GENERAL REVIEW

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Risk factors for cardiovascular disease in children on chronic hemodialysis – Traditional (general) risk factors, Part I

Faktori rizika od nastanka kardiovaskularnih bolesti kod dece na hroničnoj hemodijalizi: tradicionalni (opšti) faktori rizika, I deo

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Introduction

Cardiovascular complications are almost always present in children with chronic kidney diseases (CKD) who are being treated with hemodialysis (HD). As in adults, the risk factors responsible for the onset of cardiovascular diseases in childen with CKD can be divided in two basic groups: traditional (general) risk factors related to the arteriosclerosis and nontraditional (uremia-related) risk factors, which are especially present in HD patients.

Arterial hypertension

Arterial hypertension is one of the main risk factors in patients with CKD who are being treated with HD. The presence of hypertension increases the risk of cardiovascular mortality in patients on HD. In end-stage renal disease (ESRD), almost all children and adolescents are hypertensive. In the first weeks or months after the commencement of treatment, HD blood pressure rapidly decreases and it is being reduced by the use of antihypertensive therapy, however, in many children on HD the hypertension persists [1,2].

Apart from that, it is difficult to precisely define the hypertensive status in children on dialysis, due to the frequent changes in the volume of the circulating fluid and the changes in the circadian rhythm [3,4].

Most would argue that the two major pathogenetic mechanisms of hypertension are hypovolaemia and vasoconstriction. Preload volume (preload) is responsible for many cases of hypertension. This is related to the retention of salt and water, as well as to the reduction in the mechanism for excretion of sodium. Insufficient elimination of the fluids (body weight above the "dry weight") leads to the state of chronic hyperhydration. Chronic salt and water retention in children with chronic renal insufficiency leads towards hypertrophy and dilatation of the left ventricle [5–7]. The presence of an arteriovenous fistula (AVF) in dialysis patients increases the venous flow to the heart and it increases the pressure of the volume. AVF additionally increases the preload, since it has the effect of the left-to-right shunt, thus the chronic hypovolaemia is almost always present in patients on HD, even when the "dry weight" is reached at the end of the dialysis treatment [4,5].

Vasoconstriction or rather the increase in peripheral vascular resistance may occur as the result of the activation of the sympathetic nervous system or due to the vasoconstrictor ofthe endothelial origin (e.g. endothelin-1). Another possible mechanism is the reduction in the production of vasodilators (e.g. nitric oxide, NO). Increased vascular rigidity may occur due to the increase in collagen glycosylation, which leads to a reduced compliance of the arteries and the increase of intracellular calcium (e.g., hyperparathyroidism) [6,7].

The incidence of arterial hypertension

According to various sources, the prevalence of hypertension in children on dialysis ranges from 40% to 90% [2–4]. A study by Tkaczyk et al. [8] shows that the prevalence of hypertension is 55% in the entire group of children on HD in Poland. In our study, conducted at the University

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Children's Hospital in Belgrade on 20 patients on HD, hypertension was present in 60% of the patient [5, 6, 9]. In a recent research, Mitsnefes et al. [4] have shown that the prevalence of hypertension is 76.6% of cases in the pediatric population (period 1992–2004). Other recent studies have shown a high prevalence of hypertension in children on HD (Halbach et al. [10] 67.9%, Hölttä et al. [11] 52%, Lingens et al. [12] 47%). The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [13] shows that hypertension develops early in chronic renal disease. The increase in the incidence of hypertension from 48% in the early stage of CKD to 50–75% in terminal renal failure is very significant. Recent data from a study Chronic Kidney Disease in Children (CkiD) [4], on 586 children aged 1–16 years, from 46 pediatric nephrology centers in North America, show that the frequency of hypertension is 54% in patients in the early stages of CKD, with an increase by 25% in the end-stage renal disease and those treated with chronic HD (Table 1). The fact that children on antihypertensive therapy continue to have high blood pressure in 48% of cases is even more worrisome [14, 15].

tors are chosen as the first choice drugs for the treatment in the majority of children on HD. Besides, these two drugs present the most popular combination in most countries. Previous studies clearly describe that in patients on chronic HD, the antihypertensive therapy is often inefficient (60–70%). Most authors suggest that for this population, the selection of medication is not the only thing which is important, but also other non-pharmacologic therapies, for instance dietary salt restriction, maintaining adequate volemia and dry weight [15].

Control volume overload in patients on HD is essential in controlling hypertension. Experiences in adult patients on chronic HD are that significant help in controlling hypertension, and left ventricular hypertrophy regression can achieve HD every day, or the introduction of HD during the night 5–7 nights a week [16] (although data for children are still limited).

