intermittent peritoneal dialysis (NIPD) and Tidal dialysis. CAPD technique is most often used. It is based on a dialysate that is present continuously within peritoneal cavity, except when it is being exchanged. Dialysate exchanges are performed three to five times a day by connecting 1.5-3 L bags of dialysate to the catheter. Each exchange takes 20-40 minutes (2, 3). NIPD uses automated device to perform exchanges each night while the patient is asleep. In tidal dialysis, a residual volume is left within the peritoneal cavity with continuous cycling of smaller volumes in and out. These are simpler techniques compared to haemodialysis (2). Choice of peritoneal dialysis over haemodialysis depends on medical, social and psychological factors (4).

Most serious complication of PD is bacterial peritonitis. Clinical presentations include abdominal pain, fever, nausea and vomiting together with cloudy peritoneal effluent (2). Empiric antibiotic treatment that covers both gram negative and gram positive organisms is necessary and mostly is delivered by intraperitoneal route (13).
1.2.3. Hemofiltration

During hemofiltration, a patient's blood is passed through the machine to a semipermeable membrane where waste products are removed by convection. Hemofiltration is used for both acute and chronic kidney disease, but mainly for those patients that are not hemodinamically stable. It involves removal of plasma water by flow across a high-flux semipermeable membrane and replacing it with a solution of desired biochemical composition. Hemofiltration is most commonly used in an intensive care unit setting, where it is either given as 8-hour to 12-hour treatment, so called SLEF (slow extended hemofiltration) three times a week for maintenance purpose or as continuous venovenous hemofiltration (CVVH) in acute kidney injury. It is much more expensive than haemodialysis owing to the special filters with larger pores and solutions that are needed for this process. Lactate is used as a buffer because rapid infusion is needed, whereas a rapid infusion of acetate or bicarbonate could lead to vasodilation or precipitation of calcium carbonate, respectively (2).

Hemofiltration can be used in combination with dialysis as haemodiafiltration to increase middle molecule clearance, such as beta 2 microglobulins and prevent long-term dialysis complications such as dialysis related amyloidosis, especially in young, highly sensitized, non-transplantable patients (2, 14).
1.2.4. Renal transplantation

This form of RRT has a significant survival advantage compared to other forms of RRTs. It allows freedom from dietary and fluid restriction, correct anaemia, infertility and other complications of chronic kidney disease. The supply of donor organs greatly exceeds demand and therefore this therapy must be used optimally. The technique involves the anastomosis of an explanted human kidney onto the iliac vessels of the recipient and placement of donor ureter into the recipient’s bladder. Factors affecting success are ABO blood group compatibility between donor and recipient, matching for HLA antigen types, type of a primary kidney disease in the recipient and type of immunosuppressive treatment (15).

Croatia is one of the leading countries with regard to the number of donor kidneys and number of kidney transplantations. In 2016 there were 45.2 kidneys transplanted per million population (5). Renal transplantation is the only method of RRT that constantly rises. This is significant and means that the number of successful transplantations increases as well. Regardless of decrease in treatment of CKD by haemodialysis and peritoneal dialysis, there is an increase in overall RRT due to increase in transplantation (5, 15).

Immunosuppressive drugs are needed in all cases of transplanted kidney except in a genetically identical donor and recipient. Most regimens involve cyclosporine or tacrolimus combined with azathioprine or mycophenolate with or without prednisolone. Virology status (CMV, Hepatitis B and C, HIV, EBV, Varicella-zoster) of the recipient and donor should be assessed before the procedure because of potential development of severe disease when in immunocompromised state. Urine output and cardiovascular disease should be assessed as well. Absolute contraindications for this type of RRT are severe heart disease, active infection, malignant disease, other comorbidities with life expectancy less than two years and noncompliance (2, 15).
1.2.4.1 Deceased donors

This is the most common source of donor kidneys in Croatia according to 2017 Newsletter Transplant, with 96.46% (43.6 pmp) of all transplanted kidneys coming from a deceased donor (16). Deceased donation is obtained most often from brainstem dead donors with supported circulation and ventilation or less often from non-heart beating donors in which grafts are retrieved from patients without active circulation, hence rapid intervention is needed to prevent ischemia. Expanded criteria donors (ECD) are increasingly used. ECD include elderly donors (age over 60) and those between ages of 55 and 59 years, but with comorbidity such as hypertension, diabetes, AKI and intracranial haemorrhage as a cause of death (2).

1.2.4.2 Living donors

Kidneys from living donors generally provide superior results to those obtained from deceased donors (17, 18). Living donation is obtained from either living related donor that offers the advantage in HLA haplotype matching and optimally timed surgical procedure or living unrelated donor who satisfies the complex rules of transplant regulations. Potential living donors are subjected to an intensive preoperative evaluation, including clinical examination and renal function measurement, tests for carriage of HIV, hepatitis B, C, cytomegalovirus and detailed examination of renal anatomy, to be sure that transplantation will be technically feasible (2). In Croatia 3.76% (1,7 pmp) of donor kidneys in 2017 were from living donors (16).

In the best centres survival rate of a graft is 80% for 5-10 years and 50% for 10-30 years. However, half-life of renal allografts is still 13-16 years (4).
2. Hypothesis

Underdiagnosed rare diseases affecting the kidney have a huge impact on the post-transplantation period.

3. Objectives

The goal of this study is to determine occurrence of rare diseases in a population of patients with transplanted kidney and the outcome of transplantation in this group of patients.

With this study, we want to increase awareness of how important is to diagnose rare diseases considering their influence on post-transplantation period and potentially available treatment of primary disease itself.
4. Patients and Methods

This case-series study was conducted at Department of nephrology, arterial hypertension, dialysis and transplantation at the University Hospital Centre Zagreb.

A total of 7 patients, both male and female, the youngest being 23 years old and the oldest being 56 years old, have been retrospectively reviewed and reported here. The common link is underlying rare disease that affects the kidney. Rare diseases that are being discussed influence the kidney by various mechanisms, but with the same consequence - progressive renal insufficiency and need for renal replacement therapy.

