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Editorial comment

Renal Transplantation in Croatia: A Personal View

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History of renal transplantation in Croatia

Renal transplantation in Croatia has a long history. First transplantation from the living donor was performed in Rijeka in 1971 by Professor Vinko Franciskovic. Next year, first renal transplantation from deceased donor was also performed in Rijeka. University hospital centre Zagreb started with renal transplantation in 1972. First combined kidney-pancreas transplantation was performed in Rijeka in 1993, while the first kidney-liver combined transplantation was done in University hospital Merkur in Zagreb in 2005.

Patients on renal replacement therapy in Croatia

According to the data from Croatian registry for renal replacement therapy 4009 patients had been treated with renal replacement therapy on December 31st 2008. Out of this number (prevalence of 904 per million population), 68% were treated with hemodialysis, 6% with peritoneal dialysis and 26% of patients had functioning renal allograft. The most common primary renal disease was diabetic nephropathy (31%), followed by vascular diseases (22%) and glomerulonephritis (15%) [1].

Transplantation centers

There are currently 4 renal transplantation centers in Croatia: two in Zagreb (University hospital centre Zagreb and Clinical hospital Merkur), one in Rijeka and Osijek. Tissue typing centers are situated in Zagreb, Rijeka and Split.

Establishment of renal transplant program

Significant efforts were needed to establish a successful renal transplant program. A well trained and experienced personnel was already available, but as all surroundding countries, Croatia suffered from lack of donors. In 2003 Ministry of health of Republic of Croatia recognized the importance of renal transplantation for the benefit of patients but also of the whole society and started with strong support for organ donation. Previous isolated efforts (donor network, donor cards, renal transplant personnel efforts...) get additional strength. Promotion in different media like television and magazines, series of lectures held for medical doctors resulted in increasing number of donors. It is well known that positive stories in media result in increase of organ donation, and Croatia succeeded to avoid any possibility of wrong interpretation of organ allocation. All decisions were brought by a team consisted of a nephrologist, transplant surgeon and immunologist. Organ allocation was primarily based on HLA matching.

One of the most important measures in favor of transplantation occurs when Ministry of health decided to financially cover renal transplantation separately from the usual hospital limits. These measures enable introducetion of novel immunosuppressive drugs and protocols in renal transplantation, as well as performance of immunologically „high risk“ transplantations which need more intensive and thus more expensive immunosuppressive treatment.

From the point of organ donation, very important measure was introduction of national and hospital coordinators for organ donation who are responsible for identifycation and further processing of potential donors. Larger hospitals have dedicated transplant coordinators, while in smaller hospitals this function is usually performed by intensivists or anestesiologists. It is interesting that the second most active hospital is small general hospital in Varaždin, city on the north of Croatia. This situation clearly demonstrates the importance of the so called „human factor“ in success of any process.

Clinical coordinators for renal transplantation work in renal transplant centers and are responsible for the maintenance of the waiting-list and for cooperation with Eurotransplant. They coordinate evaluation before wait-listing and reevaluations of the patients during their waiting for renal transplantation. These are nephrologists who work in close collaboration with transplant surgeons.

Based on the previous actions Croatia succeeded to establish a solid renal transplant program and to increase number of donors, thus becoming interesting for other countries in the region for organ exchange. Eurotransplant is organization for organ allocation which allocates organs in 7 different European countries. Croatia joined Eurotransplant in June 2007, and from August 15th 2007 first organs were transplanted via this organization.

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From that point of time significant changes have occurred. First of all, a stringent administrative support was necessary to maintain the whole structure, starting from the Ministry of health with a national coordinator, across the hospital coordinators, clinical coordinators, finishing with doctors working in dialysis centers, and finally with a renal transplant recipient. Thus, excellent organization available 24 hours per day was necessary for this project. Once when this organizational scheme was established, everyday work becomes much easier than before.

Second, a significant change in organ allocation was implemented. From the HLA based organ allocation we switched to Eurotransplants' scheme of allocation which counts waiting time, HLA matching and country balance (export and import of organs between the countries). This allocation scheme resulted in high number of renal transplantations being performed in the long-term dialysis patients who gained lots of points for the waiting-time. During the first three days in Eurotransplant, 9 transplantations were performed just in Clinical Hospital Centre Zagreb.

Statistics

Based on increased organ donation (Figure 1), from 1998 to 2008, significant increase in number of renal transplantations was recorded (Figure 2). Number of living donors ranged from 7 to 24 per year (11-28 % of all transplantations), what demonstrates that there is still possibility to increase number of renal transplantations in Croatia by promotion of living organ donation. In 2009, University hospital centre Zagreb performed 105 renal transplantations thus becoming the 6th biggest centre in Eurotransplant.

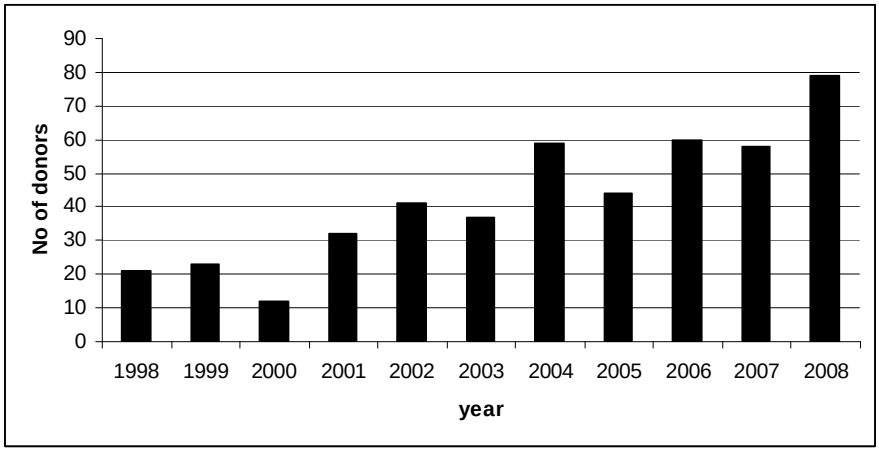

Fig. 1. Number of deceased donors from 1998 to 2008

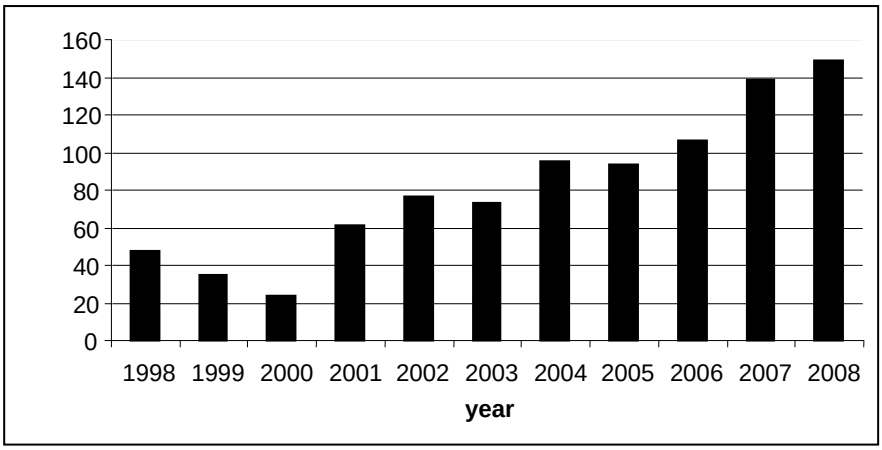

Fig. 2. Number of renal transplantations in Croatia from 1998 to 2008

Changing trend in characteristics of renal allograft recipients

First year in Eurotransplant was characterized by renal transplantations performed in very long-term dialysis pati-

Table 1. Changing trend in characteristics of renal allograft recipients. HBV – hepatitis B, HCV – hepatitis C

	2007	2008	2009
HBV +	0	2(2.19%)	0
HCV +	8(20.5%)	17(18.68%)	2(2.7%)
Age	48	47	48
Years on dialysis	12	8	6
Second transplantation	0	6	7

ents (Table 1). High proportions of patients were hepatitis C or B positive. In the succeeding years, "normalization" of renal transplantation had occurred, while most of the long-term dialysis patients received kidney allograft during the first year.

Conclusion

Pathway for establishment of deceased donor renal transplant program is hard with inclusion of all society. Promotion of organ donation, transparency of allocation, devotion of transplant stuff and financial support are all necessary for successful transplantation.

Conflict of interest statement. None declared.

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Review

Peritoneal Dialysis in Acute Kidney Injury

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Abstract

The role of peritoneal dialysis in the treatment of acute kidney injury is still under debate and it is underused in many countries. Most of the studies performed in 1970s and 1980s have reported that patients with ARF treated by PD had mortality and incidence of renal recovery at least equal to similar patients treated by hemodialysis (HD) and possibly better. Over the past decade, continuous renal replacement therapies (CRRT) have achieved better cardiovascular stability, and decreased risk of bleeding by the use of low-dose heparinization. These advantages have reduced the indication for PD in critically ill patients. In the meantime, some comparative studies have not demonstrated that CRRT achieves any reduction in mortality compared to IHD. Disadvantages of CRRT were also apparent: although described as 'gentle' forms of therapy, continuous blood therapies require considerable attention by nurses to assure adequate blood flow, monitor anticoagulation status, adjust ultrafiltration rate and calculate fluid balance; the patient is immobilized during therapy and vascular access catheters often provide insufficient blood flow and have a risk of infection leading to sepsis. By contrast, PD is a continuous dialysis therapy with less risk and less nursing effort than CVVH or CVVHD providing more mobility during therapy. PD should be considered as a valuable method for ARF since it offers several advantages over HD such as technical simplicity, no extracorporeal circuit and no bleeding risk; it offers gradual and continuous solute and liquid removal with good cardiovascular tolerance and less cardiovascular instability thus reducing kidney aggression by ischaemia and hydroelectrolytic imbalance.
CAPD may help to maintain renal perfusion by smaller daily variation in body weight, more constant blood pressure and continuous mild overhydration, persistant high blood osmolality and by continuous removal of proteins from the blood including β2-microglobulin, albumin, plasminogen-activator inhibitor type 1 (PAI-1) and immunoglobulins. These physiologic and chemical benefits may account for the highest recovery of renal function in patients with ARF treated by PD than with HD. In resource-poor countries, the cost, practicability and feasibility of CRRT may be a limiting factor whereas peritoneal dialysis is relatively simple and inexpensive and is more widely used. Finally, even in developed countries a major catastrophe can cause severe damage to the infrastructure. PD is an alternative when reliable power, clean water supply and facilities for water treatment are unavailable. Various techniques of peritoneal dialysis have been developed and these have been adapted for use in ARF.
While waiting for better, multicenter comparative studies, there are many patients with acute kidney injury that may benefit from continuous, gentle, affordable and efficient peritoneal dialysis.

Key words: acute kidney injury, peritoneal dialysis, mortality

Introduction

Despite the initial decline in mortality from 90% to 50% with the introduction of acute dialysis more than 55 years ago, [1] the mortality rate of patients with acute renal failure (ARF) remains very high: it is 40%-50% [2] overall but rises to approximately 70%-80% when ARF occurs in the intensive care unit (ICU) [3].
There are many factors contributing to the extremely high death rate seen in ARF. While most patients die from causes unrelated to their renal failure, age, comorbid condition, and severity of illness in patients with ARF have all increased in the last 20 years. Therefore, recent studies suggest that the relatively constant unadjusted mortality rate paradoxically represents better management of this syndrome [4]. Still, understanding of all factors that might influence survival in ARF is critical.
The most important question in the management of ARF probably relate to modality selection, dialysis dose, adequate start and stop of dialysis and the consequence of therapy on residual renal function.

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Peritoneal dialysis as a method of treatment for patients with acute renal failure

As with all dialysis techniques, peritoneal dialysis (PD) was first used in therapy of acute renal failure [5]. Most of the studies performed in 1970s and 1980s have reported that patients with ARF treated by PD had mortality and incidence of renal recovery at least equal to similar patients treated by hemodialysis (HD) and possibly better [5-9]. The article by Firmat reviewed literature reports including over 1,100 patients and in summation the mortality rate was identical for ARF patients receiving PD and HD [7]. In study of 100 patients with ARF in two community hospitals reported in 1983, there was a higher rate of recovery of renal function (and survival) in those treated by PD *vs*. HD. Similar results were obtained 10 years later by the same authors: 10% higher patient survival was recorded for patients treated by PD.

In the meantime, both, PD and HD have improved. Still, among intermittent treatments of ARF patients, IPD and IHD was considered equal [10]. In addition, continuous PD may give even superior results to those of conventional HD including better control of toxic metabolites and volume abnormalities in critically ill patients [11-13].

For many years the standard of practice in treating ARF was intermittent hemodialysis (IHD), three or more times per week for 3 to 4 hours. Over the past decade, continuous renal replacement therapies (CRRT) have achieved better cardiovascular stability, and decreased risk of bleeding by use of low-dose heparinization. These advantages have reduced the indication for PD in critically ill patients. In the meantime, some comparative studies have not demonstrated that CRRT achieves any reduction in mortality compared to IHD [14-16]. Disadvantages of CRRT were also apparent. Although described as 'gentle' forms of therapy, continuous blood therapies require considerable attention by nurses to assure adequate blood flow, monitor anticoagulation status, adjust ultrafiltration rate and calculate fluid balance of the patients. The patient is immobilized during therapy and vascular access catheters often provide insufficient blood flow and have a risk of infection leading to sepsis. By contrast, PD is a continuous dialysis therapy with less risk and less nursing effort than CVVH or CVVHD providing more mobility during therapy. Even so, there is a trend of using CRRT with a progressive decline in use of PD in patients with ARF. Survey of Canadian adult nephrology centers compared two periods (1999-2000 and 1994-2000) and found that the largest increase was in CRRT (from 9% to 26%), while the use of PD decreased from 8% to 3% [17]. In a study involving 54 nephrology centers distributed over five countries, Uchino *et al*. reported that CVVH were the major methods used in patients with ARF in almost 80% of services, while PD was used in 3.2% of these centers and intermittent HD in 16.8% [18]. In Latin America, particularly in Brasil, PD was used in 23% of patients with ARF and in Europe in 21% [19]. Peritoneal dialysis for ARF still constitutes the mainstay of therapy in many developing countries [20].

Indication and contraindications for acute peritoneal dialysis in acute renal failure

Despite its decreasing use, PD should be considered as a valuable method for ARF since it offers several advantages over HD such as technical simplicity, no extracorporeal circuit and no bleeding risk. Because of its gradual and continuous nature, it leads to solute and liquid removal with good cardiovascular tolerance and less cardiovascular instability thus reducing kidney aggression by ischaemia and hydroelectrolytic imbalance. Therefore, peritoneal dialysis proved to be a valuable renal replacement therapy in many instances but mainly in patients with cardiovascular problems and active bleeding (Table 1).

Several reports suggest that patients with ARF seconddary to atheroembolic renal disease may have a better chance of recovery if PD is used over HD [21]. Also, it has been reported that PD has a beneficial role in recovery of renal function in patients with renal failure due to malignant hypertension [22]. In resource-poor countries, the cost, practicability and feasibility of CRRT may be a limiting factor whereas peritoneal dialysis is relatively simple and inexpensive and is more widely used. Simplicity of PD permits interns and postgraduate students to be trained to manage ARF earlier at primary care centers, thus avoiding the delay caused by referring critically ill patients to nephrologist or ICU. Finally, even in developed countries a major catastrophe can cause severe damage to the infrastructure. PD is an alternative when reliable power, clean water supply and facilities for water treatment are unavailable.

Table 1. Indications and relative contraindications for peritoneal dialysis in patients with acute renal failure

Indications for acute peritoneal dialysis	Relative contraindication for acute peritoneal dialysis
Hemodynamically unstable patients	Recent abdominal or cardiothoracic surgery
Bleeding diathesis or active hemorrhage	Diaphragmatic pleuroperitoneal connections
Problem with vascular access	Fecal or fungal peritonitis
Pediatric ICU	Severe respiratory failure
Atheroembolic renal disease?	Abdominal wall celulitis
ARF due to malignant hypertension?	Severe reflux disease
Unavailability of other continuous therapies	Extremely high catabolic status with hyperK
	Pulmonary edema
Special circumstances (disasters)	Peritoneal adhesions

PD is still a very suitable method of treatment for pediatric ICU, especially in critically ill infants and children with ARF and post-cardiovascular surgery [23-24].
There are several relative contraindications to acute PD (Table 1): recent operation with abdominal drainage, peritonitis (fecal or fungal), known pleuroperitoneal fistula (after cardiothoracic surgery). The presence of abdominal hernia or intra-abdominal adhesions might make PD difficult. PD may be relatively contraindicated in the presence of abdominal wall cellulitis or severe gastroesophageal reflux disease, adynamic ileus and recent aortic graft (< 6 months).

Techniques of peritoneal dialysis and dialysis dose

Various techniques of peritoneal dialysis have been described in the literature and these have been adapted for use in ARF (Table 2).

Table 2. Techniques of peritoneal dialysis for ARF treatment

Technique	Description
Acute Intermittent Peritoneal Dialysis (AIPD)	Most often used in the past. Frequent and short exchanges with volumes 1-2 liters and dialysate flows of 2-6 liters/h. Each session lasts 16-20 h, usually tri session per week. The solute clearance is likely inadequate due to its intermittent nature
Chronic Equilibrated Peritoneal Dialysis (CEPD)	Long dwells of 2-6 h with up to 2 liters of dialysate each (similar to CAPD). The clearance of small molecules may be also inadequate but clearance of middle molecules is possibly higher due to the long dwells
Tidal Peritoneal Dialysis (TPD)	Typically involves an initial infusion of 3 liters of dialysate into the peritoneal cavity. A portion of dialysate, tidal drain volume (usually 1-1.5 liters) is drained and replaced with fresh dialysate (tidal fill volume)The reserve volume always remains in the peritoneal cavity throughout the tidal cycle
High Volume Peritoneal Dialysis (HVPD)	Continuous therapy proposed to increase high small solute clearances. Frequent exchanges, usually with cycler (18-48 exchanges per 24 h, 2 liters per exchange). The total dialysate volume range from 36-70 liters a day
Continuous Flow Peritoneal Dialysis (CFPD)	In-flow and out-flow of dialysate occurs simultaneously through two access routes. By inflow of 300 ml/min it is possible to achieve a high peritoneal urea clearance

Patients with ARF are hypercatabolic and require adequate clearance of toxins to avoid complications. Part of the reason for underuse of PD may be related to the perception that PD is not adequate for treatment of ARF. However, studies in literature report efficient fluid removal and metabolic control in patients on CPD [20,25,26]. These studies have limitations such as small sample size and inadequate parameters for measuring catabolism and dialysis adequacy.
Adequacy of dialysis dose is controversial since many authors believe that there is no satisfactory marker for dialysis adequacy in ARF. Katirtzoglou *et al*, reported blood urea nitrogen levels below 100 mg/dL, which were considered satisfactory at that time for ARF patients on CPD [27]. Mehta and Letteri reported that intermittent peritoneal dialysis was not adequate for treating ARF patients, as it maintained BUN levels higher than 75 mg/dl.[28] Phu *et al*, showed that PD failed to keep optimal control of BUN and creatinine levels compared with CVVH, the later having significantly lower mortality rate [29]. However, this study was frequently commented by others since their peritoneal dialysis technique was not optimal: they produced PD solutions locally by using acetate buffer, they used rigid peritoneal catheter, performed manual PD exchanges with short dwell time leading to inadequate solute clearance and dialysis adequacy.
The adequacy of PD in ARF was evaluated in a prospective, randomized, crossover trial that included 87 hypercatabolic patients [25]. This study showed that tidal PD and continuous equilibrated PD (CEPD), which is similar to but more intensive than CAPD, were adequate methods of maintaining BUN levels at about 65 mg/dl in mild and moderate hypercatabolic ARF patients in developing countries. Tidal PD provided better clearances at the same dialysis volume for a lower inpatient cost and only limitation was greater protein loss. In a prospective study, Gabriel *et al*, treated 30 ARF patients who received 236 dialysis sessions of CPD with encouraging results for metabolic, electrolytic and acid-base control [30]. They showed that high doses and CPD using flexible catheter and cycler was an effective treatment of ARF providing high solute removal, sufficient dialysis dose with higher values than described in previous literature.
An old but good idea is about the use of continuous flow PD (CFPD) [31]. This variant of PD utilizes two access points: one for inflow of dialysate and other for outflow. Since there is no interruption of inflow to outflow, flow rates are determined only by the rate at which the draining catheter can reproducibly drain the abdomen. With CFPD dialysate flow rates of up to 300 ml/min can be maintained through the peritoneum.
Besides removal of uremic toxins, dialysis must also remove fluid and salt from the patient. With a properly functioning PD catheter, exchanges of 2 liters of dialysate with 2.5 or 4.25% glucose concentration provides daily fluid removal at the same or greater rate than other regimens without causing hypotension in most patients.

