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Contents

I. Editorials

II. Original Articles

III. Short Communications

IV. Case Reports

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BJ

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Editorial Comments

Urinary Protein Biomarkers in Chronic Kidney Disease

Katerina Markoska[1], Jelka Masin-Spasovska[2], Momir Polenakovic[3] and Goce Spasovski[2]

[1]PhD student, Medical Faculty, University "Ss. Cyril and Methodius" of Skopje, Macedonia, [2]Department of Nephrology, University "Ss. Cyril and Methodius", Medical Faculty, Skopje, [3]Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia

Introduction - Chronic kidney disease

Chronic kidney disease (CKD) is increasingly recognized as an important national and worldwide public health problem because of its consequences on quality of life and high prevalence, existing in up to one-tenth of the adults in developed countries and 13% of the general population [1,2].
Currently used diagnostic and staging tools are mostly based on non-invasive analysis of serum creatinine and/ or urinary albumin and estimation of glomerular filtration rate (eGFR). These biomarkers although widely accepted, frequently fail to identify patients at higher risk of progression or death [3,4]. They are also not reliable parameters for early diagnosis, as rising of serum creatinine levels above normal is only evident after substantial loss of renal function and its level may be affected by additional factors, such as the loss of muscle mass [5]. On the other hand, urinary albumin levels are highly variable and lack of specificity, as patients with reduced eGFR can have normal urinary albumin levels [6,7]. Still, albuminuria has been suggested to be a better predictor of accelerated loss in renal function than eGFR [8]. This is also the case in patients with diabetes mellitus, where microalbuminuria is considered as a risk for development diabetic nephropathy (DN) [9]. Nevertheless, it is still challenging to predict which diabetic patients with normoalbuminuria will develop microalbuminuria and even more, to identify those in whom GFR will decline without ever developing overt albuminuria [3]. According to KDIGO guidelines, all individuals with an estimated GFR <60 mL/min/1.73m^2 for ≥3 months are classified as having CKD, irrespective of the presence or absence of kidney damage. Conversely, in patients with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2, additional evidence of kidney damage is required in order to diagnose them with CKD. This additional evidence may be provided by a renal biopsy or detected by abnormalities present in blood, urine or on kidney imaging tests [10].
Renal biopsy is the current standard for diagnosing patients with glomerular disorders and it is also used for directing and monitoring their therapy [11]. Renal histology parameters such as glomerulosclerosis, vascular sclerosis, interstitial inflammation and fibrosis are considered as valuable indicators of the disease severity [12], but as renal biopsy is invasive procedure, it is not feasible to be used for early diagnosis in patients at risk [13] or repeatedly performed to follow the progress of the disease.
There is an evident link between the kidney dysfunction and cardiovascular risk, where along with the disease progression CKD associated morbidity and mortality is increasing. Hence, it is important for the nephrologists, to be able to detect patients that are at risk for a disease progression. Additionally, there is a lack of understanding why some of the CKD patients progress to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT), while others die prematurely due to cardiovascular diseases (CVD) instead of progressing to ESRD [3, 14-17].
Ultimately, it is important to identify additional noninvasive diagnostic biomarkers for early detection of renal diseases and possible timely therapeutical interventions and prognostics biomarkers as reliable predictors of progression towards ESRD and/or death outcomes [3,4,11,18-20].

Urinary biomarkers

Urine is one of the potential sources for biomarkers having many advantages. It can be collected non-invasively, repeatedly and in large quantities, which allows their use for repeated analysis [21]. Furthermore, the fact that approximately 70% of the proteins and peptides in urine originate from the kidney [22], makes it suitable source of biomarkers associated with kidney diseases and could be considered a "liquid biopsy" [13]. Those are the main reasons why the urine is widely used for proteomic biomarkers discovery [17,23,24].
Single-protein biomarkers are not effective and suitable to reflect complex diseases, such as CKD and therefore combination and simultaneous use of multiple biomarkers should improve the diagnostic performance [4,17,25]. Combination of multiple biomarkers in high-dimensional classifiers, substantially outperform linear combination of biomarkers [26].

Correspondence to: Goce Spasovski, University clinic of nephrology, "Vodnjanska" 17, 1000 Skopje, R. Macedonia; Phone: +389 70 268 232; Faks: +389 2 3220 935; E-mail: spasovski.goce@gmail.com

Electrophoresis coupled to mass spectrometry (CE-MS) appears to be an applicable method for urinary proteome analysis and has been extensively used in discovering and validating biomarkers for CKD [17,27].

CKD273 classifier

CKD273 classifier is a successful example of CKD-specific urinary biomarker model established by using this approach. The classifier is based on 273 sequenced peptides, combined by using support vector machines (SVM), which were identified that differed significantly between 230 patients with CKD of various etiologies and 379 controls in the initial cross-sectional study. In the first blinded validation, CKD 273 classifier significantly outperformed albuminuria, showing sensitivity of 86% and a specificity of 100% [28]. It was also validated in another cohort of CKD patients with different disease etiologies and healthy controls [29], and in diabetic patients with or without overt diabetic nephropathy [27,30]. Besides proving its capability to identify patients with established CKD in independent studies, CKD273 classifier was also able to predict progression of CKD. Overall, the classifier was able to predict development of micro-or macroalbuminuria and rapid eGFR decrease (i.e. >−5% decline per year), demonstrating its utility and advantage over the currently used clinical tools for predicting CKD progression [17,31-33].

Clinical implementation

CKD is a major challenge and financial burden for the public healthcare systems [34] which can be diminished with recent advances in urinary proteomic analyses, showing potential to improve the care of patients with renal diseases [11].

Since CKD is known to be asymptomatic at early stages, screening for the disease is one of the potential solutions to timely identify CKD patients, trying to reduce the risk of progression and developing further complications. If properly applied, screening tests should identify a large number of patients with minimum costs. In practice, population-based screening does not turn up to be cost-effective and instead, targeted screening is suggested to be more beneficial, especially in patients with high-risk factors such as hypertension, diabetes, obesity, and those from African American race [35-37].

Nowadays, it is evident that urinary proteome analyses are the most suitable approach for early detection, prediction and following the progression of CKD. Hopefully, proteomics could be able to replace kidney biopsies as an invasive procedure that neither can be applied for screening and early detection nor repeatedly performed for following the progression and response to treatment in the near future.

Although urinary proteome analysis is becoming a routine tool in research and a large number of proteomic biomarkers have been described, their transition towards clinical implementation is still hampered [3,13]. Their implementation should involve a wide variety of stakeholders (clinicians, statisticians, health economists, and representatives of patient groups, health insurance, pharmaceutical companies, biobanks, and regulatory agencies). Finally, besides investing efforts for clinical adoption and routine application, their cost-effectiveness has to be also evaluated, as the last point on road map towards clinical implementation [38].

Therefore, beside its utility, CKD273 classifier needs supporting evidence for its cost-effectiveness as compared with the costs of hospitalization, RRT (haemodialysis and/or renal transplantation) and patients' quality of life [31].

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Original article

Epidemiological Review of Kidney Biopsy during 30 years - Single Center Experience

Aleksandar Jankovic[1], Jovan Ikonomovski[1], Petar Djuric[1], Milos Mitrovic[1], Jelena Tosic-Dragovic[1], Ana Bulatovic[1], Jasmina Lipkovski-Markovic[2], Gordana Basta-Jovanovic[2], Danica Vujic[1] and Nada Dimkovic[1,3]

[1]Clinical Department for Renal Diseases, Zvezdara University Medical Center, Belgrade, [2]Institute of Pathology, Medical Faculty, Belgrade University, Serbia, [3]Medical Faculty, Belgrade University, Serbia

Abstract

Introduction. Renal biopsy represents a diagnostic method that provides an acurrate diagnosis and adequate treatment of different renal diseases. The first biopsy in our Center was done in June 1982, but it has been performing routinely since 1984. The aim of this study was to report the histopathological features of biopsy proven kidney disease during the past 30 years.

Methods. During 30 years, a total of 563 biopsies were performed, of which 530(94%) were succesfull. Data about gender, age, clinical syndrome and histopatological finding were collected from the medical records.

Results. The mean age of our patients was 48±11 years, 53% were man (No=272). In the first decade (1982-1994) we performed 118(mean age 50±13), in the second (1995-2004) 208 (mean age 46±14), and in the third decade (2005-2014) 189 renal biopsies (mean age 50±16). Mean number of glomeruli per biopsy was 18±11. There were only two serious complications. The most common clinical syndromes as indication for renal biopsy were: nephrotic proteinuria (41%) followed by asymptomatic urinary abnormalities (AUA-14.8%), chronic renal failure (CRF-13.8%), acute kidney injury (AKI-12.8%), nephritic syndrome (7.6%), systemic lupus erytematosus (SLE-4.5%), isolated haematuria (2.7% of the cases) and other (2.9%). The major histological groups identified were: primary glomerulonephritis (GN) (62.3%), secondary GN (21.2%), and other (16.5% of the cases). The most common primary glomerulonephritis (PGN) were focal segmental glomerulosclerosis-FSGS (19.4%) followed by IgA nephropathy-IgAN (18.8%), membranous GN-MGN (16.4%) and mesangial proliferation-MesGN (16%). Interstitial changes were present in 55% of biopsy samples in the first, in 66% in the second and in 63% in the third decade. Blood vessel changes were present in 39% of biopsy samples in the first, in 62% in the second and in 72% in the third decade.

Conclusions. The most frequent finding among PGN was mesangioproliferative GN (including IgAN, alltogether 34.8%) followed by FSGS and MGN. Apart from succesful biopsies, there are several aspects to be improved in the future including expanding indications and earlier procedure during the course of chronic kidney disease-CKD.

Key words: kidney biopsy, epidemiology, single center experience

Introduction

Renal biopsy represents a diagnostic method that provides acurrate diagnosis and also adequate treatment of different renal diseases. The first renal biopsy was performed in 1901, but its' usage as a routine procedure started in the 1950s [1,2]. Since glomerulonephritis (GN) is a relatively rare disease with a large number of subtypes, many nephrology centers are seeing a limited number of certain histological forms of glomerulonephritis annually. Therefore the collection of data for extended periods is of great help in the study of the epidemiology of GN. Establishment of national renal biopsy registers modeled on Italian or Spanish register, should be the main objective regarding understanding local GN epidemiology [3,4]. The aim of this single Center study was to report clinical syndromes at the time of renal biopsy and histopathological features over the past three decades.

Materials and methods

The first biopsy in our Center was done in June 1982, but it has been routinely performing since 1984. Over te last 30 years, a total of 563 biopsies were done. Data collected from medical records included gender, age, clinical syndrome at the time of renal biopsy and histopathological finding. For better epidemiological analysis, the re-

Correspondence to: Nada Dimkovic, Clinical Department for Renal Diseases, Zvezdara University Medical Center, Belgrade, Serbia; E-mail: dim@eunet.rs

porting period was divided into three decades: Ist decade (1982-1994), IInd decade (1995-2004) and IIIrd decade (2005-2014).

Clinical and laboratory parameters observed at the time of renal biopsy were reported as follows:

1. nephrotic proteinuria: >3.5 g/24h;
2. asymptomatic urinary abnormalities (AUA): persistent low-grade proteinuria (<3.5 g/24 h) with or without microhaematuria;
3. chronic renal failure (CRF): elevated serum creatinine for more than 6 months;
4. isolated haematuria: presence of micro-or macrohaematuria, without any proteinuria;
5. nephritic syndrome: combination of haematuria, arterial hypertension and reduced renal function (sCr >110 mmol/l);
6. acute kidney injury (AKI) defined as sudden and rapid deterioration of renal function;
7. systemic lupus erythematosus (SLE): already diagnosed SLE with onset of renal symptoms;
8. other; in some patients, more than one clinical syndrome was found but the most prominent was taken as dominant clinical syndrome.

Histopathological analysis of the biopsy samples was based on light microscopy and immunohistochemistry except during the period 1992-1999, when it was made only on the basis of light microscopy (71 biopsy samples, 13.7%).

Histological diagnoses were clasiffied into three main categories:

1. Primary glomerulonephritides (PGN) including membranous GN (MGN), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranoproliferative GN (MPGN), minimal change disease (MCD), crescentic GN (CGN, defined as CGN not fulfilling the criteria for systemic disease), proliferative endocapillary GN (PEGN), mesangioproliferative non-IgA GN (MesGN) and unclassified GN.
2. Secondary Glomerulonephritides (SGN) including immune-mediated GN such as systemic lupus erythematosus (SLE), Henoch–Schonlein purpura (HSP), necrotizing vasculititis (NV) and Goodpasture's syndrome (GPS); GN caused by dysgammaglobulinemia or paraproteinemia such as renal amyloidosis (AM), light-chain deposit disease (LCDD), myeloma kidney (MM) and essential mixed cryoglobulinemia; GN associated with infectious diseases (non-streptoccocal GN, endocarditis, shunt GN and others); metabolic disorders, particularly diabetic nephropathy (DN).
3. Other types of GN including vascular diseases benign and malignant nephroangiosclerosis (NAS), hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (HUS/TTP), renal scleroderma and cortical necrosis; acute and chronic tubulointerstitial nephritis (TIN) and acute tubular necrosis; hereditary nephropathies, i.e. Alport syndrome (AS), Fabry's disease, thin basement membrane glomerulopathy (TBM) or other hereditary diseases; end-stage renal disease (ESRD) of undetermined cause; miscellaneous and unclassified nephropathies and normal histopathological findings.

Pediatric patients were not included since our Center does not cover pediatric level of care.

Statistical calculations were performed using the SPSS 20.0 software program. The Kolmogorov-Smirnov test was performed for making assumptions about the distribution of data which were expressed as percentages for categorical values and mean values for continuous variables. Chi-square test and one-way ANOVA test were used to analyze the differences in various baseline variables between the groups of patients. Chi-square (or Fishers' exact test where appropiate) followed by post-hoc analysis of adjusted residuals were used for analysis of variable differences overall and between three decades. A p-value <0.05 was considered statistically significant, and z-value >1.96.

Results

Out of 563 biopsies, 530 were successful (515 primary and 15 re-biopsy) and 33 were unsuccessful due to inadequate samples. We have recorded only two serious complications that were related to the procedure: one led to splenectomy and one to nephrectomy. During the first 12 years, we made about 118 biopsies and then the

Table 1. General data about patients and biopsies performed in our Center during the past three decades (re-biopsies excluded)

	Total	Decades (years)			p***
		1982-1994	1995-2004	2005-2014	
Biopsy No	515	118	208	189	
Gender (men/women)	272/243 (53%/47%)	61/57 (52%/48%)	111/97 (53%/47%)	100/89 (53%/47%)	0.958
Age, years (mean±SD)	48±11	50±13	46±14	50±16	0.163
Glomeruli No / biopsy	18±11	10.5±6.1	16.8±9.1	22.3±11.4	<0.00
Interstitial changes (yes/no)*	260/149 (63%/37%)	18/15 (55%/45%)	124/64 (66%/34%)	118/70 (63%/37%)	0.433
Blood vessel changes (yes/no)**	259/141 (65%/35%)	11/17 (39%/61%)	114/71 (62%/38%)	134/53 (72%/28%)	0.002

* data were available for 409 biopsies, ** data were available for 400 biopsies, *** according to Chi-square test or one-way ANOVA where appropriate

number increased to about 200 biopsies in the next two decades. Of all patients, 272 (53%) were men, and 243 (47%) women; mean age 48±11 years. Mean age at the moment of renal biopsy was slightly decreasing from 50 years in the first decade to 46 years in the second and than in the third it was almost similar as in the first. The average number of glomeruli per biopsy was significantly increasing over the years (10.5 in the first decade, 16.8 in the second and 22.3 in the third) and interstital changes were present in 63.6% of biopsy samples with the peak in the second decade (66%). Blood vessel changes were found in 39% of biopsy samples in the first, in 62% in the second and in 72% in the third decade with a statistical significance (χ^2=12.66) (Table 1).

The most common clinical syndromes at the time of renal biopsy are presented in Table 2. During the entire period of observation, nephrotic syndrome was the most common indication for renal biopsy (211 patients, 41%) followed by AUA (15%), CRF (14%) and ARF (13%). Over time, the representation of individual indications for renal biopsy changed significantly (χ2=24.88; p=0.036) due to increase in the number of patients with a biopsy performed for nephrotic proteinuria and chronic renal failure (in the second and the third decade) and also lupus in the third decade and significantly decreased number of biopsy in patients who had isolated hematuria in the second and the third decade. Number of patietns with AUA also decreased but without statistical significance (Table 2).

Table 2. Clinical syndromes at the time of renal biospy in past three decades (re-biopsies excluded)

	Total	Decades (years)		
	No 515	1982-1994	1995-2004	2005-2014
Nephrotic proteinuria	211(41%)	49(41.5%)	70(33.7%)*	92(48.7%)*
Asymptomatic urinary abnormalities	76(14.8%)	21(17.8%)	32(15.4%)	23(12.2%)
Chronic renal failure	71(13.8%)	13(11.0%)	39(18.8%)*	19(10.1%)
Nephritic syndrome	39(7.6%)	10(8.5%)	19(9.1%)	10(5.3%)
Isolated hematuria	14(2.7%)	6(5.1%)	4(1.9%)**	4(2.1%)**
Acute kidney injury	66(12.8%)	14(11.9%)	31(14.9%)	21(11.1%)
Systemic lupus erythematosus	23(4.5%)	3(2.5%)	7(3.4%)	13(6.9%)*
Other	15(2.9%)	2(1.7%)	6(2.9%)	7(3.7%)

*significantly increased vs. other decades, **significantly decreased vs. other decades

Table 3. Presence of major groups of biopsy proven renal diseases in past three decades (re-biopsies excluded)

Group	Total	Decades (years)		
	No 515	1982-1994	1995-2004	2005-2014
Primary glomerulo-nephritides (PGN)	321(62.3%)	83(70.3%)	126(60.6%)	112(59.3%)*
Secondary glomerulo-nephritides (SGN)	109(21.2%)	19(16.1%)	38(18.3%)	52(27.5%)**
Other	85(16.5%)	16(13.6%)	44(21.2%)	25(13.2%)

*significant decrease vs. first decade, **significant increase vs. first decade

Table 3 shows the presence of the three major biopsy proven groups of renal diseases. The most common finding was PGN in 62.3% of patients. During the years this number changed (χ^2=12.01; p=0.017) due to a significant decrease in the prevalence of PGN from 70.3% in the first to 59.3% in the third decade. At the same time the presence of SGN significantly increased from 16.1% to 27.5% of patients.

Table 4. Presence of primary glomerulonephritis in past three decades (re-biopsies excluded)

Primary glomerulonephritides	Total	Decades (years)		
	No 321	1982-1994	1995-2004	2005-2014
Membranous GN (MGN)	53(16.4%)	16(19.3%)	16(11.8%)	22(19.6%)
Focal segmental glomerulosclerosis (FSGS)	62(19.4%)	15(18.0%)	28(22.0%)	19(17.0%)
IgA nephropathy (IgAN)	61(18.8%)	12(14.4%)	29(22.8%)	20(17.9%)
Membranoproliferative GN (MPGN)	25(7.7%)	4(4.8%)	9(7.1%)	12(10.7%)
Minimal change disease (MCD)	12(3.7%)	7(8.4%)	2(1.6%)	3(2.7%)
Crescentic GN (CGN)	31(9.9%)	5(6.0%)	13(10.2%)	14(12.5%)
Proliferative endocapillary GN (PEGN)	22(6.9%)	8(9.6%)	11(8.7%)	3(2.7%)
Mesangioproliferative non-IgA GN (MesGN)	51(16.0%)	15(18.0%)	20(15.7%)	16(14.3%)
Unclassified GN	4(1.2%)	1(1.2%)	0(0%)	3(2.7%)

Among PGN, the most common finding was mesangial PGN (IgA and non-IgA 34.8%) followed by FSGS (19.4%) and MGN (16.4%). During the years, the number of patients with different histologically confirmed PGN did not differ significantly (χ^2=25.135; p=0.067). Although without statistical significance, the number of patients with MCD, PEGN and MesGN decreased and the number of patients with histologically confirmed IgAN, MPGN and CGN increased (Table 4).

Among 515 biopsies, SGN was found in 109 biopsy samples and during the years the number significantly increased from 19 to 52 (Table 3). Over the time, incidence of different SGN did not change significantly (χ^2= 0.281; p=0.991). Most of them were immune-mediated GN (60.7%). Diabetic nephropathy was confirmed in 15 patients with increase in incidence over the years (14% overall; decade I: 11.8%; decade II: 15.1%; decade III: 13.7%) (Figure 1).

