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Original Article

ANEMIA AND LEFT VENTRICULAR HYPERTROPHY IN CHRONIC RENAL FAILURE

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Summary

Chronic renal failure (CRF) syndrome significantly alters patients' quality of life. Anaemia, hypertension, and cardiovascular diseases are common complications of CRF. The study aimed to determine the incidence of arterial hypertension (AH), anaemia, and left ventricular hypertrophy (LVH) in patients with CRF and to analyze the relationship between them. The study included 212 patients with CRF, treated at the Clinic of Nephrology and Dialysis at the University Hospital "Dr. G. Stranski," Pleven, during 2008-2020. The AH accounted for 88.2% of the patients with CRF. The incidence of AH is comparable to that in patients in the predialysis period – 88.6% and among patients on dialysis – 87.9%. LVH was diagnosed in 94.3% of patients with CRF. The incidence of LVH in the predialysis period was 94.3%, and among dialysis patients - 94.4%. The incidence of LVH among hypertensive and normotensive patients was comparable. The incidence of anaemia among patients with CRF was 86.3%. Anaemia was present in 94.4% of the patients on dialysis and in 78.1% of the patients in the predialysis period. The difference was significant ($p < 0.05$). There was no correlation between anaemia and AH, nor between AH and LVH. A significant dependence of LVH on the duration of chronic renal failure and dialysis treatment was established.

Keywords: chronic renal failure, renal anaemia, left ventricular hypertrophy, arterial hypertension, dialysis.

Introduction

Anaemia is the most common complication of chronic renal failure (CRF) and is characterized by a decrease in hemoglobin and red blood cells, which leads to reduced capacity of the blood to deliver oxygen to all tissues and organs. According to the WHO definition, anaemia is a decrease in hemoglobin below 130 g/l in men and below 120 g/l in women. NKF/KDOQI defines anaemia as a hemoglobin level below 120 g/l in men and women after menopause [1].

Anaemia in CRF has a complex aaetiology, including erythropoietin deficiency, iron and

vitamin deficiency, suppressed bone marrow function, and blood loss. The leading cause of anaemia in CRF is the reduced production of erythropoietin, which stimulates the production of erythrocytes. This anaemia is also called „renal“ because the decreased production of erythropoietin results from nephrosclerosis, which is usually the morphological substrate of CRF. Anaemia also leads to sleep disorders, increased cardiovascular risk, cognitive impairment, and increased mortality. Anaemia is also considered an independent risk factor for the progression of CRF and potentiates the development of left ventricular hypertrophy (LVH) [2, 3].

Worldwide, 1.2 million people died of CRF in 2017. The global prevalence of CRF in all ages has increased by 29.3% since 1990. In 2017, more than 35.8 million people worldwide suffered from CRF, with diabetic nephropathy causing almost a third of them [4].

In CRF, there is an acceleration of endothelial dysfunction, severe hemodynamic disorders, and damage to the cardiovascular system under the influence of many vasoactive substances, uremic toxins, and mediators of inflammation. Cardiovascular diseases are the leading cause of death among patients with end-stage CRF – in over 25% of children and about 50% of adults on dialysis. They account for about 30% of hospitalizations in the dialysis population, with a tendency to increase. Cardiovascular mortality in dialysis patients is, on average, 30-40 times higher than in the general population. In patients over the age of 75, it is about five times higher, but between the ages of 25 and 30, this increase is 375 times [5-7].

During the last 25 years, heart failure has been the only category in cardiovascular pathology in which morbidity, mortality, hospitalizations, and financial costs have been rising. This „epidemic“ is paradoxically fuelled by increased survival and reduced mortality in other cardiovascular diseases. Another contributing factor is the growing number of adult patients developing left ventricular hypertrophy and insufficiency based on chronic coronary heart disease and hypertension [8].

LVH is a pathophysiological adaptation of the myocardium during its prolonged and increased work, volume, and pressure. In LVH, the myocardium undergoes significant changes, disrupting its anatomical architecture and physiological function. Age, anaemia, and arteriovenous fistula in hemodialysis patients more often lead to eccentric hypertrophy, while arterial hypertension in most cases is the cause of concentric hypertrophy. Both hypoxia (caused by anaemia) and hypertension can stimulate the renin-angiotensin system, which, in turn, enables myocyte growth as well as calcium intake into cells. Hypertension is not the sole cause of the high incidence of LVH in patients with kidney disease. Capillary density and subendocardial perfusion decrease as hypertrophy progresses. Myocardial fibrosis can develop, and myocyte death can occur with persistent maladaptive changes. Because LVH increases oxygen demand and anaemia reduces oxygen transport, the combination of these two risk factors is considered particularly dangerous [2, 3, 9-11].