Peritoneal dialysis and renal outcome in patients with acute renal failure

In many of the studies of PD versus HD for ARF, the reason for improved survival in the PD group was related to an increased rate of renal recovery. It is already known that in patients with ESRD, treatment by CAPD resulted in better preservation of intrinsic renal function than treatment by intermittent HD. This preservation of renal function is important because it maintains endocrine function of the kidneys, diminishes the clearance requirements for dialysis, minimizes ultrafiltration and physiologic stress during dialysis. On the other hand, hemodialysis has several known nephrotoxic effects such as generation of inflammatory mediators by extracorporeal circuit, rapid decrease in osmolality and vascular volume, diminishing renal perfusion. All of the above may influence renal recovery during the course of ARF [32].

By contrast, CAPD may help to maintain renal perfusion by smaller daily variation in body weight, more constant blood pressure and continuous mild overhydration, persistent high blood osmolality and by continuous removal of proteins from the blood including β2 - micoglobulin, albumin, plasminogen-activator inhibitor type 1 (PAI-1) and immunoglobulins [33]. These some physiologic and chemical benefits may account for the highest recovery of renal function in most studies, in patients with ARF treated by PD than HD.

Limitations of peritoneal dialysis in patients with acute renal failure

The major criticism of PD is low clearance of uremic toxins; the clearance of low-molecular weight toxins is lower than for other therapies (CAVH, CVVH and daily HD). It is apparent that PD with a modest dialysate use of 1 liter/h is less efficient than other modalities for urea and creatinine but is similarly efficient in removal of larger molecules such as vitamin B_{12}. It is likely that larger molecular weight toxins are the real cause of uremic illness and PD is quite effective in removing various anionic organic compounds that function as middle molecules. Small molecular clearance may be increased by increasing flow rate of dialysate to 1.5-1.0liters/h or more. Tidal peritoneal dialysis can easily deliver 2 liters/h into and out of peritoneum.

Infectious, mechanical and metabolic complications may be major problems. The incidence of peritonitis in PD therapy of ARF is much different than in CAPD therapy. Previous studies have reported a 12%-25% incidence of peritonitis [13]. If peritonitis is detected during therapy of ARF it usually occurs within 2 or 3 days of starting therapy [6,34]. This indicates that PD may detect contamination of the peritoneum that predates the implementation of PD. There is predominance of Staphylococcus epidermidis and Candida (in debilitated patients undergoing antibiotic therapies) but also mixed infections [35]. Peritonitis during PD therapy does not result in septicemia in ARF patients. This is a much different outcome than catheter-related infections during hemodialysis or continuous therapies which frequently result in septicemia. The increasing use of automated PD via flexible catheter has led to a reduction in peritonitis frequency.

Studies have shown that mechanical complications occur in fewer than 10% of patients due to immediate use just after catheter insertion [30]. Also, there is controversy about abdominal distension leading to reduced diaphragm mobilization and consequently about pulmonary compliance.

Protein losses may play an important role, mainly during peritonitis. It may exacerbate conditions in undernourished, critically ill patients with ARF. It was measured that total weekly protein losses were around 45 g in intermittent and 62 g in CPD; albumin accounted for approximately half of this loss. Despite this depletion, plasma albumin and total protein levels were not decreased [36]. However, large variability among individuals was seen and peritonitis was the only factor influencing these losses. This observation was reported by Gabriel *et al.* [30] who reported no significant difference between median plasma albumin values obtained before and after CPD session (median 2.6 g/dL) despite considerable losses in protein (median 21.7 g/day). The authors concluded that dialysate protein loss, although significant, was not a limiting factor for using CPD. In these situations it is necessary to increase patient's protein ingestion which should be 1.5 g/kg/day.

The fact that PD results in protein loss is generally considered a nutritional problem. However, this loss may contribute to the chemical effectiveness of the PD. In patients with hemolytic uremic syndrome, PD significantly reduces plasminogen-activator inhibitor type 1 (PAI-1) which inhibits fibrinolysis in hemolytic uremic syndrome [37]. Most of the organic anions removed by PD in uremic patients are in fact strongly bound to protein, so protein loss increases their clearance. These protein-bound organic anions act as middle molecules and the presence of protein within the dialysate facilitates the transfer of these compounds into the peritoneum. The peritoneal transfer of proteins can be increased by application of hypertonic solutions; the globulin removal by PD on a daily basis could equal or exceed daily therapeutic plasmapheresis [33].

Hyperglycemia is another metabolic complication resulting from PD with glucose-based solutions. Therefore, it is necessary to closely monitor glucose metabolism even by using insulin via continuous infusion pump [25].

When comparing the overall risk of each type of therapy for ARF, there are marked differences between CVVH, CVVHD, HD and PD. The blood treatment therapies have a significant risk of septicemia, low flow from blood access, hypotension, membrane clothing and bleeding. PD therapy includes risk of PD catheter outflow failure, hyperglycemia and asymptomatic peritonitis.

There are controversies about the influence of PD on respiratory system in critically ill patients. Bazari reported that PD impairs diaphragm mobilization because of increased intra-abdominal pressure [38]. As a result, pulmonary compliance and ventilation are impaired. Venous return is also reduced leading to hypotension and consequently to organ and tissue hypoperfusion which favor acidosis However, Epstein *et al.* [39] showed that although it reduces pulmonary volume, characteristics of vital capacity and expiratory volume remain unaltered. They con-

cluded that PD is rarely associated with ventilatory impairment in patients without pulmonary pathologies.

Conclusions

In conclusion, while waiting for better, multicenter comparative studies, there are many patients with acute kidney injury that may benefit from continuous, gentle affordable and efficient peritoneal dialysis.

Conflict of interest statement. None declared.

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Original article

The Onset and Prognosis of Hepatorenal Syndrome – A Three Year Single Center Experience

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Abstract

Introduction. The hepatorenal syndrome (HRS) refers to the development of acute renal failure in the setting of advanced liver disease. It can occur in a substantial proportion of patients with fulminate hepatic failure from any cause. The aim of our study was to investigate the onset, outcome and prognosis of patients with hepatorenal syndrome hospitalized at our unit.
Methods. This is a cross-sectional retrospective study in a cohort of 543 cirrhotic patients, during a period of 3 years (January, 2008-December, 2010). Hepatorenal syndrome was detected in 20 (3.7%) patients and in all of them a few variables such as: age, gender, history of cirrhosis or other liver disease, etiology of cirrhosis, Child-Pugh classification, other complications of the cirrhosis except for HRS, treatment and survival were analyzed.
Results. The average preceding time up to the occurrence of HRS was around 3 years (36.8±47.8 months), although there were 4 patients who developed HRS only a month after the onset of cirrhotic symptoms. A group of seven patients with HRS diagnosed during the first year of the onset of symptoms. The mean age of patients was 55.5±13.3 years. There was a significant difference in the gender distribution, three quarters of patients being males. With regard to the etiology, 12 patients had alcoholic abuse, and a half of them (50%) were with mixed etiology (Hepatitis B plus alcohol abuse). Two patients had a pure chronic hepatitis B virus (HBV) infection as a cause of cirrhosis. Four were with chronic liver disease of unknown etiology (2 of them with confirmed histology of chronic hepatitis). All of the cirrhotic patients were scored as grade C according to the Child-Pugh classification. Hepatic encephalopathy was the most predominant concomitant complication present in 17 (85%) patients with HRS. Only 2 showed signs of malignancy with suspected hepatocellular carcinoma (HCC). The estimated average hospital stay was 6.15 days, ranging from 1-14 days. The applied treatment was generally unsuccessful. Majority of cases (14) were supported with albumin and fresh frozen plasma transfusion and haemodialysis was performed in 4 patients. The mortality rate was high, reaching 80% (16 patients) with an average time of death at 6.8±4.4 days after the hospital admission. Although the evaluation period was short, there is a clear raising trend in number of detected patients with HRS at our Clinical Center.
Conclusion. Compared to other reports, our single centre experience shows lower occurrence rate. Despite the use of available conservative medical treatment, there was no recovery of the hepatic failure in any of HRS patients. The absence of liver transplantation or TIPS in our country is the second contributing factor related to the high mortality rate in our cohort.
Finally, gastroenterohepatologists should be aware and try to prevent iatrogenic precipitants of HRS as an aggressive diuretic treatment or removal of large volumes of ascitic fluid by paracentesis without compensating for fluid depletion by intravenous replacement could additionally impair the renal failure.

Key words: hepatorenal syndrome, hepatic failure, renal failure

Introduction

The hepatorenal syndrome (HRS) refers to the development of acute renal failure in the setting of advanced liver disease due to cirrhosis, severe alcoholic or other acute hepatitis, or less often in the presence of liver metastases. Nevertheless, it can occur in a substantial proportion of patients with fulminate hepatic failure from any cause. It is a life threatening medical condition that consists of rapid deterioration in kidney function of individuals with cirrhosis or fulminate liver failure [1,2].
HRS is usually fatal unless a liver transplant is performed, although various conservative treatments (including dialysis), can prevent worsening of the condition. Regardless of the etiology (cirrhosis, severe alcoholic hepatitis

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or fulminate hepatic failure), it usually occurs when liver function deteriorates rapidly triggered by an acute injury such as infection, bleeding in the gastrointestinal tract, or abuse of diuretic medications. HRS as relatively common complication of cirrhosis occurs in 18% and 39% of cirrhotics within one and five years of their diagnosis, respecttively [3-6].

Deteriorating liver function cause changes altering blood flow and blood vessel tonus in the kidneys, although hepatorenal syndrome may be a consequence of these changes in the blood flow, rather than direct damage to the kidney. In fact, the HRS involves constriction of the blood vessels of the kidneys and dilation of blood vessels in the splanchnic circulation, which supplies the intestines. The kidneys themselves appear with regular size and form and tissue is normal when viewed under the microscope. The kidney function could be also normal when placed in an otherwise healthy environment. The diagnosis of hepatorenal syndrome is based on laboratory tests of individuals susceptible to the condition. The classification of hepatorenal syndrome identifies two categories of renal failure termed as type 1 and type 2 HRS, occuring in individuals with either cirrhosis or fulminant liver failure. In both categories, the deterioration in kidney function is quantified either by an elevation in serum creatinine levels, or by a decreased creatinine clearance in the urine. Type 1 HRS entails a rapidly progressive decline in kidney function and is most commonly precipitated by spontaneous bacterial peritonitis (SBP). It occurs in approximately 25% of patients with SBP. Type 2 HRS is associated with an ascites that does not improve with standard diuretic medication and commonly occurs in patients with relatively presserved hepatic function. These patients are often diuretic-resistant [7-11].

The aim of our study was to investigate the onset, outcome and prognosis of patients with HRS hospitalized at the University Department of Gastroenterohepatology in Skopje.

Patients and methods

This is a cross-sectional retrospective study of 543 cirrhotic patients hospitalized at our Department during the period of 3 years (January, 2008-December, 2010) with HRS detected in 20 patients (3.7%). All of them were analyzed according to a few variables such as: age, gender, history of cirrhosis or other liver disease, etiology of cirrhosis, Child-Pugh classification, other complications of the cirrhosis except for HRS, treatment and survival. The average preceding time up to the occurrence of hepatorenal syndrome in these patients was around 3 years (36.8±47.8 months) since the disease was diagnosed, although there were 4 patients who developed HRS only a month after the onset of cirrhotic symptoms. One of them was determined as a patient with acute alcoholic heaptitis superimposed over the alcoholic cirrhosis. These patients plus another 3 composed a group of seven patients with HRS diagnosed during the first year of the onset of symptoms. The mean age of the patients was 55.5±13.3 years. There was a significant difference in the gender distribution, three quarters of patients being males.

Results

The mean age of our cohort of 543 patients was 53.4± 2.57 years (range 19-78 year), 362 men and 181 women. They have been hospitalized 665 times, and the total amount of hospital stay was 5736 days (Table 1).

Table 1. Distribution of patients with liver cirrhosis in the period 2008-2010

Year	No of pts.	Age	No of hospital	Overall in-hospital days	Average duration of hospital stay per patient
2008	206	57,2	245	1776	8.62
2009	205	55,7	274	2131	10.39
2010	132	53,1	146	1829	9.72
Total	543	/	665	5736	/
Mean	138.75±52.3	53.39	170.5±67.1	1912	9.57

The underlined etiology of our hospitalized cirrhotic patients was HBV, hepatitis C virus (HCV), mixed infections of HBV + HCV, alcohol, nonalcoholic steatohepatitis (NASH), immunological, primary biliary cirrhosis (PBC), secondary biliary cirrhosis (SBC) etc. (Table 2).

Patients were scored according to Child-Pugh classifycation. Child A was found in 215 patients, Child B in 164, and Child C in 164 patients. Hepatocellular carcinoma (HCC) was found in 66 patients, and 67 patients out of 543 died during follow up (Table 3).

Hepatorenal syndrome was detected in 20 patients (15 men) with mean age 55.5±13.3 years (range 21-78). In order to prove the medical history considered for liver cirrhosis in those patients, a complete laboratory, endoscopy, ultrasound examination and chest X-ray were performed. Patients with positive findings have been treated with stan-

Table 2. Distribution of the etiology of liver cirrhosis in the hospitalized patients over the observed period

Year	HBV	HCV	HBV+HCV	Alcohol	Other
2008	38(18.5%)	11(5%)	3(1.5%)	78(38%)	76(37%)
2009	43(21%)	10(5%)	5(2.5%)	61(29.5%)	86(42%)
2010	35(27%)	7 (5%)	29 (22%)	45 (34%)	16 (12%)
Total	**116**	**28**	**37**	**184**	**178**

Table 3. Distribution of patients according to the Child–Pugh classification in the observed period

Year	Child A	Child B	Child C	HCC	Lethal
2008	88(43%)	66(32%)	52(25%)	24(12%)	24(12%)
2009	90(44%)	46(22%)	69(34%)	23(11%)	28(14%)
2010	37(28%)	52(39%)	43(33%)	19(14%)	15(11%)
Total	**215**	**164**	**164**	**66**	**67**

dard therapy for liver cirrhosis.

The investigation of the etiology of liver cirrhosis in HRS patients showed 12 of them with alcoholic abuse. One half (50%) had mixed etiology (Hepatitis B plus alcohol). Two patients had a pure chronic HBV infection as a cause of cirrhosis. Out of four patients with chronic liver disease of unknown etiology 2 had a confirmed histology of chronic hepatitis on liver biopsy.

While most of the patients (n=19) had chronic liver disease, only one suffered from an acute liver disease caused by serologically confirmed leptospirosis infection-Weil's syndrome. All of the cirrhotic patients were scored as grade C according to the Child-Pugh classification, being at end stage liver disease. As a complication of the cirrhosis eight patients had upper gastrointestinal bleeding and ascites was found in 13 of them. Hepatic encephalopathy was the most predominant concomitant complication. Only 2 patients showed signs of malignancy with suspected HCC (Table 4). The estimated average hospital stay was 6.15±4.4 days, ranging from 1-14 days.

Regarding the other characteristics of the HRS patients, spontaneous bacterial peritonitis or any other infection were excluded in all of them. Beside the one with the Weil's syndrome all others were treated with diuretics, either spironolactone alone or combination of spironolactone and furosemide, before admission to our clinics. Higher doses, up to 200mg/24h of spironolactone and 40 mg/24h of furosemide were used in 13 patients with evident ascites. Large volume abdominal paracentesis (exceeding 5 liters per session) was initiated and performed in 4 of them in their regional medical centers. Interestingly, at the same time these 4 patients with prominent ascites had no peripheral edema. Diuretic therapy was interrupted immediately after admission to our hospital in all patients with HRS and chronic liver disease, and fluid repletion was initiated. However, there was no improvement in renal function and degradation products reduction in any of them. In contrast, it was gradually worsened, thus confirming the ensuing hepatorenal syndrome.

Table 4. Distribution by the etiology and Child-Pugh classification plus complications found in the group of 20 patients with HRS

Etiology			Child-Pugh classification			Complications			
HBV	**HCV**	**Alcohol**	**A**	**B**	**C**	**Bleeding**	**Ascites**	**Encephalopathy**	**HCC**
8	0	12	1	0	19	8	13	17	2

Unfortunately, we could admit that the applied treatment was generally unsuccessful. Majority of cases (n=14) were treated with albumin and fresh frozen plasma as a supportive regimen. Due to the general poor condition, severe thrombocytopenia and coagulopathy, haemodialysis was performed in only four patients.

The mortality rate in this population was very high, reaching 80% (16 patients) with average time until death of 6.8± 4.4 days after the admission. Two patients were dismissed from hospital without any improvement of their condition. One was transferred to the University Department of Nephrology for further treatment and the last one to the University Department of Infectious diseases. Although the evaluation period was short, there is a clear increasing trend in the number of detected patients with HRS at our Clinical Center.

Discusion

Epidemiological data about HRS incidence differ from study to study and are little bit confusing. According to Chan, Tai and Lam, the exact incidence of HRS is unknown. It is estimated to occur in approximately 8-10 percent of individuals with the accumulation of fluid in the abdomen and cirrhosis [7]. Conversely, Betrosian considers HRS as common condition, with a reported incidence of 10% among hospitalized patients with cirrhosis and ascites. In decompensated cirrhotics, the probability of developing HRS with ascites is even higher and ranges between 8-20% per year and increases to 40% at 5 years [12]. Gines A, Escorsell and Gines P in the follow-up investigational study of 234 nonazotemic patients with cirrhosis and ascites, concerning the incidence, predictive factors, and prognosis of the HRS, estimate the probability of occurrence to 18% at 1 year and 39% at 5 years [5]. Furthermore Sandeep and Hemant comment that incidence of HRS is globally similar [11]. Our results show HRS occurrence rate of only 3.7% in hospitalized patients. At present, we cannot comment precisely on causes of this difference in our small cohort.

Frequency is equal in both sexes and most patients with chronic liver disease and HRS are in their fourth to eighth decade of life, as said by Sandeep and Hemant [11]. In contrast to similar age occurrence in our study, we established that HRS dominantly occurs in males.