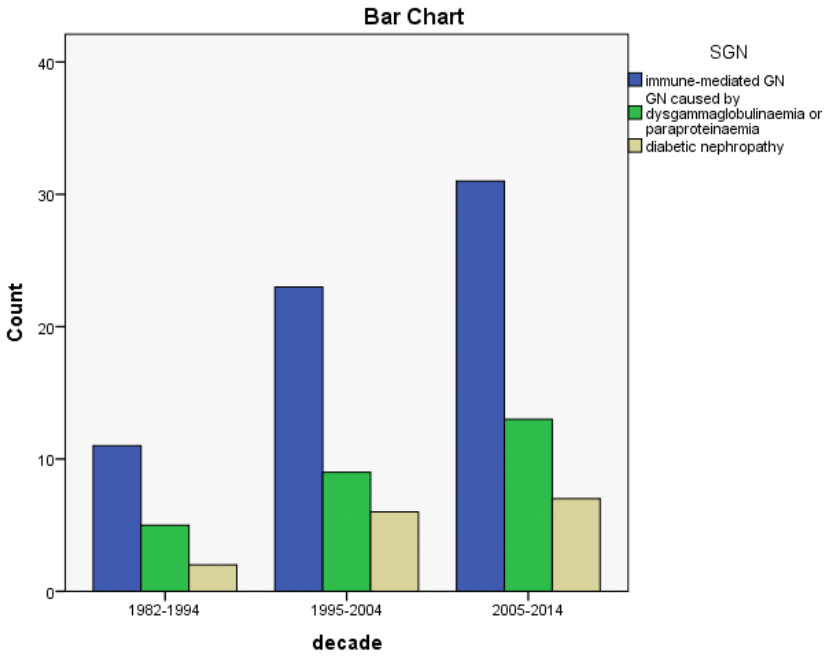

Fig. 1. Number of different SGN in the past three decades (No=109)

Table 5 represents the incidence of GN from the third category. Over time, there were no statistically significant changes in overall incidence in different types of these GNs (χ^2=10.461; p=0.401) although TIN finding decreased over time (25% in the first, 14% in the second and 7.7% in the third decade) and ESRD increased (6.2% of biopsy samples in the first decade and then increased up to 23.3% and 19.2% in the second and third decade, respectively). Vascular nephropathy is the major finding in this category (25.0% in the first, 34.9% in the second and 30.8% in the third decade).

Table 5. Presence of non-primary and non-secondary GN

Variable	Total	Decades (years)		
	N^0=85	1982-1994	1995-2004	2005-2014
Vascular diseases	27(31.8%)	4(25%)	15(34.9%)	8(30.8%)
Tubulointerstitial nephritis (TIN)	12(14.1%)	4(25%)	6(14.0%)	2(7.7%)
Hereditary nephropathies	2(2.4%)	0(0%)	0(0%)	2(7.7%)
End-stage renal disease (ESRD)	16(18.8%)	1(6.2%)	10(23.3%)	5(19.2%)
Miscellaneous	19(22.4%)	4(25%)	9(20.9%)	6(23.1%)
Unclassified nephropathies	9(10.6%)	3(18.8%)	3(7.0%)	3(11.5%)

Discussion

This report provides insight in the diagnosis obtained by renal biopsies performed in a single Center for more than 30 years. There were few serious complications and a small number of glomeruli per sample indicating the efficiency of the method applied in our Ccenter. We found a slight predominance of male patients and the mean age at the moment of renal biopsy was 48 years. According to some other reports, male patients were also bioptied more frequently than female (Romanian data-51.5%; Clinical Center Serbia-51.2%; Pisa, Italy-59%; Czech data-57.9%; Turkish data-55%). The mean age at the moment of renal biopsy was almost one decade higher in our patients than in that reported by others (two Romanian Centers-38.5±15.2; Clinical Center Serbia-

39.1±13.8 years, Turkey-40.8±14.6 years) (5-9). This difference can be explained by different attitudes regarding the biopsy of the elderly.

The main clinical syndrome as indication for renal biopsy in our patients was nephrotic proteinuria (41%), followed by AUA (14.8%), CRF (13.8%) and AKI (12.8%). Our result is similar to that from other registries and studies [4-6,8,9]. Some differences could be explained by the differences in local policies regarding kidney biopsy and by different understanding/interpretation of overlaping clinical syndromes as the main indication for renal biopsy. Also, some of the studies included pediatric patients which may explain the difference in age between our and their findings.

Our data are in concordance with other reports regarding the incidence of PGN and SGN (3,5-8,10). In our study PGN was found in 62.3% of patients and over the years this number decreased from 70.3% in the first to 59.3% in the third decade. At the same time the presence of SGN increased from 16.1% to 27.5% of biopsy samples. Simillar data have been shown in Chinese single center study where PGN desreased from 78.3% in 1985 to 66.8% in 1999 while SGN increased from 21.7% to 33.2% of biopsy samples [10].

The most frequent PGN in our patients was FSGS (19.4%) followed by IgAN (18.8%), MGN (16.4%) and MesGN (16%). Altogether, the mesangial proliferation was the most common finding (IgAN and MesGN, 34.8%). Schena *et al.* also reported that IgAN (36.9%) and FSGS (21.7%) were the most frequent PGN [3]. Single center experience from the Nephrology Clinic, Clinical Center Serbia also showed that the majority of patients had mesangial proliferation (IgAN 12.2% and non-IgAN 25.1%) followed by FSGS and MGN with the same percentage (both 18.9%) [6]. Spanish register also revealed that IgAN (15.2%) and FSGS (10%) were the most common PGN as well as Autralian data where IgAN participated with 34.1% of all PGN followed by FSGS (16.9%). According to data from Finland, IgAN was found in 34.9% of biopsy samples, followed by MesGN (11.6%) and MGN (11.6%) [4,11,12]. Chinese single center study analyzed over 13,000 biopsies and IgAN and MesGN had the highest incidence (IgAN 45.2%, MesGN 25.6%). On the other hand, Romanian investigators have shown that MPGN was the most common PGN in their patients (29.4%), followed by MesGN (incuding IgAN, 28.9%) and FSGS (11.5%). Also they reported that annual prevalence of MPGN was constantly decreasing during the study period (from 1995 to 2004). They agreed with the French authors' hypothesis that the socioeconomic conditions are strongly related to MPGN prevalence and that improvement in income, sanitation, social and medical infrastructure are followed by a decrease in MPGN [5,13]. In our group of patients MPGN had a constant increase in incidence over the years (from 4.8% to 10.7%) despite the fact that our country was under economic sanctions in the second decade, but not at the end of the study period and these 10.7% in the last decade can be still compared to data from some western European countries such is Italy [3]. According to Czech data IgAN accounted for 34.5% of all PGN, followed by MCD (12.5%) and MesGN (11.3%). Turkish register revealed somewhat different results since MGN was the most frequent PGN with prevalence of 28.8%, followed by FSGS (19.3%) and IgAN (17.2%) [9]. This finding could be explained by their indications for renal biopsy where 57.8% of patients (vs. ours 41%) underwent renal biopsy due to NS. It is well known that FSGS is the most common cause of NS.

According to our report, immune-mediated GN was the most common SGN. The incidence in our group was 60.7% while in the Czech register it was 71.6% and in the Chinese report over 90%.

In the group of patients with non-PGN non-SGN, vascular nephropathy was the most common finding (31.8%), followed by miscellaneous (22.4%), ESRD (18.8%) and TIN (14.1%). In the study of Naumovic *et al.* VN was also the most frequent finding (40.1%) followed by TIN (28%) and miscellaneous (13%) non-PGN non-SGN [6]. According to the Romanian register, 48% of patients from this group were 'miscellaneous' followed by VN (31%) and TIN (21%) [5]. The small numbers of TIN could possibly be explained by the fact that diagnosis of TIN is based mainly on clinical data and by procedures that are less invasive than renal biopsy.

One of the limitations of this study is its retrospective design. The novel biopsy analyses include more precise data (index of chronicity, index of activity, different scoring systems), however these data could not be compared over decades. In addition, therapy, follow-up and patients' outcome are not provided by this analysis.

Conclusion

In conclusion, we have shown that primary and secondary GNs have similar incidence and the similar distribution of major histological forms to other European countries. The most frequent PGN was mesangioproloferative GN (including IgAN, alltogether 34.8%), followed by FSGS and MGN. Apart from succesful biopsies, there are several aspects to be improved in the future including expanding indications and earlier procedure during the course of CKD.

Conflict of interest statement. None declared.

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Original article

Contrast Induced Nephropathy in Patients with Acute Coronary Syndrome

Mehmet Can Ugur, Ferhat Ekinci, Utku Erdem Soyaltın and Harun Akar

Tepecik Training and Research Hospital, Internal Medicine Clinic, Izmir, Turkey

Abstract

Introduction. Contrast-induced nephropathy (CIN) is associated with increased morbidity and mortality after percutaneous coronary intervention (PCI). On the other hand, CIN is a serious complication in patients with diabetes or renal impairment undergoing percutaneous coronary intervention (PCI). CIN after PCI may be associated with prolonged hospitalization, increased rates of kidney injury, and short- and long-term mortality. Factors that have been associated with CIN include: diabetes mellitus, congestive heart failure, recent acute myfocardial infarction, cardiogenic shock, and pre-existing renal impairment. In this study, we investigated contrast nephropathy development after coronary angiography (CAG) in patients presenting with acute coronary syndrome, who were hospitalized initially in the Coronary Care Unit and subsequenttly referred to the Internal Medicine Clinic in a tertiary care hospital.
Methods. We've analyzed 335 patients' records retrospectively in 1 year that were followed-up with acute coronary syndrome (ACS) in the Coronary Care Unit (CCU) and transferred to the Internal Medicine Clinic (IMC). The following parameters were evaluated: age, gender, chronic disease and drug history, biochemical values evaluated before hospitalization to CCU, ejection fraction (EF) and left atrium diameter (LA), with or without previous CAG; values of serum creatinine (sCr) levels before CAG and after 48 hours. Values of $p < 0.05$ were considered to be significant.
Results. 126 of 335 patients were female and 209 were male. The average age of patients was 64.2 years. 122 patients used angiotensin converting enzyme inhibitor (ACEI), 54 patients used furosemide. CIN development rate of CAG patients was 22.8% (n=54). There was no significant relationship with age, gender and chronic disease history in CIN patients. When laboratory findings were compared, there was no significant relationship except for potassium value before CAG. However, potassium values were significantly higher in CIN patients (p=0.001). When drug usage of patients was compared, 48.1% (n=26) of CIN patients used ACEI and there was a significant relationship between ACEI use and CIN development (p=0.026).
Conclusions. CIN development rate was 22.8% and it was relatively high when compared with literature data. Awareness about contrast nephropathy develepment risk and assessment of risk factors before the procedure should be increased in our Center.

Key words: nephropathy, acute coronary syndrome, angiography

Introduction

Contrast-induced nephropathy (CIN) is defined as either a 50% increase in serum creatinine level from baseline or 0.5 mg/dL and even more in absolute value, measured within 48 hours of intravenous contrast administration [1]. The development of acute renal failure (ARF) is a significant complication of intravascular contrast medium use and is associated with excess morbidity and mortality. An overall incidence of CIN in the general population is reported to be 0.6-2.3% [2]. We have assessed contrast nephropathy development after coronary angiography (CAG) in patients with acute coronary syndrome in the Coronary Care Unit and subsequently referred to the Internal Medicine Clinic in a tertiary care hospital.

Material and methods

Between January and December 2013, we analyzed 335 patients' records retrospectively that were followed-up with acute coronary syndrome in the Coronary Care Unit and subsequently were transferred to the Internal Medicine Clinic. After an evaluation according to inclusion and exclusion criteria, 335 patients were enrolled in our study. The parameters used and evaluated with statistical methods were: age, gender, history of chronic disease and drug usage, biochemical values evaluated before hospitalization to coronary care unit, ejection fraction (EF) and left atrium diameter (LA), with or

Correspondence to: Mehmet Can Ugur, Department of Internal Medicine, Tepecik Education and Training Hospital, Izmir, Turkey; E-mail: med.can@hotmail.com

without CAG; values of serum urea and creatinine levels before and 48 hours after CAG.

Statistical analyses

Compliance with the normal distribution for continuous variables was analyzed with the Shapiro-Wilk test. Descriptive statistics was used for defining continuous variables. Student's t-test was used to compare the two groups with independent and continuous variables showing normal distribution. Mann-Whitney U test was used for comparison of the two groups independent and continuous variables showing normal distribution. Wilcoxon Signed Rank test was used for comparison of not normally distributed dependent variables. Statistical significance was set at 0.05. Statistical analysis was performed by using the MedCalc Software Program, version 12.7.7 (MedCalc Software bvba, Ostend, Belgium).

Findings

A hundred and twenty-six of 335 patients were female and 209 were male. The average age of patients was 64.2 years. Fifty-two patients had congestive heart failure (CHF), 12 patients had malignancy, 79 patients had chronic renal failure (CRF), 108 patients had diabetes mellitus (DM) and 168 patients had hypertension (HT). 122 patients used angiotensin converting enzyme inhibitor (ACEI), 54 patients used furosemide. Three hundred and eleven patients were discharged, 6 of patients were transferred to another unit, 11 of patients were voluntarily discharged, 7 of patients died. Four of these deceased patients had CRF history and mortality might be related to CRF (p= 0.027). There was no significant relationship with the other parameters concerning mortality.

Table 1. Laboratory findings and mean EF values before CAG

	Average	Median	St Deviation	Minimum	Maximum	N
Glucose	131.5	107	70.9	11	441	335
HbA1C	7.3	6.6	2.2	1.5	12.5	33
Uric Acid	7.9	6.4	9.9	3	113	268
Total Cholesterol	185.5	182	51.5	14	350	274
HDL	40.4	38	15.5	18	207	274
LDL	122.7	113	62.8	12	400	272
Triglyceride	167.3	139.5	116	40	854	272
AST	83.3	37	116.2	4	851	329
ALT	30	21.5	93.1	3	1320	330
Albumin	3.8	3.8	0	1.7	17	269
Sodium	137.6	138	3.9	117	147	335
Potassium	4.5	4.4	0.7	0.9	7	335
Calcium	9.1	9.1	0.7	6.5	11.4	331
Phosphorus	3.6	3.5	1.1	1.3	100.8	263
LDH	424.9	337	268.3	5.3	1852	269
Troponin	7379.8	4.9	17732.1	0	50000	333
Hemoglobin	12.7	12.9	2.2	5.9	18.7	335
EF %	49.4	50	10.9	15	70	310
Urea	53.4	42	35.6	16	228	334
Creatinine	1.6	1.1	1.6	0.5	15	335

EF: Cardiac ejection fraction, LDH: Lactate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate amino transferase, HDL: High-density lipoprotein, LDL: Low- density lipoprotein, CAG: Coronary angiography

Among these 335 patients that were transferred to the Internal Medicine Clinic from the Cardiology Coronary Care Unit with the diagnosis of acute coronary syndrome, CAG had been performed in 237 patients. Laboratory findings and mean EF values before CAG in these 237 patients with CAG are shown in table 1. CIN development rate in these 237 patients with CAG was 22.8% (n=54). Before and after CAG average creatinine values of patients with CIN were 1.2 mg/dL and 1.7 mg/dL, respectively. There was no significant relationship with age, gender and chronic disease history in CIN patients. When laboratory findings were compared, there was no significant relationship except for serum potassium values before CAG (Table 2). Serum potassium values were significantly higher in patients with CIN (with Mann-Whitney U test, p= 0.001). We evaluated the drug usage of patients. We found that 48.1% (n= 26) of CIN patients used ACEI and there was a significant relationship between ACEI use and CIN development (p= 0.026). A significant relationship was not found between the use furosemide and CIN development.

Table 2. Comparison of laboratory findings before and after CAG

	Nephropathy positive		Nephropathy negative		P value
	Avg±St Deviation	Med (min-max)	Avg±St Deviation	Med (min-max)	
Glucose	145.6±79.7	111.5(58-415)	130.3±66.5	109(47-440)	0.291**
HbA1C	7.1±2.6	6.8(1.5-11)	7.4±2	6.8(5.4-12.5)	0.913**
Urea (before CAG)	42.8±23.7	36(20-159)	43.4±28.9	36(16-228)	0.883*
Urea (after CAG)	63.6±34.1	60(20-185)	45±26.6	35(14-170)	<0.001**
Uric Acid	7.4±8.4	5.9(3.7-9.3)	7.2±9.2	6.2(3-9.4)	0.712**
Total Cholesterol	203.9±46.7	188(107-346)	191.2±51.6	186(14-350)	0.132*
HDL	40.4±9.4	39(24-74)	41.6±19.2	39(19-207)	0.876**
LDL	143.3±77	121(60-400)	128.5±60	115(35-400)	0.251**
Triglyceride	198.5±157.1	151(50-854)	173±107.2	146(40-719)	0.591**
AST	66.2±53	48.5(15-244)	100.7±132	48(11-851)	0.839**
ALT	24.1±13.3	20(3-82)	36.4±32	26(11-205)	0.065**
Albumin	3.8±0.4	3.9(2.9-4.6)	4±1.2	3.9(2.9-4.7)	0.385*
Sodium	136.9±3.3	137(129-146)	138.1±3.7	138(126-147)	0.030*
Potassium	4.7±0.5	4.6(3.8-6.4)	4.3±0.6	4.2(2.9-6.5)	<0.001**
Calcium	9.1±0.6	9.1(8-11)	9.2±0.6	9.2(6.5-11)	0.491**
Phosphorus	3.2±0.8	3.2(1.4-5.1)	3.4±0.8	4.3(1.3-6.2)	0.191*
LDH	423.5±321.6	320(5-1852)	457.8±279.7	362(165-1664)	0.287**
Troponin	3714.7±13214	7.6(0-50000)	11298±20930	9.24(0-50000)	0.521**
Hemoglobin	13.1±2.1	13.2(7.9-16.6)	13.4±1.8	13.6(7.2-18.7)	0.354*
EF %	50.1±8.8	50(28-63)	49.4±10.2	50(20-70)	0.679*
LA	36.5±5.7	37(22-47)	37.1±5.6	37(26-61)	0.521*

EF: Cardiac ejection fraction, LA: Left atrium diameter, LDH: Lactate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate amino transferase, HDL: High-density lipoprotein, LDL: Low- density lipoprotein, CAG: Coronary angiography
*Student t-test, **Mann-Whitney U test

Discussion

Contrast-induced nephropathy is a growing issue in the field of interventional cardiology. CIN is one cause of acute renal injury, resulting in a decrease in the glomerular filtration rate (GFR), reduced excretion of nitrogenous waste, hypervolemia, and hyperkalemia. CIN is associated with significant increases in mortality. However, mortality in patients who develop CIN is rarely due to renal failure. Patients with CIN also have significantly higher hospital mortality than those without CIN. CIN is one of the important reasons of hospital-acquired acute kidney injury [3]. As a widely accepted method, either a 50% increase in serum creatinine level from baseline or 0.5 mg/dL and more increase in absolute value, measured within 48 hours of intravenous contrast administration can be considered as CIN [1,3-7]. We have diagnosed CIN according to this definition. Risk factors for CIN include pre-existing renal insufficiency, diabetes mellitus, older age, reduced left-ventricle systolic function, advanced heart failure, acute myocardial infarction, shock, concomitant use of nephrotoxic drugs, hypotension, dehydration, hypoalbuminemia, anemia, use of intra-aortic balloon pump, volume and type of contrast material (Table 3) [8]. In our study, the use of ACEIs and hyperkalemia were found to be associated with the development of CIN (p=0.026 and p<0.001, respectively) (Table 4). However, conflicting results exist regarding the effects of RAS blockers in the pathophysiology of CIN. Some studies reported RAAS blockers were preventive for CIN [9,10]. The study by Gupta *et al*. [10] included patients randomised to receive captopril (a sulfhydryl group containing angiotensin-converting enzyme inhibitor at a dose of 25 mg thrice a day for three days, starting one hour prior to angiography) while patients in the control group underwent angiography without receiving captopril. They reported that captopril reduced the risk of development of contrast-induced nephrotoxicity in diabetic patients by 79% [10]. They speculated that abnormalities of renal perfusion possibly mediated by RAS were responsible for development of CIN and administration of captopril offers protection against development of CIN. Holscher *et al.* [11] prospectively assessed predictors of CIN within 72 h and long-term outcomes of 412 consecutive patients with serum creatinine levels of 1.3 mg/dL to 3.5 mg/dL undergoing elective CAG. In their study, patients were randomly assigned to periprocedural hydration alone, hydration plus one-time hemodialysis or hydration plus N-acetylcysteine [11]. Multivariate logistic regression identified the predictors of CIN as prophylactic postprocedural hemodialysis (OR 2.86, 95% CI 1.07 to 7.69), use of angiotensin-converting enzyme inhibitors (OR 6.16, 95% CI 2.01 to 18.93), baseline glomerular filtration rate (OR 0.94, 95% CI 0.90 to 0.98) and the amount of contrast material (OR 1.01, 95% CI 1.00 to 1.01). In addition, they found that independent predictors for death during follow-up included left ventricular ejection fraction lower than 35% (HRR 4.01, 95% CI 2.22 to 7.26), serum phosphate (HRR 1.64, 95% CI 1.10 to 2.43) and hemoglobin (HRR 0.80, 95% CI 0.67 to 0.96) [11]. From their prospective trial, Holscher *et al*. [11] concluded that postprocedural he-

modialysis, use of angiotensin-converting enzyme inhibitors, reduced baseline glomerular filtration rate and amount of contrast media were independent predictors of CIN within 72 h after coronary procedure Assessing renal function after 30 days, rather than within 72 h, seemed to be more predictive for patients' long-term survival.