Every patient is presented with the history of a disease, history of renal replacement therapy, as well as the data about renal transplantation and post-transplantation period. Some of them have a good graft function, whereas the others have acute or chronic renal rejection.
5. Results

5.1. Primary hyperoxaluria type I

Primary hyperoxaluria type I (PH type I) is a rare disorder caused by mutation in alanine-glyoxylate and serine-pyruvate aminotransferase gene (AGXT gene). This gene provides instructions for making an enzyme serine-pyruvate aminotransferase that is responsible for a conversion of a compound called glyoxylate into amino acid glycine in peroxisomes in the liver. It results in the accumulation of glyoxylate, which is converted to oxalate instead of glycine. The oxalate is filtered through the kidneys and is either excreted in urine as a waste product or combines with calcium to form calcium oxalate, a hard compound that is the main component of kidney and bladder stones (19). This is one of the three existing types of primary hyperoxaluria, characterized mainly by recurrent kidney stones. Signs and symptoms of PH type I vary in severity and may begin at any time from infancy to early adulthood. About 19% of people with PH type I have a severe, very early-onset form that becomes apparent within a few months after birth. At the milder end of the spectrum, some people with PH type I go without any symptoms for over 40 or 50 years (20, 21). The median age of onset is about 4-7 years. Other signs and symptoms include blood in the urine and urinary tract infections, anaemia and metabolic acidosis. Left untreated, PH type I can result in end-stage renal disease, which is life-threatening. This disease is inherited in autosomal recessive pattern (19, 22).

PH type I affects males and females in equal numbers. The exact incidence and prevalence of these disorders is unknown because some cases are undiagnosed or misdiagnosed. Estimated incidence is 1 case per 10,000 live births per year in Europe (19).

To diagnose PH1, high index of suspicion is needed. Initial steps would include a thorough physical examination and patient history, tests such as urine analysis to
measure oxalate and other metabolite levels, complete blood count to show kidney function, stone composition examination and imaging of the kidney to check for deposits. Further investigation such as DNA testing, kidney and liver biopsy are needed to confirm diagnosis. Nowadays, biochemical genetics tests such as Analyte and Enzyme assay and molecular genetics tests such as Sequence analysis of the entire coding region, Sequence analysis of select exons, Deletion/duplication analysis, and Targeted variant analysis exist (23).

Early treatment is important for maintaining kidney function. Treatment plan depends on symptoms and the severity of the condition. The goal of treatment for PH1 is to minimize calcium oxalate deposition and maintain renal function. General therapies for preventing kidney stones benefit all people with PH1. This involves high fluid intake, calcium-oxalate crystallization inhibitors (citrate, pyrophosphate, and magnesium) and avoiding significant intake of vitamin C or D which promote stone formation (24). Reducing the body's production of oxalate involves treatment with pyridoxine (Vitamin B$_6$). Most of the patients do not respond to this treatment, but it is still recommended at the time of initial diagnosis as a minimum 3 month trial (25). Treatment for kidney stones may involve shock wave lithotripsy, percutaneous nephrolithotomy or ureteroscopy. Dialysis to remove oxalate in people with PH type I has limitations, but may be indicated in specific circumstances in some people with PH type I. Oxalate removal is much more effective with hemodialysis than peritoneal dialysis. For that reason, peritoneal dialysis should not be relied on as the primary dialysis modality (26). The last option is kidney transplantation. There has been much discussion among experts regarding the best transplantation strategy for people with PH type I. Depending on each person's response to other therapies and the disease severity, options may include combined liver-kidney transplant, sequential liver-kidney transplant, an isolated kidney transplant, or an isolated liver transplant (26).
5.1.1. Case presentation of a patient with PH1

A male patient born in 1988 was previously diagnosed with PH1. As a 3 year old child he started having kidney stones. The patient was on RRT for many years and it included peritoneal dialysis and haemodialysis. Family history includes hypertension in parents.

In 2000 he was transplanted due to end-stage renal failure as a long term consequence of PH1. The surgical procedure included transplantation of both liver and kidney. In 2002 he was hospitalized due to CMV infection. In 2014 thympanoplasty of the left ear was done due to cholesteatoma. In 2015 an ear ventilation tube was placed in the right ear due to serous otitis.

This patient was followed and urine analysis was checked regularly. In February of 2017 a patient had proteinuria for two consecutive months. The patient had good appearance, normal stool and urine, no loss of weight and a good appetite. He was taking his medications regularly, did not smoke and was drinking alcohol occasionally. Physical examination was normal. Complete blood count was taken where a few parameters were not at the appropriate level (Hb 127 g/L, Hct 0.370 L/L, MCV 81.7 fL, MCH 27.3 pg). Daily urine analysis results were not satisfying as well. Renal biopsy was done where two samples were taken, one for the pathohistological analysis and the other for immunofluorescence and electron microscopy analysis. Pathohistological analysis showed segmental duplications of glomerular basement membrane that involved 50% of glomerulus with perihilar segment of sclerosis. Around 5% of taken sample shows fibrosis, followed by atrophy of tubules. There is no significant inflammatory infiltrate to be found. There are many arterioles showing segmental or concentric hyalinosis of tunica intima. Findings on immunoflorescence show no deposits, but there are signs that would suggest moderate graft-glumerulopathy. Analysis of the sample under electron microscopy shows GBMs that are mostly damaged and duplicated with endothelium that is hypertrophic. Inflammatory cells can be found in
certain capillaries suggesting peritubular capillaropathy. Podocytes and foot processes are damaged. In the interstitum many inflammatory cells together with collagen deposits can be noted.

Final conclusion was that in a given samples there are changes in the structure suggesting chronic graft rejection mediated by antibody deposition. His allograft function has further deteriorated and he is in preparation to start with dialysis.