Recent data from the CkiD [4] emphasize the importance of the presence of masked hypertension, which was present in 25% of patients with CKD [2–4]. The presence of camouflage hypertension doubles the incidence of left ventricular hypertrophy. Therefore, routine ambulatory blood pressure

Table 1

Traditional risk factors for the onset of cardiovascular disease (CVD) in children with chronic kidney disease (CKD) [4]

Risk factors	CKD (%)	Dialysis (%)	Transplant (%)
Hypertension	47–54	52–75	63–81
Dyslipidemia	45	33–87	55–84
Obesity	15	8-11	12–22
Hyperglycemia	4	11	22

Note: Data are from the Chronic Kidney Disease in Children (CkiD) study.

Apart from that, arterial hypertension persists in most patients on HD, despite of the fact that nephrologists are aware of this problem. It is possible that high blood pressure in patients treated with dialysis is the consequence of untreated or inadequately treated ones. According to the European Dialysis and Transplant Association 55% of children on chronic HD receive antihypertensive therapy. Despite of this treatment, one third of all patients maintain the level of blood pressure 10 mmHg or more, above the 95th percentile for their age, gender and height [15, 16].

After kidney transplantation, hypertension is more frequently present in children than in adults. Successful transplantation leads to a significant improvement of the renal function and elimination of many risk factors, however, even after transplantation the prevalence of hypertension remains in 50–80% of patients [14].

Treatment of arterial hypertension

In most of recent studies, the majority of hypertensive children on chronic HD were treated with two or more medications. Lately, the majority of pediatric nephrologists tend to treat aggressively hypertension in their dialysis patients to achieve better control of hypertension. Calcium channel antagonists and angiotensin-converting enzyme (ACE) inhibi-

monitoring in children with CKD should begin at an early stage of CKD. This can significantly improve the control of hypertension [17].

Dyslipidemia

It is well-known that children on HD have an abnormal lipid status. It is reflected in the increase of the levels of lipoprotein of very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL) and of the total cholesterol and in the decrease of the levels of high density lipoprotein (HDL). The level of triglycerides is usually elevated, especially in patients with terminal renal insufficiency who are treated with HD and in patients after kidney transplantation [18].

It is believed that the basic mechanisms for the onset of dyslipidemia in CKD is a disorder in the break down of triglycerides which is associated with the increased levels of apolipoprotein C-III (an inhibitor of lipoprotein lipase) and with a decrease of the insulin sensitivity in the vascular endothelium of the blood vessels in skeletal muscle and adipose tissue. In children with CKD and those who are treated with HD, in almost half of the cases a combined dyslipidemia is present while in general population it is present in 20% of patients [18, 19].

The NAPRTCS shows that the prevalence of dyslipidemia is 70–90% in children on HD [16], however, dyslipidemia is common in the earlier stages of CKD (stages 2–4) [20]. The data of the aforementioned CKiD study show that dyslipidemia was found in 45% of children with CKD [5].

The CKiD study shows that 21% of children with CKD had total cholesterol greater than 200 mg/dL, in 21% HDL cholesterol was lower than 40 mg/dL and in 16% the VLDL cholesterol was greater than 160 mg/dL. Disorders of the lipid fraction may remain after kidney transplantation [19].

The treatment of dyslipidemia

The latest guidelines for monitoring and treatment of lipid status in children over 8 years of age and adults with diabetes show that the statin therapy should be considered in patients with LDL cholesterol ≥ 130 mg / dL [20]. Although these guidelines do not refer exclusively to children with CKD, they can be applied to them. Since 2006 the American Heart Association has been placing these patients in the high CV risk group, like patients with diabetes mellitus or a heart transplant. One could say that statin therapy will be a standard part of care for patients with chronic renal insufficiency older than 8 years, with LDL cholesterol ≥ 130 mg/dL, although this is not explicitly stated in the guidelines [21]. There is a few data on the improvement of long-term outcomes in children with CKD, if good control of the lipid status is performed [22, 23]. It is believed that statin therapy reduces the incidence of transplant vasculopathy. Serón et al. [24] show a significant reduction in the incidence of vasculopathy after kidney transplantation (33% compared to 7%) in the first 6 months after transplantation with statin therapy as compared to placebo. Recently, two large clinical studies (SHARP and AURORA) [25, 26] have tried to answer the question whether statin therapy benefits the patients with CKD and ESRD. The results of the AURORA study indicate that rosuvastatin has no effect on the development of atherosclerotic lesions and no significant effect on the reduction of mortality in patients undergoing HD, while the SHARP study is still in progress. Based on the data regarding the prevalence of the dyslipidemia in children, which was published as a part of the CKiD study, the NKF / KDOQI in 2008 issued the guidelines for the necessary screening of dyslipidemia in children with CKD since the beginning of puberty [27].