Table 3. Risk factors for renal impairment or development of CIN

• Diabetes mellitus	• Dehydration or volume contraction
• Renal disease or solitary kidney	• Age >70 years
• Sepsis or acute hypotension	• Previous chemotherapy
• Cardiovascular disease	• Organ transplant
• Human immunodeficiency syndrome	• Nephrotoxic drugs (amphotericin B, aminoglycosides, vancomycin, NSAIDs, chemotherapy agents such as cisplatin)
Hypercholesterolemia	Administration of >100 mL of contrast medium
Anemia	

Table 4. Comparison of drugs usage

	Drug Usage	Nephropathy			P value
		Developed	No Developed	Total	
Use of ACEI	Yes	58(%31.7)	26(%48.1)	84(%35.4)	0.026*
	No	125(%68.3)	28(%51.9)	153 (%64.6)	
	Total	183(%100)	54(%100)	237(%100)	
Use of Furosemid	Yes	16(%8.7)	5(%9.3)	21(%8.9)	1.00**
	No	167(%91.3)	49(%90.7)	216(%91.1)	
	Total	183(%100)	54(%100)	237(%100)	

ACEI: Angiotensin converting enzyme inhibitor, *Ki-Kare, **Fisher Exact test

Treatment with RAAS blockers does not usually cause renal dysfunction or hyperkalemia in patients with normal renal function. These complications can be observed in patients with high CV risk and generalized atheromatous disease such as, of course, renal atheromatosis and/or abnormal renal function. Blood pressure should be held steady before the procedure, as the patient will receive intense fluid intake. Avoid blood pressure levels 20 to 30 mmHg lower than normal and, do not administer contrast media if blood pressure is unacceptably low. ACEIs and ARBs are most frequently associated with CIN, especially in patients with depletion. Hyperkalemia was found to be associated with CIN in our study and may be due to the use of ACEI. On the other hand, there is limited information about the serum electrolyte levels in patients with CIN in the literature.

Conclusions

Coronary artery interventions are most frequently associated with CIN among the procedures in which intravenous contrast material is used. While in prospective studies CIN incidence is around 3.3%, in the subgroup of patients that has had myocardial infarction and required primary angioplasty, CIN incidence rises to 19% [12]. In our study, CIN development rate was 22.8% and this rate is considerably high. Our awareness about contrast nephropathy and assessment of risk factors before the process has to be optimized. Consequently, a thorough understanding and pathophysiology of CIN along with the drug interactions have to be studied in future by including a larger series of patients with high cardiovascular risk.

Conflict of interest statement. None declared.

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Original article

Effect of Initial PET Status on Clinical Course in Peritoneal Dialysis Patients

Tamer Sakaci[1], Yener Koc[2], Taner Basturk[2], Mustafa Sevinc[3], Elbis Ahbap[1], Ayse Sinangil[4], Ekrem Kara[1], Zuhal Atan Ucar[3], Cuneyt Akgol[3], Arzu Ozdemir Kayalar[3], Feyza Bayraktar Caglayan[3], Tuncay Sahutoglu[3] and Abdulkadir Unsal[5]

[1]Department of Nephrology, Sisli Etfal Research and Educational Hospital, [2]Division of Nephrology, Department of Internal Medicine, Istanbul Bilim University, Istanbul, Turkey

Abstract

Introduction. To investigate the effect on mortality of initial peritoneal equilibration test (PET) in PD patients (pts).
Methods. We included patients who initiated therapy between 2001-2014. Patients underwent initial PET in the first three months. They were divided into four groups according to the initial PET (high, high-average, low-average, low transport). Sociodemographic data, clinical courses and infectious complications between groups were compared, and the reasons for PD withdrawal were obtained. Technique survival analyses of patients were done.
Results. In a total of 367 pts were PD was started, 104 pts were excluded. Data of the remaining 263 patients were evaluated. Thirty-seven pts (23F, mean age 44.6±16.5 years, mean follow-up 30.5±20.8 months) had high transport, 90 pts (49F, mean age 41.5±16 years, mean follow-up 42.6±27.7 months) had high-average transport, 91 pts (55F, mean age 44.5±14.9 years, mean follow-up 50±29.2 months) had low-average transport and 45 pts (17F, mean age 43.5±14 years, mean follow-up (63.4±34.5 months) had low transport. There was no difference between groups in terms of age, gender, body mass index, initial daily urine and ultrafiltration volume, initial albumin levels, presence of diabetes mellitus ($p>0.05$). Peritonitis and catheter exit-site/tunnel infection attacks were higher in patients with high transport ($p=0.01$ and 0.008, respectively). There was a difference between groups with respect to the last status of patients ($p< 0.009$). The major causes of deaths were peritonitis and/or sepsis and cardiovascular causes in all patients. The mortality and technique survival rate was found higher in patients with high transport (log rank: 0.004 and 0.027, respectively). Age (OR:1.045, $p<0.001$), initial albumin (OR: 0.482, $p= 0.007$), daily urine volume (OR: 1.045, $p<0.001$) and presence of catheter exit-site/tunnel infection (OR: 0.249, $p<0.001$) were found to predict patient survival. Only presence of catheter exit-site/tunnel infection (OR: 0.452, $p=0.013$) were found to predict patient survival.
Conclusions. Initial PET has effects on PD patient survival; patients with high transport have the worst survival and frequent infectious complications.

Key words: peritoneal dialysis, PET, mortality

Introduction

Patients with end-stage renal disease (ESRD), including those who are on peritoneal dialysis (PD), are at a much higher risk for premature death than the general population. Well-accepted risk factors for early mortality that have been identified in the PD population include age, diabetes, preexisting cardiovascular disease, and malnutrition/hypoalbuminemia [1-6].
The relationship between peritoneal membrane transport characteristics and the outcomes of patients receiving peritoneal dialysis [5,7-17] has been the subject of several studies. It was found that, in the CANUSA study population, ANZDATA registry and several other studies, high transport status was associated with mortality risk [5,7-13]. However, other studies such as ADEMEX and EAPOS, have found peritoneal membrane properties are not associated with patient survival [14-17].
Peritoneal equilibration test (PET) developed by Twardowski [18] characterizes the transport nature of the patient's peritoneal membrane. The transport character not only helps to decide the dwell time, but also plays a crucial role in determining the morbidity and mortality of patients on PD.
The aim of this study was to evaluate whether initial PET status had an effect on patients' and technique survival or not and to show presence of any other factors other than PET status in patients performing peritoneal dialysis in our Center.

Correspondence to: Yener Koc, Clinic of nephrology, Sisli etfal research and educational hospital, Istanbul, Turkey; Mobile: 090 532 3715585; Fax: 090 212 2312209; E-mail: dryenerkoc@mynet.com

Material and methods

The records of 367 patients who underwent PD therapy due to ESRD in our PD unit between 2001 and 2014 were evaluated retrospectively. Patients younger than 18 years, with history of PD less than 90 days, unknown PET status within 3 months after initiation of PD, recovering renal function and no longer need for dialysis were excluded from the study. Remaining 263 patients' data were evaluated.
All patients had a PET within 3 months after initiation of PD as Twardovski *et al*. described [18]. They were divided into 4 groups according to the PET results including low, low-average, high-average, high transport.
Age, gender, educational level, sociodemographic characteristics such as presence of someone to administer PD [Self or Assisted PD (their children or other persons like health caregivers)], nature of the decision for PD (patient's own preference or compulsory choice), etiology of ESRD were investigated in-depth from patients' records. If present, duration of hemodialysis (HD) history before PD therapy was noted.
Systolic and diastolic blood pressure measurements, daily urine volumes, daily mean ultrafiltration (UF) amount, and cardiothoracic indices of all patients were recorded both at the beginning and at the end of the study.
Serum urea, creatinine, calcium, phosphorus, albumin, intact parathyroid hormone (iPTH), hemoglobin, and ferritin values were recorded at the beginning of PD treatment and during the last monitoring. Infectious complications such as peritonitis, exit site/tunnel infections were recorded and their incidences were calculated. All parameters were compared among groups.
The factors associated with mortality, patient and technique survival were examined for all of the patients. The effect of initial PET status on mortality was also investigated. Technique failure was defined as transfer to HD due to peritonitis, ultrafiltration failure, inadequate dialysis, exit-site and/or tunnel infection, and mechanical problems.
We performed statistical analyses with the Scientific Package for Social Science (version 17.0; SPSS Inc., Chicago, IL, USA). Kruskal-Wallis and Mann-Withney U tests were used for nonparametric variables. One Way ANOVA test was used for analyzing clinical and biochemical parameters among groups (post-hoc analysis, Tukey's test). The Kaplan–Meier method was used for patient and technique survival. A comparison of outcomes was done by the log rank test. Independent risk factors were also analyzed for patients' mortality and technique survival and hazard ratio (HR) was calculated by using backward logistic regression of the Cox proportional hazards method. Differences were considered statistically significant for the p values less than 0.05.

Results

Out of 367 patients 104 were excluded from the study. The remaining 263 patients were divided into 4 groups according to PET results. Groups with low transport, low-average, high-average and high transport consisted of 45, 91, 90 and 37 patients, respectively. Sociodemographic, biochemical and clinical data of groups are given in Tables 1 and 2. Glomerulonephritis (23.9%) and

Table 1. Demographic and clinical data of patients

PET Status	Low (n:45)	Low-average (n:91)	High-average (n:90)	High (n:37)	p
Mean age (years)	43.5±14	44.5±14.9	41.5±16	44.6±16.5	0.59
Gender (female)	17	55	49	23	0.06
Mean follow-up (months)	63.4±34.5	50±29.2	42.6±27.6	30.5±20.8	<0.001
Kt/V_{Urea}	2.3±0.5	2.2±0.5	2.0±0.4	1.9±0.5	<0.001
Body mass index (kg/m²)	23.2±4.2	23.3±4.3	21.9±4.8	23.3±5.4	0.15
History of HD (presence, %)	14.3	25.3	15.9	24.2	0.30
Urine volume, initial (ml/day)	475±454	365±462	407±461	280±256	0.54
Urine volume, last visit (ml/day)	106±251	89±229	159±315	132±333	0.43
Ultrafiltration volume, initial (ml/day)	1074±359	1064±483	1030±457	893±353	0.51
Ultrafiltration volume, last visit (ml/day)	1166±507	1227±602	1052±470	891±533	0.009
Systolic blood pressure, initial (mmHg)	120±27	117±28	112±23	120±24	0.20
Systolic blood pressure, last visit (mmHg)	125±36	121±27	111±27	106±26	0.009
Diastolic blood pressure, initial (mmHg)	79±16	74±16	71±14	69±14	0.04
Diastolic blood pressure, last visit (mmHg)	75±18	75±16	70±16	68±17	0.09
Incidence of peritonitis (patient-months)	37.7±31	33.8±26	28.1±21	20.7±19	0.01
Incidence of catheter exit site/tunnel infection (patient-months)	48.2±32	40.7±27	36±25	27.6±18.9	0.008

Table 2. Laboratory data of patients

PET Status	Low (n:45)	Low-average (n:91)	High-average (n:90)	High (n:37)	P
Urea level, initial (mg/dl)	112±34	122±54	121±42	112±45	0.52
Urea level, last visit (mg/dl)	86±37	95±38	99±42	88±39	0.25
Creatinine level, initial (mg/dl)	8.5±2.9	8.9±3.0	9.5±3.1	8.8±2.6	0.24
Creatinine level, last visit (mg/dl)	8.5±2.3	8.8±2.7	9.7±2.6	8.4±2.2	0.03
Albumin level, initial (g/dl)	3.5±0.6	3.7±0.5	3.7±0.5	3.6±0.5	0.11
Albumin level, last visit (g/dl)	3.6±0.7	3.6±0.5	3.7±0.5	3.3±0.5	0.03
Hemoglobin level, initial (gr/dl)	10.6±1.8	10.7±1.7	10.5±1.8	11±1.9	0.62
Hemoglobin level, last visit (gr/dl)	11.3±2.3	11.3±2	11.3±1.9	11.6±1.9	0.89
Ferritin, initial (ng/mL)	335±259	482±436	363±274	376±418	0.08
Ferritin, last visit (ng/mL)	308±233	405±414	381±375	452±729	0.53
Calcium level, initial (mg/dl)	9.0±1.0	9.1±1.0	9.0±0.7	8.8±1.0	0.50
Calcium level, last visit (mg/dl)	9.2±0.9	9.2±0.9	9.2±0.8	9.0±0.8	0.93
Phosphorus level, initial (mg/dl)	4.9±1.5	4.9±1.8	5.2±1.7	5.3±2.0	0.50
Phosphorus level, last visit (mg/dl)	4.3±1.3	4.3±1.3	5.0±1.4	4.6±1.4	0.004
Parathyroid hormone level, initial (pg/dl)	303±355	326±321	387±555	248±203	0.39
Parathyroid hormone level, last visit (pg/dl)	393±395	437±528	483±529	397±308	0.75

diabetic nephropathy (21.9%) were the leading causes of ESRD in all patients. There was no difference in terms of etiology of kidney disease among groups (p=0.35). Most of the patients had completed primary school: 57.1% of low transport group, 51.7% of low-average transport group, 62.7% of high-average and of high transport groups. Education level was similar among groups (p=0.52).

PD was performed by patients themselves in 92.9% of low, 90.8% of low-average, 90% and 72.7% of high-average and of high transport groups, respectively. In other words, high transporters were performing assisted PD more frequently compared to other groups. (p=0.02).

PD therapy was done mandatory in 30% of high transporters (p=0.04) while it was 7.1% in low, 13.8% in low-average, 14.8% in high-average transport patients. History of hemodialysis was similar among groups (p=0.3).

Peritonitis and catheter exit site/tunnel infections were significantly frequent in high transport group patients (p=0.01 and 0.008, respectively).

A total of 201 patients were withdrawn from PD during the follow-up period. Eighty patients were transferred to HD, 73 patients had died, 42 patients had transplantation, and 6 patients were dropped out due to transfer to another PD unit. The remaining 62 patients were still performing PD.

Twenty patients were transferred to HD, 15 patients had died, 5 had transplantation, 1 patients dropped out in low transport group. Sixteen patients were transferred to HD, 28 died, 14 were transplanted, and 2 were dropped out in the low-average transporters. In the high-average transporters, 31 were transferred to HD, 16 diede, 14 had transplantation while 2 were dropped out from the study. Thirteen patients were transferred to HD, 14 patients died, 9 patients had transplantation and only 1 patient was dropped out in high transport group. Low transporters had the lowest rate of transplantation and the highest rate of transfer to HD while death rate was higher in high transport patients. There was a statistically significant difference in terms of the last status of patients among groups (p=0.009).

The most frequent causes of death in all patients were peritonitis/sepsis (42.1%) and cardiac reasons (35.8%). Causes for transfer to HD were mostly due to peritonitis/sepsis (62.4%) and inadequate dialysis (28.2%). PET

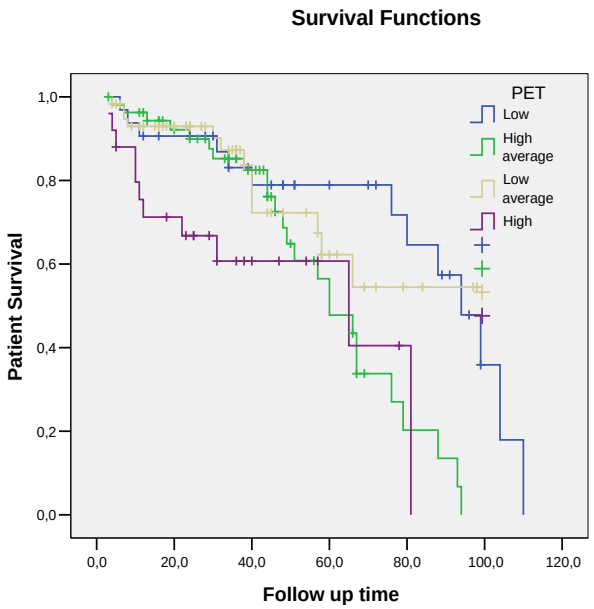

Fig. 1. Patient survival according to PET characteristics

groups were similar when causes of death and transfer to HD were compared among groups.

Mean survival time was 81.6±6.6 months in Kaplan-Meier analysis and survival rate was 90.6%, 83.1%, and 71.7% at 1, 3, and 5 years, respectively in patients with low transport status. Mean survival time was 72.4±5.6 months and survival rate was 92.9%, 87.3%, and 54.5% at 1, 3, and 5 years, respectively in low-average transport group. In high-average transport group, mean survival time was 60.1±4.1 months and survival rate was 96.3%, 82.5%, and 47.8% at 1, 3, and 5 years, respectively. Mean survival time was 51.0±7.3 months and survival rate was 71.2%, 60.7%, and 40.5% at 1, 3, and 5 years, respectively in patients with high transport status. Patients' survival was the worst in high transport group (log rank: 0.004) (Figure 1). The factors affecting patients' survival by Cox proportional hazard model backward stepwise LR (Likelihood Ratio) analysis method was found to be advanced age (OR:1.045, 95%[CI]:1.019-1.071, p<0.001), daily urine volume OR:1.045, 95%[CI]: 1.019-1.071, p<0.001), initial serum albumin level (OR:0.482, 95%[CI]:0.284-0.817, p=0.007), and number of catheter exit site/tunnel infection episodes (OR:0.249, 95%[CI]: 0.119-0.524, p<0.001).

Mean technique survival duration was found to be 72.8±6.4 months and survival rate was 96.6%, 75.4%, and 51.6% at 1, 3, and 5 years, respectively in low transport group. Mean technique survival duration was found to be 43.7±3.9 months and survival rate was 91.2%, 48.5%, and 25.1% at 1, 3, and 5 years, respectively in patients with low-average transport status. In high-average transport group, mean technique survival duration was found to be 54.4±4.5 months and survival rate was 92.6%, 66.2%, and 38.4% at 1, 3, and 5 years, respectively. Mean technique survival duration was found to be 43.2±5.3 months and technique survival rate was 95.7%, 53.3%, and 20% at 1, 3, and 5 years, respectively in high transport group. Comparison of technique survival among groups yielded a statistically different significance (log rank: 0.027) (Figure 2). The only factor effective on technique survival was found to be number of catheter exit site/ tunnel infection episodes (OR:0.452, 95%[CI]:0.241-0.847, p= 0.013) by means of Cox proportional hazard model backward stepwise LR (Likelihood Ratio) analysis method.

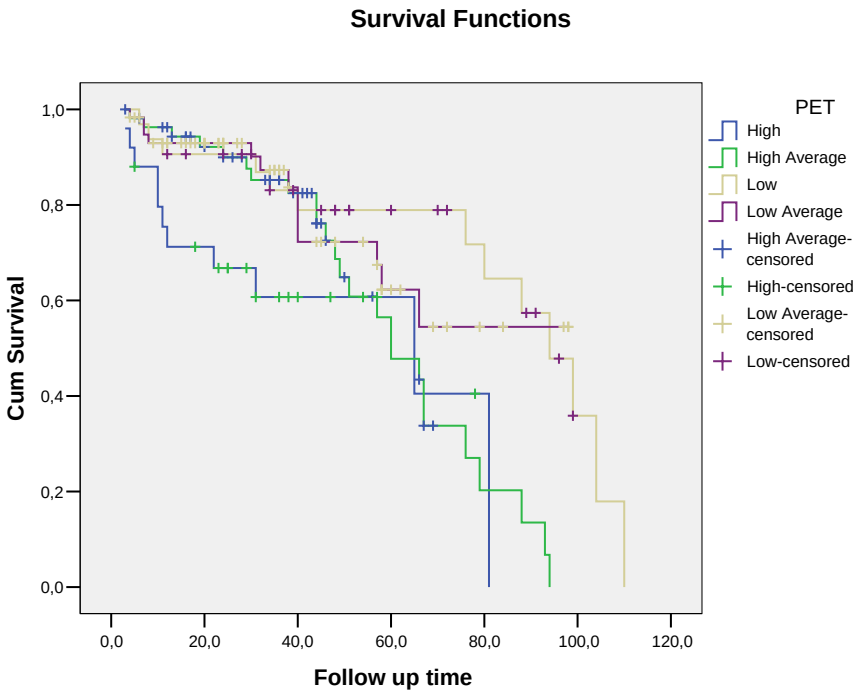

Fig. 2. Technique survival according to PET characteristics

Discussion

The results of this study demonstrated that patients with high transport status had increased mortality rates, worse technique survival rate and frequent infectious complications than the other groups. Older age, number of catheter exit size/tunnel infection attacks, hypoalbuminemia, and low daily urine volume at the beginning of PD were predictors of mortality. Only number of catheter exit size/ tunnel infection attacks was found to predict technique survival.

Many conflicting results have been reported on the relationship between high peritoneal transport and mortality in PD patients [5,7-17]. Some studies have found that high transporters have increased mortality [7-13] while other studies such as ADEMEX and EAPOS, have found peritoneal membrane properties were not associated with patient survival [14-17]. Analysis from the ANZDATA registry has confirmed the association of high transport rates with increased mortality and technique failure [19]. An analysis of the CANUSA data,

Churchill [5] *et al*. demonstrated that the relative risk of technique failure or death was increased by 19% for each 0.1 increase in D: P Cr 4 hour. Two-year survival probabilities of high, high-average, low-average and low transporters were 70.5, 72.4, 80.4 and 90.9%, respectively. The two-year probabilities of both patients and technique survival were increased in high transporters. Another study demonstrated that patient survival for years 1, 3, and 5 were 85%, 64%, and 35%, respectively for high transporters [20]. However, other studies such as ADEMEX and EAPOS, have found that peritoneal membrane properties were not associated with poor patient survival [14,16]. The ADAMEX trial assessed peritoneal transport status by the dialysis adequacy and transport test which may have given different results compared with PET test [16]. In addition, EAPOS study has included patients without residual urine volume and performing only automated peritoneal dialysis (APD). The number of deaths was a few in this study [14]. These factors might lead to differences in study population. We found patient survival rate to be 71.2%, 60.7%, and 40.5% at 1, 3, and 5 years, respectively. They were lower than in the other PET transport groups.