Figure 1. Bone biopsy revealing oxalate crystals.
5.2. Fabry disease

Fabry disease (FD) is caused by mutations in the galactosidase alpha gene (GLA gene). This gene provides instructions for making an enzyme called alpha-galactosidase A (α-Gal A), that is active in lysosomes. This enzyme usually breaks down a fatty substance called globotriaosylceramide, but in FD this function is prevented and causes build-up of globotriaosylceramide (GL-3) throughout the body, particularly in the cells lining blood vessels of the skin, kidneys, heart, and nervous system. There are many variants of GLA mutation (27). GLA gene mutations that result in an absence of alpha-galactosidase A activity lead to the classic, severe form of Fabry disease. Mutations that decrease but do not eliminate the enzyme's activity usually cause the milder, late-onset forms of Fabry disease that affect only the heart or kidneys. This condition is inherited in an X-linked pattern. Milder, late-onset forms of the disorder are more common than the classic, severe form. The classic form, occurring in males with less than 1% α-Gal A enzyme activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesia), the appearance of vascular cutaneous lesions (angiokeratomas), sweating abnormalities (anhidrosis, hypohidrosis, and rarely hyperhidrosis), problems with the gastrointestinal system (abdominal pain), characteristic corneal and lenticular opacities, arthralgia, anaemia and proteinuria (28). Gradual deterioration of renal function to end-stage renal disease (ESRD) usually occurs in men in the third to fifth decade (29). In middle age, most males successfully treated for ESRD develop cardiac or cerebrovascular disease, a major cause of morbidity and mortality. Heterozygous females typically have milder symptoms at a later age of onset than males (28).

Identification of deficient α-Gal A enzyme activity in plasma, isolated leukocytes, or cultured cells is the most efficient and reliable method of diagnosing Fabry disease in males. Identification of a hemizygous GLA pathogenic variant by molecular genetic testing confirms the diagnosis in a male proband. Identification of a heterozygous GLA pathogenic variant by molecular genetic testing confirms the diagnosis in a
heterozygous female. Males with Fabry disease are more uniformly affected, whereas females, due to random X-inactivation, may be asymptomatic or as severely affected as males (28). It is estimated that type 1 classic Fabry disease affects approximately one in 50,000 males (30). The type 2 later-onset phenotype is more frequent, and in some populations may occur as frequently as about 1 in 1,500 to 4,000 males (31).

Management of Fabry disease should include treatment of specific signs and symptoms, as well as prevention of secondary complications. Phenytoin, carbamazepine or gabapentin can be used to treat the episodes of severe burning pain in the hands and feet. Chronic haemodialysis or renal transplantation has become lifesaving procedure for people with Fabry disease and kidney involvement. The transplanted kidney remains free of the harmful fatty substance deposition. Therefore, after successful kidney transplantation, kidney function will be normal. It is recommended to initiate Enzyme Replacement Therapy (ERT) as soon as possible. Human α-Gal A enzyme is generally used to improve some of the signs and symptoms associated with Fabry disease and to stabilize organ function. All of these individuals are at high risk for cardiac, cerebrovascular and neurologic complications, such as transient ischemic attacks and strokes. Measures taken may include ACE inhibitors or ARB drugs for proteinuria or albuminuria, blood pressure control and cholesterol control. Aspirin and other medications may be recommended for the prevention of stroke (32).
5.2.1. Case presentation of a patient with FD

A male patient born in 1962 had meningitis when he was 1 year old and since then he lost hearing. With 12 years of age he was diagnosed with slowly progressive glomerulonephritis and since 2003 he has arterial hypertension. He had chronic macrohematuria and microhematuria. Since 2005 he had AV fistula and from 2006 to 2010 he was on a regular haemodialysis due to progressive renal insufficiency. In 2006 diagnosis of Fabry disease was established and since then this patient is on ERT.

In 2010 he received a renal allograft from a deceased donor. The post-transplant course was uneventful until the March of 2013 when he required hospitalization due to suspected graft failure. The patient had normal urine and stool laboratory analysis and his appetite was good. Acute graft rejection was confirmed by biopsy. He received three boluses of methylprednisolone. After that creatinine was 210mmol/l and remained stable.

In 2015 patient presented with palpitations that have lasted for two days. He was tachycardic without any other signs or symptoms. He denied chest pain and syncope. Atrial fibrillation with rapid ventricular response was established. In February of 2018 patient developed skin lesions (porokeratosis) which may be associated with enzyme replacement therapy. At that time, a function of the graft was stable. The patient was in good physical health.
Figure 2. Electron microscopy showing myelene figures in the kidney of a patient with Fabry disease. X4400.
5.3. Atypical haemolytic-uremic syndrome

Atypical haemolytic-uremic syndrome (aHUS) results from a combination of environmental and genetic factors. Mutations in a gene called complement factor H (CFH) are most common. The complement system is a group of proteins that work together to trigger the inflammatory response. This system must be carefully regulated so it targets only unwanted materials and does not damage the body's healthy cells. Complement factor H protects healthy cells by preventing the complement system from being turned on when it is not needed. Mutations in the other genes have been identified as well, but CFH represents 70% of cases in childhood and 30% of all cases in adulthood (33). Although gene mutations increase the risk of atypical haemolytic-uremic syndrome, studies suggest that they are often not sufficient to cause the disease. In people with certain genetic changes, the signs and symptoms of the disorder may be triggered by factors including certain medications (such as anticancer drugs), chronic diseases (systemic sclerosis and malignant hypertension), viral or bacterial infections, cancers, organ transplantation or pregnancy (34). Most cases of aHUS are sporadic. When disorder is familial, it can have an autosomal dominant or an autosomal recessive pattern of inheritance. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode and 60% of genetic aHUS progresses to ESRD. Diagnosis of aHUS can be suggested if some of the family members were previously diagnosed with aHUS, if exclusion of HUS was made by normal activity of ADAMTS13 and negative STEC O157:H7 and if patient’s history suggest exposure to some of the triggering factors (33).