In LVH patients on dialysis treatment, the risk factors are often interrelated, creating a kind of vicious circle, significantly reducing the duration and quality of life. Arterial hypertension accelerates the development of LVH. The incidence of LVH, even before HD treatment, is also significantly increased [12]. According to some authors, 75% of patients have initial left ventricular hypertrophy when initiating renal replacement therapy [11, 13].

Anaemia is a crucial factor closely related to cardiovascular complications, left ventricular hypertrophy in particular, which significantly worsens the prognosis of these patients. There is also a significant correlation between anaemia, cardiovascular complications, and hospitalizations. Numerous pieces of evidence have been found to improve the quality of life and prognosis in patients with cardiovascular diseases and CRF with timely and adequate treatment of anemic syndrome [10, 11, 13, 14].

Materials and methods

The study is retrospective and includes 212 patients with CRF treated at the Clinic of Nephrology and Dialysis of UMHAT “Dr. G. Stransky”- Pleven in the period January 2008-December 2020. Data on major kidney disease, duration of CRF, severity were analyzed of anemia, renal replacement therapy and its duration. LVH was assessed by echocardiography, assessing left ventricular

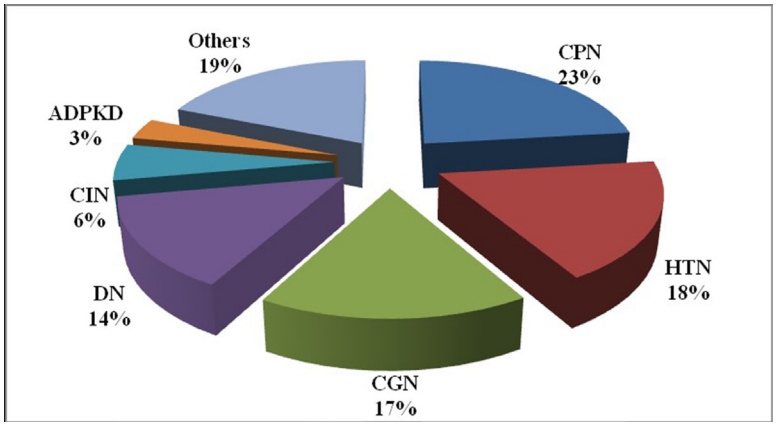

Figure 1. Aetiology of chronic renal failure (CPN – chronic pyelonephrirtis, HTN – hypertensive nephropathy, CGN – chronic glomerulonephrirtis, DN – diabetic nephropathy, CIN – chronic interstitial nephritis, ADPKD – autosomal dominant polycystic kidney disease)

wall thickness, left ventricular mass, and left ventricular geometry. The echocardiography is the gold standard for the diagnosis of LVH [13].

Statistical analysis

Alternative, variational and correlation methods were used for statistical analysis. Qualitative variables are presented as absolute frequencies and relative proportions, and continuous quantitative variables as median with 1-3 quartiles or minimum-maximum value (asymmetric distribution) and mean±standard deviation (normally distributed variables). Demographic, clinical, laboratory, medical history data were compared using McNemar's test, Fisher's exact test and Hotelling's T-squared distribution. A $p<0.05$ value was accepted as statistically significant.

Results

The studied patients were at different stages of CRF – from initial to end- stage, including those undergoing renal replacement therapy.

We studied 100 women (47.2%) and 112 men (52.8%). The patients' age range was 20-89 years (mean 60.3±14.3). The group's registered CRF duration varied from 4 to 436 months (average 72.1±56.5). Analysis of the CRF aetiology showed that the most common were chronic pyelonephritis, hypertensive nephropathy, chronic glomerulonephritis, and diabetic nephropathy. The autosomal dominant renal polycystic kidney disease (ADPKD), Balkan endemic nephropathy (BEN), and congenital anomalies of the urinary tract have the smallest share (Figure 1). In 14 (6.6%) cases, the aetiology remained unclear, as some of the patients sought advice from a nephrologist for the first time and were with terminal uremia and advanced nephrosclerosis.

The aetiology of renal failure was complex in 31% of the patients. The data is included in Fig. 1, and distribution presents the leading aetiology.

Regarding therapy, 107 of the patients were treated with renal replacement therapy 97 patients (45.7%) were on hemodialysis (HD), and 10 (4.7%) were on continuous ambulatory peritoneal dialysis (CAPD). The average duration of hemodialysis treatment was 56.2±61.4 months, and that of CAPD was 49±48.1 months.