The peritoneal equilibration test characterizes the peritoneal membrane transport properties by determining the ratio of the creatinine concentration in the dialysate to that in the plasma after a 4-h dwell (D/Pc) and has been shown to vary considerably among individuals [18]. The relationship between reduced survival on PD and high transport status may relate to properties of the peritoneal membrane that predispose to the development of conditions associated with a poor prognosis. This is more common in high transporters [21], as rapid solute transport leads to early dissipation of the osmotic gradient for fluid removal [22] hence, reduced drain volumes [5], left ventricular hypertrophy and hypertension are more common in high transporters [23], and are both interrelated with intravascular volume overload [24,25]. We found that high transporters had lower amounts of daily urine volume and ultrafiltration volume even though there was no statistical significance. All of our patients admitted to out PD unit were under strict salt restriction. Acceptable blood pressure values even in high transport group may be the result of our strict salt restriction policy.

High transporters will have greater peritoneal losses of protein [26]. Other markers of a poor prognosis such as hypoalbuminemia [27] and elevated inflammatory markers [28] are also more common in higher transport groups. Factors like these may play a role in the higher rate of adverse outcomes observed in high transporters [26]. Our high transporters had similar serum albumin levels at initiation of PD compared to other groups. Albumin level decreased significantly afterwards. We could not measure amount of peritoneal protein loss so we cannot speculate its effect on hypoalbuminemia. It can be said that high transport patients with hypoalbuminemia at initiation of PD may face with further decreases in albumin levels to the level that it may affect their mortality.

The leading cause of death and transfer to HD was peritonitis/sepsis in our study. The rates of both conditions were similar in groups. However, high transporters had more often peritonitis and catheter exit site infections. Some factors were found to increase peritonitis risk. A meta-analysis found that non-modifiable peritonitis risk factors were ethnicity, female gender, chronic lung disease, coronary artery disease, congestive heart failure, cardiovascular disease, hypertension, antihepatitis C virus antibody positivity, diabetes mellitus, lupus nephritis or glomerulonephritis as underlying renal disease, no residual renal function while modifiable ones were malnutrition, overweight, smoking, immunosuppression, no use of oral active vitamin D, psychosocial factors, low socioeconomic status, PD against patient's choice, and hemodialysis as former modality [29]. We showed that in high transport group, presence of someone to perform PD was more likely and also percentage of patients performing PD due to vascular problems were more common than in the other transport groups. These factors may enlighten the increased peritonitis incidence in high transport group.

The single-center Stroke PD study [11,30] and the multicenter CANUSA study [5] found that high transport was associated with worse technique survival independent of other important risk factors, such as age, comorbidities, and residual renal function. A meta-analysis of 20 observational studies [31] also demonstrated that a higher peritoneal membrane solute transport rate was associated with a trend to higher technique failure. The 2-yr probabilities of technique survival were increased in high transporters [5]. Another study showed that cumulative combined technique survival at the end of 1, 3, and 5 yr were 76%, 57%, and 16% for high transport group, and 83%, 66%, and 30% for non-high group. There were no significant differences in the risk of either technique failure between patients in two transport groups [20]. This study revealed worse technique survival in high transport group and technique survival rate was 95.7%, 53.3%, and 20% at 1, 3, and 5 years, respectively.

The most significant limitation of this study is its retrospective design. In addition, changes in transport status of peritoneal membrane as the times passes can not be considered. Sum of renal and peritoneal clearances were given, unfortunately the summands were not known separately. Amount of protein loss from urine and peritoneal fluid could not be assessed and hence presence of any possible effect on serum albumin level could not be predicted.

Conclusions

In conclusion, it was shown that high transporters had worse patient and technique survival. Infectious complications were also more frequent in this group. Mortality was higher in patients with advanced age, hypoalbumine-

mia at initiation of PD, decreased amount of daily urine volume, frequent catheter infections. Transfer to HD can be an option in high transport patients if they have hypoalbuminemia, frequent infectious complications and no urine output.

Conflict of interest statement. None declared.

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Original article

Impact of Different Variables on Recovery Time in Patients Receiving Hemodialysis

Nikolina Smokovska[1], Risto Grozdanovski[1] and Goce Spasovski[2]

[1]Special Hospital for Nephrology and Hemodialysis-Diamed, Skopje, Republic of Macedonia; [2]University Department of Nephrology, University "Ss. Cyril and Methodius" Medical Faculty Skopje, Republic of Macedonia

Abstract

Introduction. Patients on hemodialysis (HD) are proven to have impaired Health Related Quality of Life (HRQoL) compared to the general population. Recovery from the hemodialysis session is a permanent problem among majority of patients receiving HD treatment. A partial explanation may be the osmotic imbalance between different compartments of the body due to the fluid and electrolyte movement across the cell membrane which is a part of the HD process itself. The aim of our study was to see whether the length of recovery time (RT) is associated with different clinically relevant variables and dialysis treatment features in our HD population.

Methods. We performed a cross-sectional study on patients receiving trice weekly HD in a single hemodialysis center. The recovery time was defined by posing a single question "How long does it take you to recover after a hemodialysis session?" and was calculated in hours (up to 2, 2-6, 6-12, and 12-24 hours) / minutes. Various demographic and clinical characteristics were analyzed for association with the RT.

Results. The mean RT was 364.62±339.24 minutes. From all of the analyzed variables a significant statistical correlation was obtained with the level of albumin, urea, interdialytic weight gain (IDWG), protein catabolic rate (PCR), body mass index (BMI) and the level of hemoglobin ($p<0.05$ for all parameters). The longest mean RT had patients with hypertension and glomerulonephritis as a primary cause of ESRD and the shortest, patients with an adult dominant polycystic kidney disease. With the multiple regression analysis a significant correlation was obtained only for the level of hemoglobin (Hb) with a coefficient for partial regression analysis – 0.2635. The t-test showed that the influence of the level of hemoglobin on recovery time in patients was statistically significant ($p = 0.039$).

Conclusions. RT in our study was associated with IDWG, albumin, urea, BMI, and PCR, while the level of hemoglobin was also shown to have a significant impact on the RT and on patients' overall health status. Hence, we could conclude that maintaining Hb levels in dialysis patients within reference values among the other benefits, may improve the recovery time and HRQoL of our patients.

Key words: hemodialysis, recovery time, hemoglobin

Introduction

The majority of patients with an impaired renal function may be classified as to a certain stage of chronic kidney disease (CKD) progressing to end-stage renal disease (ESRD) and requiring renal replacement therapy (RRT). Patients on hemodialysis (HD) are proven to have impaired Health Related Quality of Life (HRQoL) compared to the general population [1-3]. There are multifactorial reasons for this condition but the time needed to recover after each hemodialysis session was found to be highly associated with HRQoL [4,5].

Recovery from the hemodialysis session is a permanent problem among majority of patients receiving HD treatment. They describe this condition as feeling "washed out", weak or without energy. The pathophysiology of this process is investigated but not completely understood. A partial explanation may be the osmotic imbalance between different compartments of the body due to the fluid and electrolyte movement across the cell membrane which is a part of the HD process itself. These changes appear more frequently after HD sessions with a higher ultrafiltration, which may lead to a longer recovery thereafter [6].

The aim of our study was to see whether the length of recovery time (RT) is associated with different clinically relevant variables and dialysis treatment features in our HD population in order to have an easier decision for patients' treatment choice and to possibly improve patients' everyday life.

Correspondence to: Nikolina Smokovska, Special Hospital for nephrology and dialysis Diamed, St. "Gorce Petrov" No 23, 1000 Skopje, R. Macedonia; Mob. 00 389 75 21 08 32; E-mail: nikolinasmokovska@gmail.com

Material and methods

We performed a cross-sectional study of our patients receiving trice weekly HD in the Special Hospital for Nephrology and Hemodialysis-Diamed, Skopje, R. Macedonia. Exclusion criteria were: diagnosis of dementia, intellectual impairment, less than one year dialysis duration, and clinical instability requiring hospital admission. After inclusion into the study, all patients were assessed for the recovery time after dialysis. The recovery time was defined by posing the question "How long does it take you to recover after a hemodialysis session?" The patients were asked in their native language, Macedonian or Albanian, excluding the language barrier. This question is proven to be a reliable assessment tool for HRQoL in HD patients [4].

The recovery time was calculated using the methods of Lindsay *et al*. [4]. Answers were obtained in hours (up to 2, 2-6, 6-12, and 12-24 hours). Afterwards they were converted and calculated in minutes. Then we collected patients' different demographic and clinical characteristics. This included age, gender, elapsed time on hemodialysis and duration of hemodialysis session, interdialytic weight gain (IDWG), biochemical parameters (urea, creatinine, albumin, hemoglobin, triglyceride, cholesterol, phosphate, calcium etc.), eKT/V. The Charlson's Comorbidity Score (CCS) was used since it included reviewing the patients' recovery time for each of the co-morbidities (congestive heart failure, diabetes mellitus, periphery artery disease, coronary artery disease, chronic obstructive pulmonary disease, malignancies and liver disease) [7].

Within the statistical analysis all continuous data were expressed as mean±SD and proportions for categorical variables. Spearman's correlation coefficient was used to assess the association between the recovery time and each separate variable. Univariate linear regression was performed with the recovery time as a dependent variable and all other variables. Afterwards, multivariate regression analysis was performed from the variables that significantly correlated within the univariate analysis. Variables with P value less than 0.05 were considered significant.

Results

Patients included in the study had been on dialysis for at least 1 year, and were up to 22 years old, with an average of 6.5 years. The youngest patient was 35 years of age, and the oldest 83 (average of 59.04±9.72 years). HD frequency was thrice-weekly with individualized sessions from 3.5 to 5 hours (average 4.22 hours) targeting desired eKT/V >1.2 [8].

We delivered a screening questionnaire to a total of 108 patients treated in our HD center for the purpose of this study. The answers were considered successful in 78 patients, i.e. 72.2% response rate (not including patients who were intellectually impaired, not willing to participate, or had to be hospitalized) and were included for analysis. Their demographic, clinical and laboratory characteristics are shown in Table 1.

Table 1. Characteristics of patients (n=78)

Age, years	59.04 ± 9.7
Dialysis age, years	6.55± 6.0
Sex (M/F)	51 / 27
Dialysis session, hours	4.22 ± 0.27
Primary cause of ESRD	
- HTA nephropathy	20
- Glomerulonephritis	21
- Diabetic nephropathy	10
- ADPKD	9
- Obstructive nephropathy	12
- Sy Alport	1
- Unknown	5
Body mass index	27.08 ± 4.8
Albumin (mmol/L)	40.15 ± 2.7
Creatinine (μmol/L)	446.64 ±466.8
Urea (mmol/L)	31.8 ± 24.9
eKt/V	1.35 ± 0.28
TG (mmol/L)	1.93 ± 1.2
Cholesterol (mmol/L)	4.03 ± 0.9
Calcium (mmol/L)	2.12 ± 0.2
Phosphorus (mmol/L)	1.27 ±0.39
Hb (mmol/L)	121 ± 13.5
IDWG (L)	2.17 ± 0.73
PCR	0.96 ± 0.22
CCS	2.04± 1.32

Data are expressed as mean±SD. ESDR=end-stage renal disease; HTA=hypertension; ADPKD=adult dominant polycystic kidney disease; eKt/V=equilibrated Kt/V; TG=triglycerides; Hb=hemoglobin; IDWG=interdialytic weight gain (L); PCR=protein catabolic rate; CCS= Charlson's comorbidity score.

The mean RT was 364.62±339.24 min. Majority of patients (n=34) reported RT between 2-6 hours, and only

Table 2. Correlations among time of recovery after hemodialysis and different variables

Independent variables	Spearman correlation coefficient	p Value
Age	0.128	0.131
Dialysis age	- 0.147	0.1
Dialysis session	- 0.191	0.095
Body mass index	0.226	**0.023**
Albumin	- 0.457	0.0003
Creatinine	- 0.002	0.433
Urea	- 0.214	**0.03**
eKt/V	0.148	0.099
TG	0.05	0.334
Cholesterol	- 0.052	0.323
Calcium	- 0.039	0.367
Phosphorus	- 0.039	0.367
Hb	- 0.457	**0.00001**
IDWG	- 0.265	0.019
PCR	- 0.254	**0.012**
CCS	0.105	0.180

ESDR=end-stage renal disease; HTA=hypertension; ADPKD =adult dominant polycystic kidney disease; AKI=acute kidney injury; eKt/V=equilibrated Kt/V; TG=triglycerides; Hb=hemoglobin; IDWG=interdialytic weight gain (L); PCR= protein catabolic rate; CCS=Charlson's Comorbidity Score.

13 patients had recovery time more than 12 hours. The mean RT for males was significantly shorter 311.76±300.5 compared to females 464.44±389.1 min. The correlation matrix between different variables is presented in table 2.
From all of the analyzed variables a significant statistical correlation with the recovery time had the level of albumin (p=0.0003), urea (p=0.03); IDWG (p=0.019), PCR (p=0.012), BMI (p=0.023) and the level of hemoglobin (p=0.00001).The longest mean RT had patients with unknown etiology as a primary cause of ESRD and it was 564±341 min. Patients who had an adult dominant polycystic kidney disease (ADPCD) had the shortest RT, 160 min ±60 min. (Table 3). We did a comparison of the RT between each of the groups against all others and found that patients with ADPKD had the shortest RT.

Table 3. Comparison of RT between each particular groups vs all others

Primary cause of ESRD (n=78)	RT (min.) ± SD	p value
- HTA nephropathy	420±355.23	0.2
- Glomerulonephritis	405.71±389.73	0.26
- Diabetic nephropathy	294±305.22	0.24
- ADPKD	160±60	0.03
- Obstructive nephropathy	340±350.17	0.39
- Unknown	564±341	0.09

Data are expressed as means ±SD. ADPKD=adult dominant polycystic kidney disease

Univariate linear regression was performed with the recovery time as a dependent variable associated with each of the normally distributed variables. The RT showed a significant predictability with the variables which had a correlation with the Spearman's correlation coefficient (Table 4).

Table 4. Univariate linear regression analysis for the association of RT and clinical and biochemical variables

Independent variables	r	p value
Age	- 0.055	0.315
Dialysis age	- 0.128	0.132
Dialysis session	- 0.155	0.088
Body mass Index	0.275	**0.008**
Albumin	- 0.353	0.0008
Creatinine	- 0.07	0.37
Urea	- 0.309	**0.003**
eKt/V	0.111	0.167
TG	0.036	0.376
Cholesterol	- 0.038	0.372
Calcium	0.065	0.287
Phosphorus	- 0.175	0.063
Hb	- 0.412	**0.0001**
IDWG	- 0.218	0.028
PCR	- 0.241	**0.017**
CCS	0.052	0.327

eKt/V = equilibrated Kt/V; TG = triglycerides; Hb = hemoglobin; IDWG = interdialytic weight gain (L); PCR = protein catabolic rate; CCS = Charlson's Comorbidity Score.

When the multiple regression analysis with the RT and all other patients' independent variables was performed, the multiple regression coefficient (R) was 0.559. Determination coefficient (R^2) was 0.313 showing that all independent variables as one influence the variability of the recovery time with 31.3%, while 68.7% of the influence is coming from other factors. Additionally, the coefficient of multiple correlation based on F-distribution showed that the influence of the predictable group of variables on the recovery time (dependent variable) was statistically significant (p=0.027). When analyzing all the individual variables, a significant correlation was obtained only for the level of hemoglobin (Hb) with a coefficient for partial regression analysis - 0.2635. The t-test showed that the influence of the level of hemoglobin on recovery time in patients was statistically significant (p=0.039). The influence of other predicative variables of interest on the recovery time was not statistically significant (Table 5).

Table 5. Multiple regression analysis for the association of rt and clinical and biochemical variables

Independent variables	**R** = 0,559		**R^2** = 0,313
	F = 2.47		p = 0.027755
	Beta	**t - test**	**p - level**
Urea	-0.051	-0.395	0.694
Albumin	-0.182	-1.364	0.177
IDWG	-0.206	-1.652	0.104
Hb	**-0.263**	**-2.100**	**0.039***
PCR	-0.080	-0.668	0.506
BMI	0.160	1.437	0.156
Gender	0.098	0.737	0.464
Age	0.160	1.197	0.236
eKT/V	0.057	0.443	0.659
Phosphorus	0.149	1.196	0.236
TG	0.086	0.684	0.496
Cholesterol	-0.116	-0.812	0.420
Calcium	0.063	0.550	0.584
Creatinine	0.072	0.579	0.565

* statistical significance

Discussion

There were several studies evaluating the possible associations between various demographic, laboratory and clinical variables with RT [4,8-10]. Lindsay *et al.* pointed out that not only the test-retest consistency of the question measuring RT proved to be stable over time, but at the same time it correlated well with the HRQoL measurements [4].
In our study we investigated whether recovery time is influenced by different characteristics related to patients' characteristics or within the HD process itself. This might be important in treatment modifying decision about the hemodialysis regimen for sole purpose of improving patients' well-being despite their burden of ESRD.
Unexpectedly, the reported RT was not affected by patients' age, years spent on HD or the length of the HD session previously observed in the work of Kwabena *et al.* [9]. Our findings suggest that RT may be independent from these variables. However, there is no clear explana-

tion why it happens. It may be partially explained by the wide range of patients' age and years spent on HD. Surprisingly, there was no correlation between the recovery time and the adequacy of HD. The explanation for this might be that eKT/V is a number which is highly sensitive to change based on the technician's skill to pin point the exact moment for blood extraction and varying session by session because of many reasons that are not considered of interest for our study aim.

Maurizio *et al.* [10] showed no association between the recovery time and different laboratory variables. In our study, from all investigated laboratory variables (creatinine, albumin, urea, TG, cholesterol, Ca, P, Hb) only the level of albumin ($p=0.0003$), urea ($p=0.03$) and hemoglobin ($p<0.001$) showed a significant but inverse correlation. In contrast to our results, Dreisbach *et al*. found no difference in IDWG and recovery time [11]. A possible explanation may be that variables reflecting patients' nutritional status BMI and PCR (but may also include albumin, urea, IDWG and Hb), showed significant correlations. These variables may contribute to patients' overall better physical conditions which render them to be more capable of reducing the stress of the HD treatment.

We also analyzed the association between the recovery time and primary cause for ESRD (Table 3) pointing out that only ADPKD could have an impact on the length of RT. This may be in line with the fact that the Hb level may influence patients' recovery time, given that ADPKD patients have the highest Hb level compared to all other primary causes of ESRD [12]. Interestingly, there was no association with CCS that may be partially explained by the fact that we could not assess the severity or acuity of the co-morbidities but only their presence.

Despite the significant findings of association with certain variables in the univariate regression analysis, it was not shown in the multivariate regression analysis. The Hb level was the sole variable that significantly influenced patients' RT. Furthermore, all independent variables taken together influenced the variability of the RT with 31.3%, while 68.7% of the influence belonged to other factors that should be investigated in further studies.

The present study has some limitations. The number of comprised patients was relatively small and from a single dialysis unit. Nevertheless, we may say that it is a representative sample of HD patients in our region. Secondly, this study is a cross-sectional showing only one point in time, but continuing prospective, longitudinal investigation should most probably give a better insight into the aim of a similar research. Finally, we did not investigate the influence of each of the co-morbidities on RT and their association with patients' characteristics.

Conclusions

Considering the impact of dialysis on patients' well-being it is recognized that for its possible improval an assessment of the recovery time and better characterization of variables associated with the RT is required. Our study did not associate with many of the variables included in the analysis but answered our question which variables have weak correlation and which are strongly correlated (IDWG, albumin, urea, BMI, PCR). The level of hemoglobin was shown to have a significant impact on the RT and on patients' overall health status. Hence, we could recommend maintaining Hb levels in dialysis patients within reference values [13] given that among other benefits it may improve the recovery time and HRQoL of our patients.

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Conflict of interest statement. None declared.

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Original article

Impact of Interdialytic Weight Gain (IDWG) on Nutritional Parameters, Cardiovascular Risk Factors and Quality of Life in Hemodialysis Patients

Aysegul Kahraman[1], Hakan Akdam[2], Alper Alp[2], Mustafa Ahmet Huyut[3], Cagdas Akgullu[3], Tuba Balaban[1], Fadime Dinleyen[1], Aynur Topcu[1], Husniye Gelmez[1], Nevin Atakan[1], Harun Akar[2] and Yavuz Yenicerioglu[2]

[1]Adnan Menderes University Hospital, Hemodialysis Unit, [2]Adnan Menderes University, Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, [3]Adnan Menderes University, Faculty of Medicine, Department of Cardiology, Aydın, Turkey

Abstract

Introduction. The amount of interdialytic weight gain (IDWG) considering body weight is of great importance in hemodialysis patients. In general practice, patients are asked to get standard weight between two hemodialysis sessions. However, it should be individualized considering patient's weight. We aimed to determine the association between the IDWG and the nutritional parameters, cardiovascular risk factors, and quality of life.

Methods. Thrity-two patients receiving hemodialysis at least for one year were enrolled into the study. Patients were monitored for 12 consecutive hemodialysis sessions; and the arithmetic mean of IDWG was calculated. IDWG% was calculated in accordance with patients' dry weight. Data of patients with IDWG<3% (Group I) and IDWG≥3 (Group II) were compared. Sociodemographic variables, laboratory, anthropometric measurements, blood pressure, left ventricular mass index, Subjective Global Assessment Scale and SF-36 Quality of Life Scale were applied to evaluate the patients.

Results. 59.4% (n=19) and 40.6% (n=13) of patients were included in Group I and Group II, respectively. In Group II, albumin (p=0.02), potassium (p=0.02), phosphorus (p=0.04), nPCR (p=0.03), physical function (p=0.04), role limitations caused by physical problems (p=0.04), general health (p=0.03), physical quality of life (p=0.04) scores were significantly higher. A significant correlation was detected between IDWG and physical and mental quality of life, total score SF-36, albumin, total protein and the potassium values.