The overactive system attacks cells that line blood vessels in the kidneys, causing inflammation and the formation of abnormal clots. Atypical haemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: haemolytic anaemia, thrombocytopenia, and kidney failure. Anaemia occurs if erythrocytes are destroyed faster than the body can replace them. They are usually prematurely broken down while squeezing past the clots within small vessels. In people
with aHUS, fewer platelets are available in the bloodstream because a large number of platelets are used to make abnormal clots. Thrombocytopenia in this patient causes easy bruising and abnormal bleeding (35, 36). As a result of clot formation in small blood vessels, people with atypical haemolytic-uremic syndrome experience kidney damage and acute kidney failure that lead to end-stage renal disease (ESRD) in about half of all cases. These life-threatening complications prevent the kidneys from filtering fluids and waste products from the body effectively (36).

In childhood, aHUS affects males and females in equal numbers. In adulthood, females are affected more often than males, most likely because pregnancy is a triggering event. It is estimated that disorder affects 2 people per 1 million individuals in United States (34). In Europe, the disorder is estimated to affect approximately 0.11 per 1 million individuals between the ages of 0-18 and it accounts for approximately 5-10% of all cases of haemolytic uremic syndrome (37).

Current management of aHUS includes fresh frozen plasma and apheresis while awaiting confirmatory tests if TTP is a plausible diagnosis. Treatment includes blood transfusions, dialysis if indicated, and blood pressure control. Patients on dialysis may develop malignant hypertension, and bilateral nephrectomy may be needed to achieve blood pressure control in some of these patients (38). Eculizumab is a humanized monoclonal antibody that inhibits the production of the terminal complement components and the membrane attack complex C5b-9 by binding to complement C5. This blocks the proinflammatory and cytolytic effects of terminal complement activation. Ideal outcome criteria for the use of eculizumab would be cessation of acute haemolysis, normalization of low platelet counts, stabilization or improvement in renal function, prevention of recurrences prior to and after renal transplant, reduction in mortality rate and normalization of complement proteins. Eculizumab treatment achieved all these outcomes in nearly all patients in various trials. The problem is that eculizumab is not always available (38, 39). The last possible option is kidney transplantation or both kidney and liver transplantation in these patients.
### 5.3.1. Case presentation of a patient with aHUS

A female patient born in 1967 was previously diagnosed with atypical haemolytic-uremic syndrome. She has bronchitis since she was 4 years old. In early childhood she had tonsillectomy. In 1999 she was hospitalized because of tuberculosis of the lungs. She took antituberculosis drugs for 10 months, and pyrazinamide was excluded from therapy in the early beginning of treatment due to allergic reaction manifested as a skin rash. Since 2006 she has been treated for arterial hypertension that would occasionally increase to 240/120 mmHg. She has high risk HPV changes on the cervix resembling Carcinoma in situ or Cervical Intraepithelial Neoplasia grade III. She has hyperlipidaemia. This patient is a smoker for 30 years. Her family history includes a father that had myocardial infarction two times and was treated for colon cancer and a mother who had thyroid cancer. Mother has arterial hypertension and DM. The patient has allergies to vitamin B6, ACE inhibitors, pyrazinamide and fresh frozen plasma.

In 2009 she was hospitalized at Haematology ward due to profound anaemia, thrombocytopenia, proteinuria, headache and weakness and was treated with corticosteroids. She was admitted to Immunology ward in 2010 where kidney biopsy was done and first time chronic thrombotic thrombocytopenic purpura (TTP) in the setting of aHUS was diagnosed. CKD grade 3 was established at the same time. She was treated with plasmapheresis and corticosteroids. During the first plasmapheresis procedure, she developed dyspnea due to fresh frozen plasma allergy. Further treatments were done with premedication. In laboratory test results in 2011 urea is found to be 13.5 mmol/L and creatinine 183 umol/L.

She was regularly followed by nephrologist and at the beginning of 2012 the patient was hospitalized at the Nephrology Department due to worsening of anaemia, thrombocytopenia and renal function. After the thorough examination and testing it is confirmed that a patient has a relapse of the primary disease (aHUS) and worsening of kidney function due to TTP. The therapy included daily plasmapheresis and
methylprednisolone every second day. Even after 30 plasmaphereses, number of thrombocytes did not improve. Therefore, on the recommendation of hematologist, it was necessary to start the treatment with biological therapy. It included rituximab once weekly throughout 4 weeks with premedication. Improvement was noted and plasmapheresis is reduced to once weekly. Considering the progression of kidney disease, it was requisite to start hemodialysis through CVC in February of 2012. An AV fistula, positioned in the left forearm, was made in March 2012. During 2013 parameters of haemolysis gradually had stabilized along with progressive loss of kidney function. Overall, 157 plasmaphereses were done, with the last one in September of 2013.

In 2014 genetic testing was done and 3 mutations were found and diagnosis of aHUS was confirmed. On April the 6th of 2016 patient had deceased kidney transplanted with insertion of Double-J stent. Before transplantation surgery treatment with eculizumab was initiated. One day after surgery, she received another dose of eculizumab. This therapy was continued to be given once every week. On May the 17th of 2016 this patient was hospitalized at Nephrology Department because of haematuria and increased LDH. The biopsy was performed and pathohistological analysis showed signs of acute graft rejection grade II A according to Banff’s classification. On the 7th day of hospitalization, the patient had fever and meropenem was introduced in the therapy. Escherichia coli was isolated from urine culture. After the CRP has decreased, 3 boluses of methylprednisolone were given. On CT, a collection of liquid material (8.9 x 3.6 cm) was seen in subcutaneous fat tissue, at the level of previous surgical cut. Puncture and evacuation of subcutaneous material was performed by urologist. Therapy with eculizumab was continued after the patient was released from the hospital. On July the 12th of 2016, kidney scintigraphy was performed and the results were normal.

Patient had continued with eculizumab treatment until the end of the first posttransplant year. At that time, further treatment was rejected by the hospital pharmacy committee due to financial concerns. One year later she has stable allograft function without laboratory signs of hemolysis.
5.4. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystem disorder characterized by the formation of hamartomas in multiple organ systems, most commonly the brain, skin, kidney, and eye. It is caused by a mutation in the TSC1 and TSC2 (tuberous sclerosis complex) genes that are responsible for production of proteins hamartin and tuberin, respectively (40). Estimated birth incidence of TSC is 1:6000 (41).