The classification of hepatorenal syndrome identifies two categories of renal failure, termed as type 1 and type 2 HRS, occurring in individuals with either cirrhosis or fulminant liver failure. Type 1 HRS occurs in approximately 25% of patients with SBP, despite rapid resolution of the infection with antibiotics. Without treatment, median survival of patients with type 1 HRS is less than 2 weeks, and virtually all patients die within 10 weeks after the onset of renal failure. Type 2 HRS is associated with an ascites that does not improve with standard diuretic medication, and commonly occurs in patients with relatively preserved hepatic function. These patients are often diuretic-resistant with a median survival of 3-6 months. Although this is markedly longer than type 1 HRS, it is still shorter compared to patients with cirrhosis and ascites who do not have renal failure [7-11]. Appenrodt refers that type 1 HRS has a median survival of 2 weeks, with few patients surviving more than 10 weeks. Type 2 HRS has a median survival of 3-6 months [13]. Having in mind that there was no patient with confirmed SBP, we cannot discus about two types of HRS in our study, but median survival of 6.8±4.4 days after admission, suggests that most of them probably suffer from type 1 HRS. The other possibility is that majority of our patients sought for medical help too late or were misdiagnosed for a longer period. In our surrounding, further prospective trials are clearly warranted, if we want to draw definitive conclusions about all issues that could not have been clearly explained from our study.

Progressive liver failure, as manifested by most frequent complications like worsening encephalopathy, jaundice, and coagulopathy, is a preterminal condition if liver transplantation is not performed [11]. In our opinion, hepatic encephalopathy is the most predominant concomitant complication in cirrhotic patients with HRS, reaching 85% [13].

Repeated abdominal paracentesis in neither cirrhotic patients, nor other therapies will prevent insidious progression to HRS type II, nor the precipitation of HRS type I. In contrast, liver transplantation, or transjugular intrahepatic hepatoportal stent shunt (TIPS) in patients with refractory ascites, may prevent the onset of, or reverse the fatal clinical outcome [1]. Due to the deficiency of these treatment modalities in our country, unfortunately, we have to admit that the applied treatment was generally unsuccessful and the prognosis of our patients with HRS is very poor.

Conclusions

Compared to other reports, our single centre experience shows lower occurrence rate. The outcome of patients with HRS, as well as recovery of kidney function, is highly dependent on the possible reversal of the hepatic failure, be it spontaneous, following medical therapy, or after successful liver transplantation. Despite the use of available conservative medical treatment, there was no recovery of the hepatic failure in any of HRS patients. The absence of liver transplantation or TIPS in our country is the second contributing factor related to the high mortality rate in our cohort.

From all identifiable characteristics of HRS patients with cirrhosis or fulminate hepatic failure as bacterial infection, acute alcoholic hepatitis, or bleeding in the upper gastrointestinal tract, according to our modest experience upper gastrointestinal bleeding is the dominant one. Hepatic encephalopathy seems to be the most frequent concomitant complication in predominantly cirrhotic patients with HRS. Males seem at greater risk for HRS development. Finally, gastroenterohepatologists should be aware and try to prevent iatrogenic precipitants of HRS as an aggressive diuretic treatment or removal of large volumes of ascitic fluid by paracentesis without compensating for fluid depletion by intravenous replacement could additionally impair the renal failure.

Conflict of interest statement. None declared.

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Original article

Microbiological Diagnosis of Peritonitis in Patients Undergoing Peritoneal Dialysis: Review of 10 Years at Ege University Single Centre Experience

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Abstract

Introduction. Peritonitis as a complication of peritoneal dialysis (PD) may cause a technique failure, hospitalization, and even death and the responsible microorganisms have to be evaluated to direct the treatment.
Methods. Three hundred and four patients with the mean age of 48±14 years, 51.6% male, 16.8% diabetics, 14.8% on automated PD program, with mean PD time of 28±26 months, were recruited in this retrospective, observational cohort study.
Results. A total of 384 episodes of peritonitis occurred from January 1999 to June 2009. The peritonitis incidence has been 1 episode every 22.1 patient–months. Gram positive microorganisms were the leading cause 173 (45.1%), in which 111 (28.9%) of Coagulase negative staphylococcus (CoNS), 28(7.3%) of Staphylococcus aureus followed by gram negatives 67 (17.4%), composed mostly of E. coli 23(6%) and Klebsiella pneumoniae 8(2.1%) as causative agents of peritonitis. Proportion of negative dialysate cultures was 24.6 % at 1999 but reduced to 10% at 2009. Methicilline resistant CoNS were found in 50.5% of cases. There was a significant decrease in the proportion of peritonitis due to MR-CoNS from 61.8% (34/55) in 1999-2003, to 39.3% (22/56) in 2004-2009 ($p<0.05$). The proportion of strains resistant to Ampicilline among E. coli was 36.4% (4/11) in 1999-2003 to 75% (9/12) in 2004-2009 ($p<0.05$).
Our policy regarding the initial treatment was cefazoline plus ceftazidime or aminoglycosides so there were no vancomycine resistance in the staphylococci infections.
Conclusion. There has been an increasing resistance to antimicrobials in the world so it is important to determine causative agents of peritoneal attacks and their susceptibilities to antibiotics in order to develop current treatment protocols.

Key words: peritoneal dialysis, peritonitis, culture and antibiogram

Introduction

Peritonitis is a serious complication of peritoneal dialysis (PD) [1-3]; it probably is the most important cause of technique failure in PD [2-5]. Eighteen percent of the infection related mortality in PD patients is the result of peritonitis in the United States [6].
Although the incidence of peritonitis varies from center to center, it decreased dramatically in the 1990s to 1 episode/24 patient-months [7-10]. Widely used treatment guidelines have continually been modified by the International Society for Peritoneal Dialysis (ISPD), and the most recent modification being made in 2010 [11].
Treatment guidelines should be changed depending on the causative organisms because empirical antimicrobial regimens for peritonitis are established by the major causative organisms. Even though cross-sectional studies on the causative organisms of peritonitis have been reported frequently, long-term studies on changes in the causative organisms of peritonitis are scarce [12,13]. There have been only a few studies, conducted at a single center, which analyzed the changes in infecting pathogens and also their antimicrobial sensitivities [14,15].
In the present study, from 474 patient's files, we investigated the causative organisms, antimicrobial susceptibility, and catheter removal rates relative to the causative organisms in all available records of 304 PD patients with peritonitis, who were followed up at Ege University Medical Faculty Hospital, Izmir, between 1999 and 2009. Changes in the causative organisms and antimicrobial susceptibility of each causative organism were also examined.

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Patients and Methods

Between January 1999 and June 2009 at Ege University Medical Faculty Division of Nephrology PD unit Three hundred and four patients being on PD for more than 6 months were recruited in this retrospective, observational cohort study. The mean age was 48±14 years, 51.6% were male, 16.8% diabetics, 14.8% on automated PD program with dry day, the rest CAPD with the 2 liters of dialysate solutions 4 times a day. The mean PD duration was 28±26 months. The data recorded included causative organisms of peritonitis, antimicrobial susceptibility of each organism.

PD was performed by means of disconnect systems (Baxter Healthcare, Deerfield, Illinois, USA, and Fresenius Medical Care, Deutschland GmbH, Germany), with lactate-buffered glucose-containing dialysate solutions.

Prophylactic antimicrobial was not routinely administerred prior to Tenckhoff catheter placement. PD was initiated after a break-in period of 4 weeks following whether percutaneous or surgical placement of the catheter. The standard PD training program lasted generally for a week.

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface. A positive culture in the absence of an abnormal appearance is accepted as colonization rather than infection [16].

A tunnel infection was diagnosed if erythema, edema, or tenderness present over the subcutaneous pathway. A tunnel infection was usually diagnosed in the presence of an exitsite infection but rarely occurred alone.

Patients were classified as having peritonitis if they satisfied at least two of the following criteria: (1) presence of clinical symptoms (pain, fever, cloudy dialysate); (2) presence of more than 100 leukocytes/mm^3 dialysate, with at least 50% polymorphonuclear neutrophils; and (3) positive culture or Gram stain. Since 1999, culture of the dialysate has been performed as recommended by the ISPD [17]. Whole dialysate (50 mL) is concentrated by centrifugation, resuspended in sterile saline, inoculated into blood culture media, and observed for at least 72 hours to document pathogens. Antimicrobial susceptibility is determined by standard disk-diffusion and automatised (api strips/VITEK 2, bioMérieux) microbiological methods.

When peritonitis was diagnosed, empirical therapy with a combination of cefazolin and cefdazidime (or amikacin) was initiated. Within 72 hours, the empirical antibiotics were adjusted based on the results of the dialysate culture and antimicrobial susceptibility test. In culture-negative peritonitis with no response to initial therapy after 72 hours, cefazolin and cefdazidime were substituted by vancomycin and amikacin. If peritonitis did not respond to adequate antibiotics after 96 hours, the catheter was removed. In addition, the catheter was removed in cases of frequent relapsing peritonitis, fungal peritonitis, and tuberculosis peritonitis.

Data are expressed as episodes/patient-months, percent, and mean±standard deviation (SD) Antimicrobial susceptibilities and catheter removal rates according to the pathogens were analyzed using chi-square analysis or Fischer's exact test.

All probabilities were two-tailed and the level of significance was set at 0.05. To further explore the effect of individual factors after excluding potential confounding variables, a Binary Logistic Regression model was constructed.

Table 1. Clinical Characteristics of Patients

Patients (n)	304
Sex (male/female)	157/147
Age (years)	48±17a
APD (%)	45 (14.8)
Mean duration of follow-up (months)	28±26
≥1 peritonitis attacks (%)	165 (54.2)
≥2 peritonitis attacks (%)	67 (40.6)
Peritonitis attacks/patients	384 / 251
Underlying disease (%)	
Others or unknown (%)	135 (44.4)
Diabetes mellitus (%)	51 (16.8)
Glomerulonephritis (%)	32 (10.5)
Amyloidosis (%)	16 (5.3)
Hypertension (%)	28 (9.2)
Polycystic kidney disease (%)	16 (5.3)
TIN (%)	13 (4.3)
Pyelonephritis (%)	8 (2.6)
Systemic lupus erythematosus (%)	5 (1.6)

a Mean ± standard deviation

Table 2. Causative Organisms of PD Peritonitis (n = 384)

	Microorganism	1999-2003		2004-2009	
		n	%	n	%
Peritonitis (patient-months)		21.4		24.4	
Dialysate cultures (+)		122	61.3	129	70
Dialysate cultures (-)		77	38.7	56	30
Gram (+) m.o		85	42.7	88	47.6
	CoNS	55	27.6	56	30
	MR-CoNS	34	17.1	22	12
	S. aureus	15	7.5	13	7
	Other gram (+)	15	7.5	19	10.3
Gram (-) m.o		35	17.6	32	17.3
	Escherichia coli	11	5.5	12	6.5
	K. pneumoniae	3	1.5	5	2.7
	P. aeruginosa	5	2.5	2	1.1
	Other gram (-)	16	8	13	7
Other	Tbc, fungi, etc.	2	1	9	4.9

Results

Demographic and clinical characteristics of patients

Of the 304 patients examined, 157 were men and 147 women, the mean age at the initiation of PD was 48±17 years, and they were followed up for a mean period of 28± 26 months. The causes of ESRD are listed in Table 1.

Causative organisms of peritonitis

A total of 384 episodes of peritonitis were recorded during this 10-year study period. The causative organisms of peritonitis are listed in Table 2.

Peritonitis rates and causative organisms

The incidence of peritonitis decreased significantly, from 1 episode/21.4 patient-months in 1999-2003 to 1 episode / 24.4 patient-months in 2004-2009. Gram positive microorganizms were the leading cause 173(45.1%), in which 111 (28.9%) of Coagulase negative staphylococcus (CoNS), 28(7.3%) of Staphylococcus aureus were followed by gram negatives 67(17.4%), composed mostly by E. coli 23(6%) and Klebsiella pneumoniae 8(2.1%) as causative agents of peritonitis. Overall proportion of negative dialysate cultures was 34.6% but decreased to 10% abruptly by the time (Figure 1).

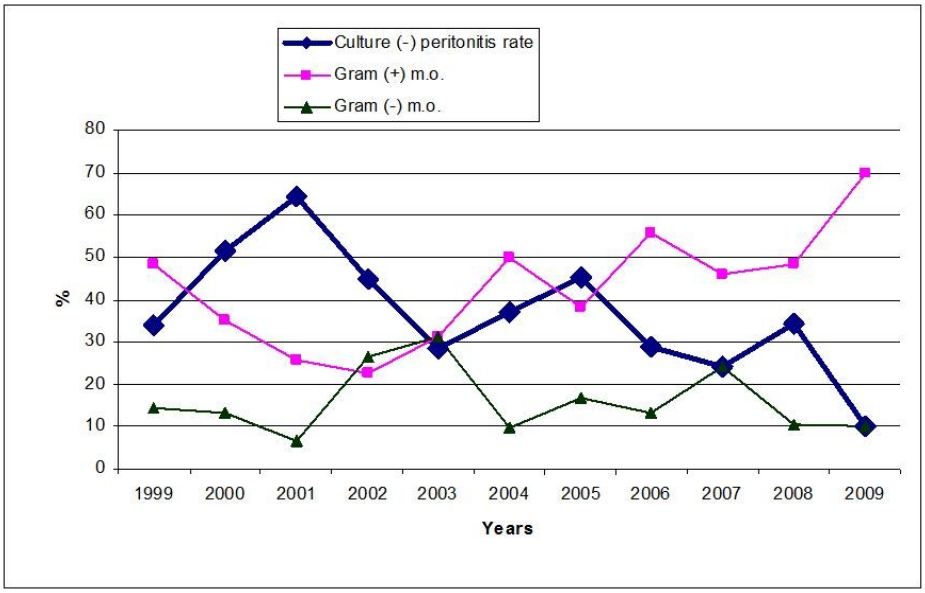

Fig. 1. Culture Negative, Gram-Positive and Gram-Negative Peritonitis Rates in Peritoneal Dialysis

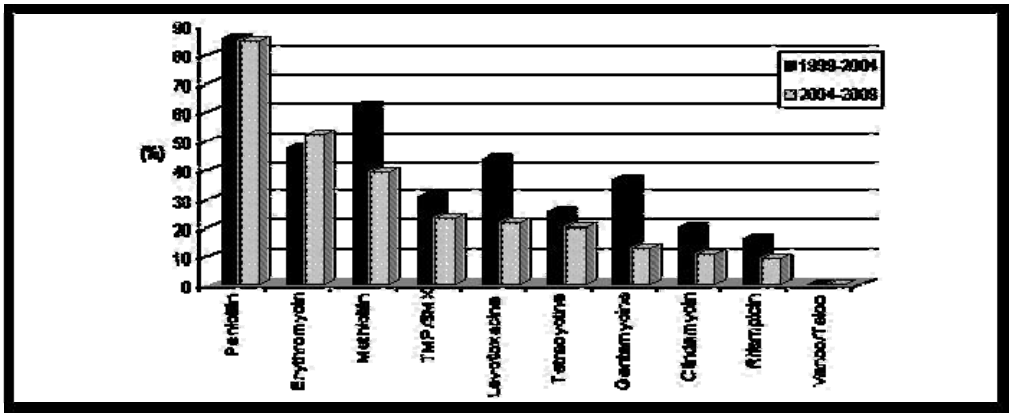

Fig. 2. Susceptibility Profile for Antibiotics in Coagulase negative staphylococcus Species in Peritonitis Episodes in Peritoneal Dialysis ***Abbreviations***: Vanco/Teico - Vancomycin/Teicoplanin

Antimicrobial resistance of gram-positive organisms decreased (Figure 2).

Coagulase-Negative Staphylococcus: Of the 111 episodes of peritonitis caused by CoNS, 49.5% (55/111) were caused by methicillin-sensitive (MS-) CoNS and 50.5% (56/111) by methicillin-resistant (MR-) CoNS. There was a significant decrease in the proportion of peritonitis due to MR-CoNS from 61.8% (34/55) in 1999-2003, to 39.3% (22/56) in 2004-2009 ($p<0.05$). There was also a significant decrease in the proportion of peritonitis

resistance to levoflaxacine from 43.6% (24/55) in 1999-2003, to 21.4% (12/56) in 2004-2009 ($p<0.05$) (Table 3).

Table 3. Susceptibility Profile for Antibiotics in Gram-Positive Species in Peritonitis Episodes in Peritoneal Dialysis

		1999-2003			2004-2009		
	Organism	**Resistance (n)**	**Isolates (n)**	**%**	**Resistance (n)**	**Isolates (n)**	**%**
Penicillin	CoNS	47	55	85,5	47	56	83,9
Methicillin*	CoNS	34	55	61,8	22	56	39,3
Erythromycin	CoNS	26	55	47,3	29	56	51,8
Levofloxacine*	CoNS	24	55	43,6	12	56	21,4
Gentamycine	CoNS	20	55	36,4	7	56	12,5
TMP/SMX	CoNS	17	55	30,9	13	56	23,2
Tetracycline	CoNS	14	55	25,5	11	56	19,6
Clindamycin	CoNS	11	55	20	6	56	10,7
Rifampicin	CoNS	9	55	16,4	5	56	8,9
Vanco/Teico	CoNS	0	55	0	0	56	0
Penicillin	S. aureus	14	15	93,3	12	13	92,3
Methicillin	S. aureus	5	15	33,3	0	13	0
Rifampicin	S. aureus	2	15	13,3	1	13	7,7
Clindamycin	S. aureus	1	15	6,7	2	13	15,4
Erythromycin	S. aureus	4	15	26,7	2	13	15,4
Levofloxacine	S. aureus	4	15	26,7	1	13	7,7
TMP/SMX	S. aureus	3	15	20	1	13	7,7
Tetracycline	S. aureus	3	15	20	3	13	23,1
Vanco/Teico	S. aureus	0	15	0	0	13	0
Penicillin	Enterococcus	4	4	100	2	2	100
Gentamycine	Enterococcus	2	4	50	2	2	100
Levofloxacine	Enterococcus	3	4	75	1	2	50
Vanco/Teico	Enterococcus	1	4	25	1	2	50

$p< 0.05$, TMP/SMX: Trimethoprim/sulfamethoxazole, Vanco/Teico: Vancomycin/teicoplanin, CoNS = coagulase-negative staphylococcus

Staphylococcus aureus: Staphylococcus aureus was the etiologic agent in 7.3% (28) episodes of peritonitis. Methicilline resistance was decreased from 33.3% (5/15) to 0% (0/13) ($p>0.05$) (Table 3). Importantly, there was no Vancomycine resistance to CoNS and S. aureus.

Enterococcus: Enterococcus species were resistant to penicilline and the resistance to aminoglycosides was increased from 50% (2/4) to 100% (2/2) ($p>0.05$) (Table 3). Of the 23 episodes of peritonitis caused by E. coli were 6%. The proportion of strains resistant to Ampicilline among

Antimicrobial resistance of gram-negative organisms increased (Figure 3).