Conclusions. Patients with an IDWG ≥ 3% have better nutritional parameters and quality of life scales. The limiting of IDWG to 1-2 kg, ingoring patient weight may give rise to malnutrition and a reduced quality of life.

Key words: hemodialysis, interdialytic weight gain, nutritional parameters, SF-36, triceps skinfold thickness

Introduction

The weight gain occurring in hemodialysis patients during the interval between the two hemodialysis sessions is called "interdialytic weight gain" (IDWG). Interdialytic weight gain is used as a measure to limit the weight gain between the two consequent dialysis sessions; however the values identified for this measure have been restricted to an absolute value of 1-2 kg [1,2]. Interdialytic weight gain usually tends to be relatively constant for each patient [1-3] and is affected by the dialytic factors (hypernatremia, the NaCl solution infusion during the hemodialysis), residual renal function, nutritional habits, hyperglycemia, environmental factors, the level of self-care and compliance with treatment [2-4]. Interdialytic weight gain may vary individually, while in the majority of the patients the IDGW is less than 5% of the body weight and is usually in the range of 2 and 3.5 kg [5].

In general, IDGW is thought to result from salt and water intake between the two dialysis sessions [2,3,6]. Liquid and salt are commonly consumed with carbohydrates, fats and proteins, suggesting that high IDWGs could be associated with a better nutritional state [2].

Despite the recent advances in hemodialysis, the mortality in dialysis patients is still very high, when compared to the normal population [1,7-9]. Malnutrition is one of the most significant risk factor for mortality in dialysis patients with no other concomitant systemic disease [1,7-11]. Malnutrition is defined as a state of nutrition, where inadequate, excessive or imbalanced intake of protein, energy and other nutrients cause measurable side effects on the tissues, whole body functions and the

Correspondence to: Aysegul Kahraman, Adnan Menderes University Hospital, Hemodialysis Unit, 09100 Aydın, Turkey; Phone: +90 256 444 1256; Fax: +90 256 214 4086; E-mail: kahramanaysegul@yahoo.com

clinical outcomes [10]. Malnutrition may lead to suppression of the immune system, increased susceptibility to the infections, reduced wound healing, reduced functional capacity, anemia, erythropoietin resistance, and vascular access complications [1,7,11].
Malnutrition is multifactorial in chronic renal disease. Loss of protein, increased protein catabolism, endocrine causes and inadequate intake may be summarized as the etiologic factors [1,7-11]. In dialysis patients, strict diet, dysgeusia, nausea-vomiting, inadequate dialysis, psychological and socio-economical causes contribute to malnutrition [1,8-10].
The end-stage renal disease (ESRD) itself is also associated with many unfavorable factors such as hypertension, dyslipidemia and inflammation, which are also established as risk factors for cardiovascular diseases [12].
Using the percentage of the weight gain instead of a fixed number, is more correct to be in accordance between the body weight and weight gain. The weight gain per body weight takes into account patient's measures. For example, a 3 kg weight gain is excessive for a patient weighing 50 kg (6%) but it is normal for a patient weighing 50 kg (3% increase) [1].
The amount of IDWG considering body weight is of great importance in hemodialysis patients. Thereof, the IDGW should be individualized as IDWG%: weight gain per body weight. In this descriptive and correlative and cross-sectional study, we aimed to analyze the possible correlation between IDGW% and sociodemographic variables, disease variables, nutritional state variables, cardiovascular risk factors and the quality of life in hemodialysis patients.

Material and methods

This study was conducted at the Adnan Menderes University Medical Faculty Hospital Hemodialysis Unit between February 2013 and April 2013.

Ethical Considerations

This study was performed in accordance with the principles of the Helsinki Declaration. The study was submitted to the local ethics committee of clinical research and was granted approval with decision number B.30.2. ADU.0.20.05.00/050.04-220, dated 31.08.2012.
The objectives, methods, targets and the potential hazards of the study were explained to all individuals. The participants were informed and gave their informed consent before participating in the study.

The study population

Chronic hemodialysis patients for at least ond year, aged 18- 75 years, without overt hypervolemia, active infection or malignancy were considered to be eligible for the study. Forty patients were evaluated for eligibility and 32 patients fulfilled the criteria.

Study Group

The IDWG were recorded during 12 consecutive hemodialysis sessions. The IDWG (the current pre-dialysis weight minus the preceding post-dialytic weight) was measured in each hemodialysis session and the mean IDWG of 12 consecutive hemodialysis sessions was used for statistical analysis. The IDWG% was expressed as a proportion of the current dry weight [3,14]. Patients were grouped into 2 groups based on the percent IDWG considering the dry weight: Group I and Group II were composed of patients with IDWG less than 3% of dry weight and IDWG equal or greater than 3% of dry weight, respectively.

Data Collection Tools

Patients' height, mid-arm circumference, and triceps skinfold thickness and pre-dialysis and post-dialysis weight were measured. A skin caliper was used for measuring triceps skinfold thickness. Mid-arm muscle circumference, arm muscle area were calculated by the Heymsfield formula [13]. Mid-arm fat area was calculated as [(mid-arm circumference-triceps skinfold thickness) /2]-[(π x triceps skinfold thickness^2)/4], and body mass index (BMI) was calculated using the weight (kg)/ height (m^2) formula.
Blood pressure was measured throughout the 12 sessions, recorded and the arithmetic means were calculated. The "General data form" intended for the hemodialysis patients, and the "Session data form", "Subjective Global Assessment (SGA) Scale", "The Medical Outcomes Study Short Form 36-Item Health Survey (SF-36)" intended for the dialysis session, were used as data collection tools.
The SGA consisted of 5 components, including weight change, dietary intake, GI symptoms, functional capacity, subcutaneous fat and signs of muscle wasting. Each component was scored as A (normal), B (mild to moderate malnutrition) or C (severe malnutrition). Based on the data from all forms, the physician grouped the patients into 3 in accordance with the total SGA score as well-nourished (A), mildly-moderately malnourished (B) and severely malnourished (C) [15]. The SF-36 is designed as 2 main-topic scales that include 36 expressions and assess 8 health dimensions. The main topics are the quality of life and the global quality of life. The 8 dimensions are the Physical function (PF), Role limitations caused by physical problems, Pain, General health, Vitality/energy, Social function, Mental health/emotional well-being and Role limitations caused by emotional problems/mental health. Each dimension was scored as 0-100, with a higher score indicating better quality of life [16]. The SF-36 and the SGA forms completed

by the investigator used the personal expressions and the patient file records through face-to-face interviews.

Biochemical Analysis

During the initial session of the study, a 12-hour fasting blood sampling was performed before the hemodialysis for measuring urea, creatinine, sodium, potassium, calcium, phosphorus, total protein, albumin, lipid panel and hemoglobin. At the end of the hemodialysis session, post-dialysis serum urea, serum creatinine and potassium measurements were obtained. Urea reduction rate (URR) was calculated as follows: [(pre dialysis urea-post dialysis urea) x 100] / (pre dialysis urea). Single pool Kt/V was calculated, using the Daugridas formula, and the normalized protein catabolic rate (nPCR) calculated via kinetic urea model [17].

Echocardiographic Evaluation

An experienced cardiologist conducted the echocardiographic investigations at the Cardiology department of our Faculty. Measuring the parameters by the Devereux formula, the left ventricular mass was divided by the body surface area to calculate the left ventricular mass index (LVMI) [18]. A left ventricular mass index >131 gr/m^2 and >100 gr/m^2 was accepted to indicate the presence of left ventricular hypertrophy (LVH) for males and females, respectively [19]. The patients were divided into 2 groups as those with and without LVH.

Statistical Data Analysis

Statistical assessments were performed using the Statistical Package for Social Sciences for Windows, version 17 [SPSS Inc; Chicago, IL, USA]. The descriptive statistics was expressed in number (n, %) and the mean ± standard deviation.
The quantitative variables were expressed as mean ± standard deviation (SD), and the qualitative variables as percentage (%) or proportion. The compliance of the variables with the normal distribution was assessed by the Kolmogorov-Smirnov test. For comparison of the variables between the groups, the Student's t-test and the Mann-Whitney U test were used respectively in case of normal and abnormal distribution. As for the quailtative variables, the chi-square test was used, or the Fisher's exact test if the expected values were below 5 in the cross tables. The correlations between the variables were investigated using the Pearson's correlation test. A value of $p<0.05$ was considered significant.

Results

Thirty-two patients were included in the study. The mean age was 64.3±8.3 years. 40.6% were males (13), 93.8% were married, 62.5% were primary school graduates, 96.9% lived with the family, 50% were retired, 31.3% were housewives and 87.5% had a moderate income.

Table 1. Sociodemographic features of the groups

Sociodemographic features	**Group I (n=19)** (IDWG < 3%)	**Group II (n=13)** (IDWG ≥ 3%)	**P**
Age (mean±sd)	64.1 ± 7.8	64.6 ± 9.3	0.954
Gender (n,%)			
Male	12(37.5%)	7(21.9%)	0.598
Female	7(21.9%)	6(18.8%)	
Marital status (n,%)			
Single	1(3.1%)	0(0%)	
Married	17(53.1%)	13(40.6%)	0.482
Divorced/Widow	1(3.1%)	0(0%)	
Education (n,%)			
Literate	1(3.1%)	1(3.1%)	
Primary school	13(40.6%)	7(21.9%)	0.162
Middle school	3(9.4%)	0(0%)	
High school and higher	2(6.2%)	5(15.6%)	
Profession (n,%)			
Housewife	6(18.8%)	4(12.5%)	
Retired	10(31.2%)	6(18.8%)	
Self-employed	2(6.2%)	2(6.2%)	0.670
Civil servants	0(0%)	1(3.1%)	
Laborer	1(3.1%)	0(0%)	
Live with (n,%)			
Alone	1(3.1%)	0(0%)	0.401
With family	18(56.2%)	13(40.6%)	
Income level (n,%)			
Low-income	3(9.4%)	1(3.1%)	0.458
Moderate	16(50.0%)	12(37.5%)	

With respect to the primary disease, 37.5% of them had hypertensive nephropathy and 25% had diabetic nephropathy. The mean dialysis duration was 24 months. In addition to ESRD, 34.4% of the patients had concomitant hypertension, 25% had diabetes and 12.5% had cardiac diseases.

Table 2. Laboratory and cardiovascular features of the groups

Parameter	Group I (n=19) (IDWG < 3%)	Group II (n=13) (IDKA ≥ 3%)	*P*
BUN (mg/dL)	53.3±14.3	56.4±7.6	0.156
Creatinine (mg/dL)	6.7±1.8	7.8±2.1	0.140
Total protein (gr/dL)	6.9±0.4	7±0.5	0.758
Albumin (gr/dL)	3.4±0.4	3.7±0.2	0.026*
CRP (ng/dL)	10.6±10.6	8.1±7.1	0.759
Phosphorus (mg/dL)	4.1±1.3	4.7±0.9	0.040*
Potassium (mg/dL)	4.5±0.7	4.9±0.5	0.025*
Total cholesterol (mg/dL)	193.6±82.5	193±52.8	1
Triglycerides (mg/dL)	180.2±143.6	180.6±96.8	0.242
Hemoglobin (g/dL)	11.4±1.5	11.2±1.6	0.734
Fe (mg/dL)	61.7±26	68.9±20	0.234
Transferrin saturation (%)	28.5±10	32.2±12	0.274
Ferritin (ng/dL)	524±527	386±274	0.454
HCO_3 (mEq/L)	20.5±2.0	21.6±1.8	0.124
Kt/V	1.7±0.3	1.75±0.2	0.847
URR (%)	77.7±6.9	77.4±4.1	0.478
nPCR (gr/kg/day)	0.9±0,2	1.1±0.1	0.032*
Systolic BP (mmHg)	120.3±18.6	115.2±14.2	0.398
Diastolic BP (mmHg)	70.3±8.5	68.3±6.4	0.551
MAP (mmHg)	90.8±13.1	94.6±13.2	0,425
Ejection fraction (%)	58.1±6.2	56.0±10.7	0.654
LVMI (gr/m²)	115.9±52.4	105.4±29.2	0.939
Cardiothoracic ratio (%)	47.1±4.1	49.4±4.4	0.123

Abbreviations: BUN - Blood urea nitrogen, CRP- C-reactive protein, URR - Urea reduction rate; nPCR - normalized protein catabolic rate; BP - Blood pressure; MAP - Mean arterial pressure; LVMI - Left ventricule mass index

The hemodialysis patients were grouped into 2 based on their IDWG: 19 patients (54.9%) were in Group I (IDWG less than 3% body weight) and 13 patients (40.6%) were in Group II (IDWG equal or greater than 3% body weight). There were no differences between the two groups with respect to sociodemographic features (Table 1).

Group I had significantly lower values of albumin (p=0.02), potassium (p=0.02), phosphorus (p=0.04) and nPCR (p=0.03) in comparison to Group II. There was no difference in mean age, Kt/V, URR, serum iron, transferrin saturation, and ferritin levels between the groups (Table 2).

The BMI and mid-arm circumference values were 24.2±4.4, 25.3±3.9 kg/m^2, and 26.7±3.3, 27.5±3.2 cm in Group 1 and Group II, respectively. As for the anthropometric parameters, BMI, mid-arm circumference, triceps skinfold thickness, arm muscle area, midarm muscle circumference, mid-arm fat area did not differ between the groups (Figure 1).

Ejection fraction, systolic and diastolic blood pressure were similar between the groups. LVMI was 115.9±52.4 gr/m² and 105.4±29.2 gr/m² in Group I and II, respecttively; no significant difference was detected (p=0.939) (Table 2). Left ventricular hypertrophy was present at a rate of 68.4% (13/19) in group I and 69.2% (9/13) in Group II.

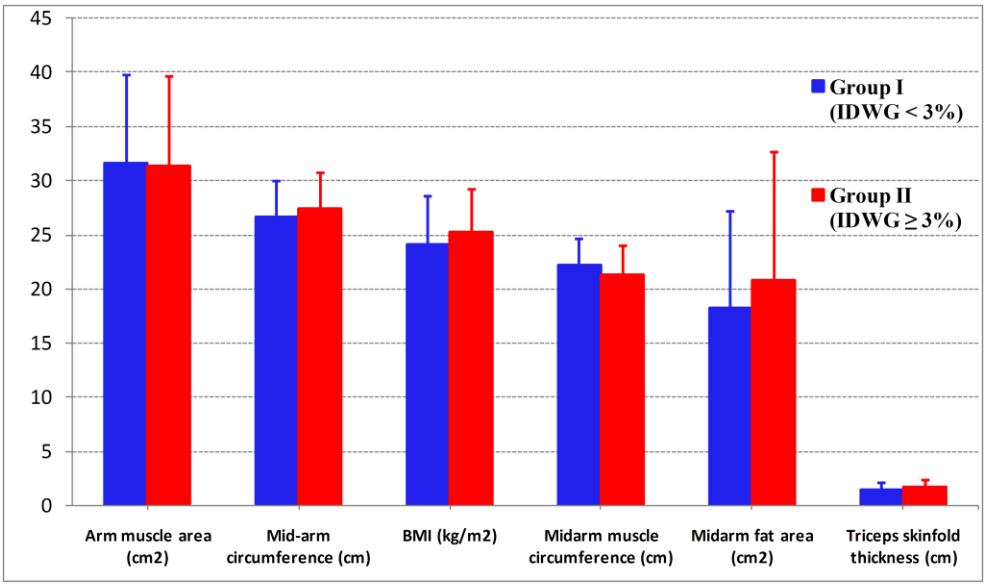

Fig. 1. Anthropometric parameters of the two groups
(BMI - Body mass index, no difference found between two groups, p>0.05)

The rate of well-nourished patients (A) was 68.4% in Group I (13/9) and 69.2% (9/13) in Group II; there was no difference between the two groups with respect to SGA. There were no severely malnourished (C) patients in either group.

Table 3. SF-36 scores of the groups

Health dimensions	**Grup I** (IDWG < 3%, n=19)	**Grup II** (IDWG ≥ 3%, n=13)	***P***
Physical function	51.5±32.1	74.7±23.2	0.043*
Role limitations physical (RP)	34.2±40.1	66.1±35.0	0.040*
Pain	59.2±27.2	64.6±23.3	0.801
General health	50.6±25.4	69.3±30.5	0.034*
Vitality/Energy	59.7±23.0	68.0±24.2	0.240
Social function	63.4±24.3	65.9±31.8	0.643
Mental health (MH)	44.1±38.7	63.9±28.1	0.150
Role limitations emotional (RE)	63.4±15.9	70.0±23.2	0.233
Physical component summary	48.1±25.3	69.0±24.3	0.046*
Mental component summary	55.9±20.5	68.3±23.6	0.107
Total score of SF-36	52.1±21.6	63.3±29.5	0.173

Abbreviations: RP - Role limitations caused by physical problems; MH - Mental health/emotional well-being; RE - Role limitations caused by emotional problems/mental health

The SF-36 overall score in Group I and Group II was 52.1±21.6 and 63.3±29.5, respectively (p=0.173). Compared to Group I, Group II had a significantly higher Physical function (PF) (p=0.04), Role limitations caused by physical problems (p=0.04), General health (p=0.03) scores among the quality of life sub-dimensions, and a significantly higher physical quality of life (p=0.04) from the main topic (Table 3). In correlation analysis, IDWG was positively correlated with total protein, albumin and potassium (Figure 2). In addition, IDWG was positively correlated with the main topics of quality of life (physical and mental quality of life). The IDWG was not correlated with the anthropometric measurements, and cardiovascular findings (Table 4).

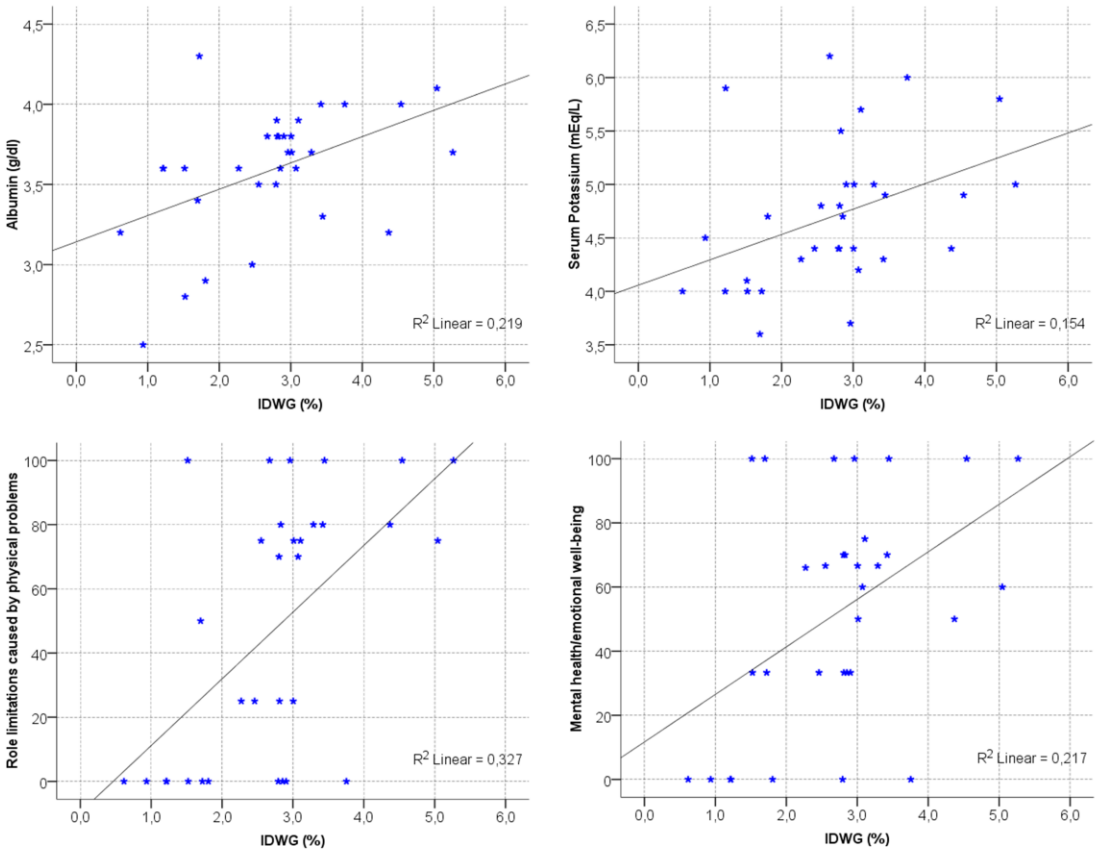

Fig. 2. Intradialytic weight gain (IDWG) correlation between the variables

Table 4. Interdialytic weight gain correlation with laboratory, anthropometric, cardiovascular parameters and SF-36 scores

Parameter	*R*	*P*	Parameter	*R*	*P*
Age (year)	0.195	0.284	Cardiothoracic ratio (%)	0.205	0.262
BUN (mg/dL)	0.09	0.625	Triceps skinfold thickness (cm)	-0.097	0.599
Creatinine (mg/dL)	0.304	0.091	Mid-arm muscle circumference (cm)	-0.065	0.722
Total protein (gr/dL)	0.351	0.049*	Arm muscle area (cm²)	0.020	0.913
Albumin (g/dL)	0.468	0.007*	Mid-arm fat area (cm²)	-0.131	0.476
Phosphorus (mg/dL)	0.325	0.069	Mid-arm circumference (cm)	-0.069	0.706
Potasssium (mg/dL)	0.393	0.026*	Physicial function	0.433	0.013*
Kt/V	-0.013	0.943	Role limitations physical (RP)	0.572	0.001*
URR	-0.126	0.494	Pain	0.146	0.425
nPCR (gr/kg/day)	0.300	0.095	General health	0.365	0.040*
Total cholesterol (mg/dL)	-0.008	0.966	Vitality/Energy	0.277	0.125
HCO_3 (mEq/L)	-0.280	0.120	Social function	-0.139	0.447
BMI(kg/m²)	0.091	0.621	Emotional	0.466	0.007*
LVMI (gr/m²)	-0.009	0.960	Mental health (MH)	0.275	0.128
Ejection fraction (%)	-0.185	0.310	Physical component summary	0.436	0.013*
Systolic BP (mmHg)	-0.011	0.983	Mental component summary	0.357	0.045*
Diastolic BP (mmHg)	0.083	0.652	Total score of SF-36	0.358	0.044*

Abbreviations: BUN - Blood urea nitrogen; URR - Urea reduction rate; nPCR - Normalized protein catabolic rate; BMI - Body mass index; LVMI - Left ventricule mass index; BP - Blood pressure; RP - Role limitations caused by physical problems; MH - Mental health/emotional well-being

Discussion

Interdialytic weight gain is regarded as an indicator for treatment compliance for a long time [2,3]. The effect of IDGW is unclear in the dialysis patients. No consensus was achieved on the fact that a higher IDWG was beneficial for the dialysis patients [3,5,9,20,21]. Various trials have reported on the association between the nutritional parameters and the IDWG [2,3,6,9,14,21]. A study reported better five-year actuarial survival with high IDWG [3]. However, in a retrospective study, 255 patients who had recently started hemodialysis, a high IDWG was reported not to be an indicator of nutrition; and in contrast, a high IDWG was indicated to

increase mortality by resulting in LVH, hypertension and intradialytic hypotension [20].