TSC is a clinical diagnosis and without specific signs and symptoms can be diagnosed only some time later in life. We search for major and minor features of TSC. One of the major features is the skin that is affected by multiple facial angiofibromas or fibrous cephalic plaques, ungual fibromas, hypomelanotic macules and Shagreen patches. Multiple hamartomas can be found in the retina of the eye (42). The brain is affected by cortical dysplasia prenatally and this can result in seizures early in childhood. Epilepsy occurs in more than 90% of TSC patients and is a major sign that calls for further investigation of a potential TSC diagnosis. Subependymal nodules (SENs) and Subependymal Giant Cell Astrocytomas (SEGAs) are benign tumors that can be found in the brain of a patient with TS (43). Rhabdomyoma can be found in the heart of a patient with TS, but this tumor regresses with age. The most common kidney presentation of TS is angiomyolipoma, but rarely renal cell carcinoma can occur. Lymphangioleiomyomatosis (LAMs) is a condition that is occurring primarily in adult women with TS in which normal lung tissue is replaced by numerous cysts and muscle cells (42). Minor features of TSC include cysts and hamartomas in other organs. Behavioral problems are common in children with TSC (42, 43).

Diagnosis of the disorder is based on a careful clinical examination in combination with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, which may show tubers in the brain, and an ultrasound of the heart, liver, and kidneys, which may show tumors in those organs. Since there is no existing curative treatment, goals of different pharmacotherapy in TSC are to reduce morbidity and to
prevent complications. The main complication of TSC requiring long-term medical therapy is epilepsy. Antiepileptic medication such as vigabatrin is the mainstay of therapy for patients with TSC. Drug everolimus is approved to treat subependymal giant cell astrocytomas (SEGAs) and angiomyolipoma kidney tumors. Surgery may be needed in case of complications connected to tubers, SENs or SEGAs, as well as in risk of haemorrhage from kidney tumors. Respiratory insufficiency due to LAM can be treated with supplemental oxygen therapy or lung transplantation if severe (43, 44).
5.4.1. Case presentation of a patient with TSC (I)

A female patient born in 1982 was diagnosed with TSC in childhood following multiple epileptic attacks. She is being monitored regularly by neurologist. Family history includes grandmother with DM and grandfather with CVI.

Since 2009 she is being monitored at the Nephrology Department due to decrease in renal function as a consequence of the primary disease and arterial hypertension. In January of 2010 right nephrectomy was performed due to the bleeding from angiomyolipoma. In June of the same year, segmental embolization of the left renal artery was performed. In September of 2011 patient had haemorrhagic shock following the embolization of left renal artery and was treated with volume expanders and blood substitutes. In October of 2011 an emergency left nephrectomy was done because of the renal bleeding and development of retroperitoneal hematoma. Dialysis was initiated, first with the temporary vascular access by CVC and then by created AV fistula.

In November of 2011 this patient was hospitalized and treated for acute myopericarditis and bilateral pneumonia. A month later, she was hospitalized due to bilateral pleural effusions around hilum of the lung and dyspnea, whereat a treatment with intensive dialysis improved her condition. On a few more occasions, she was hospitalized due to the same cause, pleural effusion with mediastinal lymphadenopathy. In 2013 thyroidectomy was done due to the malignant variant of papillary thyroid carcinoma followed by radioiodine ablation. In 2015 extirpation of submandibular gland was done due to the sialolithiasis.

On December the 31st of 2016 renal transplantation from a deceased donor was performed. Double-J stent was placed in the ureter during the surgery. On January the 27th of 2017 she was hospitalized due to edema of left leg that developed as a result of the lymphocele verified on US and CT. Lymphocele is a common complication after the surgery in retroperitoneal space. In February of 2017 lymphocele puncture and drainage was performed through simple percutaneous catheter. In March of 2017 the patient is
once again hospitalized due to edema of left leg as a result of the lymphocele that was compressing iliac vessels. The urologist recommended conservative measures of treatment such as resting and edema went into regression. It was also recommended to introduce anticoagulative treatment with warfarin. In April of 2017 she was treated with cefepime for urinary infection caused by Pseudomonas aeruginosa. A month later patient had again urinary infection caused by Vancomycin-resistant enterococci (VRE) and Pseudomonas aeruginosa, and was treated with linezolid and cefepime, respectively. At this period, Double-J stent was removed. On August 27th of 2017 she was hospitalized due to graft pyelonephritis. The day before the admission she had fever, shaking and chills. She felt pain in suprapubic region and had urinary urgency. On the admission a treatment with cefepime, linezolid and meropenem in duration of 14 days was initiated. Infection was cured, but the state is complicated by recurring edema of the left leg. Emergency US examination of the transplanted kidney and Doppler of renal vessels were normal. Control CT of the abdomen and pelvis showed lymphocele below the transplanted kidney that is compressing iliac blood vessels on the left side. Considering that there is no clear outline of the external iliac vein on CT, a Colour Doppler of iliac vessels was recommended owing to the suspicion of thrombosis. Among other finding on CT, ovarian cysts, liver lesions and pleural effusions at the base of the lungs were observed. Colour Doppler of ileocecal region showed narrow partially occluded external iliac vessel in the close proximity of lymphocele that is mechanically compressing iliac vessels. The meeting was held on behalf of removal of the lymphocele that could potentially endanger the leg. It was stated that the lymphocele is out of reach for endovascular intervention or puncture, but then again there is no indication for surgical reconstruction of the vessel. It is concluded that the patient should keep up with conservative measures such as elastic-compressive bandages with avoidance of being in the sitting or standing position for a longer period of time. Treatment with warfarin was replaced with low molecular weight heparin due to the high levels of INR. During the regular check up on March the 19th patient was in a good general condition with stabile kidney function and without leg edema.
5.4.2. Case presentation of a patient with TSC (II)

A female patient born in 1995 was diagnosed with TSC when she was 2. Since when she was a new-born baby she has polycystic kidneys. This resulted gradually in progressive renal insufficiency. In October of 2015 peritoneal dialysis catheter was implanted, but never used because in February of 2016 she was transplanted with deceased kidney and insertion of Double-J stent in the ureter. Afterward she gained 27 kg owing to corticosteroid treatment. In October of 2016 extirpation of peritoneal catheter was done. The patient is allergic to acetylsalicylic acid. Her heart is dilated and she often has increased levels of blood pressure.