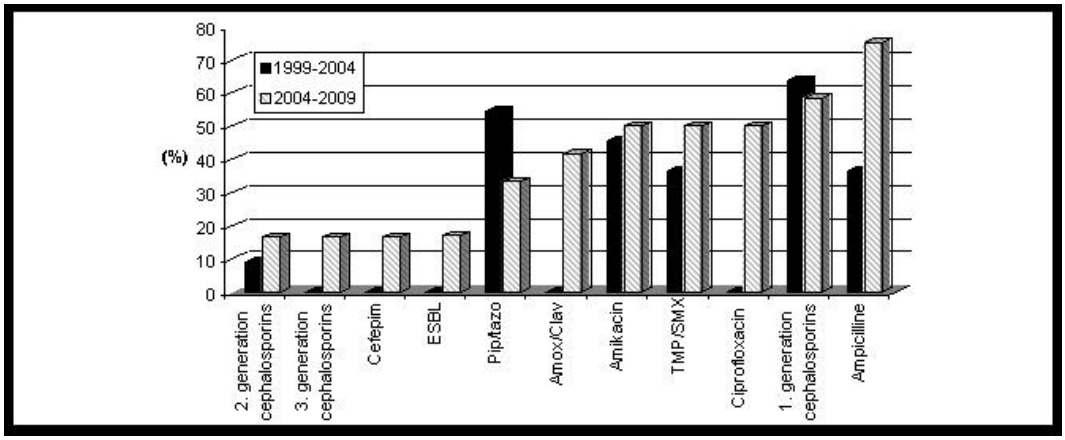

Fig. 3. Susceptibility Profile for Antibiotics in Escherichia coli Species in Peritonitis Episodes in Peritoneal Dialysis ***Abbreviations***: TMP/SMX: Trimethoprim/sulfamethoxazole

E. coli was 36.4% (4/11) in 1999-2003 and 75% (9/12) in 2004-2009, respectively (p<0.05) (Table 4).
Of the 8 episodes of peritonitis caused by K. pneumoniae were only 2.1%. Although there was no resistance to various antibiotics (Cephalosporins, Cefepim, ESBL, and Amikacin) in 1999-2003, by the time resistance reached 20%, while there was a 100% resistance to Ampicilline.

Table 4. Susceptibility Profile for Antibiotics in Gram-Negative Species in Peritonitis Episodes in Peritoneal Dialysis

		1999-2003			2004-2009		
	Organism	**Resistance (n)**	**Isolates (n)**	**%**	**Resistance (n)**	**Isolates (n)**	**%**
1. generation cephalosporins	E.coli	7	11	63,6	7	12	58,3
Pip/tazo	E.coli	6	11	54,5	4	12	33,3
Amikacin	E.coli	5	11	45,5	6	12	50
Ampicilline*	E.coli	4	11	36,4	9	12	75
TMP/SMX	E.coli	4	11	36,4	6	12	50
2. generation cephalosporins	E.coli	1	11	9,1	2	12	16,7
3. generation cephalosporins	E.coli	0	11	0	2	12	16,7
Cefepim	E.coli	0	11	0	2	12	16,7
Ciprofloxacin	E.coli	0	11	0	6	12	50
Amox/Clav	E.coli	0	11	0	5	12	41,7
1. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
Pip/tazo	K. pneumoniae	0	3	0	1	5	20
Amikacin	K. pneumoniae	0	3	0	1	5	20
Ampicilline	K. pneumoniae	3	3	100	5	5	100
TMP/SMX	K. pneumoniae	0	3	0	0	5	0
2. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
3. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
Cefepim	K. pneumoniae	0	3	0	1	5	20
Ciprofloxacin	K. pneumoniae	0	3	0	0	5	0
Amox/Clav	K. pneumoniae	0	3	0	0	5	0
Ceftazidime	P. aeruginosa	1	5	20	0	2	0
Ciprofloxacin	P. aeruginosa	2	5	40	0	2	0
Gentamycine	P. aeruginosa	0	5	0	0	2	0
Carbapenem	P. aeruginosa	1	5	20	0	2	0
Pip/tazo	P. aeruginosa	0	5	0	0	2	0

*p<0.05, Pip/tazo: Piperacillin/tazobactum, TMP/SMX: Trimethoprim/sulfamethoxazole, Amox/Clav: Amoxicilline/Clavulanic acid

Of the 7 episodes of peritonitis, the cause in 1.8% was P. aeruginosa. In the second period althought there was a decrease of Ceftazidime, Ciprofloxacin and Carbapenem resistance, it was not significant (Table 4). In addition, the proportion of strains resistant to the extended spectrum beta-lactamase among E. coli and Klebsiella was 0% to 17% (2/12) and 0% to 20% (1/5) from 1999-2003 to 2004-2009, respectively (p>0.05) (Table 4).
Our policy regarding the initial treatment was cefazoline plus ceftazidime or aminoglycosides as guidelines recommended so there were no vancomycine resistance in staphylococci.

As described in the Methods section, we constructed a Binary Logistic Regression model for the analysis of time to the first peritonitis episode. Variables used for modeling were patient Age, Dialysis mode whether CAPD or APD, Sex, Diabetes mellitus, Catheter insertion technique, PD time (months), Previous transplant history. Using this model, two independent factors that predicted peritonitis -free survival among our cohort were identified, namely, age (hazard ratio -0.98, 95% confidence interval 0.96-0.99; p=0.01) and PD time (hazard ratio -0.98, 95% confidence interval 0.97-0.99; p = 0.000) (Table 5).

Table 5. Binary Logistic Regression Analysis Showing Factors Associated with Dialysis-Related Peritonitis

Variables	**Hazard ratio (95% CI) of developing peritonitis**	**p Value**
Age (per 1 year decrease)	0.98 (0.96-0.99)	0.01
Sex (male vs female)	0.94 (0.57-1.58)	0.83
Diabetes mellitus	1.06 (0.52-2.14)	0.88
Catheter insertion technique	1.29 (0.78-2.15)	0.32

(medical vs surgical)		
PD time (per 1 month decrease)	0.98 (0.97-0.99)	0.000
Previous tx history	-0.68 (0.31–1.48)	0.33

Discussions

There were a few studies investigating changes in the causative organisms of peritonitis and their antimicrobial susceptibilities in PD patients for a decade [15]. This is the first study in Turkey in this field, concerning more than 300 PD patients, for 10 years follow up at a single center. Peritoneal dialysis has been performed in Turkey since 1981. The provider of renal replacement therapy in Turkey is public.

The incidence of peritonitis decreased significantly, from 1 episode/21.4 patient-months in 1999-2003 to 1 episode/ 24.4 patient-months in 2004-2009 years. It was good enough if we compare with the ISPD recommendation rate of 1 episode every 18 months (0.67/year at risk) [11]. This change may be due to the increased experience of our institution, improvement in connecting systems (usage of the double-bag system), development of the new peritoneal dialysis solutions, improvement in living environments, and finally education of patients.

The incidence of peritonitis differs according to patient characteristics, such as race [18], age [19], mode of PD (CAPD vs. automated PD) [20], and composition of dialysis solutions [21]. In the present study, all subjects were Turks, and there was a small decrease in the proportion of diabetics and the age of patients after 2003. All patients used lactate-based solutions. Therefore, we consider that the specially trained nurses and technicians at our institution, who participated in training of new PD patients and in education of patients who visited our PD unit due to peritonitis, along with the patient education program, which has been operational since 2004, all contributed to this decrease. Our education program for new PD patients consists of 1 hour for 7-10 days according to patients intelligence and learning ability. On the first day, patients learn the basic knowledge about renal replacement treatments and physiology of PD; on the second day, how to exchange dialysate and on the following days they learn PD complications and how to deal with these problems and last days perform PD with our team.

Our policy regarding the initial treatment was cefazoline plus ceftazidime (if preserved residual renal function) or aminoglycosides into peritoneal dialysate. Nevertheless, only a few studies have attempted to examine the epidemiology of the causative organisms and their antimicrobial susceptibilities [22], and there have been only two reports at a single center on changes in antimicrobial susceptibility according to each organism [14,15].

We found gram-positive microrganisms incidence and the proportion of peritonitis increased from 1999-2003 to 2004-2009 (Figure 1). However, MR-CoNS, and levofloxacine resistance to CoNS were decreased signifycantly. This may be due to our more effective education program especially avoiding the hand contact of the connecting systems and hygiene. In view of the significant changes in the antimicrobial susceptibility of CoNS observed in our present study, we suggest the use of first-generation cephalosporin as the initial empirical antibiotic, as also recommended by the ISPD [23]. In the literature for the effect of S. aureus prophylaxis on the prevention of peritonitis there have been many studies, but the results are controversial [24-27]. In our study, we could not reveal the effect of S. aureus prophylaxis in our patients because it has never been performed at our unit.

The proportion of peritonitis due to E. coli and P. aeruginosa among gram-negative organisms was found to be the second most common causative microorganisms as similar to previous studies [28,29]. On the other hand, overall proportions of peritonitis due to gram negative microorganisms were decreased, but resistance to Ampicilline was increased significantly. This high resistance to Ampicilline may be due to over use of this drug for upper respiratory tract infections in our country. Nevertheless, it's not the first choice of empiric therapy regimen.

We used BACTEC aerobic bottles (Becton Dickinson) for culture of PD fluid and encountered a high percentage of culture negativity (35%) in PD in 1999-2003 peritonitis cases but it has been decreased to 10% (Figure 1) which was in line with the recommendations by the ISPD guidelines [11].

In the present study, younger age was associated with peritonitis risk reduction. In the literature some studies support [30], some not [31,32] and in our study decreasing the PD duration time was also associated with peritonitis risk reduction. There were no significant difference among gender, diabetes mellitus, type of dialysis treatment (CAPD or APD), type of catheter and its surgical implant, and previous renal transplantation history.

The role of diabetes in peritonitis is not clear; Although Chow *et al*. showed diabetics had a higher risk of first peritonitis episode [33]. Viglino *et al*. did not observe any difference [34].

Locatelli *et al*. showed that, in Argentina, transfer of patients from CAPD to APD resulted in a significant reduction in peritonitis rate: from 1/8.3 to 1/18.9 patient-months [35]. Bevilacqua *et al*. showed in Brazil, a lower peritonitis rate in prevalent APD patients [36]. Fernandez *et al*. in Chile, a peritonitis rate of 1/75 patient-moths with APD, the lowest ever reported in Latin America [37]. In contrast, Oo *et al*. analyzing data from the United States Renal Data System (USRDS), found CAPD was associated with a slightly lower risk than APD for a first peritonitis episode [38].

Conclusions

In conclusion, the proportion of peritonitis due to gram-positive organisms increased, while gram negative organisms were decreased. Antimicrobial resistance decreesed in gram-positive organisms (CoNS) and increased in gram-negative organisms (E.coli and K. pneumoniae) during the study period.

We recommend cefazoline plus ceftazidime (if presserved residual renal function) or aminoglycosides into peritoneal dialysate as initial treatment and to avoid vancomycine as an empirical approach and tailoring the treatment according to the culture results. Consequently, it is necessary to prepare new center-based treatment guidelines for PD peritonitis.

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Conflict of interest statement. None declared.

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Original article

Obstructive Nephropathy as a Result of Malignant Neoplasms: A Single Centre Experience

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Abstract

Introductıon. The aim of our study was to assess the significance of the problem of obstructive nephropathy as a result of malignant diseases in a single nephrology centre.
Methods. The medical histories of patients hospitalized at the Clinic of nephrology, Faculty of Medicine in Skopje, due to malignant disease associated with obstructive nephropathy during January 2000-May 2003, have been retrospectively analyzed.
Results. Out of 42 patients with obstructive nephropathy due to malignancies, the obstruction was a result of cervical carcinoma in 12(28.6%), bladder tumor in 9(21.4%), colorectal tumor in 7(16.7%), prostate cancer in 7(16.7%), endometrial cancer in 4(9.52%), ovarian in 2(4.7%) and lymphoma in 1 patient (2.4%). Double J stent has been inserted in only 5 patients (11.9%) and percutaneous nephrostomy in 14(33.3%). Hemodialysis was discontinued in 8(19%) patients after a successful urinary diversion. In 6 patients (14.3%) maintenance hemodialysis followed after ineffective urinary diversion. Seventeen patients (40,5%) were not adequate for urinary diversion and remained on maintenance hemodialysis and 7 (16.7%), independent of urinary diversion, but all with reduced renal function, had no need for dialysis. All the patients with percutaneous nephrostomy experienced some kind of complications, the most frequent being dislodgment of the tube, obstruction and bleeding (42.8%, 21.4 and 21.5% respectively). Out of 19 attempts, only 5 have been successful in placing double J stent, and only one patient had urosepsis. Hemodialysis was associated with ileofemoral thrombophlebitis in 4 patients (17.4%), and only one patient (4.3%) had catheter associated sepsis.
Conclusion. Hemodialysis is a safe method to relieve signs and symptoms of obstructive nephropathy due to malignancies and may provide a relatively fair quality of life, but is costly and should not be considered if a timely endourologic procedure is possible as palliative treatment for obstructive nephropathy due to malignanices.

Key words: complications; hemodialysis; malignancies; obstructive nephropathy; urinary diversion

Introduction

Three terms are used to describe a disease as a consequence of urinary tract obstruction: obstructive uropathy, obstructive nephropathy and hydronephrosis, but each in different connotation. If ureteral dilatation due to impaired flow of urine is associated with renal parenchimal damage, it is described as obstructive nephropathy [1]. Obstructive nephropathy as a result of malignant neoplasms (ONM) is becoming increasingly a great problem for urologists and nephrologists, and is one of the major emergencies in urology and oncology. The obstruction may be caused by prostate cancer, bladder cancer, colorectal, cervical, uterine, ovarian, testicular tumor, embrionic tumor, lymphoma, and metastatic breast cancer. Two to three percent of the cases with obstructive nephropathy may be benign, as a result of a previous radiation therapy. It is a result of ureteral stricture and usually has a long latent period of 14 years (10-21 years). The malignant obstruction developes in a much shorter period, usually one month, but sometimes might occur as late as after 14 years. It is either due to spread of the primary tumor in the pelvic cavity, or recurrence of the tumor, or due to enlarged metastatic lymph nodes close to the ureters. If the obstruction occurs gradually and in a long term, then cortical atrophy of the kidney ensues, leading to deterioration of renal function and uremia.
Despite advancements in surgical techniques, radiotherapy and chemotherapy for treatment of urogenital malignancies, these neoplasms often progress with obstructive nephropathy due to local spreading or pelvic metastases and if the obstruction is not removed, the patient's clinical conditions will deteriorate at a fast pace through uremia, water-electrolyte abnormalities and urinary infections with a consequent reduction of alertness and subsequent death. Retrograde ureteral clearing with double-J ureteral stents is

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the most widely used technique for relieving obstructtions of the urinary tract, but as it is frequently impossible in cancer patients due to the presence of anatomic deformities, bleeding or ureteral compression, percutaneous nephrostomy (PNS) is the method of choice. Ultrasonography has made this procedure safe and effective obtainning immediate improvement in the biochemical and laboratorial parameters of renal function. Although simple, PNS can be associated with complications leading to significant morbidity. Therefore, in patients with poor prognosis, the indication for PNS is more complex [2].
Most frequent complications associated with ureteral diversion are dislodgment, kinking, blockade and infection from nephrostomy tubes and failed reinsertion of double-J [3]. Sometimes bleeding at the nephrostomy and even haemorrhagic shock is possible.
Many urologists and radiologists have found no differrence in clinical efficacy between placing retrograde ureteral stenting and PNS [4].
The aim of the study was to assess the significance and the scope of the problem of obstructive nephropathy as a result of malignant diseases at the Clinic of nephrology in Skopje by assessment of hospitalized patients with ONM in the period of January 2000-May 2003.

Patients and Methods

All the medical histories of patients hospitalized at the Clinic of nephrology due to malignant disease associated with obstructive nephropathy during January 2000-May 2003, have been retrospectively analyzed. A total of 42 patients have been admitted to hospital due to ONM within this period. Obstructive nephropathy has been diagnosed by ultrasound, intravenous pyelogram or computerized tomography, and the malignancy by histopathologic confirmation prior to hospitalization. The type of malignancy, presence of obstruction (uni-or bilateral), the urologic diversion, nephrologic therapy and complications associated with urologic diversions are summarized in tables. All the patients with ONM were admitted to the Clinic of nephrology either for severely reduced glomerular filtration rate and requirement for urgent hemodialysis, or due to failed attempt for placing double J stent by a urologist, and at the same time having been assessed by nephrologist as progressors toward uremia and need for subsequent hemodialysis. In all the patients that have been assessed adequate for PNS while hospitalized at the Clinic of nephrology, the nephrostomy has been placed either by a nephrologist or gastroenterologist under the guidance of ultrasound.

Results

A total of 42 patients have been diagnosed to have ONM within the study period. Male-female ratio was 20:22. Mean age of patients was 60.4 years (range 29-85 years).

Presentation of ONM according to tumor site and type

Out of 42, in 12 patients (28.6%) the obstruction was a result of cervical carcinoma, followed by 9(21.4%) with bladder tumor, 7(16.7%) with colorectal tumor, 7(16.7%) prostate cancer, 4(9.52%) endometrial cancer, 2(4.7%) ovarian cancer and 1(2.4%) lymphoma).
Table 1 shows the treatment procedure prior to hospitalization and type of obstruction. Only 26.2% have been operated and have their tumor removed and have undergone irradiation. In the majority of patients with ONM, 88.2%, the obstruction was a result of malignant spread.

Table 1. Type of treatment before hospitalization and type of obstruction

Type of treatment	Number of patients (% of total)
Surgical treatment	22(52.4)
Radiation treatment	20(47.6)
Surgery + radiation	11(26.2)
Without surgery or radiation	11(26.2)
Type of obstruction	
Benign obstruction	5(11.9) [latency 5.75years; 3-276 months]
Malignant obstruction	37(88.1) [latency 12.8 months: 0-96 months]

Urinary diversions

Out of 42, in only 5(11.9%) double J has been successfully inserted, and in 14 patients, the attempt failed. In 14 patients (33.3%) percutaneous nephrostomy has been placed. Surgical diversion has been performed in only 2 cases (4.8%) (Table 2).

Table 2. Urinary diversions, hemodialysis and outcome in hospitalized patients with obstructive nephropathy

Primary tumor	JJ- stent n (%)	PNS n (%)	Surgical diversion n (%)	Remained on HD n (%)	Died n (%)
Cervical n =12	1(8.33)	3(25)	1(8.33)	6(50)	1(8.33)
Bladder n =9	1(11.1)	3(33.3)	1(11.1)	3(33.3)	1(11.1)
Colorectal n =7	2(28.6)	5(71.4)	0	4(57.1)	1(14.3)
Prostate n =7	0	1(14.3)	0	4(57.1)	0
Endometrial n=4	0	1(25)	0	3(75)	1(25)
Ovarian n =2	0	1(50)	0	2(100)	0
Lymphoma n =1	1(50)	0	0	1(100)	0
Total n =42	**5(11.9)**	**14(33.3)**	**2(4.8)**	**23(54.8)**	**4(9.5)**

Patient outcome regarding renal function

Out of 42, 23(54.8%) patients remained on maintenance hemodialysis, independent of whether urinary diversion has been performed or not. Out of them, hemodialysis was inevitable in 8 patients prior to urinary diversion, and it was discontinued in all after a successful urinary diversion (19%). Six patients (14.3%) where the urinary diversion had been ineffective remained on maintenance hemodialysis. Seventeen patients (40.5%) were not adequate for urinary diversion and therefore remained on maintenance hemodialysis. Seven patients (16.7%) independent of whether urinary diversion has been performed or not, all with reduced renal function, had no need for dialysis (Table 3).

Table 3. Patient outcome regarding renal function after management of obstruction

Treatment and outcome	Cervical n=12	Bladder n=9	Colorectal n=7	Prostate n=7	Endometrial n=4	Ovarian n=2	Lympoma n=1	Total n=42(%)
HD before UD; Without HD after UD	1	3	2	1	1	0	0	8(19)
With UD, but remained on HD	2	0	2	0	0	1	1	6(14.3)
No UD Remained on HD	6	3	1	4	2	1	0	17(40.5)
With or without UD, no need for HD	2	2	1	2	0	0	0	7(16.7)
Died	1	1	1	0	1	0	0	4(9.5)

Complications of urinary diversions In a total of 14 patients, PNS have been placed, and all of them experienced some kind of complication: in 6 dislodgment occurred and the PNS had to be replaced, in 1 urosepsis was the final outcome, in 3 obstruction of the percutaneous tube, in 3 bleeding and in 1 the attempt to place a PNS failed. In only 5 patients a retrograde double-J stent has been successfully placed. In 14 patients the attempt to place a double-J stent failed, and in one patient with double-J stent, urosepsis occurred. A total of 23 patients remained on maintenance hemodialysis. Out of these 23, in only 4 ileofemoral thrombophlebitis occurred, and in 1, catheter-associated urosepsis (Table 4).