The mean IDWG was 2.7±1.1 in our study and IDWG values presented similarity with the other studies [3-5,9]. As previous studies have defined IDWG a cutoff value of 3% showed that less than 3% have poor prognosis and poor nutrition [3,9]. Therefore, in our study this 3% value was used as a cutoff value for identifying the groups. Interdialytic weight gain is directly in line with the body weight; this explains the higher absolute IDGW (expressed in kg) in males [5] Lopez *et al*. [3] detected that IGWG was higher in males than in females. Patients below 65 years of age were reported to have a higher appetite; in addition, younger patients were observed to have a quite high level of sodium and fluid loading and thus their IDWG were higher [1,3-5,14,21]. Even if this is true for the overall population, it may also result from a low comorbidity associated with young age [3].

Various methods are applied to detect malnutrition. These primarily include the anthropometric measurements, assessment of serum albumin level, SGA and nPCR [10]. Particularly, serum albumin level is a valuable parameter in hemodialysis patients; a low serum albumin level (<3.5 gr/dl) is known to be a significant indicator of malnutrition and thus mortality [7]. Mortality and morbidity is high in hemodialysis patients with a low serum urea and albumin level [8]. Many studies have reported a high albumin level in patients with a high IDWG; on the other hand a retrospective study in 283 patients detected a negative correlation between IDWG and albumin [3,4,6,9,21]. While albumin is used as an indicator in assessment of nutrition, there is a considerable extent of suspicion on its sensitivity. Albumin is a negative acute phase reactant; under conditions of inflammation, sepsis or stress, serum albumin level generally does not respond to nutritional support or responds slightly [8,10]. In our study, the level of CRP, an inflammation indicator, was similar between the two groups. Albumin levels were detected to be significantly high in the high IDWG group. We attributed it to good nutritional status.

Likewise, nPCR, measured via kinetic urea model, is an index of protein intake [3]. It is also a practically ideal nutrition parameter since it is mildly affected by inflammation [8,10,17]. Patients with a high IDWG were shown to have a higher nPCR [3,4,6,9,21]. Phosphorus level is an indicator of protein intake; potassium level is likewise related to nutritional state. We found signifycantly high levels of nPCR, phosphorus and potassium levels in the high IDWG group. These findings supported the fact that patients were well-nourished. There are relevant studies with findings that are in line with ours [3,4,9]. There are a large number of studies reporting a positive correlation between IDWG and the nutritional indicators of pre-dialysis BUN, creatinine and pre-albumin levels [3,9,21].

Kt/V indicates the sufficiency of dialysis. Severely high levels may result from a reduced urea distribution volume, due to a latent malnutrition presence. Kt/V values >1.7 were reported to potentially indicate malnutrition [22,23]. While a negative correlation was detected between IDWG and Kt/V, there are also studies reporting a positive correlation [3,4,6,21]. In our study, the groups did not differ in Kt/V and URR values and the values were above the target value; and thus additional factors such as dialysis insufficiency, which could impair the analysis of IDWG and nutrition correlation, were excluded.

Dialysis patients with a higher IDWG were detected to have lower serum HCO_3 values compared to those with a low IDGW. This was attributed to the high acid production in concomitance with higher protein intake and dilution was indicated to potentially contribute to this reduction [2,3,24]. In contrast, we detected no relationship between HCO_3 and IDWG.

Subjective global assessment is a simple method used to demonstrate the state of nutrition in ESRD patients, which involves parameters such as medical history, state of nutrition, and acute stress. The subjective global assessment was reported to be closely associated with morbidity and mortality [8,11,15]. Modified SGA score was shown to be negatively correlated with triceps skinfold thickness, mid-arm muscle circumference, pre-albumin, ferritin, transferrin and the total iron binding capacity in hemodialysis patients [15,25]. The IDWG% values were detected to be high in hemodialysis patients with malnutrition as defined by SGA [26]. In our study, we did not find a correlation between SGA and IDGW.

Anthropometric measurements are convenient, fast and safe to administer [8,11]. The body mass index is an important indicator of the state of nutrition [3]. Different from the general population, dialysis patients are reported to have a reduction in mortality as the BMI increases; this has been potentially attributed to better nutrition [11]. Another study revealed a mortality in the form of *j* curve in similarity to the general society and the mortality was the lowest in those with a BMI of 25-27.5 kg/m^2 [27]. A strong correlation was detected between BMI and IDWG% [9]. In patients IDWG less than 3% were found significantly lower BMI. Considering that the changes in BMI occur slowly in each patient, one could assume IDWG has a large effect on the state of nutrition in hemodialysis patients. There was no difference between the two groups in anthropometric measurements in our study and there was no correlation with IDWG. Similarly, in a previous study, there was a negative correlation between IDWG and mid-arm circumference and no association found with IDWG and arm muscle area. It was indicated that the findings could be misleading in ESRD patients due to the inadequacy of the sensitivity of the anthropometric measurements and the variable tissue hydration or myopathy [4]. We agree with this opinion.

The risk of cardiovascular events has increased 5 to 30-fold in dialysis patients relative to the overall population [28,29]. The target blood pressure values in the absence of cardiovascular risk, recommended for renal patients are as follows: systolic <130 mmHg, diastolic <80 mmHg. We detected systolic and diastolic blood pressure values as 120.3±18.6, 115.2±14.2, 70.3±8.5, 68.3±6.4 mmHg in group I and II, respectively; the values were within the target range. Blood pressure did not significantly differ between the two groups. There are trials showing no relationship between blood pressure and IDWG, and interdialytic blood pressure in normotensive or hypertensive patients does not correlate with the rise in IDWG [2,28,30]. There are also studies indicating that blood pressure was positively correlated with IDWG [3,21,31]. Cardiovascular and overall mortality was observed to be high in those with an IDGW > 5.7 [1]. Each 1% increase in IDGW was detected to increase the blood pressure by 1 mmHg; however, patients with IDGW less than 3% were observed to have a higher mortality after 5 years [31]. A prospective, observational study reported that the 5-year survival increased with the IDWG increase and the two-year mortality rate was higher in patients with a lower IDGW [3,9]. The investigators concluded that the favorable effects of IDGW on nutrition outweighed the unfavorable effects of blood pressure. They also underlined the fact that patients needed to maintain dietary salt restriction for blood pressure management [3].

In dialysis patients, LVH is the first condition occurring with a potential to lead to other complications over time including ischemic cardiac disease and cardiac failure. Anemia, hypertension, secondary hyperparathyroidism, volume overload, AV fistula, uremia and malnutrition are among the factors that contribute to the development of LVH. Repetitive volume overload may lead to early mortality by contributing to LVH and left ventricular dilatation [10,12].

There was no significant difference between the groups with respect to LVH. In a different study, LVH was observed to be significantly high in patients with an IDWG >5%; IDWG was reported to potentially cause LVH via non-blood pressure-mediated mechanisms [32]. We used the 3% value; therefore, the results were considered to lack similarity with 5% of findings. Our study showed no correlation between LVMI and IDWG; this finding is consistent with those from the previous study [32].

There are no quality of life comparisons with IDWG in the literature. However, association between state of nutrition and quality of life showed that patients with a better nutritional state had a better physical condition [33-35]. In diabetic patients, an adequate maintenance of life is defined as fulfillment of all individual requirements, satisfaction with life, adequate social behaviors, enough recreational time spared, sufficient emotional and physical state, and maintenance of interindividual relations. The quality of life is lower in ESRD with regard to the normal population due to the dialysis procedure, nutrition, and other risk factors such as the presence of concomitant diseases [33].

In our high-IDWG group (group II), physical function, role limitations caused by physical problems, general health and physical quality of life, included in the quality of life scale were detected to be higher. Physical and mental quality of life items of the quality of life scale, and overall SF-36 score were significantly correlated with IDWG. Our findings suggest a potential correlation between the increase in quality of life and the IDWG.

Conclusions

Based on our results, we can conclude that an IDWG less than 3% of the body weight could result in undesirable nutritional effects and secondary malnutrition and reduced quality of life. Therefore, awareness of the fact that IDWG% is a good indicator of nutrition should be established, and caution exercised to avoid the potential negative effects of nutrition. 3-5% IDWG seems to be most suitable weight gain due to mortality and nutrition.

Conflict of interest statement. None declared.

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Short communication

Patients with Primary Brain Tumors as Organ Donors

Lidija Orlic[1], Branka Sladoje-Martinovic[1], Ivana Mikolasevic[1], Zeljko Zupan[2] and Sanjin Racki[1]

[1]Department of Nephrology and Dialysis, Division of Internal Medicine, [2] Department of Anesthesiology and Intensive Care Medicine, University Hospital Rijeka, Croatia

Abstract

Organ transplant is now the treatment of choice for many end-stage diseases. The success of solid organ transplantation is accompained by a severe shortage of available organs for those currently awaiting transplantation. In recent years, there has been an increasing demand for organs, but not a similar increase in the supply leading to a severe shortage of organs for transplant that resulted in increasing waiting times for recipients. This has resulted in expanded donor criteria to include older donors and donors with mild diseases. Malignancy is considered a contra-indication to organ donation, with a few possible exceptions. There is a significant controversy in the transplant literature around the use of organs from donors with primary brain tumors (PBT). While case reports and registry data have certainly documented transmission of PBT with resultant morbidity and even mortality, the loss of quality and quantity of life by those on the waiting list remains a staggering and sobering reality. Ultimately the decision regarding transplantation from such donors lies with the transplanting team that should weigh the risk of donor tumor transmission against the risk of their patient dying on the waiting list.

Key words: organ donors, brain tumors, kidney transplantation

Introduction

Organ transplant is now the treatment of choice for many end-stage diseases. The success of solid organ transplantation is accompained by a severe shortage of available organs for those currently awaiting transplantation. In recent years, there has been an increasing demand for organs, but not a similar increase in the supply leading to a severe shortage of organs for transplant that resulted in increasing waiting times for recipients. Therefore, many programs have implemented the aggressive use of extended criteria donors. Consequently, this has resulted in expanded donor criteria to include older donors and donors with mild diseases. But, recent data reported the discovery of hepatocellular carcinoma in a recipient who received an organ from a serologically positive donor with hepatitis. Furthermore, the use of donors up to 80 years of age will potentially increase the incidence of donor tumor transmission. Malignancy is now considered as a contraindication to solid organ donation, with a few possible exceptions. Malignancy after transplantation can occur in three different ways [1-4]:

- De-novo occurrence;
- Recurrence of malignancy;
- Donor-related malignancy.

Also, there is a potential for development of tumors in recipients due to transmission of oncogenic viruses like human papiloma virus (HPV), human T-lymphotropic virus (HTLV), hepatitis C virus (HCV), hepatitis B virus (HBV), human herpes virus 8 (HHV-8), Epstein-barr virus (EBV) and cytomegalovirus (CMV). The donor malignancy may have been indentified at the time of the organ procurement or may be identified after transplantation [1,2]. Malignant tumors can be transmitted to immunosuppressed patients when organs from donors with neoplastic disease are unknowingly or knowingly transplanted into recipients. But, the actual prevalence of donors with malignant neoplasms and the donor-recipient tumor transmission risk are not well-known. Although, there are some published data on tumor transmission, taking into account the high number of solid organ transplants performed, only a minimum percentage of graft recipients have developed a transmitted tumor disease [1,5]. For example, according to the ONT registry (Spain) the frequency of donors from 1990 until 2006 with an undetected tumors was 5.8 per thousand donors in the ONT registry. Of these donors, only 5 (2.9 per 10.000 donors) transmitted the tumor to the recipients. Only 10 recipients out of the 155 who received a graft from a donor with a tumor developed tumor transmission (6.4%) [6]. Furthermore, according to the Danish registry that studied a 27-year history of Danish transplant registry, 13 malignant tumors were found among 626 donors, of which eight were detected after the organs had been transplanted [7]. But, due to the

Correspondence to: Lidija Orlic, Department of Nephrology and Dialysis, Division of Internal medicine, University Hospital Center Rijeka, Rijeka, Croatia; Phone: 0038551/407-487, Fax: 0038551/407-156; E-mail: lidija.orlic@ri.t-com.hr

potentially serious consequences, it is mandatory to carefully select all potential donors with the intention of avoiding the transmission of tumor disease. The number of expanded criteria donors (ECD) and especially of older donors has increased due to organ shortages. Actually, there is no age limit for organ donation, but only for organ-specific functional parameters. The rate of tumor occurrence in the donor population increases concomitantly with increasing donor age. Although transplant coordinators and members of transplant teams need guidelines to assist in the management of such complex situations, the treatment of each case will often require an individual approach [1-5].

Some general recommendations to follow in the donation process to prevent transmission of tumors are listed below.

During the work-up of obtaining an organ, the complete clinical history of the donor should be recorded, taking into account several basic points:

- Records of any previously diagnosed tumors (or tumors removed without medical documentations of the definitive diagnosis).
- History of menstrual irregularities.
- Intra-cranial tumors or metastases should always be excluded in donors diagnosed with intra-cranial hemorrhage. This is especially important in the cases if no evidence of hypertension or arterio-venous malformation exists.
- If it is possible, the donor's general practitioner and family members should be contacted to provide detailed medical records.
- Standard laboratory investigations sholud be performed in all potential donors with the objective of detecting specific disease that may contra-indicate organ donation. Routine screening of tumor markers is not recommended.
- Abdominal ultrasound and chest-x rays must be carefully investigated, together with the complete clinical history and physical examination. Further imaging methods (e.g. CT-scans) may be necessary for thorough donor evaluation, especially in patients with suspected tumors. In donors with any history of tumor disease, CT-scans of the thorax and abdomen should be carried out to evaluate current disease status and to ensure the highest possible safety for organ recipients.
- During organ procurement, surgeons should examine all intra-thoracic and intra-abdominal organs in order to detect possible hidden tumors or pathological lymphadenopathies. Any suspect lesion must be investigated by a pathologist.
- If no precise histological diagnosis of a suspicious mass can be obtained, the donor should be excluded; although the final decision should be made on the basis of an individual risk-benefit analysis. Transplantation can only be performed in fully-informed recipients [1-5,8].
- According to these observations, the acceptance of organs from donors with tumors differs to a great extent throughout Europe. Countries with organ shortages, long waiting times and significant waiting list mortality are more likely to consider a donor with a malignancy as an acceptable risk than countries with a higher donor rate and shorter waiting times.

A particular problem in the donation process represent primary tumors of the central nervous system (CNS). Therefore, in the text below we will focus on this relatively controversial topic.

Primary tumors of the central nervous system

Approximately 17.500 primary CNS tumors occur annually in the United States, accounting for 1.4% of all tumors and 2.3% of cancer-related deaths [9]. As mentioned above, the use of organs from donors with other malignancy remains generally unacceptable. But, the use of organs from donors with primary tumors of the central nervous system (CNS), where the risk of spread outside the central nervous system, and hence the risk to transplant recipients, is low, remains an exception from this rule. There is a significant controversy in the transplant literature about the use of organs from donors with primary brain tumors. Organs from such donors have been used for transplantation over many years, on the basis that disease transmission was rare. But, according to the literature, there have been some data where transmission of malignancy has occurred from donors with primary malignancy of the central nervous system. The risk of extracranial metastasis of these tumors was recognized first, most commonly with high grade astrocytoma/glioblastoma, medulloblastoma, and ependymoma [10]. According to the Council of Europe guidelines, organs from donors with high-grade brain tumors should not be used because of the perceived high risk of cancer transmission, especially where the integrity of the blood brain barrier is compromised. Therefore, they should no longer be considered safe for transplantation. On the other hand, they stated that donors with low-grade malignant tumors should be used only in very special circumstances. Furthermore, donors with primary CNS tumors have historically been regarded as suitable, but cumulative data suggesting that aggressive intervenetions (craniotomy and ventricular shunting) and/or unfavorable histology (glioblastoma and medulloblastoma) may pose a prohibitive transmission risk has refined our practice over time. Furthermore, case reports of donor brain tumor transmission with transplant subsequently began to appear in the literature and have led to a reassessment of this donor [1-5,8].

In generally, primary tumors of CNS represent 3-4% of the causes of brain death of organ donors. Although CNS tumors rarely develop extra-cranial metastases, these have been described in 0.4-2.3% of cases. These metastases can develop in the lungs, pleura, lymphatic

glands, bone, liver, adrenal glands, kidneys, mediastinum, pancreas, thyroids and peritoneum. The tumors that most often produce extra-cranial metastasis are multiform glioblastoma, meduloblastoma and also ependymoma. Although aggressive interventions and prior derivations are the principal causes of dissemination of CNS tumors, there are cases of spontaneous dissemination to the cranial and cervical lymphatic glands, and even distant metastases [11,12].

According to the literature, the risk factors for transmission of primary CNS tumors are:

- High-grade malignancy tumors;
- The presence of ventriculo-peritoneal or ventriculo-atrial derivations;
- Previous chemotherapy;
- Previous radiotherapy;
- Previous craniotomy;
- Duration of disease may also be important [8,11,12].

According to the literature, the Australian and New Zealand Registry (ANZODR) reported 46/1.781 donors (2.6%) with PBT providing 153 organs. Of these donors, there were eight with a high-grade glioma and five with a medulloblastoma. They reported no cases of donor-derived malignancy at mean follow-up of 40 months [13]. Furthermore, according to the UNOS registry (USA) review from 2002 of 397 donors with a history of primary CNS tumors, from whom 1220 organs were transplanted and after the follow-up of 36-months, no tumor transmission to the recipient was observed. But, UNOS itself warns that some tumors, such as multi-forme glioblastoma (GBM) and medulloblastoma, can potentially have a high transmission risk and therefore donors presenting with a history of these tumors should not be used [14]. Furthermore, Israel Penn International Tumor Registry (IPITTR) (USA) states that, when there are no risk factors (listed above) the rate of transmission from donors with primary CNS tumors to organs recipients is 7%. But, if one or more risk factors are present, the rate of transmission to recipients rises to 36-43%. Also, they suggested that organs from donors with low-grade malignant or benign primary CNS tumors can be used for transplantation. Furthermore, donors that have one or more risk factors should be avoided as donor candidates or used only when there is a need for an emergency transplant [15]. On the other hand, the retrospective study of UK registry data has shown that none of the 177 donors with primary intracranial malignancy transmitted the malignancy to the 448 recipients who received their organs. There were many donors with high-grade tumors, including 23 grade IV gliomas (glioblastoma multiforme) and 9 with medulloblastoma who provided organs for 85 traceable recipients [10]. In contrast to all reports, the IPITTR reported 36 donors with malignant primary brain tumors, including 31 with astrocytoma/GBM and three with medulloblastoma. Fourteen out of 62 recipients (23%) developed presumed donor derived tumor. Ten of the 14 recipients died from disseminated disease [16,17]. Because the denominator in this series remains unknown, it is difficult to interpret these results.

Histological classification of common primary central nervous system tumors is shown in Table 1 and 2.

Table 1. Histological classification of common primary central nervous system tumors

Cell of origin	Tumor type	Grade/tumor subtype
Glial	Oligodendroglioma	Grade 2: Low grade Grade 3: Anaplastic
	Astrocytoma	Grade 1: Pilocytic Grade 2: Low grade Grade 3: Anaplastic Grade 4: Glioblastoma variants; gliosarcoma and giant T-cell glioblastoma
	Mixed glioma	Grade 2 or 3 having features of both astrocytoma & oligodendroglioma differentiation
Neuronal	Medulloblastoma Neuroblastoma Esthesioneuroblastoma	

Table 2. Clinical grades of astrocyte gliomas and their histological criteria

Grade	Designation	Histological criteria
1	Pilocytic astrocytoma	Rosenthal fibers, piloid cells; no criteria
2	Diffuse astrocytoma	One criterion, usually nuclear atypia
3	Anaplastic astrocytoma	Two criteria, usually nuclear atypia and mitosis
4	Glioblastoma multiforme	Three or four criteria; the two above plus endothelial proliferation and/or necrosis

Meduloblastoma

Meduloblastoma represents 6% of all CNS gliomas and 44% of gliomas in children. Meduloblastoma metastazises more often in bones, bone marrow and lymphatic glands and less frequently in the lungs, pleura, liver and breast. Tumor transmission from organ donors with this type of tumor has been documented. Therefore, potential donors with medulloblastoma should not be considered for organ donation and should be used only in cases of life-threatening emergency transplants. In these cases, it is recommended that donors who have previously undergone craniotomies and/or peritoneal ventricular derivations are not used [8,15].