She has been treated in psychiatric hospital because of behavioural problems since she was 16 years old. The patient was hospitalized from August the 24th to September the 1st of 2017 because of attempted suicide due to depression. The patient was diagnosed with adjustment disorder, personality disorder and antisocial personality disorder. During the hospitalization she acquired respiratory infection that was successfully treated. She is under the control of the neurologist because of the seizures, the last one occurring in January of 2016.

Laboratory values show oscillations in the level of creatinine since August. On September the 15th of 2016 Colour Doppler was performed and it was normal. On September the 28th she was hospitalized due to worsening of renal graft function. On admission, high levels of creatinine and tacrolimus were verified and dose adjustment was initiated. Thereafter, laboratory levels had normalized and she was released home. The patient had microcytic anaemia and high levels of blood pressure that were managed accordingly. During the regular check-up on March the 28th of 2018 the patient was in a good health and renal graft was stable.
5.5. **Turner syndrome**

Turner syndrome is a disorder in females characterized by the absence of all or part of a normal second sex chromosome. Approximately half have monosomy X (45, X), and 5-10% have a duplication of the long arm of one X (46, X, i(Xq)). Most of the rest have mosaicism for 45, X, with one or more additional cell lineages (45).

One fifth to one third of affected girls receives a diagnosis as new-borns because of puffy hands and feet or redundant nuchal skin, the residual effect of cystic hygromas in utero. Turner syndrome should be suspected in any new-born girl with edema or hypoplastic left heart or coarctation of the aorta, since the frequency of both conditions is increased among children with Turner syndrome. Approximately one third of girls with Turner syndrome receive the diagnosis in middle childhood on investigation of short stature. In most other patients with Turner syndrome, the condition is diagnosed either in adolescence when they fail to enter puberty or in adulthood because of recurrent pregnancy loss. A diagnosis of Turner syndrome is confirmed by chromosomal analysis through karyotyping. It is estimated that Turner syndrome affects approximately 1 female in 2,000-2,500 live female births (45).

Most of the patients develop a variety of distinctive physical features including a short neck with a webbed appearance, a low hairline at the back of the head, low-set ears, and narrow fingernails, toenails that are turned upward, and obesity. A broad chest with widely spaced nipples may be observed. Another common feature of Turner syndrome is gonadal dysgenesis. Many patients have learning disabilities. Bicuspid aortic valve is another feature of a patient with TS. Liver abnormalities may include a fatty liver. Some affected individuals may have hypothyroidism (46). Structural renal malformations, including horseshoe kidney and duplication of the collecting system, are found in up to 40% of patients with Turner’s syndrome. Whereas most structural malformations do not cause renal dysfunction, silent hydronephrosis resulting from obstruction of a duplicated collecting system may occur. Screening renal US is
necessary for all patients with Turner syndrome. Kidney abnormalities increase the risk of urinary tract infections and high blood pressure (45, 46).

The treatment of Turner syndrome is directed toward the apparent symptoms. Individuals with Turner syndrome may benefit from growth hormone therapy, which can help to normalize height. Sex hormone replacement therapy is needed in order to undergo normal development associated with puberty, including the menstruation. Despite hormone replacement therapy, most of the patients will not be able to conceive children and in vitro fertilization would be a treatment option (47).
5.5.1. Case presentation of a patient with TS

A female patient born in 1992 was diagnosed with Turner syndrome as a baby. She has multiple comorbidities. Diagnoses of many cardiovascular abnormalities were verified, such as aortic coarctation, abnormal drainage of right pulmonary veins into superior vena cava, aortic valve stenosis and ventricular septum aneurysm. She has damaged hearing since the birth. She has been given antiepileptic therapy because of febrile convulsions since 1993. She has been treated for autoimmune thyroiditis and has known allergies to vancomycin, gentamicin and amphotericin.

First surgery was due to fallopian tube incarceration when she was 3 months old. With 6 months she had first heart surgery where patch aortoplasty was performed for aortic coarctation. At the age of 6 months second cardiac surgery on aortic valve was done where commissurotomy of the valve was performed. In 1998 heart catheterization was performed by which they excluded atrial septal defect. In 1999 partially anomalous drainage from pulmonary veins to superior vena cava was surgically corrected. Valvuloplasty of aortic valve was performed three times. In the age of 14 months she had instrumental dilation of bronchi due to emphysema. In 2005 she underwent surgical correction of scoliosis. The surgery was complicated by cardiomyopathy development and cardiopulmonary resuscitation whereupon she was hospitalized at intensive care unit. After the treatment, she was completely recovered.

Renal problems have been occurring since October of 1993 when Double-J stent was inserted into the left ureter due to the bilateral hydronephrosis. In November of the same year, the patient got urosepsis after which left ureteropyelonephrostomy was performed by Bergmann-Israel lumbotomy incision. Since this time chronic renal insufficiency persists. Because of the retention of liquid in renal pelvis, prophylaxis with trimethoprim and sulfamethoxazole was initiated. In 1999 an Anderson-Hynes pyeloplasty was performed. She was hospitalized in 2005 due to severe kidney damage with the progression of aortic stenosis, aortic insufficiency and cardiomyopathy. In 2005
she started with peritoneal dialysis. She had 5 episodes of acute peritonitis. She was on peritoneal dialysis for 9 years. In February of 2015 MSCT was performed where exclusion of peritoneal sclerosis was made. On MSCT venography was established that the access to the neck veins is possible only on the right side since there is hypoplasia of jugular, axillary, subclavian and brachiocephalic veins on the left side.