Table 4. Complications associated with urinary diversions and hemodialysis

Treatment	Complications	Patients n=42 (%)
PNS (14 pts)		
	♦ movement/dislodgement	6 (42.8)
	♦ urosepsis	1 (7.2)
	♦ tube obstruction	3 (21.4)
	♦ bleeding	3 (21.4)
	♦ failed attempt	1 (7.2)
JJ-stent (19 pts)		
	♦ failed attempt	14 (73.7)
	♦ urosepsis	1 (5.3)
HD (23 pts)		
	♦ ileofemoral thrombophlebitis	4(17.4)
	♦ catheter associated sepsis	1 (4.3)

PNS-percutaneous nephrostomy, HD-hemodialysis, UD-urinary diversion

Causes of death

Four patients (9.5%) died during hospitalization. Causes of death were pulmonary oedema in two patients who have undergone surgical therapy for the primary tumor (no urinary diversion, treated by hemodialysis only), liver insufficiency in one patient with metastatic liver disease (palliative surgery of the primary tumor, obstruction of the JJ-stent and hemodialysis), and sepsis in 1 patient (only radiation for the primary tumor, no urinary diversion, treated by hemodialysis).
Four patients out of the remaining have been taken home by family members in a very poor general condition. One patient have been transferred to the Reanimatology clinic in chemorragic shock as a result of severe bleeding from the neprhostomy, and a total of 7 patients have been transferred to Gynaecology or Urology for surgical procedure of the primary tumor or palliative surgery.

Discussion

If obstructive uropathy resulting from malignancy is not timely and effectively treated, it may progress to uremia, electrolyte imbalances, persistent urinary infections and death. Reports from literature show a poor prognosis of these patients with a median survival of 3 to 7 months. This accentuates the importance of quality of life (QOL) in these patients. QOL is very often poor additionaly, after urinary diversions, due to frequent complications (tube movement and dislodgement, leaking, bleeding etc.) and moreover, placing a PNS or urinary stent may not necesserialy resolve the obstruction, thus requiring hemodialysis in the end [5]. We observed complications in our study group associated with placement of PNS to a certain

extent. But, the procedure was carried out under guidance of ultrasound only. Carrafiello *et al*. [6] reported no major complications associated with placement of PNS, 14.4% dislodgements, 1.33% rupture of the catheter and 0.67% kinking of catheters, but the procedures were carried out under ultrasound and fluoroscopy. We observed some kind of complications in all the 14 patients with placement of PNS in our study: 42.8% dislodgements, 21.4% obstruction of the percutaneous tube, 7.2% urosepsis, 21.4% bleeding and 7.2% failure to place the PNS. Shekarriz *et al*. [7] also reported high percentage of complications after endourologic palliative urinary diversion (stent or nephrostomy), 68.4% in patients with advanced malignancy and obstructive nephropathy. They also had a high failure rate for primary endourologic procedures and additional procedures were required. Pappas *et al*. [8] on the other hand, reported highly successful and effective desobstruction in patients with ONM, 99% success rate with PNS and 81% with antegrade ureteral stenting. Both procedures have been performed under ultrasound and radiologic guidance in his study. Only 6% of patients had no improvement of renal function, and the rest returned to normal, or significantly improved and had no need for dialysis. Hyppolite *et al*. [9] out of 34 patients with obstructive uropathy due to gynecological malignancy and renal failure (obstructive nephropathy) in a 5-year period, reported that 7 had stent catheter placement and 86% of them developed urosepsis, 17 had PNS (uni-or bilateral) with no complications and renal failure was reversed, and only 6% were dialyzed. They concluded that PNS was a superior procedure for ONM. On the other hand, Wong *et al.* [10] in his study of 102 patients with ONM, concluded that in spite of improved technical success of decompression, subsequent complication rate was still high in these patients, particularly if they had therapy after decompression, and one of the factors associated with inferior overall survival was placement of PNS.

In our study, 45.5% of patients had urinary diversions (33.3% of total had PNS) and the success rate was only 19%. In 19% of patients, hemodialysis was discontinued after urinary diversion, but high number of patients left on maintenance hemodialysis (54.8%). This is the highest percentage of patients treated by hemodialysis compared to other studies (3, 6-10). It might be probably a result to the selection of patients. The study analyzes hospitalized patients in a nephrology clinic where all of them had already obstructive nephropathy with some extent of renal failure. Therefore, the complication rate associated with placement of ureteral stents and PNS was high. But, only 4.3% of patients on hemodialysis (1 patient) had catheter associated urosepsis, and 17.4% had minor complications that were overcome.

As the study analysis patient medical histories retrospectively, sufficient additional data are lacking to clarify the causes why these patients have not timely undergone endourologic procedures. It can be speculated that comorbiditities might be partly a cause of late referral to a urologist, as well as patient incompliance. But, also, one can not disregard a possibility of inadequate cooperation among gynecologists, surgeons, oncologists and urologists.

Conclusion

Hemodialysis is a safe method to relieve the signs and symptoms of obstructive nephropathy due to malignancies, but is costly. Concerning the poor prognosis these patients have and the high percentage of complications associated with endourologic palliative urinary diversions, hemodialysis as palliative therapy to relieve symptoms of uremia is obligatory, but only where all the other endourologic procedures fail. In order to reduce the number of patients with obstructive nephropathy as a result of malignanices on maintenance hemodialysis, establishing a good and devoted team consisting of surgeons, oncologists, urologists and nephrologists is required. Careful follow-up of these patients might enable timely referral to urologist for endourologic procedure, less complications and prevention of loss of renal function followed by maintenance hemodialysis.

Conflict of interest statement. None declared.

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Original article

Clinical Appearance and Management of Fabry Nephropathy in Greece

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Abstract

Introduction. Fabry disease is a rare, X-linked sphingolipidosis caused by an insufficient activity of the lysosomal enzyme alpha-galactosidase-A. Renal involvement is a major cause of morbidity and mortality in these patients.
Methods. We performed a multi-center study, in which almost the entire population of Fabry patients in Greece 20 patients (15 men and 5 women) from 10 independent families] participated and we assessed the clinical manifestations of the disease in our country, focusing on renal involvement. In addition we studied the clinical course of the disease during enzyme replacement therapy (ERT).
Results. The mean age at diagnosis was 37.6 (ranging between 11 and 67) years for males and 38.6 (ranging between 21 and 70) years for females. The diagnosis of the disease was made late, within approximately 18 years after the onset of the symptoms. Almost all patients showed renal involvement upon referral (90% of them presented with albuminuria, 50% with decreased glomerular filtration rate (GFR) and 25% in end-stage renal disease (ESRD). Three years after the initiation of ERT the renal function, as well as proteinuria levels remained stable.
Conclusion. Renal involvement represents one of the most common and particularly serious complications of Fabry disease. Timely diagnosis and early beginning of ERT may provide greater clinical benefit.

Key words: agalsidase beta, alpha-galactosidase-A, Fabry nephropathy, chronic kidney disease, proteinuria

Introduction

Fabry disease is a rare disorder of glycosphingolipids (GSLs) metabolism [1]. It is caused by complete or partial deficiency of the lysosomal enzyme alpha-galactosidase-A (α-Gal A), which leads to gradual accumulation of GSLs in the tissues and the plasma of patients [2]. Clinical diagnosis in affecting hemizygotes is confirmed by demonstrating very low or undetectable α-Gal A enzyme activity in plasma or leucocytes. Identification of disease-causing mutation rather than enzyme activity testing is required in females with either a positive family history or symptoms suggesting Fabry disease [3].

Renal involvement is a major cause of morbidity and mortality in Fabry patients and typically starts during the 2nd -3rd decade of patients life [4]. Urinary concentration defects may be the earliest sign of renal functional abnormalities leading to polyuria and nocturia. Proteinuria, lipiduria and GFR deterioration could also be the initial manifestations [5]. Gradually, the progressive accumulation of GSLs in nearly all renal cell types causes deterioration in renal function; [6] ESRD is usually apparent between the 4th and 5th decade of life, leading to the initiation of renal replacement therapy (RRT) [7,8].

Renal involvement occurs almost in all hemizygotes men, but often in heterozygotes women, too. The clinical manifestation of Fabry nephropathy in males shows increased diversity regarding the degree and the intensity of symptoms: the type of the patient's mutation and the α-Gal A residual activity seem to be related to the clinical expression of the renal involvement [9]. In female patients, variable X-inactivation within renal tissue, as well as the other tissues, along with different thresholds of α-Gal A enzyme required for normal tissue function, may be responsible for the observed phenotypic heterogeneity [10,11].

Aim of the present study was to assess the clinical manifestations of Fabry disease in our country, focusing on

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the renal involvement and to study its clinical course after the initiation of enzyme replacement therapy (ERT).

Patients and Methods

The disease has been already diagnosed in 10 families. The total number of documented patients is 20 (15 males and 5 females). Diagnosis was based on residual enzyme's activity measurement and genetic control-identification of the responsible mutations. Initial symptoms, clinical and biochemical evaluation and disease progression were also recorded. Patient's age at the time of diagnosis ranged between 11 and 70; mean age for males was 37.6 (ranging between 11 and 67) and for females 38.6 (ranging between 21 and 70) years. No statistically significant difference noted in age between males and females (p=0.89). The diagnosis of Fabry disease was made approximately 18 years after the onset of the symptoms.
Currently, 16 patients (3 females and 13 males) are on ERT. Half of them started ERT within the last two years, whereas and 2 out of 16 are at the treatment initiation stage. Eight patients have completed three years of follow-up and treatment results have been recorded based on a proposed protocol. Clinical evaluations were performed every 2 months and all adverse reactions were assessed for the degree of severity, in relation to the treatment regimen. Renal function was evaluated on monthly basis by serum creatinine and eGFR calculated by the Modification of Diet in Renal Disease Study equation [12]. Proteinuria (24 hours urine protein) was evaluated every 6 months of follow-up. Blood chemistries, which also included mass spectrometric quantification of GL-3 in the plasma, using standardized method [13], were performed every 6 months. Serum samples for recombinant human α-Gal A, IgG antibody testing were collected at baseline and every 6-month after ERT initiation.
We have studied the outcome of eight patients in ERT, who have completed three years of follow-up, receiving a common treatment regimen [intravenous administration of 1mg/kg of body weight agalsidase beta (Fabrazyme®, Genzyme Corp) every 2 weeks] in accordance to international guidelines.

Results

Renal involvement

In the vast majority of our patients the diagnosis was made when renal complications occurred. With the exception of two teenagers, a boy and a girl, to whom the disease was diagnosed via the investigation of the respective pedigree trees, the rest 18 patients had already developed clinical and laboratory manifestations of renal involvement upon disease diagnosis. The most common finding was proteinuria (90%), which usually did not exceed 1g/24h (Figure 1). Only one patient was reported with nephrotic syndrome at the time of diagnosis. Kidney biopsies were performed in four patients and were useful to document the diagnosis in three of them.

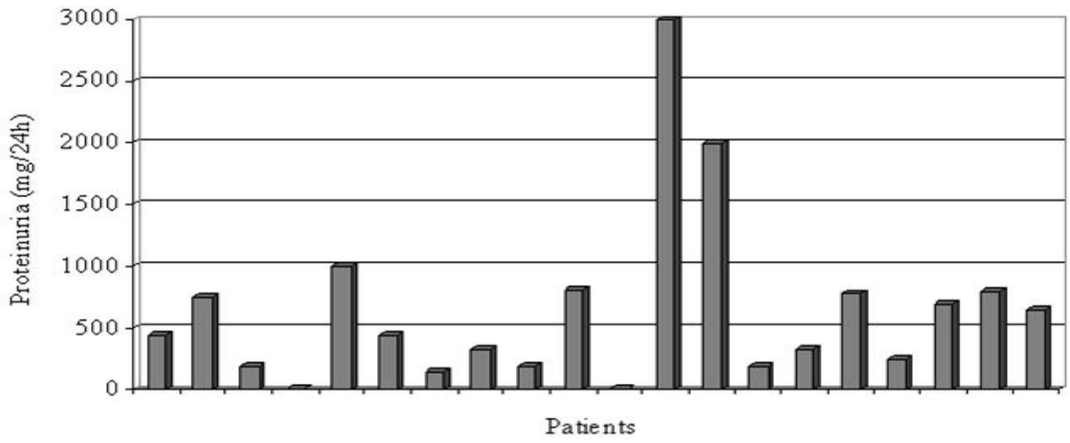

Fig. 1. Levels of Proteinuria of Greek patients at the time of diagnosis of Fabrydisease

We have to underline that, 50% of patients, at the time of diagnosis, had already deterioration of GFR at a relatively young age (39±9 years); three patients presented with stage II CKD, while in other three patients the renal disease had already progressed significantly (stages III-IV) and four male patients presented with ESRD (Figure 2). Three of the ESRD patients were on chronic haemodialysis program (one underwent a successful kidney transplant), whereas the fourth was on peritoneal dialysis.

Enzyme replacement therapy

ERT was invariable during the whole study period and the patients follow up was completed in accordance with the current protocol. No patient withdrawals were reported during the follow up period. Mean plasma GL-3 levels showed a decrease to normal levels (≤7.03 μg/ml) within 6 months of treatment with recombinant α-Gal A in all patients included in the study and these levels remained stable throughout the three years of follow-up (Figure 3).

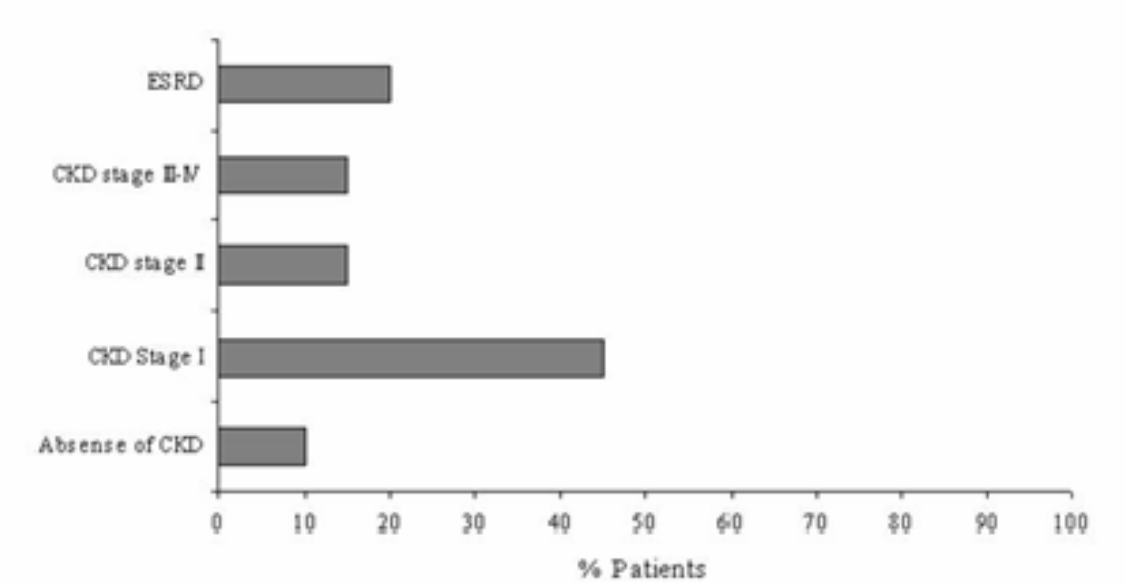

Fig. 2. CKD at the time of diagnosis of Fabry disease in Greece

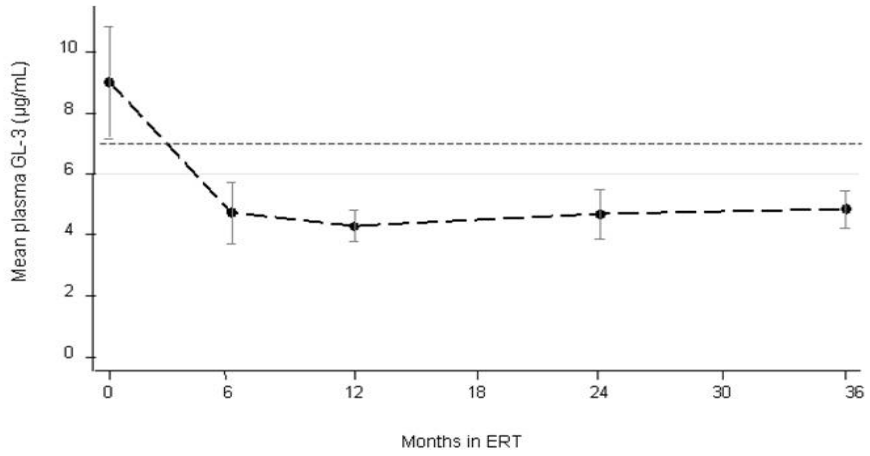

Fig. 3. Mean (±SD) plasma GL-3 concentration (µg/ml), at baseline and at 6, 12, 24, and 36 mo, showing normalization (≤7.03 µg/ml) after ERT

Mean serum creatinine and 24 hours mean proteinuria levels remained stable from baseline in patients receiving ERT during the 3 years of follow-up as shown in figure 4 (A) and (B), respectively. Interestingly in one 51-years-old man patient in ERT, renal function was ameliorated. He was about 39 years old when mild CKD was diagnosed (serum creatinine: 1.3 mg/dL). At the same time, he presented with microalbuminuria (≈150 mg/24h), which remained unchanged during the years of follow-up. During a follow-up of about 10 years his creatinine clearance (Ccr) decreased at a rate of 2.4 mL/min/year. At the initiation of ERT his Ccr was 45 mL/min and rose gradually during the 36 months of treatment and reached 65 mL/min; microalbuminuria remained stable at 150mg/24hours.

In our cohort, ERT was well tolerated; the adverse reactions were mild (fever, rigors, headache) and the majority of them was observed during the treatment and was managed by increasing the infusion time. The development of specific IgG antibodies (seroconversion) against agalsidase beta, as expected [14], occurred in 7 out of 8 patients during the first semester of treatment. However it did not alter the rate of adverse effects during enzyme administration.

Only one patient was reported with significant hypersensitivity reaction despite the pre-medication treatment (antihistamines and corticosteroids). We decided to modify the enzyme administration schedules: for the following-after the reaction-period of six months, the patient received the treatment every week instead of every 15 days with a particularly slow infusion rate (about 12 hours). This modification was absolutely effective and six months later the patient returned to the initial schedule of ERT without developing any other complication ever since.