Gliomas

The incidence of extra-cranial glioma dissemination is from 0.4 to 2.3%, mainly in the lung, lymphatic glands, bone and liver. Astrocytomas are divided into low-grade tumors such as pilocytic astrocytomas (grade I) and diffuse astrocytomas (grade II); and malignant astrocytomas, namely anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV) (Table 2) [18].
Low-grade astrocytomas often appear in young adults. They rarely metastazise, but up to 30% of low-grade astrocytomas may be associated with histological grades of greater malignancy. These tumors have a tendency to relapse and often present a higher grade of malignancy. Therefore, potential donors with low-grade astrocytomas may be considered for organ donation depending on the histological results of the tumor and local invasiveness.
At least 80% of malignant gliomas are multiforme glioblastomas. Anaplastic astrocytomas appear more often in adults aged in their 30s and 40s, while GBM is more often present in adults aged in their 50s and 60s. Extracranial metastases of anaplastic astrocytomas and GBM have been reported even in the absence of prior surgery. Also, transmission of these tumors from donors has been reported. Therefore, potential donors with anaplastic astrocytomas and GBM should not be considered for organ donation. They could be used only in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with high risk of tumor transmission (prior surgical intervention) should not be used [8,18,19].

Oligodendrogliomas

These tumors represent 20% of gliomas. According to the histological type there are four types of oligodendrogliomas: low grade (Schmidt grades A and B) oligodendrogliomas and anaplastic (Schmidt grades C and D) oligodendrogliomas. Low grade tumors are the most frequent and typically appear in adults in their 20s and 30s. In most cases they present as spontaneous cerebral hemorrhages. On the other hand, anaplastic forms of these tumors are very aggressive tumors and extracranial metastases of anaplastic oligodendrogliomas have been documented after surgical interventions. Therefore, potential donors with low grade oligodendroglioma could be considered for organ donation, while anaplastic forms should not be considered. They can be only used in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with high risk of tumor transmission (prior surgical intervention) should not be used [8].

Ependymomas

Ependymomas represent 6% of all CNS glioma. Their metastases are rare and the cases documented correspond to recurrent tumors or those treated with radiotherapy and/or chemotherapy. Therefore, donors with these tumors can be considered for organ donation [8,20].
Furthermore, it is important to note that the brain is also the site of secondary brain tumors, many of which may present as a spontaneous intra-cerebral hemorrhage with no evident primary tumor and at times can be diagnosed as a primary brain tumor without any available histology. Namely, studies have shown that a wrong diagnosis can be disastrous. For example, Buell *et al*. reported 42 organ recipients who received organs from 29 donors who were misdiagnosed to have a primary brain tumor. The most common diagnostic error was intracranial hemorrhage and CNS metastasis misdiagnosed as a primary brain tumor. Following transplantation, the donors were identified with melanoma, renal cell carcinoma, choriocarcinoma, sarcoma and Kaposi's sarcoma, and variable tumors. Therefore, beside a detailed history in such cases, it is important to perform additional imaging methods, frozen sections as well as various laboratory testing [1,21].

Final considerations

- Group I tumors do not contraindicate organ donation.
- Group II CNS tumors can be considered for organ donation when there is an absence of other risk factors.
- Group III tumors should not be considered for organ donation. They can be only used in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with a high risk of tumor transmission (prior surgical intervention) should not be used [8].

According to all of these observations, the available literature remains incomplete. In a perfect world without organ donor shortage, all extended criteria donors would be avoided as they carry an increased risk of graft failure and recipient death. But, in real life the members of

transplant community face the problems of long waiting lists and waiting list mortality. The current knoweldge of donor PBT transmission is incomplete and based on relatively small numbers. Some registry reports, such as UNOS and ANZODR are encouraging in documenting the absence of donor tumor transmission but may under-represent the risk because of incomplete registration. There remains a need for prospective studies which will help us to improve our understanding of real risk of tumor transmission, potential risk factors, and successful therapies for the recipients in the event of tumor transmission. Therefore, the transplant community remains uncertian about the role of PBT donors on the basis of variable practices. Ultimately, the decision regarding transplantation from such donors lies with the transplanting team that should weigh the risk of donor tumor transmission against the risk of their patient dying on the waiting list.

Conflict of interest statement. None declared.

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Short Communication

Neutrophil-Gelatinase Associated Lipocalin (N-GAL) to Assess Perioperative Acute Kidney Injury in Hand-Assisted Laparoscopic Donor Nephrectomy: A Pilot Study

Emma Aitken[1], Alex Vesey[1], Julie Glen[1], Mark Steven[2] and Marc Clancy[1]

[1]Department of Renal Surgery, [2] Department of Anaesthetics, Western Infirmary, Dumbarton Road, Glasgow

Abstract

Perioperative insults, including hypotension, hypovolaemia and pneumoperitoneum may occur during laparoscopic live donor nephrectomy. These may have deleterious effects to both donor and recipient. The extent and significance of these insults is poorly understood and difficult to quantify. The aim of this study was to evaluate acute kidney injury (AKI) in the donor using the novel biomarker neutrophil-gelatinase associated lipocalin (N-GAL). We report the results of a pilot study of 20 patients undergoing hand-assisted live donor nephrectomy. eGFR and serum NGAL measurements (Triage CardioRenal Panel, Alere) were obtained pre-operatively, immediately post-operatively, day 1 and 6 weeks post-operatively. Mean pre-operative eGFR was 105.6+/-10.1ml/min/1.73m^2. Mean eGFR 6 weeks post-operatively demonstrated a 29.4+/-8.8% reduction from baseline. Serum N-GAL increased by 34.1+/-16.7% following an overnight fast pre-operatively (day 0) (ΔNGAL 45.1+/-36.0ng/ml), by a further 14.9+/-7.2% following surgery (immediate post-op). The largest ΔNGAL was observed during the pre-operative fasting period. ΔN-GAL [day -1 to day 0] and [day -1 to post-op] were found to correlate inversely with eGFR at 6 weeks ($p<0.05$, $r^2=0.47$ and $p<0.001$, $r^2=0.52$ respectively). We conclude that clinically significant AKI does occur in the donor following live donor nephrectomy. Optimisation of perioperative fluid management is likely to have a protective role.

Key words: acute kidney injury, biomarkers, donor nephrectomy, renal transplantation, living donor, N-GAL, graft outcome

Introduction

Perioperative insults, including hypotension, hypovolaemia and pneumoperitoneum, which may occur during laparoscopic live donor nephrectomy can have deleterious effects to both donor and recipient. The extent and significance of these insults is poorly understood and difficult to quantify. Delayed graft function is uncommon following live donor renal transplantation, nevertheless a degree of acute kidney injury (AKI) in the recipient is well-recognized [1,2]. Similarly, in other laparoscopic abdominal surgery, pneumoperitoneum is known to be associated with adverse renal haemodynamic effects and acutely decreased urine output of the native kidneys [3]. The degree of acute tubular injury in the donor however has not previously been evaluated.

Until recently, a lack of sensitive biomarkers for AKI has made assessment of perioperative renal insults in the donor difficult, with any subtle changes in serum creatinine masked by the overwhelming effect of nephrectomy itself. Neutrophil-gelatinase associated lipocalin (N-GAL) is a novel biomarker of early AKI which has previously been demonstrated to be predictive of morbidity and mortality following cardiac surgery and in polytrauma [4,5]. The aim of this study was to evaluate acute kidney injury (AKI) in the donor using the novel biomarker N-GAL.

Material and methods

We report the results of a pilot study of 20 patients undergoing hand-assisted live donor nephrectomy. eGFR and serum NGAL measurements (Triage CardioRenal Panel, Alere) were obtained pre-operatively, immediately post-operatively, day 1 and 6 weeks post-operatively. Data on perioperative fluid balance was also collected. Results are presented as mean+/-S.D.

Results

Mean donor age was 40.6+/-11.1 years (65% male). Mean pre-operative eGFR was 105.6+/-10.1ml/min/1.73m^2. Day 1 post-op mean eGFR was 65.7+/10.4 ml/min/1.73m^2 (37.7+/-9.2% reduction from baseline) and mean eGFR 6 weeks post-operatively was 74.1+/-8.6ml/min/1.73m^2 (29.4+/-8.8% reduction from baseline). Pre-operative fluid

Correspondence to: Emma Aitken, Department of Renal Surgery, Western Infirmary, Dumbarton Road, Glasgow, G11 6NY; Phone: +44 141 211 1750; Fax: +44 141 211 2784; E-mail: EmmaAitken@nhs.net

loading was undertaken as was surgeon preference. Mean pre-operative intravenous fluid volume administered was 2245+/-1112.4ml in the 12 hours prior to surgery. Mean intra-operative intravenous fluid volume was 1175+/-466.6ml.

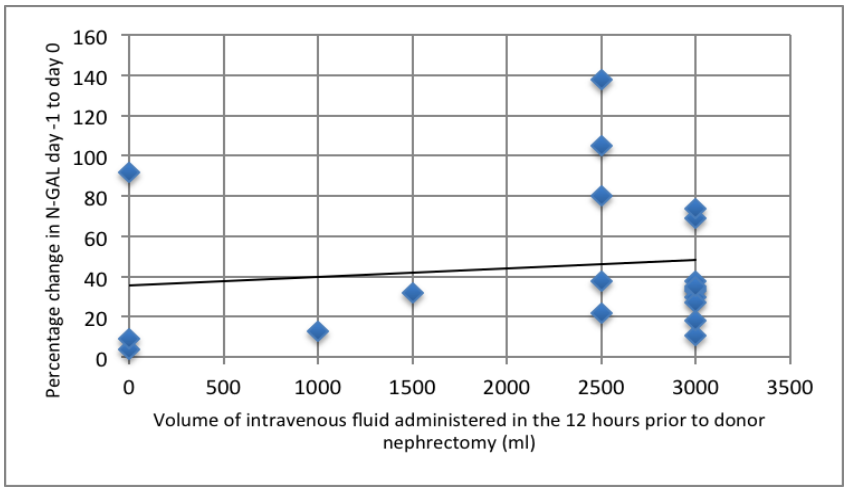

Fig. 1a. There was no association between the volume of intravenous fluid administered in the 12 hours pre-operatively and Δ N-GAL perioperatively

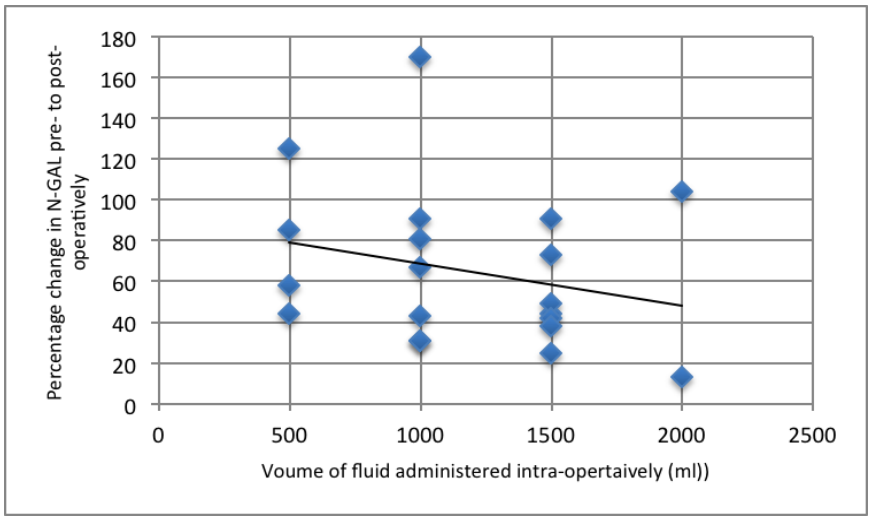

Fig. 1b. There was a trend towards liberal intra-operative fluid regimens resulting in smaller ΔN-GAL perioperatively

Mean pre-operative N-GAL was 72.2+/-14.0ng/ml (normal: <153ng/ml) on the evening prior to surgery (day-1). Serum N-GAL increased by 34.1+/-16.7% following an overnight fast pre-operatively (day 0) (ΔNGAL 45.1+/-36.0ng/ml), by a further 14.9+/-7.2% following surgery (post-op) and a further 3.1+/-1.2% by post-operative day 1. The largest ΔNGAL was observed during the pre-operative fasting period. ΔN-GAL [day -1 to day 0] and [day -1 to post-op] were found to correlate inversely with eGFR at 6 weeks ($p<0.05$, $r^2=0.47$ and $p<0.001$, $r^2=0.52$ respectively). No association was seen between pre-operative fluid balance and ΔN-GAL (Figure 1a), however liberal intra-operative fluids may be protective against post-operative AKI (Figure 1b).

Discussion

We conclude that clinically significant AKI does occur in the donor following live donor nephrectomy. This can be difficult to quantify using standard biochemistry due to the overwhelming effect which nephrectomy itself has on eGFR and serum creatinine. Perioperative AKI is associated with poorer donor eGFR at 6 weeks. Peri-operative hypovolaemia appears to play a signifycant role in the development of donor AKI. Optimisation of perioperative fluid management is likely to have a protective role.

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Conflict of interest statement. None declared.

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Case Report

Successful Continuation of Peritoneal Dialysis after "Sweet" Hydrothorax

Utku Erdem Soyaltin, Ferhat Ekinci, Denizhan Ayatan, Cihangir Turemis, Mustafa Yildirim and Harun Akar

Tepecik Education and Research Hospital, Internal Medicine Clinic, Izmir, Turkey

Abstract

A 44-year-old woman with end-stage renal disease presented with dyspnea on exertion and a vague chest pain about two weeks after commencing continuous ambulatory peritoneal dialysis (CAPD) four months ago. A chest x-ray revealed massive unilateral right-sided pleural effusion. Laboratory analysis of the effusion revealed low protein and lactate dehydrogenase but elevated glucose levels were consistent with transudate and pleuroperitoneal leakage. Pleural glucose concentration was much higher than patients' serum glucose concentration, which was suggestive of "sweet" hydrothorax because of this high glucose concentration. It is advisable to keep this condition in mind among the differential diagnoses of hydrothorax in patients on CAPD.

Key words: peritoneal dialysis, sweet hydrothorax, pleural effusion

Introduction

Pleural effusion is rarely caused by peritoneal dialysis (PD). Approximately 2% of all continuous ambulatory peritoneal dialysis (CAPD) patients develop massive transudative pleural effusion [1]. Hydrothorax in this situation is called "sweet hydrothorax" as hypertonic glucose solution fills the pleura [2,3]. Efforts to treat what is erroneously diagnosed as fluid overload with more hypertonic solutions lead to massive pleural accumulation of this solution together with ultrafiltrate. This phenomenon appears to be due to an increased intraabdominal pressure in the setting of congenital or acquired diaphragmatic defects [4]. In 2003, Tang *et al*. described a series of CAPD patients with hydrothorax due to pleuroperitoneal communications. Hydrothorax developped in this group within mean 5.8 months after the start of peritoneal dialysis [5]. Hydrothorax frequently presents as respiratory distress, particularly dyspnea, or shortness of breath. The lung collapses under extreme conditions. Approximately 25% of patients remain asymptomatic. This report describes a case of a 44-year-old female patient on peritoneal dialysis presenting with dyspnea and unilateral right-sided pleural effusion, which was eventually diagnosed as "sweet" hydothorax.

Case Report

A 44-year-old female CAPD patient was admitted to the Internal medicine clinic because of worsening dyspnea on exertion and a vague chest pain. Her past medical history revealed hypertension. She was started CAPD treatment four months ago. She was hemodynamically stable and not tachypneic, she was afebrile and her percutaneous oxygen saturation was 96% when she was breathing in ambient air. There was no jugular venous distension and there were no signs of congestive heart failure. Decreased breath sounds at auscultation and dullness on percussion were noticed at the right side. Cardiac examination was normal. A chest X-ray demonstrated a massive right-sided pleural effusion (Figure 1a and 1b). Laboratory evaluation demonstrated pronounced renal dysfunction, a white-cell count of 7.4 per cubic millimeter and a CRP value of 0.8 mg/dl (Table 1). Diagnostic thoracentesis revealed a crystal clear pleural fluid with a high glucose concentration of 271 mg/dl. The pleural-fluid protein was 0.3 g/dL and according to Light's criteria the fluid appeared to be a transudate (Table 2). Cytological and microbiological examination of the pleural fluid showed no abnormalities. The high pleural-fluid and serum-glucose ratio confirmed the clinical suspicion of a pleuroperitoneal leak. Peritoneal scintigraphy was performed and pleuroperitoneal communications were seen at the right side. Contrast-enhanced CT scanning did not show diaphragmatic hernias (Figure 2). Since the patient refused to shift to hemodialysis, we reduced peritoneal dialysis fluid volume, dwell time and increased the frequency of change. After one week chest radiography showed a complete resolution of pleural effusions and patient's symptoms.

Correspondence to: Utku Erdem Soyaltin, Tepecik Education and Research Hospital, Internal Medicine Clinic, Izmir, Turkey; E-mail: soyaltinutku@hotmail.com

The patient was followed-up for five months after discharge. Pleural effusion did not recur again.

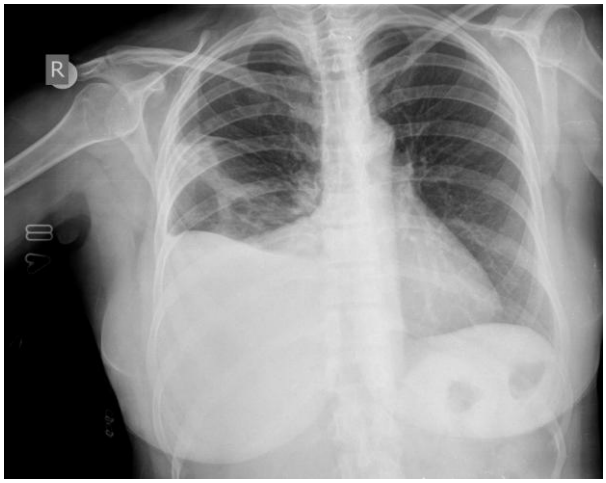

Fig. 1a. Chest radiograph demonstrating right-sided pleural effusion in patient

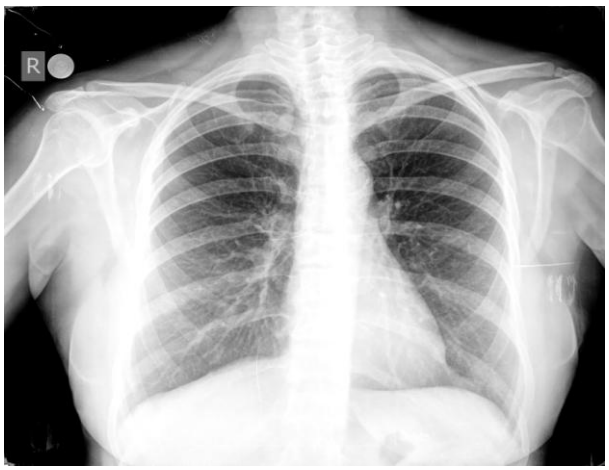

Fig. 1b. Chest X ray of the patient after one week

Table 1. Results of chemical analysis of simultaneously drawn serum and pleural fluid

	Serum	Pleural Fluid
Glucose (mg/dl)	94	271
Total protein (g/dl)	7.2	0.3
Albumin	4.2	0.1
Lactic dehydrogenase (U/L)	219	13

Table 2. Results of the laboratory parameters

Parameters	
Urea mg/dl	72
Creatinine mg/dl	8,4
Sodium mmol/L	132
Potassium mmol/L	3.63
Aspartate aminotransferase U/L	12
Alanine aminotransferase U/L	9
White Blood Cell 10^3 u/L	15.1
Hemoglobin gr/dl	12.6
Thrombocytes 10^3 u/L	390
Sedimentation mm/h	45
C-Reactive Protein mg/dL	0.8

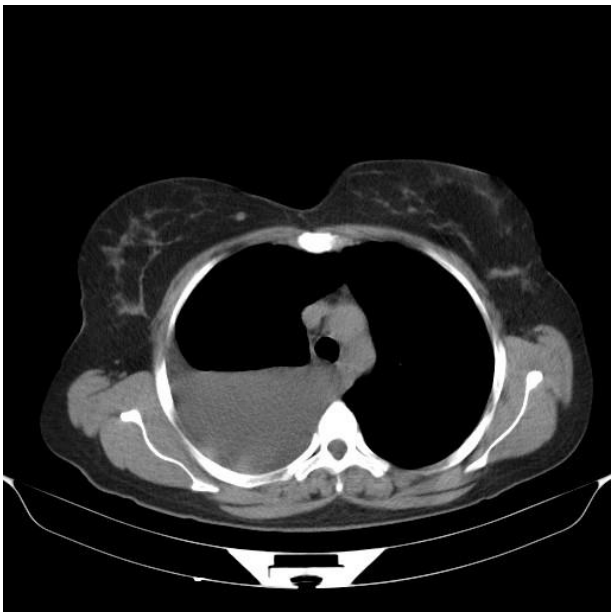

Fig. 2. Contrast enhanced CT with intraperitoneal infused contrast-mixed dialysate

Discussion

The incidence of hydrothorax in peritoneal dialysis patients is low and it usually affects the right hemithorax and there is no clear sex predominance [4]. Hydrothorax occurs uncommonly and it may occur as an acute or late complication of PD. Although the mechanism of hydrothorax is unclear, different theories have been suggested. It is proposed that in the context of chronic liver disease ascites may be transferred by lymphatics, of which the greater supply is on the right hemithorax. Alternatively there may be a direct pleuroperitoneal communication due to diaphragmatic defects [5]. Not all diaphragmatic defects leading to pleuroperitoneal communications are congenital. Some of them are acquired, due to high intraabdominal pressure.