Arterial hypertension (AH) was found in 187 (88.2%) of the CRF patients (96 men and 91 women, average age 61.2±13.6 years). The incidence of AH among patients with CRF in the predialysis period was 93/105 (88.6%), and among patients with CRF on dialysis – it was 94/107 (87.9%). The difference was insignificant ($p>0.05$). The incidence of symptomatic hypertension was highest among patients with chronic pyelonephritis, diabetic nephropathy, and chronic glomerulonephritis (Tabl. 1). The average value of hemoglobin in hypertensive patients was 97.8±16.9 g/l.

AH was not found in 25/212 patients (11.8%), with an average age of 53.7±19.0 years, 9 women and 16 men, with an average hemoglobin value of 101.9±17.1 g/l. The difference between the average hemoglobin values in hypertensive and normotensive patients was insignificant ($p>0.05$).

Table 1. Incidence of anaemia, AH and LVH among patients according the basic disease

Aetiology	All	Anaemia	AH	LVH
Chronic pyelonephrirtis	49	48	49	49
Hypertensive nephropathy	39	35	39	39
Chronic glomerulonephrirtis	35	28	31	34
Diabetic nephropathy	30	23	22	23
Chronic interstitial nephritis	12	12	10	12
Lupus nephropathy	9	7	5	7
Autosomal domi-nant polycystic kidney disease	7	4	6	7
Others	31	26	25	29

Table 2. Distribution of patients with LVH among those with AH

	With LVH	Without LVH	All
With AH	176	11	187
Without AH	24	1	25
All	200	12	212

Table 3. Distribution of patients with LVH among patients with anaemia

	With LVH	Without LVH	All
With AH	173	10	183
Without AH	27	2	29
All	200	12	212

LVH was diagnosed in 200/212 patients with CRF (94.3%). The incidence of LVH among patients with CRF in the predialysis period was 99/105 (94.3%) and among patients with CRF on dialysis was 101/107 or 94.4%. The difference is not significant ($p>0.05$).

The highest incidence of LVH was seen in patients with CRF, hypertensive nephropathy, and polycystic kidney disease – 100%, and the lowest – was among patients with lupus nephropathy – 77% (Tabl. 1). Data analysis showed that 176/187 patients (94.1%) with AH also had LVH, and only 11 patients (5.9%) were without LVH. Of the 25 patients without AH, 24 (96, 0%) had LVN. (Table 2). The incidence of LVH among hypertensive and normotensive patients was comparable. However, the difference was not significant.

We diagnosed anaemia in 183/212 patients (86.3%), and 29/212 patients were without anaemia (13.7%). Of those with CKD on dialysis, those with anaemia were 101/107 (94.4%), and in the patients in the predialysis period, anaemia was found in 82/105 (78.1%). The difference was significant ($p<0.05$). All dialysis patients with anaemia received erythropoietin. The mean hemoglobin of patients with anaemia was 95.8±17.1 g/l and that of patients without anaemia – 133.6±12.6 g/l. Among the patients with anaemia, 173/183 (94.5%) had LVH, and among the patients without anaemia, 27/29 (93.1%) had LVH (Tabl. 3), with no significant difference between the two groups ($p>0.05$).

There were 35/200 (17.5%) patients with initial LVH, 125/200 (62.5%) – with pronounced LVH, and 40/200 (20.0%) had severe LVH. (Tabl. 4).

Only 7 of the patients on hemodialysis treatment did not have LVH, and the average duration of their treatment was 22.7±25.6 months. On dialysis treatment were 13/35 with initial LVH, with an average period of 46.8±56.8

Table 4. Distribution of patients according to the presence and severity of LVH

	Patients count	Rel. share	Average age (years)	Average Hg level (g/l)	Average duration of CRF (months)
Without LVH	12/212	5.7%	51.3±15.4	91.0±18.6	38.1±26.7
With initial LKH	35/200	17.5%	49.9±15.7	100.5±17.1	60.9±65.8
With pronounced LKH	125/200	62.5%	63.2±13.1	99.0±15.8	81.4±75.8
With severe LH	40/200	20.0%	63.1±11.6	95.5±19.6	68.2±44.1

months; 63/125 with pronounced LVH, with an average duration of 56.2±65.2 months; 24/40 with severe LVH, with an average duration of 48.6±39.4 months. A significant difference was registered between the duration of CRF respectively the dialysis treatment of patients with and without LVH ($p<0.05$). The average haemoglobin level was lower in patients with severe LVH than in patients with mild LVH, but the difference was insignificant ($p>0.05$).