After the extensive pre-transplantation processing, no contraindications for kidney transplantation were found. Transplantation of deceased kidney and extraction of peritoneal catheter were done in July of 2015. On control MSCT after the procedure, a hematoma was found and was evacuated. Due to the high antibody titres and risk of acute humoral rejection of the graft, it is recommended to repeat immunological tests more often. In the early post-transplantation period thrombocytopenia was noted and immunosuppressive therapy was modified in a way that the dose of mycophenolic acid was decreased. In September 2015 kidney biopsy was performed because of oscillations in creatinine level that lasted for more than a month, but the result of the biopsy did not show any acute cellular or humoral graft rejection. After dose modification of tacrolimus drug and exclusion of potentially nephrotoxic trimethoprim and sulfamethoxazole, levels of creatinine normalized. In November of 2015 patient was admitted to the hospital because of the high fever, shaking, chills and increased inflammatory parameters. Urinary tract infection caused by E.coli was verified and treated with meropenem. The fever level dropped on the third day, but the patient started complaining about intensive itching that was present for a month, but now increased in severity. She was diagnosed with scabies and treated with benzyl benzoate. On the regular check-up in April of 2018 graft function was stable.
5.6. Dandy-Walker syndrome

Dandy-Walker syndrome is characterized by abnormal development of cerebellum and cystic enlargement of the forth ventricle. These abnormalities result in problems with movement, coordination, intellect, mood, and other neurological functions (48). It is thought that most cases are caused by a combination of genetic and environmental factors that affect early intrauterine development, but the exact cause is unknown. Dandy-Walker malformation is diagnosed with the use of ultrasound, CT and MRI. Prenatal diagnosis of Dandy-Walker malformation is sometimes made by US or fetal MRI. It is estimated to affect 1 in 25,000 to 35,000 newborns (49).

Symptoms of Dandy-Walker complex that begin in infancy may include faster than usual increase in head circumference, hypotonia or spasticity. Children might meet developmental milestones such as sitting up or walking later than expected. In older children signs and symptoms may include irritability, vomiting, nystagmus, and ataxia. These symptoms may develop slowly or appear suddenly (50). Hydrocephalus and seizures are common manifestations of this syndrome (51). Most people with Dandy-Walker complex develop symptoms within the first year of life. In 10-20%, signs and symptoms of the condition do not appear until late childhood or into adulthood (50). These individuals typically have a different range of features than those affected in infancy, including headaches, an unsteady walking gait, facial palsy, increased muscle tone, muscle spasms, and mental and behavioural changes (48). Other features include heart defects, malformations of the urogenital tract, polydactyly or syndactyly and abnormal facial features (50). Goldston syndrome is a rare entity describing the association of polycystic kidneys and Dandy Walker malformation with or without hepatic fibrosis (52).
5.6.1. Case presentation of a patient with DWM

A female patient born in 1992 was diagnosed with Dandy-Walker malformation. From the previous history we found out that she has conductive hearing loss and cysts in the right ovary. She received a kidney graft from a donor that was her family member in July of 2009. In January of 2017 she was treated with antibiotic due to the urinary infection caused by E. Coli. During the last visit patient’s general condition and graft function were normal.
6. Discussion

Diagnosis of the primary kidney disease is unknown for more than 35% of patients with ESRD. “Idiopathic chronic kidney disease” is found in a small percentage of people treated with renal replacement therapy. However, under the diagnosis of “chronic glomerulonephritis without biopsy”, “nephroangiosclerosis” or “diabetic nephropathy”, many rare diseases may be hidden. Some of these patients have mutations in genes involving normal development and function of kidneys or influence other organ systems that will in the end consequently affect the kidney as well. The best treatment option for all patients with ESRD would be renal transplantation, despite the increased risk for surgical complications and immunosuppressive treatment. The issue is that primary disease can reoccur in transplanted kidney, so there is a need for wider investigation of possible causes in pre-transplantation period.