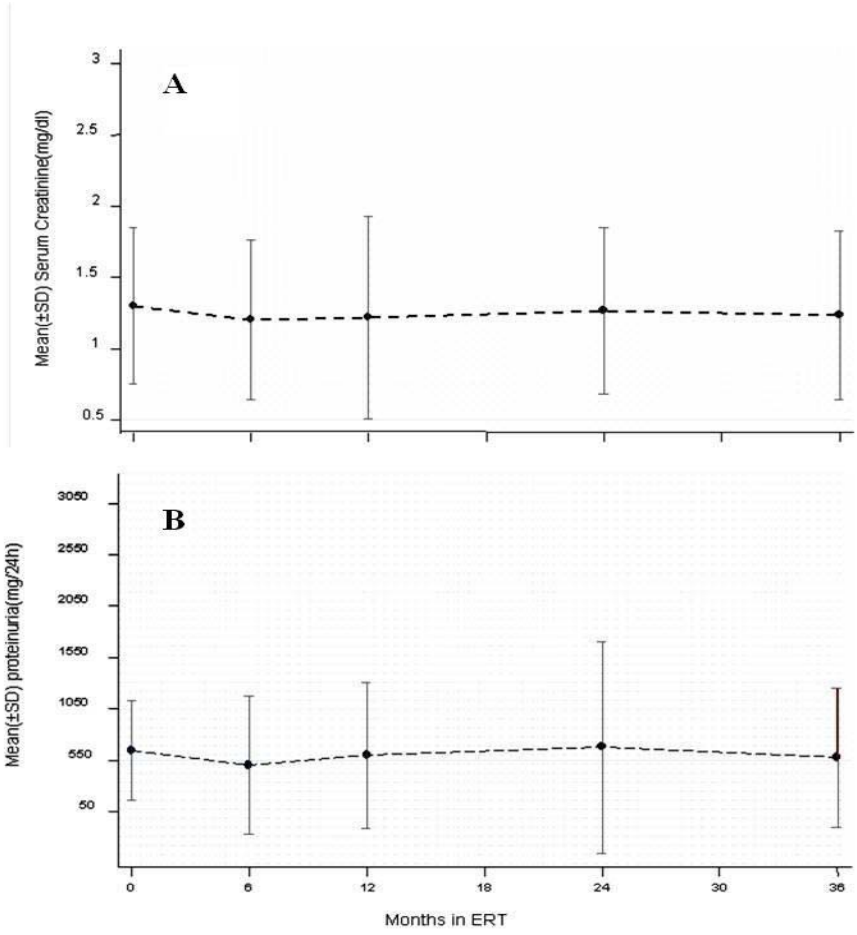

Fig. 4. (A) Stabilization of renal function (serum creatinine) during ERT-three years follow-up
(B) Stabilization of proteinuria (mg/24h) during ERT-three years follow-up

Discussion

Fabry disease is a rare inherited metabolic disorder which, if not treated appropriately and timely, could cause multiple organ failure, leading to death during the 4^{th}-5^{th} decade of patients' life [1,3]. The correlation between the genotype and phenotype of the disease is an important field of medical research and every report to this direction could contribute to the deeper understanding of the underlying pathogenesis of Fabry disease [15,16].

Conducting an epidemiological study on Fabry disease in the Greek territory is a challenging attempt given that prior to 2000 only 2 or 3 cases of Fabry disease were identifyed in our country. The ERT approval resulted in raising the awareness about this rare disease among the medical community in our country, which led to an increased rate of Fabry diagnosis: during the following 6-7 years about 20 new cases were diagnosed in Greece; in other words, every year a new family with Fabry disease is added [17]. Current data indicate a prevalence of about 1 case per 500,000 inhabitants, which is significantly higher than the respective rate at the beginning of 2000, but yet much lower compared to the rest of the world. Based on the significantly increasing rate of new cases, the increasing disease awareness and the better educational level of different medical specialties concerning the disease, we are quite optimist that, very shortly, Hellenic prevalence of Fabry disease is going to reach the levels of the other developed world.

The diagnosis in our country was mainly based on the established significant complications in the course of the disease and despite the fact that the clinical manifestations were apparent very early: the vast majority had the classical symptoms already during the childhood-adolescence period (mean age of symptoms onset: 15.6 years, ranging between 9-20 years). It is noteworthy that the definite diagnosis was delayed approximately 18 years (mean age at diagnosis 36 years, ranging between 15-60 years) [17].

Only two cases in our country were diagnosed based on a typical initial clinical manifestation of the disease such as acroparesthesias or angiokeratomas and without having any known family member with Fabry disease. Nevertheless, at the time of initial diagnosis, even these two patients had already established kidney or heart involvement, suggesting that the diagnosis was delayed. In the rest of the cases, nephrologists made the initial diagnosis during investigation of proteinuria or deterioration of GFR. In some of these cases renal biopsy confirmed the diagnosis. Four patients were presented with ESRD at the time of diagnosis. Fifty percent of Fabry cases in our country (and all the cases of women) were diagnosed through

pedigree trees. Nevertheless, there is no statistically significant difference in terms of the age at which the diagnosis is confirmed between males and females.

Renal involvement constitutes one of the most common and serious complications of the disease. In our study, almost all patients were presented with renal involvement, consisting of proteinuria, and impaired renal function (GFR<80 mL/min/1.73 m^2) at the time of diagnosis. Renal damage is caused by diffuse deposition of GSLs in glomeruli, the tubular system and vasculature and development of structural changes including glomerular sclerosis, tubular atrophy, and interstitial fibrosis [18-20]. Progressive kidney failure develops at a comparable rate as in diabetic nephropathy [21]. However, the pathogenesis of progressive chronic kidney disease in Fabry nephropathy is not yet completely understood; also the renal response to ERT is largely unknown.

Enzyme replacement therapy constitutes the most rational, effective and safe treatment for Fabry patients [22-25]. Exogenous administration of recombinant α-Gal A results in a significant reduction of the deposits of GSLs by all renal cells [26]. The encouraging results of ERT have already been shown in the first clinical trials. Indeed, the renal function in these patients seemed to stabilize in long-term and this finding was more obvious in those starting the treatment at the early stages of renal disease. Moreover, patients who presented with moderately impaired renal function at the initiation of treatment demonstrated significant improvement regarding the rate of loss of their renal function, resulting in a significant delay of renal disease progression [27-30]. In our study, after three years of ERT, patients did not increase the initial proteinuria levels preserving at the same time their renal function stable.

Conclusions

In conclusion, renal involvement constitutes one of the most common and particularly serious complications of Fabry disease. Patients with unexplained chronic renal disease at any stage or albuminuria should be examined for Fabry disease. Timely diagnosis and early initation of ERT are the most effective ways to prevent further renal deterioration due to Fabry disease.

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Conflict of interest statement. None declared.

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Short communication

Wegener's Granulomatosis with Renal and Pulmonary Involvement - Single Centre Experience

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Abstract

Introduction. Wegener's granulomatosis is a systemic necrotizing vasculitis with a potentially fatal course even in patients treated with immunosuppressive drugs. The disease is not very common but the true incidence is difficult to be determined.

Methods. We report 16 cases of Wegener's granulomatosis diagnosed at our Department during a 10-year period, between 1999 and2009. Patients age was 42.8+/-8.6 years, 9 of them were males and 7 females. All patients had severe renal and pulmonary involvement and positive ANCA. The respiratory tract involvement was characterized by multiple bilateral nodular cavitary infiltrates on the computed tomography. The characteristic lesion observed in the renal biopsy was extracapillary glomerulonephritis with crescents found in 80 % of patients.

Results. The clinical features of patients at diagnosis were the following: Upper respiratory tract infection was observed in 12 patients, pulmonary involvement in 15, conjunctivitis in 1, skin lesions in 9 patients, gastroduodenal granulomas in 1, proteinuria and hematuria in 15 and renal insufficiency in 13 patients. Although there were some differences in the clinical and laboratory findings at presentation, nearly all patients had haemoptysis, mild hypertension, leucocytosis, proteinuria and increase of serum creatinine. Fifteen out of 16 patients were treated with corticosteroids and one patient was treated by cyclophosphamide alone. In 80% of patients combination of corticosteroids with cyclophosphamide was used whereas plasmapheresis was applied in 9 of 16 patients (56%). Complete remission was observed in 3 patients, partial remission in 3 and end stage renal disease in 3 more patients. The remaining 7 patients did not survive. In 2 out of 9 patients (22%) treated by plasmapheresis, complete remission of the disease was achieved. No significant difference was observed in all the parameters examined between patients who showed remission and those who did not survive.

Conclusion. The clinical course of Wegener's granulomatosis with renal and pulmonary involvement might be poor despite the administration of immunosuppressive treatment. The early detection of the disease is very important and might be followed by a more favorable outcome.

Key words: Wegener's granulomatosis, glomerulonephritis, chronic renal failure

Introduction

Wegener's granulomatosis is a systemic necrotizing vasculitis, involving mainly the upper and lower respiratory tract and the kidneys. Without effective therapy the disease shows increased mortality rate since 82% of patients are not alive one year after the diagnosis [1-3]. The disease is not very common and the true incidence is difficult to be determined. Male-to-female ratio is 1:1. The disease can be seen at any age, but the mean age at the time of presentation is approximately 40 years old. About 15% of patients are less than 19 years old.

The kidneys are usually involved in Wegener's granulomatosis. A rapidly progressive glomerulonephritis with presence of extracapillary and intracapillary proliferation and cellular and fibrous crescents is observed in a large percentage of patients [2,4].

Prior to the introduction of dialysis, uremia was the main cause of death in these patients. Using cyclophosphamide and steroids, the patients can be successfully treated with a 5-year-survival rate between 60% and 90%. Nevertheless, 20-60% of patients with renal involvement and elevated serum creatinine at the time of initiation of immunosuppressive therapy developed end-stage renal disease during a period of observation of 5 years [5-7]. It has been speculated that, similarly to systemic lupus erythematosus, the activity of the disease decreases after the loss of renal function. Following kidney transplantation, reduction in the activity of the disease has been observed in patients with Wegener's granulomatosis and is probably due to the administration

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of immunosuppressive therapy. Relapses of Wegener's granulomatosis in patients on chronic dialysis have been described, but the number of patients included in the published studies is very small. Moreover, data concerning the dose of immunosuppressive therapy at the time of the relapse and the outcome after treatment of dialyzed patients is not available.

The aim of the study was to present our experience on patients with Wegener's granulomatosis who were diagnosed and treated at the University Clinic of Nephrology in Skopje Republic of Macedonia over a period of 10 years, between 1999 and 2009.

Patients and methods

Sixteen patients with Wegener's granulomatosis, 9 males and 7 females, aged 42.8+/-8.6 years old, were detected at the Department of Nephrology in the period between 1999 and 2009. The diagnostic criteria were: a typical presentation with involvement of the respiratory tract and positive ANCA. ANCA tested by indirect immunofluorescence were found positive at least twice during the course of the disease [4]. All sera were also tested with ELISA, using proteinase 3 and myeloperoxidase as antigens. Our Department is the single Centre in Republic of Macedonia in which a renal biopsy is performed in order to diagnose kidney diseases. All patients signed an informed consent before the renal biopsy. Light microscopy and immunofluorescence were available for the biopsy sections of 12 patients; electron microscopy was used in 2 cases. In 2 patients renal biopsy was not performed. One of them showed a lesion on epiglottis that was biopsied and proved to be granuloma, and another one died the second day of his admission at the hospital, because of the aggressive course of his disease.

Pulmonary involvement was documented using X-ray chest examination and computed tomography.

Relapse was defined as recurrence of the original manifestation of Wegener's granulomatosis with organ involvement that needed re-administration of immunosuppressive treatment.

After the diagnosis had been established, the patients were treated with oral cyclophosphamide (1-2 mg/kg BW/day) and steroids starting with pulse therapy (methylprednisolone 1 g/daily intravenously for 3 days) followed by oral administration of steroids (0.5 mg/kg/daily). The dose of cyclophosphamide was tapered off to 0.7-1 mg/kg BW/daily after 6 months and that of steroids to 20 mg/daily. The administration of corticosteroids alone was followed by some symptomatic improvement, but had only little effect in the clinical course of the disease. Instead of oral administration of cyclophosphamide, we have also used given cyclophosphamide intravenously (500 mg IV every 4-6 weeks) in combination with corticosteroids (Pronison 30 mg /daily). Side-effects of treatment were rarely seen.

Haemodialysis was started in patients with advanced renal failure. Plasma exchange was performed 2-4 times weekly, sometimes every day [8]. Different protocols, depending on the severity of the disease were used for plasmapheresis.

Statistical analysis

For statistical analysis, Student's t-test was used to compare continuous variables and chi-squared test to compare discrete variables. Fisher exact probability test was also used. Any p value below 0.05 was considered as significant.

Results

All patients visited the outpatient Clinic for consultation because of significant proteinuria and impairment of renal function as well as pulmonary involvement. One patient had a lesion in the upper respiratory tract.

Table 1. Clinical manifestations of our patients

Clinical features	Number of patients
Upper respiratory tract infection	12
Pulmonary involvement	15
Conjunctivitis	1
Skin lesions - macula, papules	8
- subcutaneous nodules	1
Gastroduodenal polipoid granulomas	1
Haematuria, proteinuria	15
Renal failure	13

Table 2. Laboratory findings at the admission in the hospital

N	Leucocytes	Urea (mmol/l)	Creatinine (μmol/l)	Proteinuria (g/24 h)	ANCA
1.	15,2	37.7	686	3.14	(+)
2.	13,5	14.0	270	2.43	(+)
3.	12,4	27.9	187	0.61	(+)
4.	14,8	12.6	171	1,04	(+)
5.	20,5	30.3	1889	0.87	(+)
6.	6,0	5.5	74	0.06	(+)
7.	7,3	31.1	891	5.35	(+)
8..	13,0	31.5	1310	0.77	(+)
9.	15,1	28.9	1114	1.67	(+)
10.	15,1	12.0	134	0.92	(+)
11.	19,7	45.7	677	0.52	(+)
12.	13,7	55.3	1116	0.50	(+)
13.	20,2	31.4	801	2.83	(+)
14.	14,3	70	1704	3.26	(+)
15.	14,5	41.9	1116	2.28	(+)

16.	12,5	30.5	872	2.62	(+)

The clinical manifestations of all patients at the time of admission in the hospital are presented in Table 1.Upper respiratory tract infection was observed in 12 patients, pulmonary involvement in 15, conjunctivitis in 1, skin lesions in 9 patients, gastroduodenal granulomas in 1, proteinuria and hematuria in 15 and renal insufficiency in 13 patients. The laboratory investigation of all patients at the admission in the hospital is shown in Table 2. Although there were some differences in the clinical and laboratory findings at presentation, nearly all patients had haemoptysis, mild hypertension, leucocytosis, proteinuria and increase of serum creatinine.

The mean age of men with Wegener's granulomatosis at the time of presentation was 46+/-10.6 years and that of women 36.33+/- 9.85. This difference was not proved to be significant (p=NS).

The main histological finding in the renal biopsies performed, was extracapillary glomerulonephritis with crescents present in 80% of cases as it is shown in Table 3. We found association between the serum creatinin levels and the severity of active glomerular lesions (crescents, necrosis).

Table 3. Histologic findings on renal biopsy

N	G	Age	Histological findings on renal biopsy
1.	f.	48 y	Rapidly progressive glomerulonephritis- diffuse extracapillary
2.	m.	44 y	Rapidly progressive glomerulonephritis
3.	f.	40 y	Diffuse mesangioprolif.glomerulonephritis with fibrocellular crescents
4.	f.	30 y	Necrotizing glomerulonephritis with extracapillary lesions
5.	m.	29 y	Rapidly progressive glomerulonephritis-extracapillary lesions
6.	f.	39 y	Endocapillary and extracapillary glomerulonephritis
7.	m.	39 y	Rapidly progressive glomerulonephritis
8.	f.	41 y	Rapidly progressive glomerulonephritis
9.	f.	20 y	Rapidly progressive glomerulonephritis
10.	m.	40 y	Extracapillary proliferative glomerulonephritis
11.	m.	52 y	Rapidly progressive glomerulonephritis – extracapillary lesions
12.	m.	63 y	Extracapillary glomerulonephritis
13.	m.	55 y	Glomerulonephritis granulomatosa
14.	m.	48 y	Rapidly progressive glomerulonephritis

Table 4. Therapeutic regimen and prognosis

N	Corticosteroids	Cyclophosphamide	PE	HD	Prognosis
1.	MP, Decortin	(+)	(+)	(+)	Death
2.	Urbason	(+)	(+)	(+)	Death
3.	Pronison	/	/	/	Remission
4.	MP, Decortin	(+)	(+)	(+)	Remission
5.	MP, Urbason	(+)	(+)	(+)	Death
6.		(+)	/	/	Remission
7.	MP, Decortin	(+)	/	(+)	Death
8.	MP, Decortin	/	/	(+)	CHD
9.	MP, Decortin	/	/	(+)	Death
10.	MP, Decortin	(+)	/	/	Remission
11.	MP	/	(+)	(+)	Death
12.	MP	(+)	(+)	(+)	Death
13.	MP, Decortin	(+)	(+)	(+)	CHD
14.	MP, Decortin	(+)	(+)	(+)	Remission
15.	MP, Decortin	(+)	(+)	(+)	CHD
16.	MP, Decortin	(+)	(+)	(+)	Remission

MP-metylprednisolone, PE plasma exchange, HD-haemodialysis, CHD-chronic haemodialysis

The therapeutic regimens used and the prognosis of the disease in all patients are shown in Table 4. Fifteen out of 16 patients were treated with corticosteroids and one patient was treated by cyclophosphamide alone. In 80% of patients cyclophosphamide was used in combination with corticosteroids whereas plasmapheresis was applied in 9 of 16 patients. Complete remission was observed in 3patients, partial remission in 3 and chronic haemodialysis was started in 3 patients. The remaining 7 patients did not survive. In 2 out of 9 patients treated by plasmapheresis, complete remission of the disease was achieved. No significant difference was observed in all the parameters examined between patients who showed remission and those who did not survive.

Discusion

In this study we present a group of patients with Wegener's granulomatosis and severe renal and pulmonary disease. The clinical outcome of the disease was different despite the same immunosuppressive regimen used in all patients. It is worth mentioning that our patients with poor prognosis died because of respiratory failure, due to severe pulmonary disease. Literature data suggest a strong correlation between renal histopathology changes and renal out-

come in patients with Wegener's granulomatosis [2,4]. In recent studies, the percentage of normal glomeruli has been found to be correlated to renal outcome, but the presence of active glomerular lesion has not been significantly correlated to the severity of renal disease. Most of our patients presented with classical crescentic glomerulonephritis whereas glomerular necrosis was noticed in only one patient (now in remission). However, glomerular necrosis has been very frequently found in other studies.

Older age and elevated serum creatinine levels at diagnosis, predicted a poor prognosis [5,9]. Most of the reported patients had general symptoms like weight loss, fatigue and/or fever. In patients on dialysis with relapses, involvement mainly of the upper and lower respiratory tract has been observed. Despite the early diagnosis of the relapses and achievement of remission in most cases, about one third of patients with respiratory relapses developed irreversible damage. These reports have stressed the fact that respiratory involvement is important for the patients' survival and renal involvement for the kidney survival. The survival rates of patients with Wegener's granulomatosis on chronic haemodialysis were comparable to those of other patients' groups with end-stage renal disease.

Survival in Wegener's granulomatosis increased dramatically after the establishment of cyclophosphamide and corticosteroids as the standard therapeutic regimen. However, Wegener's granulomatosis is still related with increased mortality rate whereas most patients develop permanent organ damage [10].

In conclusion, our findings suggest that early detection of the disease, when respiratory involvement is not severe is very important. Every patient with haematuria and symptoms of respiratory tract involvement should be immunologically tested and treated properly. However, the clinical course of the disease is not predictable and a large number of patients shows and unfavorable outcome.

Conflict of interest statement. None declared.