Discussion

The relationship between the kidneys and the heart in health and pathology has been long known. The decreased glomerular filtration rate is associated with hypervolemia and increased cardiac output. Haemodynamic loading leads to increased myocardial contractility by neurohumoral mechanisms and, over time, to LVH and heart failure [3]. The cardio-renal syndrome in patients with CKD was first described by R. Bright in 1836 [16] but has been the subject of research and discussion since 1980, especially after the establishment of practical and widespread use of extrarenal methods for the treatment of CRF. The significant increase in the survival of patients with CRF undergoing organ replacement therapy, mainly related to the improvement of dialysis technology and the treatment of renal anaemia with epoetin after 1990, has also led to an increase in the incidence of chronic complications of CRF in which left ventricular hypertrophy and chronic heart failure play an essential role [17].

Due to the dramatic increase in the incidence and prevalence of diabetes worldwide since 1990, in many countries, the most common chronic parenchymal nephropathies leading to CRF – chronic glomerulonephritis and tubulointerstitial nephritis have been replaced by diabetic nephropathy [4]. Data from our study showed that diabetic nephropathy led to CRF in only 14% of patients and ranked only fourth after chronic tubulointerstitial nephritis, chronic glomerulonephritis, and hypertensive nephropathy.

The ratio of the patients on hemodialysis and peritoneal dialysis we studied was approximately 10:1, like in over 90% of countries worldwide [4]. Our study confirmed the known high incidence of symptomatic hypertension in patients with chronic renal failure – 88.6%. The comparison showed that the difference in incidence in the groups treated with dialysis and in the predialysis period was less than 1%. Anaemia, assessed by investigating haemoglobin values, was equally severe in patients with CRF with normal and high blood pressure. Other authors have not made such a comparison.

The incidence of LVH among patients with CRF was very high – 94.3%. The incidence of LVH among dialysis patients and in the predialysis period was similar. In the majority of the patients with LVH, it was pronounced or severe. A correlation was found between the severity of LVH and the duration of dialysis treatment. The high incidence of LVH among dialysis patients that we found is comparable to the incidence reported by K. Amann et al. [13] and L. Di Lullo [15], E. Nardi et al. [18], and V. Vishwanath [19]. Our findings regarding LVH differ from the data reported by A. Khan et al. [6], who studied patients whose average age was 46 years and the average duration of dialysis treatment was only 3.8 months.

According to L. Di Lullo et al. [15], the prevalence of LVH is estimated to be between 16 and 31% in individuals with a GFR>30 ml/min. It increases to 60-75% before renal replacement therapy and rises to 90% after initiating dialysis.

A study by A. Levin et al. found a high incidence of LVH before starting dialysis treatment and an increase of about 10% every 12 months after its onset [20]. The dependence of LVH on AH is natural: 94% of the studied

hypertensives with CRF have LVH. The incidence of LVH among patients without AH is equally high, indicating that AH is not the only cause of LVH in patients with CRF. Similar data have also been found by K. Amann et al. [13]. The importance of studying patients with CRF for the presence of LVH is determined by the fact that LVH is a predictor of premature cardiac death, despite hypertension [2, 11, 13].

The incidence of renal anaemia among the studied patients was also high – 86%. In contrast to arterial hypertension, it was significantly higher in patients on dialysis – 94%, compared with the incidence of patients in the predialysis period – 78%. This is most likely related to dialysis patients' more severe degree of nephrosclerosis. The incidence of renal anaemia was the same among patients with and without LVH.

All patients with anaemia were treated with erythropoiesis-stimulating agents according to the appropriate guidelines (NKF/KDOQI). Although anaemia is considered a risk factor for the development of LVH [2, 3], and despite data from many studies, it is still unclear to what extent the correction of anaemia leads to regression of LVH [21].

Conclusions

Unlike other countries in the world, diabetic nephropathy is not the most common cause of chronic renal failure and is the fourth most common underlying disease in Europe. About 10% of our dialysis patients were treated with peritoneal dialysis. Hypertension was equally common in patients with chronic renal failure in the predialysis and dialysis patients. There was no significant difference in LVH incidence between patients with and without anaemia and those with and without hypertension. There was a considerable dependence of left ventricular hypertrophy on the duration of chronic renal failure and dialysis treatment. A correlation was found between the severity of left ventricular hypertrophy and the duration of chronic renal failure and dialysis treatment.

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