Atherosclerosis

Accelerated atherosclerosis in children with CKD is likely. There are indirect and direct evidence for the onset of atherosclerosis in childhood. Indirect evidence is that most of these patients have an increased *c*arotid intima-media thickness (cIMT), which is a basic sign of atherosclerosis in adults. In the group of young adults who had ESRD in childhood, cIMT was increased compared to the control group and it was correlated with the duration of end-stage renal disease, duration of HD and with the increase of the serum calcium, phosphorus and products of calcium x phosphorus [28–30].

Mönckeberg sclerosis is a special form of arterial calcification of the *tunica media* that is seen in patients with CKD.

This form of sclerosis is regulated by the ratio of promoters and inhibitors of calcification. Mönckeberg sclerosis involves calcification of *tunica media*, but does not include calcification of the *tunica intima*. Calcification of *tunica media* and *tunica intima* can coexist together, or calcification of the *tunica media* is dominated, especially in young children and in patients in stage 4 or 5 CKD (before dialysis). It is important that the clinical manifestation of calcification determines localization in the blood vessel wall. Furthermore, calcification of the *tunica intima* increases the frequency of mortality compared to the calcification of the *tunica media*. Also, dialysis patients may develop uremic arteriolopathy, which is a special form of calcification of the *tunica media* of blood vessels of the skin and heart valves [28].

To detect calcification of blood vessels commonly used measurement calcification using high-resolution ultrasound or direct evidence of coronary artery calcification using CT (multislice CT scan). Functional changes in blood vessels due to an increase in the stiffness of the vessel wall or decrease in the compliance of the vessel wall can be monitored by pulse Doppler during ultrasound examination [5, 30].

Direct evidence suggesting that significant atherosclerosis may occur in young patients with CKD is shown in the study of Naiyr et al. [31] who did a biopsy of the iliac artery in 12 patients on HD, aged 11–17 years. Out of 12 histologically examined arteries, in 7 (58.3%) there were atherosclerotic changes found, while in 5 (41.6%) they found intimal fibroelastic thickening and in 2 (16.6%) cases they found atheromatous plaques. Also, the duration of the acute renal failure is an important factor in the onset of the atherosclerosis. It is interesting that the values of blood pressures were similar regardless of the cause of end-stage renal disease, but the patients with congenital causes of CKD had elevated levels of phosphate and products of calcium-phosphorus – bigger than those with acquired diseases such as glomerulonephritis. This points out the fact that vascular diseases in young patients with CKD have multifactorial origin, with dyslipidemia as just one of many factors involved in the pathogenesis [28, 29].

Obesity

Lately, the presence of obesity was noted in children with CKD. The trends of the increased prevalence of obesity, with the rates from 8% (1995) to 12% (2002) are shown in HD patients (the NAPRTCS) [32]. The survey data on the adult definition suggests that the longer survival in patients with higher body mass (128–130 kg), however, it seems that the body and muscle mass should not exceed 133 kg. According to the recommendation of the NKF/KDOQI 32 weight loss in patients should be approached cautiously, with constant monitoring by dietitian and exercise physiologist. After kidney transplantation in children obesity is associated with higher rates of graft rejection or graft dysfunction. There is evidence that obesity in children on HD reduces the efficiency of antihypertensive therapy.

Obesity is becoming present in children even after the kidney transplantation. Approximately, the prevalence ranges from 15% to 30% in the first year following transplantation (Table 1).

Disorders of glucose and insulin metabolism

Disorder of the glucose and insulin metabolism in children with CKD on therapy with HD, and especially after kidney transplant is becoming more frequent [5]. Small studies on children with CKD, stage 2–4 or on HD, show that the prevalence of hyperinsulinemia is 33% and the prevalence of insulin resistance disorder is up to 16% (measured by homeostasis model assessment-estimated insulin resistance –HOMA IR) [33, 34]. It appears that abnormalities in glucose and insulin metabolism are more prevalent than they were deemed to be. Recent publications featuring studies on children after kidney transplantation have shown that the frequency of disorders of glucose and insulin metabolism is from 16% to 18% [33, 35].

Seating lifestyle

In adults with CKD, seating lifestyle and low levels of physical activity are well documented. Painter et al. [36] show that children with CKD (specifically, those on HD) are fairly inactive as they spend less than 10% of time in extracurricular physical activities. Also, aerobic capabilities have already been reduced in children and adolescents in the early stages of CKD (stage 3) and the improvement does not come even after transplantation. Due to the evidence that regular physical activity can decrease the risk of CVD in the general population, it is reasonable to question whether increased physical activity can reduce cardiovascular risk in children with CKD [37].

Conclusion

Early recognition of the traditional risk factors and treatment of patients with asymptomatic cardiovascular changes is the key for the reduction of the mortality and morbidity of dialysis patients with a developed cardiovascular disease during childhood.

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