Peritoneal dialysis should be included in the differrential diagnosis of a hydrothorax of PD patients. Hydrothorax may develop several weeks or months after starting of PD [7]. Diagnostic thoracentesis and pleural-fluid analysis are often diagnostic, revealing a crystal clear pleural fluid with a low protein and a high glucose concentration. In the patient presented here, glucose concentration in the pleural fluid was much higher than that in the serum drawn concomitantly. Sweet hydrothorax is a suitable term to describe this high glucose concentration [1,8-10]. A glucose gradient of more than 50 mg/dL is a sensitive, specific, simple and convenient first-line screening test to detect the sweet hydrothorax [1]. Moreover, pleuroperitoneal leaks typically cause transudative effusions with a low LDH and cell count [12]. In terms of imaging, peritoneal scintigraphy or contrast CT peritoneography

may be used as a diagnostic tool to detect possible peritoneopleural communications [4,13,14].

There are several treatment options such as conservative option, pleurodesis or surgery. None of these has been shown to be superior and the decision depends on the patients' clinical status and their preference as in our case. Patients should also be informed about the risks and benefits of these options [15]. Pleuroperitoneal communication is a clinical situation with little relevance outside the context of PD. Thus, conservative treatment may be the most suitable option for patients who will be transferred to hemodialysis.

Conservative treatment methods to correct pleuroperitoneal communication range from reduction of peritoneal dialysate volume to transient interruption of PD treatment. Continuation of PD happens with a 50% success rate [1].

In patients with residual renal function, manipulation of the PD prescription to decrease intra-abdominal pressure results in using small volume PD exchange [16,17]. Alternatively, patients using a cycler could use both small volume and short dwell periods with a dry day [18,19]. These options may not offer adequate clearance in anuric patients. Hemodialysis offers a temporary or permanent alternative treatment modality for renal replacement if PD is ceased [20]. The absence of PD fluid in the abdomen decreases intra-abdominal pressure. Withholding PD for 4-6 weeks allows minor imperfections in the diaphragm to heal themselves [21]. Restoration of PD on a trial basis determines whether pleural effusion will reoccur.

Talc and tetracycline pleurodesis are safe and effective treatment options for pleuroperitoneal communication [22,23]. There are other treatment options such as pleurodesis with autologous blood, which has had inconsistent results [24-26].

Videoassisted thoracoscopic surgery allows for direct visualisation of the diaphragm and malformations in this area and it is reserved as the last treatment option as it is not devoid of risks [27,28].

In general, with both conservative and surgical treatment, up to 58% of patients can continue on PD treatment [21]. However, the relapse rate is generally high, which is why the results with the different treatments are not very encouraging [4,29] and a high percentage of cases require a definitive transfer to HD [30]. This means that it is not possible to give clear directions in favour of one treatment or the other.

The present report describes a case of conservatively treated hydrothorax due to pleuroperitoneal communication. The conservative treatment via reduction of peritoneal dialysate volume and dwell time appears safe and effective.

While our patient was anuric we succeeded in conservative treatment without HD and in 3 month follow-up pleural effusion did not recur again.

Conflict of interest statement. None declared.

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Case report

Development of Acute Peritonitis after Gynecological Procedure in a Peritoneal Dialysis Patient

Dragan Klaric

Department of dialysis and nephrology, Zadar General Hospital, Zadar, Croatia

Abstract

Although the majority of peritonitis cases in peritoneal (PD) dialysis patients are caused by gram-positive cocci, streptococcus agalactiae, a gram-positive group B β haemoliticus streptococcus, may rarely be found in this group of patients. We present a case of acute peritonitis caused by streptococcus agalactiae with bacteriemia and septic shock occurring after a curettage indicated because of gynecologic bleeding. The patient did not receive antimicrobial prophylaxis since the gynecologist considered this case as a "routine" procedure without the need to administer antibiotics. Our case demonstrate that small procedures may cause great problems and therefore one should always give priority to individual approach regardless of the protocol for "routine" surgery, especially if there are no indications for the emergency procedure.

Key words: bacteriemia, peritoneal dialysis, peritonitis, streptococcus agalactiae, gynecological procedure

Introduction

Peritonitis in patients on peritoneal dialysis (PD) may be challenging in many ways; a small initial problem may sometimes cause serious complications. Approximately 18% of infections causing mortality in PD patients are a result of peritonitis. Additionally, peritonitis and its consequences are major reasons for shifting of patients from the PD modality to hemodialysis [1]. Peritonitis as a result of the surgical procedure has been described as a complication of surgery in genitourinary tract, gynecological and urological procedures (curettage or endometrial biopsy, conization, cystoscopic procedures) but also in the gastrointestinal tract (rectoscopy, colonoscopy with polypectomy, enema) [2-8]. Careful preparation of the patient may avoid compromising complications including infection, perforation, loss of the method and death.

Case report

A 36-year-old female patient has been suffering from type 1 diabetes since the age of 2 years, with multiple complications including diabetic nephropathy. She developed end-stage renal disease (ESRD) and was treated with CAPD over 5 years. Several months prior to admission she had noticed prolonged gynecologic bleeding, and a gynecologist indicated a curettage. After the appropriate preparation (72 hours prior to gynecologic surgery the patient had an empty abdomen without dialysis fluid and was treated with hemodialysis because she also had an AV fistula), the curettage was performed under general anesthesia. Following this procedure she was transferred to the Department of nephrology for further observation. That same evening she developed a high fever (38.8°C), with intensive pain in the lower abdominal quadrants, vomiting, poor general condition and hypotension. Laboratory tests found the following septic blood count: white blood cells (WBCs) 27×10^9/L, 39×10^9/L, differential WBCs showed neutrophils-31% undivided, and 50% divided neutrophils, lymphocytes 2.0%, monocytes 3.0%, metamyelocytes 6%, C-reactive protein (CRP) 330 mg/L, procalcitonin 61.63 ng/mL), with drop in the red blood count (E1.98×10^{12}/L,2.49×10^{12}/L, Hb 58; 60 g/L) and an increase in peritoneal leukocytes (103.30×10^9/L). Due to the suspected intra-abdominal perforation a native abdominal radiography was done which showed no pathological findings. Abdominal multi-sliced computerized tomography also showed no pathological substrates, both natively and after contrast application. We consulted a gynecologist in terms of developing postoperative complications, but nothing abnormal was found. In the meantime, the patient received a PHD after obtained curettage findings suggesting chronic cervicitis.

The patient continued receiving HD treatment, but due to prolonged hypotension and poor general condition thrombosis of AVF occurred, thus HD was performed via temporary central venous catheter. Since she had a CAPD catheter, we had a window view into the abdominal cavity. Peritoneal lavage with 300 ml of dialysis fluid was performed. The obtained content was blurry, and the samples were sent for biochemical and microbiological analyses. Direct microscopy of the lavage showed Gram-positive cocci for which empirical Vancomycin 30 mg/kg

Correspondence to: Dragan Klaric, Department of dialysis and nephrology, Zadar General Hospital, 23000 Zadar, Croatia; Phone: 00 385 23 505 121; Fax: 00385 23 505 423; E-mail: dragan.klaric@.t-com.hr

body weight was applied intraperitoneally (IP) considering her clinical condition. Due to the possibility of intraperitoneal perforation, Clindamycin and Ciprofloxacin were introduced, but after arrival of microbial pathogens culture they were discontinued. The cultivation on solid medium, after 3 days, showed the following microbiological findings: beta-hemolytic streptococcus group B with good sensitivity to Meropenem, Ceftriaxone, Vancomycin, Ampicillin, Penicillin. Ampicillin IP 125mg/L in each PD exchange was applied for the following 3 weeks, with fluconazole therapy for oral prophylaxis of fungal peritonitis, and heparin intraperitoneally until the dialysis fluid was completely clear (according to the ISPD Guidelines/ recommendations) [5]. During hospitalization anemia was corrected with transfusion of washed red blood cells, and later with erythropoietin. Before the patient was discharged from the hospital new AV fistulas were formed in the right cubital region, and she continued with bimodal treatment including CAPD and hemodialysis. Now she is in the active status for multi-organ transplantation (kidney and pancreas). The assumption is that the patient, prior to the procedure had received a prophylactic antibiotic-Cephazolin, which is a common surgical protocol. Afterwards, according to the gynecologist's opinion this case was treated as a "routine" surgery, and antibiotics were not given.

Discussion

The patient had a complication following a gynecologic procedure. Microbiologically isolated pathogen, streptococcus agalactiae, is a normal inhabitant of the gynecologic vaginal tract and peritoneal cavity, and it is transmitted with micro-perforating lesion. Theoretically, a hematogenic transmission could be the cause as well, due to the fact that it was isolated in hemoculture, and transmission into blood flow was possible through a lesion in the small blood vessels [2]. It is also known that the inflammatory processes and pathogens from the vagina and cervix may spread into the peritoneal cavity over the oviduct. Uremic patients have reduced resistance to infection, atrophic mucosa, the organ walls change in the inflammation, and the procedure cannot be done in the sterile environment [3,6]. Since beta-hemolytic group B streptococci are common inhabitants of the vagina, the most ideal prophylaxis for gynecologic procedure is administration of Ampicillin. However, it is unclear whether lavage with appropriate antiseptic in pre-procedural preparation would be helpful.
Our case demonstrates that an individual approach to each patient with careful preparation for surgical procedures as well as antimicrobial prophylaxis should be applied.

Conclusions

Despite all technical improvements in the PD procedure peritonitis remains a major problem of this renal replacement modality. Our case indicates that small procedures may cause great problems and therefore one should always give priority to individual approach regardless of the protocol for "routine" surgery, especially if there are no indications for emergency procedure. Certainly this requires the nephrologist's personal contact with other professions due to the specificity of the patients with ESRD.

Conflict of interest statement. None declared.

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Case Report

Central Nervous System Involvement under Intensive Immunosuppressive Treatment in a Patient Diagnosed with Granulomatosis Polyangiitis: A Case Report

Zeynep Kendi Celebi[1], Orhan Kucuksahin[2], Elif Peker[3], Sim Kutlay[1], Gokhan Nergizoglu[1], Kenan Ates[1] and Oktay Karatan[1]

[1]Ankara University School of Medicine Nephrology Department, [2]Ankara University School of Medicine Rheumatology Department, [3]Ankara University School of Medicine Radiology Department, Ankara, Turkey

Abstract

Granulomatosis polyangiitis (Wegener's granulomatosis) is an ANCA-associated necrotising vasculitis. The disease involves upper respiratory tract, the lungs and kidneys but central nervous system (CNS) involvement is 1-5%.
A 40-year-old male patient was admitted to the hospital with joint pain, rash, aphthous lesions. The skin biopsy from the lesion showed leukocytoclastic vasculitis. The patient had c-ANCA positive and was diagnosed granulomatosis polyangiitis. He was treated with a pulse steroid and cyclophosphamide. Before the 5th session of therapy, the patient developed hemoptysis and hematuria. Thorax CT (computarized tomography) showed a diffuse alveolar hemorrhage and hence plasmapheresis and IVIG (intravenous immunoglobulin) were added to the treatment. Two days after IVIG, the patient developed globe vesical, headache and respiratory arrest. MR (magnetic resonance) showed CNS involvement. The patient was treated with a pulse steroid, but did not respond to therapy and died after 5 months since establishing the diagnosis.
More studies are needed to identify effective treatment and course of disease for patients with central nervous system involvement.

Key words: alveolar hemorrhage, central nervous system involvement, granulomatosis polyangiitis, immunosuppressive treatment, renal failure

Introduction

Granulomatosis Polyangiitis (GPA) is an ANCA- associated necrotizing vasculitis and affects small and medium-sized vessels. ANCA is positive in 82-90% of patients [1]. The disease involves upper respiratory tract, lungs and kidneys and can affect people of any age, but is more common in the 5th and 6th decade [2] Patients may be present with constitutional symptoms like fever, arthralgia, weakness or with nose bleeding, sinusitis, hematuria, hemoptysis, shortness of breath or acute renal failure. Skin involvement is seen in approximately 50% of patients, upper respiratory tract involvement in 90% and renal involvement in 20% at the beginning but at follow-up in up to 80% [2,3].
The disease affects peripheral nervous system in 50-60% of patients, but central nervous system (CNS) involvement is 1-5%. Peripheral nervous system involvement occurs as peripheral neuropathy (mononeuritis multiplex or polyneuropathy) or cranial nerve neuropathies. Involvement of the central nervous system occurs as cerebral vasculitis or involvement of meninges [4-6].
In our case, the patient was admitted to the hospital with constitutional symptoms and at the follow-up the kidneys and the lungs were affected and central nervous system involvement occurred as well.

Case report

A 40-year-old male was admitted to our hospital with joint pain, rash, aphtous lesions and hemorrhagic crusts at nasal septum following a 2 week antibiotic course for ear infection. Skin biopsy showed leucocytoclastic vasculitis with negative immunohistochemistry, and nasal septum biopsy was non-spesific. His baseline creatinine level was 0.79 mg/dl and 24-hour urine protein was 1 g/day. C-ANCA was positive, anti-PR3 level was 2.4 U/mL, thorax CT did not show any lung involvement. We could not perform a kidney biopsy, because the patient was using enoxaparine for treatment of deep venous thrombosis in vena saphena magna. Serum protein electrophoresis was normal, physical examination revealed no lymphadenopathy, ANA was negative. The patient was diagnosed with GPA and treatment with a pulse steroid (1 g/day, three days) and cyclophosphamide (500 mg/m^2/day, one day) was initiated. Three weeks later (before the

Correspondence to: Zeynep Kendi Celebi, Ankara University School of Medicine, Ibni Sina Hospital, Nephrology Department 14th Floor Samanpazari, Altindag, Ankara 06100 Turkey; Phone: +903125082603; Fax: +903125083166; E-mail: zeynepkendi@yahoo.com

2nd session of treatment) the patient was admitted to the hospital with joint pain; creatinine levels were 5.4 mg/dl and anti-proteinase 3 level was 55 U/mL. We suggested performing a kidney biopsy, but the patient refused. Four sessions of plasma exchange were performed and methylprednisolone dose increased to 1 mg/kg/day and therapy with cyclophosphamide was continued.
After treatment creatinine levels decreased to 2 mg/dl. The steroid dose tapered to 32 mg/day and before the 5th session of the pulse therapy the patient developed hemoptysis and hematuria. Thorax CT showed diffuse alveolar hemorrhage and anti-PR3 level was 59 U/mL. Sputum acid-fast bacillus was negative. We continued pulse therapy with 500 mg/day (3 days) methylprednisolone and 8 sessions of plasma exchange were performed. The patient was treated with 2 g/kg intravenous immunoglobulin (IVIG). There was no adverse event attributed to IVIG treatment. Patient's urine output decreased and he required hemodialysis. After treatment, arterial blood gas showed no hypoxia and he did not require chronic hemodialysis. However, he developed thrombocytopenia and therefore cyclophosphamide therapy was stopped and for maintenance therapy mycophenolate mofetil was initiated. After the 2nd session of IVIG treatment the patient complained on weakness in his lower extremities and urinary retention. The neurological examination revealed flask paraplegia. He suddenly developed headache, loss of consciousness and respiratory arrest. He was transferred to Intensive care unit. Cranial CT showed intraventricular hemorrhage and hydrocephalus. MR showed dural soft tissue masses, wrapping around the spinal cord at the cervical and thoracic levels consistent with disease activity (Figure 1). The patient was treated with 500 mg/day (3 days) methylprednisolone, but he did not respond to this therapy. The patient passed away after 5 months of establishing the diagnosis. There was no response to treatment.

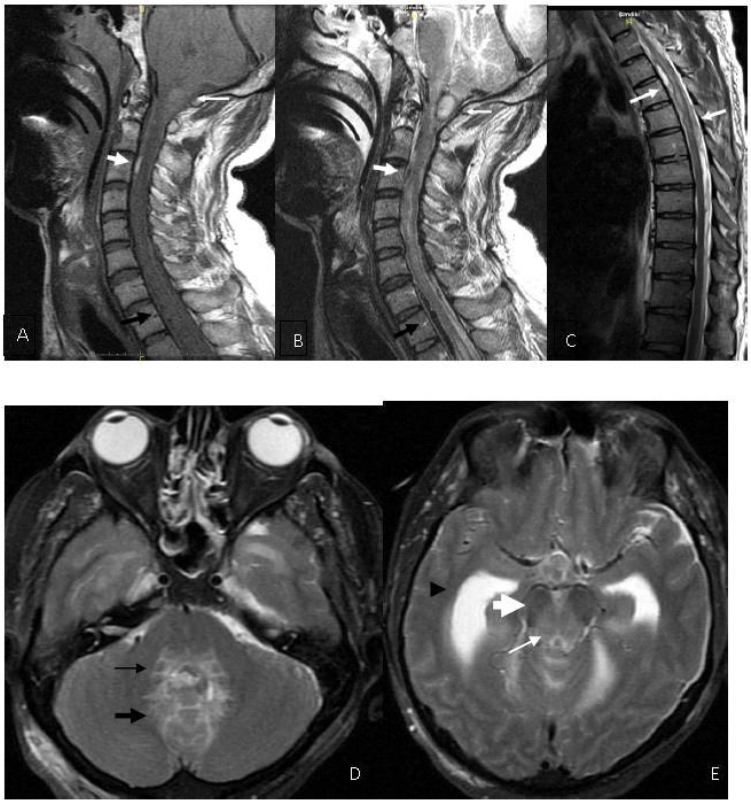

Fig. 1. MR images show dural soft tissue masses, wrapping around the spinal cord at the cervical and thoracic levels.
A. Sagital T1 weighted MR image (cervical level), B. Sagital T1 weighted MR image (thoracic level), C. Sagital T2 weighted MR image (thoracic level), D. Axial T2 weighted MR image (pons level), E. Axial T2 weighted MR image (mesencephalon level).
Spinal cord is hyperintense at the cervical and upper thoracic level. Dural masses are hyperintense on T1-weighted images and hypo- and hyperintense on T2-weighted images depending on the stage of the hemorrhage (white and black arrows). There is a hematoma at the craniocervical junction with minimal cord compression (white thin arrow). Symetrical hyperintensity of the midbrain (thick white arrow), pons (black arrow), periaqueductal gray matter (white arrow) and cerebellum (thick black arrow) is well seen on the T2 weighted scan, these findings are compatible with brainstem involvement. Hydrocephalus is present (arrowhead).

Discussion

We presented a case of a patient diagnosed with granulomatosis polyangiitis and during the course of the disease he developed CNS involvement in spite of the aggressive treatment. CNS involvement is a rare finding in the course of a disease, but in our case leptomeningeal

and cerebral vasculitis appeared concomitantly and led to death of the patient.

CNS involvement in granulomatosis polyangiitis is thought to be caused by three different mechanisms. The first mechanism is the vasculitic involvement of the small-medium sized vessels of the brain and spinal cord. The second mechanism is spread from the upper respiratory lesions to the central nervous system by bone and cartilage destruction. The third mechanism is arising from granulomatous lesions in the brain and meninges [7-9]. Cerebral involvement usually occurs with progression of the disease, but sometimes it may occur as the first manifestation of the disease. Many cases with primary CNS lesions respond well to immunosuppressive therapy and full recovery is possible [10-14]. There are some cases successfully treated with rituximab, but the data is limited [15].

Cerebral vasculitis is the most common form of central nervous system involvement as it was in our case and it may occur as intracerebral or subarachnoid hemorrhage or transient ischemic attack, ischemic infarct of brain and spinal cord, or as arterial-venous thrombosis [8,13]. It may present with neurological findings such as epileptic seizures, loss of consciousness, or neuro-psychiatric symptoms such as behavioral disorders [7,8]. Chronic hypertrophic pachymeningitis is a more common form of leptomeningeal involvement and is usually seen in localized disease [14,16]. Our case showed features of cerebral involvement. The hemorrhage was thought to be related to the vasculitic involvement of the brain tissue, and there was also a spinal cord involvement. Platelet count was below normal, but enough to prevent spontaneus hemorrhage and there was no detectable coagulation abnormality.

Treatment resistance was defined as unchanged or increased disease activity in ANCA-associated vasculitis after 4 weeks of treatment with standard therapy or a reduction of <50% in the disease activity score after 6 weeks [17]. Therefore, this case can be regarded as treatment resistant. There is no consensus about treatment of severe relapsing or treatment of resistant ANCA-associated vasculitis. There is no consensus about effective treatment and there is no study about the course of the disease and mortality in Wegener granulomatosis with neurological involvement. In clinical practice a high dose of steroid and cyclophosphamide seems to be effective to induce remission.

Conclusions

In conclusion, in addition to standard therapy in our case we used IVIG and plasmapheresis, but the course of disease was fatal. More studies are needed regarding treatment in generalized disease with neurological involvement.

Conflict of interest statement. None declared.

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