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Case Report

Pregnancy in End-stage Renal Disease Patients on Long-term Hemodialysis: Two Case Reports

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Abstract

Although still uncommon, pregnancy in haemodialysis (HD) patients does occur and frequency has been increased in the past 20 years. But unfortunately, the rates for premature delivery, neonatal death, maternal hypertension, and preeclampsia in the pregnant HD patient are much higher than in the general population. Infants are often born both prematurely and small for gestational age. We report here two cases of pregnancy in women on long-term HD, one successfully and the other unsuccessfully managed, despite the same treatment strategy. Case 1 was a 43-year-old female patient, 10th gravida, after six years of maintenance HD whose pregnancy was successfully managed up to the 33rd week of gestation with a delivery of a healthy boy weighing 2,100 g. Case 2 was a 32-year-old female patient, 2nd gravida, after five years of maintenance HD, whose pregnancy ended in spontaneous abortion with intrauterine death at week 19 of gestation. Maternal hypertension and anemia contributed partly to the unsuccessful outcome.
A successful pregnancy in HD patients requires multidisciplinary management, but considering the previous nephrological/prenatal/gynaecological/obstetric recommendations, many open questions remain when it comes to the best treatment and management of pregnancy in these women.

Key words: haemodialysis, pregnancy, anaemia, hypertension

Introduction

In 1971 Confortini *et al*. [1] reported the first successful pregnancy in a 35-year-old woman on chronic HD. Over time, the outcome of pregnancies in patients on HD has markedly improved, from only 23% live births during the 1980s based on a report from the European Dialysis and Transplant Association [2], to 50–100% (overall 76.25%) surviving infants from the systematic reviews in the recent literature (2000 through 2008) [3]. The results of 90 pregnancies reported in the new millennium confirm that pregnancy is still a challenge but also a possibility [3,4]. Nevertheless, fetal mortality in pregnant women on HD is still much higher than in the general population [4]. Polyhydramnios-possibly due to fetal solute diuresis caused by high placental blood urea nitrogen (BUN) concentration, maternal hypertension and premature rupture of the fetal membranes are suspected of causing premature delivery [5]. Shifts in acute fluid volume, electrolyte imbalance, and hypotension could also contribute to the major dialysis-related complications resuling in impairment of the uteroplacental circulation [6]. There are some recommendations for HD management of pregnant patients to improve outcomes, but systematic nephrological and prenatal/ gynaecological/obstetric treatment approach cannot be found in the literature. We report here two cases of pregnancy in women on long-term HD, one successfully and the other unsuccessfully managed.

Case presentation

Case report 1

A 43-year-old female patient, 10th gravida with three living offsprings (1988, 1990, 1993 year) and a history of five abortions before 1988. During the first trimester of her 9th pregnancy (may1996), she developed placental abruption with peripartal haemorrhage, complicated with fetal death and acute renal failure. Bilateral renal cortical necrosis was documented in a contrast-enhanced CT scan in this patient who presented with anuria and remained dependent on dialysis. Renal biopsy was not done due to patient's refusal and she was diagnosed as a case of ESRD in July 1996. She remained on maintenance HD three times a week, with no significant problems.
After six years on maintenance HD (in 2002), she presented with abdominal distension and amenorrhea and was found to be 16 weeks pregnant, diagnosed by serum HCG testing and pelvic ultrasound, but amniocentesis was not

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done due to patient's refusal. The patient was dialyzed with bicarbonate dialysate and low-flux polysulfone F6HPS membrane with 1.3m^2 effective surface dialyzers that were not reutilized. The HD schedule was increased during pregnancy to 4 hours 4 times weekly between the 16th to the 23rd week of gestation, 4 hours 5 times weekly between the 24th to the 28th week of gestation and 4 hours 6 times weekly after the 28th week of gestation. As a consequence, her pre-dialysis blood urea levels decreased from 22.1 mmol/l (20th week), 17.7 mmol/l (24th week), 15.6 mmol/l (28th week) to 14.4 mmol/l at the end of pregnancy, and serum creatinine dropped from 622 μmol/l to 455 μmol/l. As part of her medication, the required dose of erythropoietin (Epo) was increased from a mean weekly dose of 6000 units to 10000 units during pregnancy, but her haemoglobin level ranged between 90 and 72g/l. Iron was also increased from 50mg/weekly to 100 mg/weekly, but transferrin saturation was 22.8% (24th week) and 15.9% (28th week). Blood pressure was controlled by minimal dose of alpha methyldopa of 125mg two times a day, and blood pressure using the ambulatory blood pressure monitoring was 119/76 mmHg (20th week) and 114/72 mmHg (28th week). She also received calcium carbonate, 1500 mg/day as a phosphate binder, multivitamins and folic acid. On the 33rd week of gestation, the patient had a caesarean section delivery of a live boy weighing 2,100 g. After delivery, the mother returned to the schedule of three dialyses per week. The patient and her boy have remained healthy eight years after.

Case report 2

A 32-year-old female patient, 2nd gravida without living offsprings. ESRD was a result of focal segmental glomerulosclerosis proven by renal biopsy in 1996. Her first pregnancy (1997) was complicated by pre-eclamsia with abortion in the 28th week and as her renal function continued to deteriorate, maintenance HD was initiated in April 1997 (three sessions a week). In the first two years of HD she was with poor volume control and hypertensive, depressive, and developed pulmonary tuberculosis that resolved successfully within 6 months. After the first two years of maintenance HD, she remained normotensive and had a regular dialysis course.

Five years after the onset of maintenance HD (2002), the patient informed the nephrologist that she might be pregnant. Gynecological and ultrasound examination confirmed the presence of a live fetus at 13 weeks of gestation. From then onwards, HD prescription was changed to 4 days a week and 5 days a week after 16 weeks of pregnancy, with duration of 4 hours per session. The patient was dialyzed by using bicarbonate dialysate (with Enoxaparin sodium as anti-coagulant) with low-flux polysulfone F6HPS membrane (1.3m^2 effective surface). As expected, Epo and iron requirements were increased during her pregnancy (Epo, from a weekly dose of 6000 units, to a mean of 10.000 units and iron, from 50mg to 100 mg iv once every week), but her haemoglobin level ranged between 81 g/l (14th week) and 65 g/l (16th week), and transferrin saturation between 15.2% and 13.6%, thus requiring additional treatment of two units of red blood cells in the 17th week. Hypertension remained of concern during the pregnancy, and she was treated with alpha methyldopa, 250 mg three times a day, between the 13-14th week of gestation with a dose increase over the next week up to 1500 mg/day. Blood pressure using the ambulatory blood pressure monitoring was 135/91mmHg (14th week) and 156 /103mmHg (17th week). Interdialytic weight gain reached no more than 2.0 kg. She, also, received calcium carbonate 1500 mg/day as a phosphate binder, multivitamins and folic acid. She was intensively followed by the nephrologist and obstetrician, but nevertheless, the pregnancy ended in spontaneous abortion with intrauterine death at week 19 of gestation. After the delivery, the mother returned to the previous treatment strategy of three dialyses per week and within the following eight years she had no significant problems.

Discussion

It has been shown that the prognosis for successful conclusion of pregnancy is better for patients who started HD after initiation of pregnancy as compared to those who conceived after starting HD (73.6% and 40.2%), respectively [4]. Our article reports cases representing patients who conceived long after starting HD (case 1-after six years, case 2-after five years).

Most published papers report that increasing HD hours improves pregnancy outcomes, specifically with respect to gestational age, birth weight, and infant survival [4,7]. In the largest study to date, the Registry for Pregnancy in Dialysis Patients reported the better infant survival in women who received dialysis≥20 hours per week [4]. By 2002, there were enough data available to say that 75% of infants would survive if dialysis was increased to 20 or more hours per week, but that smaller increases in dialysis time were not beneficial [8]. Increasing dialysis dosage reduces predialysis BUN levels and intensified ultrafiltration may reduce the occurrence of polyhydramnios, thus lower the risk of premature labour and rupture of membranes in the later stages of pregnancy. Recommendations regarding the dialysis prescription for the pregnant woman on HD suggest maintaining predialysis BUN concentration of ≤50 mg/dl (17.85 mmol/l) is an appropriate goal [5]. Asamiya *et al*. showed that a birth weight equal to or greater than 1500g, or a gestational age equal to or exceeding 32 weeks corresponded to BUN levels of 48-49mg /dl (17.14-17.49mmol/l) or less [9]. In our case 1, we gradually increased the number of the weekly dialysis sessions and the mean pre-dialysis BUN was maintained at 22.1 mmol/l, 17.7 mmol/l, 15.6 mmol/l and 14.4 mmol/l respectively during pregnancy, which may have contributed in part to the successful outcome

Anaemia and hypertension (HTA) are the most frequent maternal complications observed in the HD population during pregnancy and require intensive management. Recommendations for anaemia management of the pregnant HD patients suggest that Epo doses need to be increased by approximately 50% in order to maintain target haemoglobin levels of 10–11 g/dl. The reason for the higher Epo

doses is unknown, but increased vascular volume with subsequent hemodilution and possibly erythropoietin resistance (due to enhanced cytokine production) during pregnancy may contribute to it [5]. New implications regarding the link between anaemia and pregnancy come from studies in rats, which suggest a possible suppressive effect of endogenous estradiol on erythropoietin induction through iron restoration [10]. This is not consistent with our observation, because, despite the increase of Epo doses for approximately 60% in both cases, the haemoglobin levels were below 90 mg/l, especially in case 2, which may have resulted partly to the unsuccessful outcome.

Common maternal complications observed in HD population during pregnancy include HTA, occurring in 42-80% of these women and polyhydramnios [11]. The pathogenesis of maternal HTA in HD patients is complex, but hypervolemia and inappropriate elevated total peripheral resistance are likely central to the refractory nature of this comorbid condition. Common to both HTA in ESRD and preeclampsia is the impairment in vascular responsiveness [12]. Antihypertensive medications are often required to maintain maternal diastolic blood pressure in the 80-90 mmHg range. The mainstays of treatment are methyldopa, B-blockers, and hydralazine [5]. The patient in case 1 with successful delivery remained normotensive on minimal dose of antihypertensive medications and intensified dialysis throughout pregnancy. However, in the other case 2, HTA was difficult to control during pregnancy despite the maximum dose of methyldopa and increased dialysis frequency, which most probably, at least partly contributed to the unsuccessful outcome. Haemoglobin level in case 2 was not achieved to the levels recently recommended for pregnant HD patients because of the risk to further increase her high blood pressure with higher doses of Epo [6]. The occurrence of HTA with Epo treatment is thought to be secondary to the increase in red blood cell mass, but the mechanism of HTA in this setting is probably multifactorial. However, studies on HTA among pregnant HD patients are lacking.

Several large surveys confirmed that infants born to women on HD are usually premature, with an average gestation of 32 week [3-5). According to the article by Hou, 82% of babies born to HD patients reported to the registry were born before term and 18% were born before 28 week of gestation with the mean gestational age of 29.5 weeks for women dialyzed less than 20 h/wk and 34 weeks for women dialyzed more than 20 h/wk. [8]. In contrast, Baua *et al.* show that the mean gestational age in nocturnal home hemodialysis (NHD) cohort was 36weeks, but what potential advantages may NHD offer to improve pregnancy outcomes is unknown [12]. Our finding in case 1 is in agreement with earlier reports regarding gestational age since we failed to prolong gestational age beyond 32 weeks.

We reported on two cases of pregnancy in women on long-term HD who had different outcomes despite the same management: successful in a 43-year-old female patient in her 10th pregnancy and unsuccessful in a 32-year-old female patient in her 2nd pregnancy. Maternal hypertension and anaemia contributed in part to the unsuccessful outcome in case 2.

Conclusions

In conclusion, our case reports illustrate that following the recommendations for dialysis management in pregnant women may result in successful outcome, but only an international registry of pregnancies in HD patients will help answer the many open questions on the best management of pregnancy in HD women.

Conflict of interest statement. None declared.

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Case Report

Arthrogryposis, Renal Tubular Dysfunction and Cholestasis (ARC) Syndrome: A Case Report

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Abstract

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome, the association of arthrogryposis, renal tubular dysfunction, and cholestasis, is a rare autosomal recessive multisystem disorder. This syndrome results from mutations in VPS33B gene. In some patients, ichthyosis, central nervous system malformations, deafness, and platelet abnormalities may be seen. Many patients with different associations of cholestasis, renal tubular acidosis, and dysmorphic morphology may be underdiagnosed. We describe novel mutations (Gly496Arg and Gly514Ser) in VPS33B gene in an affected fortyfive-month-old female infant with ARC syndrome from Turkey.

Key words: Arthrogryposis, renal tubular dysfunction, cholestasis ARC syndrome, VPS33B gene

Introduction

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome was first described in 1973 and refers to an association between arthrogryposis, tubular dysfunction and cholestasis [1]. It is an autosomal recessive multisystem disorder that may be associated with germline VPS33B mutations on chromosome 15q26 [2]. Other features variably reported include ichthyosis, failure to thrive, mild dysmorphic signs, absent corpus callosum and neurogenic muscular atrophy. Recurrent infections result in severe metabolic acidosis, worsening diabetes insipidus and rarely liver failure [1,3,4]. In the present paper, we describe a fortyfive-month-old girl with ARC syndrome who initially presented with cholestasis associated with homozygote Gly496Arg and Gly514Ser genetic mutations in VPS33B gene.

Case report

A fortyfive-month-old female infant was transferred to our hospital for further evaluation and management of hypotonia and jaundice. She was born at 40th week of gestation from non-consanguineous parents, via cesarian section because of macrosomy with a birth weight of 4100 gr. She was the second child of healthy Turkish parents. On the 8th day of life jaundice was recognized and she was hospitalized on 35th day in another hospital with the diagnosis of prolonged jaundice. On physical examination body temperature was 36.5 ^{0}C, heart rate 140 per minute, respiratory rate 28 per minute, weight 3000 gr, length 53 cm and head circumference was 37 cm. She had dry and scaly skin like ichthyosis, lax skin on the neck and jaundice. Muscle bulk

Fig. 1. Manifestation of ARC syndrome. Ichthiyosis, lax skin, reduced muscle bulk, flexion contractures of knees and limbs, equinovarus, talipes calcaneovalgus, radial deviation of the wrists, bilateral arthrogryposis

of deltoid and triceps was notably reduced. Flexion contractures of knees and limbs, equinovarus, talipes calcaneo-

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valgus, radial deviation of the wrists, bilateral arthrogryposis, proximally inserted thumps and big toes were detected (Figure 1).

Liver was palpable 4 cm from the costal margin. On laboratory examination, hemoglobin was 8.1 g/dL, leucocyte: 18.200/mm^3, platelet: 497.000/mm^3 (giant-sized platelets were seen in peripheral blood smear), serum total bilirubin level was 10 mg/dL, conjugated bilirubin level 3.8 mg/dL. Serum values of transaminases, gamma glutamil transferase, protein and albumin were within the normal limits but alkaline phosphatase was 4 times above the normal value (1438 U/L). Protrombin time (18 seconds) and activated partial tromboplastine time (76.8 seconds) were prolonged. Serologic investigations for hepatitis and viral infections were negative. Thyroid function tests were within normal limits. Plasma alpha 1 anti-tripsin, alpha feto protein, aminoacid analysis of blood and urine were all normal. Urine electrolytes were as follows: Na 40 mmol/L, K 27 mmol/L, Cl 37 mmol/L, Ca 8.2 mg/dL and P 23 mmol /L. A search of common mutations for cystic fibrosis was negative. She was diagnosed as Fanconi syndrome with blood pH of 7.32, HCO_3^- of 11 mmol/L, base excess of 14 and urine pH of 6.5 with proteinuria (> 300 mg/dL), calciuria (6.8 mg/kg/day), phosphaturia (TPR: % 45) and glucosuria (48 mg/dL) with normal serum glucose. Urinalysis showed tubular proteinuria [N-acetyl glucoseaminidase: 22 U/L (normal: 1.5-6.1 U/L), beta 2 microglobulin 77.7 mg/L (normal: 0.02-0.2 mg/L)]. Abdominal ultrasound showed bilateral moderate renal hyperechogenity, nephrolithiasis in left kidney and minimal hepatomegaly. A radionucleotide scan of biliary system (HIDA scan) revealed excretion to the bowel after 24 hours. Liver biopsy showed giant cell hepatitis. Cranial MRI and echocardiographic studies showed encephalomalacia and atrial septal defect (< 3 mm), respectively. With all signs and laboratory findings ARC syndrome was diagnosed. We have screened all 23 exons and exon–intron boundaries of the VPS33B gene and mutation analysis revealed homozygote Gly496Arg and Gly514Ser mutations in VPS33B gene.

After treatment with Scholl solution, acidosis was partially improved (blood pH: 7.38, HCO_3^-: 18 mmol/L, base excess: -4). Despite treatment with intravenous antibiotics, total parenteral nutrition and appropriate fluids, she died at the age of 4 months from dehydration and sepsis. Autopsy could not be performed because her parents did not give permission for religious reasons.

Discussion

Arthrogryposis-renal dysfunction-cholestasis syndrome is a multisystem disorder with a wide clinical spectrum. This rarely seen syndrome is characterized by arthrogryposis, renal tubular dysfunction and cholestasis [1]. To the best of our knowledge, we report the fourth patient from Turkey who presented with Fanconi syndrome, cholestasis and renal tubular acidosis.

In this syndrome, the first diagnostic criterion is arthrogryposis and it is thought to be secondary to neurogenic muscle athrophy [6]. It has been reported that fractures in extremities due to muscle athrophy and strain [7]. Evidence of denervation was obtained from electromyographic studies as well as from muscle biopsies [8]. Severity varies from talipes equinovarus to severe hip dysplasia [3]. Our patient just had flexion contractures of knees and limbs, equinovarus, talipes calcaneovalgus, radial deviation of the wrists, bilateral arthrogryposis, proximally inserted thumps and big toes (Figure 1).

Cholestatic jaundice and hepatomegaly are the most common symptoms at presentation and the second major component of the syndrome. Reportedly, all patients had conjugated hyperbiluribinemia and level of bilirubin in an individual patient fluctuated between extremely high or normal levels. Normal or mildly elevated transaminases with normal GGT level are a constant and early feature of ARC syndrome. Appropriate laboratory investigation should be done to rule out the other causes of conjugated hyperbilirubinemia in infancy. Our patient had conjugated hyperbilirubinemia with normal transaminase and GGT levels. In a study 14 out of 15 patients had non excreting biliary isotope studies suggesting biliary obstruction or severe intrahepatic cholestasis as HIDA scan of our patient revealed excretion to the bowel after 24 hours [3]. Liver biopsy shows paucity of bile ducts, lipofuscin deposition, bile plugs and giant cell hepatitis [9]. Therefore, liver biopsy has nonspecific findings and this procedure could be dangerous due to bleeding. In our patient, however, liver biopsy revealed giant cell hepatitis.

Renal dysfunction in ARC syndrome is characterized by multiple features of Fanconi syndrome including aminoaciduria, glycosuria, phosphaturia and bicarbonate wasting as well as by nephrogenic diabetes insipidus [10,11]. Gissen *et al*. [3] found poor corticomedullary differentiation in 6 patients, nephrocalcinosis in 6 patients and tubular atrophy in 2 patients. Our patient was also diagnosed as Fanconi syndrome and she showed tubular proteinuria which is the most striking clinical abnormality. Also, in our patient, renal ultrasound showed nephrolithiasis which is an occasional sign of this syndrome.

Abnormally, large platelets have been described in ARC patients as in our patient but trombocytopenia is unusual [1]. Although, despite normal clotting studies hemorrhagic events can be encountered after interventional procedures, such as kidney or liver biopsies, in our patient, we performed liver biopsy, uneventfully. However, later on, intracranial bleeding was detected during sepsis.

Congenital heart disease has been reported in ARC patients [2]. Our case had an ASD less than 3 mm. with no clinical significance.