In this study, we observed patients with rare diseases and their condition from the onset of disease to after the transplantation. Most of these patients have been diagnosed early in childhood due to some other characteristics of the disease, such as kidney stones in PH type I, multiple epileptic attacks in tuberous sclerosis or anomalies of cardiovascular system in Turner syndrome. Patient with aHUS was diagnosed later in life, but this is expected considering that this disease is usually triggered by some environmental factor, such as pregnancy, medications, chronic disease or infection. Patient with PH type I had typical signs and symptoms characteristic for the disease that led to renal insufficiency and was on renal replacement therapy for many years. He was transplanted with both liver and kidney and developed chronic graft nephropathy due to antibodies deposition. Even though this patient was treated and followed for primary disease, he had graft rejection that may be consequence of the primary disease. The diagnosis of primary hyperoxaluria is confirmed by hepatic enzyme analysis documenting deficiency of AGT or GRHPR, molecular genetic testing showing mutations in AGXT or GRHPR, or marked hyperoxaluria in an appropriate clinical setting and in the
absence of a secondary cause (23). In a study done from 1976 – 2009 outcomes of different transplantation approaches were compared using different methods to determine kidney graft survival among patients in the International Primary Hyperoxaluria Registry in USA (53). Pooling data from 84 transplants, a total of 44 kidney transplantations and 40 kidney-liver cases of transplantation were compared and 5-year kidney graft survival was 45% vs. 64% (p=0.10), respectively, but death censored graft survival was 45% vs. 78%(0.003). Significant challenges remain, such as the timely diagnosis of primary hyperoxaluria and prevention of oxalate injury to kidney allografts as a result of the marked hyperoxaluria that often persists for years following correction of the metabolic defect. The time required for resolution of hyperoxaluria following liver transplantation varies widely, occurring most rapidly in those who undergo transplantation within 6 months after reaching ESKD (54). Strategies for individual patients with type I PH based on molecular genotyping may be important in achieving the best outcome (55). High index of suspicion is needed to diagnose patient with Fabry disease, especially if a patient doesn’t have classic severe form of a disease that is apparent already in childhood. Patient in this study had slowly progressive glomerulonephritis since he was 12 that resulted in renal insufficiency and need for dialysis in the age of 43, after which diagnosis of Fabry disease was established. Enzyme replacement therapy was given for primary disease. Renal transplantation was done in the age of 48 and acute graft rejection was established 3 years later, but this was treated with boluses of corticosteroids, after which the patient’s graft function was improved and is still good today. A study was done in which patients with transplanted kidneys were screened for Fabry disease. Dried blood samples on Guthrie papers were used to analyze galactosidase A enzyme. Genetic analyses were performed in all female and male patients with low enzyme activity. In total, 648 female and 447 male patients with functioning grafts were evaluated. Among 1095 patients, 5 male patients had AGALA activity below threshold and 3 female patients had galactosidase alpha gene DNA variations. One male patient had a disease-causing mutation. The other 4 patients had polymorphisms causing low enzyme activity. All the 3 female patients had
mutations that were associated with FD (56). In another study long-term outcome of kidney transplantation in 17 patients (15 males, 3 females) with Fabry disease were followed-up. Follow-up ranged from 0.8 to 25.5 years, with a median of 11.5 years. Graft survival was similar and death-censored graft survival was superior to matched controls. Fabry patients died with functioning kidneys, mostly from cardiac causes. In 2 male patients, 14 and 23 years after the transplantation, the grafts had a few typical FD lamellar inclusions, presumably originating from invading host macrophages and vascular endothelial cells. This study shows excellent long-term outcome in patients with Fabry disease (57). Atypical haemolytic-uremic syndrome is presented here with classical signs and symptoms, such as profound anaemia, thrombocytopenia and profound kidney insufficiency that was treated with plasmapheresis, dialysis and in the end with transplantation. Specific treatment with eculizumab is available and it should be initiated as soon as possible as it was in this case. One month after the transplantation this patient had acute graft rejection associated with accumulation of liquid material at the level of surgical cut. She was treated with boluses of corticosteroids and evacuation of subcutaneous material that led to improved graft function. According to the article published in American Journal of Transplantation (58), a study was conducted with 78 patients with aHUS, among which 60% of cases manifested recurrence in post-transplantation period, 90% of whom developed graft failure (59). One-year graft survival was 32% for deceased donor transplants and 50% for living donor transplants. The percentage of graft failure from recurrence was higher in adults than in children (59). In a French cohort including 24 renal transplants in 15 children (60), recurrence was reported in 53% of patients and 33% of grafts. However, only 31% of graft failures were due to HUS recurrence (60). The time between renal transplantation and recurrences of aHUS varies from few days to 2 years, however 60% occur during the first month (59, 60). In patients with aHUS and complement gene abnormalities or anti-CFH autoantibodies kidney endothelial cells are vulnerable early after transplantation as ischemia triggers complement activation. The risk of recurrence may be increased by posttransplant viral or bacterial infections that activate complement. Further injury and inflammation are
caused by alloimmune response to the graft and indeed recurrence often occurs in concomitance with rejection episodes (58). Two female patients in this study have tuberous sclerosis and are example of how same diagnosis affects the kidneys by different mechanism. The first one had multiple nephrectomies due to the bleeding from angiomyolipoma, whereas the second had polycystic kidneys that progressed to renal insufficiency. The first patient was transplanted and month later developed lymphocele that was compressing iliac blood vessels and causing leg edema. Treatment included anticoagulation therapy together with conservative measures. In post-transplantation period, this patient had multiple graft infections that were successfully treated and graft function was preserved. The second patient had oscillations in creatinine level in post-transplantation period and at one point level of creatinine together with level of tacrolimus increased drastically whereupon the patient was hospitalized due to progressive renal failure. Dose adjustment of tacrolimus was initiated after which laboratory values went back to normal and graft function improved. Patient with Turner syndrome has many comorbidities that also included persisant chronic renal insufficiency that started with bilateral hydronephrosis in early childhood. After the transplantation she had high antibody titres that required immunological testing more often, hematoma development in retroperitoneal space that was evacuated, thrombocytopenia that was resolved after dose adjustment of mycophenolic acid and creatinine oscillations that were corrected by dose adjustment of tacrolimus and exclusion of potentially nephrotoxic trimethroprim and sulfamethoxazole that she was taking due to liquid retention in renal pelvis. Dandy-Walker malformation case presented progressive kidney failure due to multiple cysts in the kidneys. This patient still has a good kidney function, even after many years following the transplantation.

The diagnosis of recurrent renal disease in post-transplantation period is dependent on an accurate diagnosis of the primary disease and a similar determination of the cause of graft failure. Most of these diseases have huge impact on post-transplantation period and without treatment for primary disease, the failure of graft will occur earlier. Even if disease is diagnosed it represents considerable medical burden
due to poorly addressed instructions in terms of treatment. Overcoming obstacles such as the development of screening methods that efficiently improve diagnosis would lead to further investigation of a disease and wider pathology knowledge. This would increase number of patients to test and commercial interest from the industry that is another important aspect in diagnosis and treatment.
7. Conclusion

Renal transplantation is the best method of renal replacement therapy. Many factors influence graft successfulness. Some of these are age, gender, diabetic status, cardiovascular status, smoking status and HLA mismatch, but most important factor is primary disease itself. When primary disease is unknown it imposes great risk for recurrence of disease in transplanted kidney and graft failure. Screening for rare diseases in pre-transplantation period would improve overall outcome of renal transplantations in these patients. It is very likely that screening of transplanted population would show many different genetic mutations that result in deterioration of graft function.
8. Acknowledgements

I would like to express my gratitude and appreciation to my mentor, Doc.dr.sc. Nikolina Bašić Jukić, for valuable guidance, keen interest and inspiration.

To my family, thank you for your continuous and unparalleled love, help and support.
9. References


10. Biography

Tea Vukić was born on February the 2\textsuperscript{nd} in 1994 in Dubrovnik. She completed secondary education in mathematics, physics and computer sciences at Dubrovnik High School, after which she enrolled in the Medical Studies in English Program at the University of Zagreb in 2012.