Unfortunately, curative therapy for this rare syndrome has not been reported [2]. The current treatment of ARC patients includes the use of fluids and caloric administration such as total parenteral nutrition or medium-chain triglyceride-rich formulas, monthly vitamins A-D-E-K and ursodeoxyhcolic acid. Most patients do not live longer than 7 months after birth despite supportive care for metabolic acidosis and cholestasis [12]. Death usually occur secondary to sepsis and severe dehydration and acidosis [6]. Our patient died at 4 month of age, due to sepsis.

Novel identification of the mutation in VPS33B in this syndrome, which involves intracellular protein traffick-

ing by regulation of vesicle-to-target sensory nerve action potential receptor (SNARE) family, might explain the consistent combination of membrane fusion defects [5,13]. The reported cases and also mutations are few in the literature due to the new discovery of gene locus of disease. The mutation analysis for ARC syndrome is important because it eliminates the need for diagnostic organ biopsies which results in life threatening hemorrhage over 50 % of patients. The syndrome is inherited in an autosomal recessive pattern and most of the reported cases are from the regions where the consanguineous marriage rates are high, as in our country [2]. Recently, Gissen *et al*. [5] mapped the disease to 15q26.1 and identified germline mutations in the VPS33B gene in 14 kindred with ARC syndrome. Furthermore, Gissen *et al*. found that, in 7 apparently unrelated consanguineous families of Pakistani origin with ARC syndrome, a 1311C-T transition in the VPS33B gene resulting in an arg438-to-ter (R438X) mutation and in a consanguineous Pakistani family with ARC syndrome an arg532-to-ter (R532X) mutation [5]. Gissen et al. [13] also characterized clinical and molecular features of 62 individuals with ARC from 35 families (11 of which had been previously reported). Germline VPS33B mutations were present in 28 of 35 families (48 of 62 individuals); however, VPS33B mutations were not detectable in approximately 25% of patients, suggesting the possibility of a second ARC syndrome gene [13]. Our case is the forth patient reported from Turkey and twenty-first patient who was determined VPS33B mutation by this time [5,13]. Mutation analysis revealed a 1405G-C transition resulting in homozygote Gly496Arg mutation and a 1540 G-A transition resulting in Gly514Ser mutation in VPS33B gene. We, therefore, identified novel mutations in our Turkish patient with ARC. Identification of population-specific mutations improves the ability to provide rapid molecular diagnosis and makes molecular studies more affordable.

Conclusion

Arthrogryposis-renal dysfunction-cholestasis syndrome is a severe multisystem disorder leading to death in infancy. However, the traditional method of diagnosis such as liver biopsy is associated with a substantial risk of morbidity and mortality. Direct sequencing of VPS33B is a good method to provide molecular diagnosis in ARC patients.

Conflict of interest statement. None declared.

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Case report

Spontaneous Rectus Sheath Haematoma in a Renal Transplant Recipient

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Abstract

Rectus sheath hematomas are rare and generally caused either by rupture of one of the epigastric arteries or by a muscular tear with shearing of a small vessel. Anticoagulation has been described as an important etiological factor; other less frequent associations include recent abdominal surgery, medication injection, trauma, and increased abdominal pressure from straining, coughing or pregnancy.
We present a first documented case of bilateral spontaneous rectus sheath haematoma in a renal transplant recipient treated with nadroparin. Sixteen days after renal transplantation she experienced abdominal pain after twisting in bed. Urgent MSCT revealed rectus sheath haematoma which was surgically treated with ligation of epigastric arteries. Patient completely recovered with preserved renal allograft function.

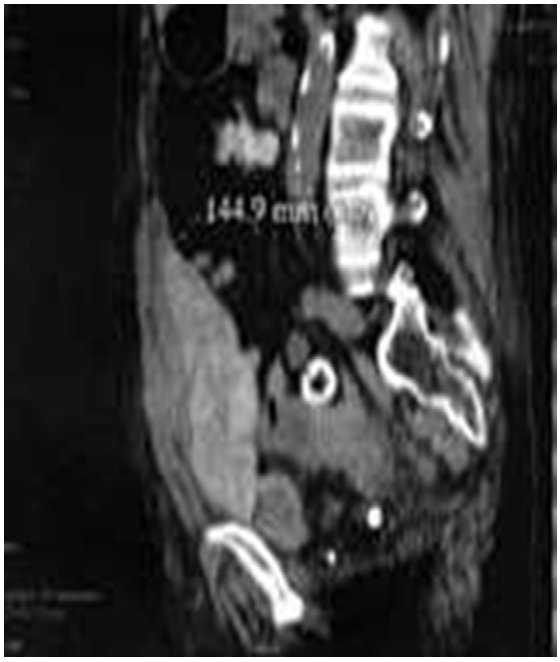
Key words: rectus sheath haematoma, renal transplanttation, LMWH, nadroparin

Introduction

Rectus sheath haematoma (RSH) is a rare and difficult to diagnose clinically, while it may mimic a number of other acute abdominal conditions. It results from bleeding into the rectus sheath from injury to the epigastric arteries or their branches, or sometimes from a direct tear of the rectus abdominis muscle [1].
We present a first documented case of spontaneous bilateral rectus sheath hematoma in a renal transplant recipient.

Case report

A 63-year-old female patient received a renal allograft with 4 mismatches from deceased donor after 4 years of haemodialysis. Primary renal disease was amyloidosis. She also suffered from hypothyreosis. Body mass index was 27 kg/m2. Immunosuppressive protocol included basiliximab (20 mg on days 0. and 4.), cyclosporine (trough concentration was 185 umol/L), mycophenolate mofetil 2x1 g and steroid. Patient received pantoprasol, beta-blocker, L-thyroxin, digoxin, and gancyclovir. In 2007 she received artificial mitral valve for correction of mitral insufficiency, and since that time had been treated with warfarine. After renal transplantation she received nadroparin (Fraxiparine®) 0.6 ml/day subcutaneously. Graft function was delayed and she required dialysis 11 days after transplantation. Sixteen days after the surgery she experienced severe left sided abdominal pain after twisting in bed. Her haemoglobin dropped from 11.4 to 9.8 g/dL. A multi-slice computed tomography (MSCT) scan of the abdomen demonstrated a large haematoma in the right rectus abdominis



1a.

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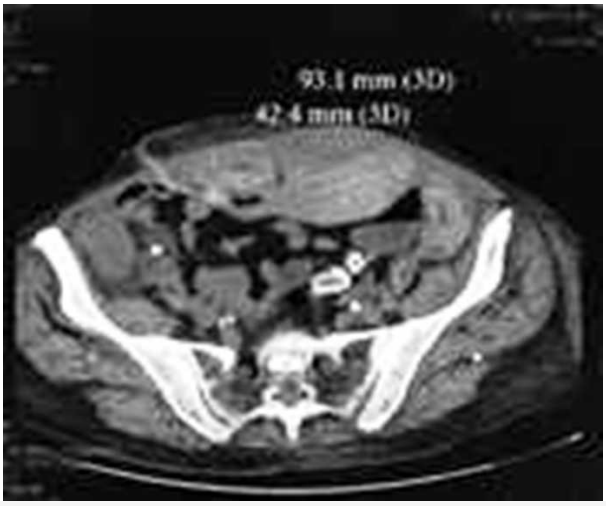

1b.
Fig. 1a and 1b. Multislice CT scan showing rectus sheath haematoma

muscle. On examination the patient was hemodynamically stable with a large haematoma palpable in the right side of her abdomen surrounded by extensive bruising. Haematoma was surgically drained, anticoagulation was ceased. The international normalized ratio (INR), activated partial thromboplastin time (APTV) and anti-Xa levels were all within the normal levels. Two days later she felt severe pain in the left side of abdomen. MSCT revealed haematoma in the left rectus abdominus muscle measuring 9.3x4.2x 14.5 cm (Figure 1a and 1b). Patient was hypotensive what urged surgical control of the bleeding. Her hemoglobin dropped to 6.9 g/dL, and she received blood transfusion. Under general anaesthesia incisions were made over the inguinal ligament and over the upper rectus abdominis muscle. The right inferior and superior epigastric arteries were identifyed and ligated. She recovered completely, and left the hospital 10 days later with good kidney function.

Discussion

Rectus sheath hematomas are generally caused either by rupture of one of the epigastric arteries or by a muscular tear with shearing of a small vessel. The immediate cause of the rupture may be external trauma to the abdominal wall, iatrogenic trauma from surgery, or excessive vigorous contractions of the rectus muscle [1]. Because the arteries supply the recti from the back side, most hematomas are posterior to the muscle, making diagnosis by means of palpation more difficult. The incidence is thought to be on the rise, with the increased use of oral anticoagulation drugs and low molecular weight heparins (LMWH) [2,3].
It is difficult to distinguish between rectus sheath haematoma and other intra-abdominal disorders what caused many unnecessary surgical abdominal explorations. Rectus sheath haematomas occur more commonly in women, with the highest incidence in the fifth decade. Anticoagulation has been described as an important aetiological factor; other rarer associations include recent abdominal surgery, medication injection, trauma, and increased abdominal pressure from straining, coughing or pregnancy. Common features in the history include acute abdominal pain, often associated with nausea, fever and vomiting [4,5].
Both ultrasonography and CT may be used for diagnosis, thus reducing unnecessary laparotomy, but CT is more sensitive and specific, and has the advantage of ruling out other abdominal pathology [6,7].
Most rectus sheath haematomas can be treated conservatively with bed rest, analgesia, treatment of predisposing conditions, transfusions and discontinuation of anticoagulation. Active bleeding can be managed either surgically by evacuating the haematoma and ligating the bleeding vessels or radiologically with catheter embolisation [8,9].
Although most are self-limiting, rectus sheath haematoma can lead to significant morbidity and has an overall mortality reported as 4%. Patients on anticoagulation therapy have the mortality as high as 25%. The morbidity of rectus sheath hematoma is primarily the result of incorrect diagnosis leading to unnecessary exploratory laparotomy or delay in cessation of anticoagulant therapy [1,4,5].
To the best of our knowledge, a case of spontaneous rectus sheah haematoma in renal transplant recipient has never been described in the literature. It resulted from the accumulation of extravasated blood into the sheath of the rectus abdominal muscles. Abrupt change in position, together with precipitating factors which in our patient included anticoagulation therapy, coagulation disorder, recent surgery, medication injection, steroid treatment, and amyloidosis as the primary renal disease, all contributed to development of this rare complication. Prompt recognition and treatment resulted in complete recovery with preserved graft function. Association between the time-duration of the use and the dose of anticoagulants as well as of corticosteroids with the incidence of RSH is, because of the rarity of this condition, unknown but possible.

Conclusion

This case demonstrates an uncommon cause of abdominal pain in a renal transplant recipient. Spontaneous abdominal rectus muscle haematoma occurred as a result of accumulation of multiple risk factors. Prompt recognition and treatment are mandatory to reduce morbidity and mortality in this rare condition.

Conflict of interest statement. None declared.

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Letter to the editor

The Measurement of Inferior Vena Cava Diameter for Assessing Volume Status in Autosomal Dominant Polycystic Kidney Disease

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Dear editor,

Hypertension is an early and frequent manifestation in ADPKD, being the presenting clinical finding in 13 up to 81% of patients [1,2]. Although the underlying mechanisms for the rise in blood pressure in individuals with ADPKD are still unclear, two principal mechanisms as elevated plasma volumes [3] and increased plasma renin activity [4] are reported. Since invasive methods for evaluation of fluid status such as measurement of central venous pressure cannot be used routinely, the measurement of the inferior vena cava diameter (IVCD) by echocardiography has been suggested to reflect the intravascular volume in adult haemodialysis patients and to correlate well with the other methods for estimation of fluid volume [5,6]. Also a significant correlation was found between IVCD and blood pressure [7]. The present cohort study was undertaken for assessing the correlation of volume status with IVCD in our ADPKD patients.

A hundred ADPKD patients included in the study were divided in two groups: first group of 52 patients without hypertension (normotensive patients) and second group of 48 patients with hypertension (hypertensive patients). Hypertension was defined as BP greater than or equal to 140 mmHg for systolic BP and greater than or equal to 90 mmHg for diastolic BP [8]. Eighty patients had normal renal function (GFR > 60 ml/min). All hypertensive patients were treated with one or more antihypertensive drugs. Only three patients received diuretics in small doses. All vasoactive medications were stopped 48 hours prior the IVCD measurement. Knowing that patients with ADPKD can be complicated with valvular abnormalities, in this study we didn't include patients with these abnormalities. IVCD was visualized two-dimensionally and measured by Doppler-echocardiography three times during a period of 18 months (every six months, divided in three periods). The anteroposterior IVCD was measured using 2-dimensional and Doppler recordings 1.5 below the diaphragm in the hepatic segment in the supine position after 5–10 min of rest during normal expiration and inspiration. The same examiner performed all the measurements of IVCD. Mean IVCD was expressed as (IVCD in inspiration+IVCD in expiration)/2. The referee values for IVCD were those defined by Mandelbaum *et al.* (normal range 8-11 mm/m^2) [6]. Results are reported as mean±SD. *P* values less or equal to 0.05 were considered statistically significant.

Table 1. Demographic and clinical data of patients

Demographic variable	Normotensive patients	Hypertensive patients
Number of patients	52	48
Gender (M/F)	23/29	22/26
Age (years)	46.4±5.7	49.1±8.9
Smoking (Yes/No)	12/40	19/29
Renal function		
- normal renal function (GFR > 60 ml/min)	42 patients	38 patients
- chronic renal failure (GFR < 60 ml/min)	10 patients	10 patients
Mean blood pressure values (mmHg)		
Mean systolic pressure	131.2	162.5
Mean diastolic pressure	88.4	97.7
Body weight (kg)	74.2±5.7	71.6±4.3
Body height (cm)	162.7±9.4	164.8±10.2

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The demographic and clinical data are presented in Table 1. The mean IVCD result was 9.8±2.3 mm/m^2 in the first group of normotensive patients, while in the second group of hypertensive patients it was 12.4±0.9 mm/m^2 ($p< 0.005$) (Table 2). An interesting fact was that in 18 patients of the first group (normotensive patients), the mean IVCD result increased and 13 of these patients developed hypertension after a mean period of 2.4±1.2 years. In addition, five patients from the last group developed left ventricular hypertrophy (LVH) after some years.

These results indicate the importance of fluid overload in the pathogenesis of hypertension in ADPKD patients. Since the volume expansion is a pathogenetic mechanism for hypertension in ADPKD patients, IVCD would be accurate assessments of the volume state in ADPKD patients. It was proved that hypertension plays an important role in cardiovascular morbidity including LVH and mortality [9].

Table 2. IVCD measurements

	Normotensive patients	**Hypertensive patients**	**P**
Mean values of IVCD	9.8 ± 2.3 mm/m^2	12.4 ± 0.9 mm/m^2	< 0.001
First measurement (mean values)	9.3 ± 2.5 mm/m^2	11.9 ± 1.3 mm/m^2	< 0.001
Second measurement (mean values)	9.5 ± 1.8 mm/m^2	11.4 ± 1.5 mm/m^2	< 0.01
Third measurement (mean values)	10.1 ± 1.9 mm/m^2	13.1 ± 1.4 mm/m^2	< 0.001

The development of LVH after some years in normotensive patients supports the fact revealed from Timio *et al*. that LVH in ADPKD patients can be caused by hemodynamic initial burden [10].

Although promising, this method has several limitations. One of the obstacles is the lack of normal values for IVCD in adults. In a study of 86 healthy adults the diameter of IVCD varied widely and did not correlate with the height, weight or body surface area (BSA) [6]. Although it is reasonable that IVCD correlates with BSA, the precise relationship is not known because other factors such as the heart rate, blood pressure and treatment with antihypertensive drugs may influence IVCD.

In conclusion, IVCD is a non-invasive and relatively convenient method for obtaining a good correlation with the intravascular fluid status in ADPKD patients. It may serve as an additional reliable parameter in estimation of the hydration status in ADPKD patients, but it cannot be used as a single parameter for fluid status. The increased IVCD could be an early predictor of developing hypertension and sometimes aslo LVH.

Conflict of interest statement. None declared.

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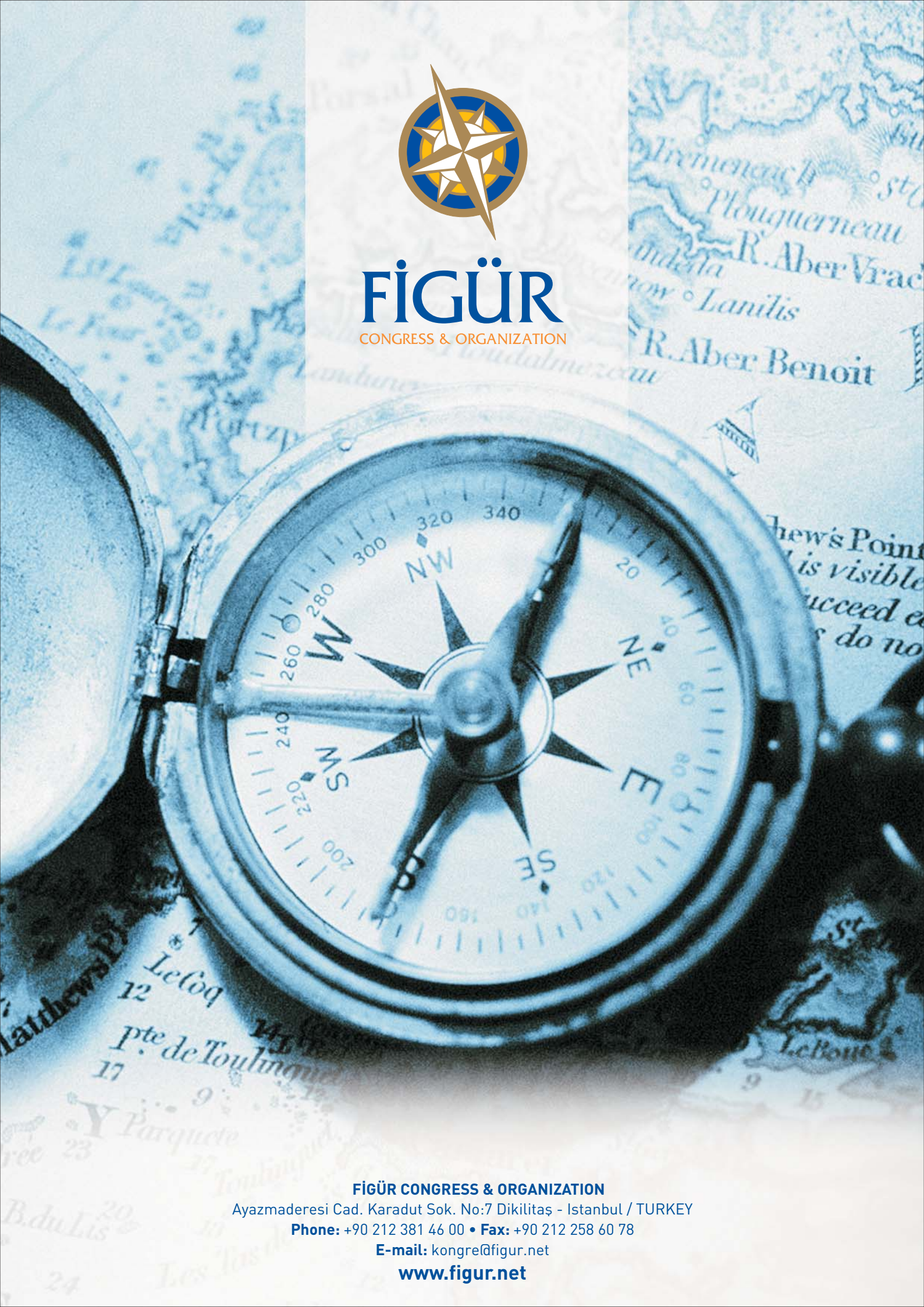

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