Influence of nephrectomy on solitary kidney function in children with non-malignant diseases

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KEY WORDS

unilateral nephrectomy ◗ compensatory hypertrophy ◗ solitary kidney ◗ biomarkers of renal injury ◗ time after nephrectomy

ABSTRACT

Introduction. Removal of a kidney with abnormal structure and impaired excretory function causes compensatory hypertrophy of the „normal" kidney. Aim:
1. Does nephrectomy of a unilateral multicystic dysplastic or hydronephrotic kidney correspondingly influence biomarkers of renal injury of the solitary kidney?
2. To what extent are duration after nephrectomy and kind of renal pathology pathogenic factors that may impair function of the solitary kidney?

Material and methods. In 27 children after unilateral nephrectomy (11 – congenital hydronephrosis, 16 – multicystic kidney dysplasia) the following parameters were evaluated: kidney length; renal cortex thickness; mean arterial pressure; body mass index; glomerular filtration rate (GFR); plasma creatinine and cystatin C concentration and clearance; albuminuria; urinary excretion of: IgG, transferrin, α1-microglobulin, α2-macroglobulin, and β2-microglobulin.

Results. Most estimated parameters were of similar magnitude in both examined groups. Only renal creatinine clearance and renal cortex thickness were significantly higher in the group with hydronephrosis. There was a positive correlation between duration after nephrectomy and albuminuria in children with multicystic dysplastic kidney.

Conclusions.
1. In the majority of children an appropriate compensatory overgrowth of the solitary kidney was found.
2. In children with a multicystic dysplastic kidney the duration after nephrectomy of the diseased kidney seems to be a promoter of albuminuria.
3. Prolonged and careful follow-up of these children is mandatory.

INTRODUCTION

Congenital unilateral multicystic dysplastic or nonfunctioning hydronephrotic kidneys are frequent indications for nephrectomy with the aim of preventing malignant transformation of the dysplastic organ or recurrent infection respectively. As may be expected, unilateral nephrectomy is often accompanied by compensatory hypertrophy of the solitary functioning kidney which in turn may be the cause of renal parenchymal injury and hypertension. Nephrectomy effectively prevents relapses of urinary system infections, generalized infections caused by purulent processes in the damaged kidney, eliminates the potentially higher risk of Wilms' tumor development in the dysplastic kidney, and may also prevent the development of arterial hypertension. At the same time, nephrectomy does not cause premature mortality of patients subjected to that form of therapy [1]. The first unilateral nephrectomy in a human was performed in 1869 by Simon [2] and has since become a treatment accepted in specific clinical situations in both adults and children. Some authors suggest that removing even more than a half of the total weight of renal tissue does not cause impairment of the function of the remaining kidney; nevertheless, such patients show increased risk of proteinuria, glomerulopathy, and progressive renal insufficiency [3, 4]. Similar risk also concerns patients with unilateral renal agenesis [5]. What is essential, the consequences of the reduction of the total weight of active kidney parenchyma do not occur in all patients and are highly dependent on the morphological and functional state of the other kidney. The available publications do not report any possibilities of predicting the development of the aforesaid complications in an individual patient based on the generally used diagnostic methods.

Insufficient knowledge of the compensatory hypertrophy, pathophysiology, the phenomenon of hyperfiltration and lack of reliable predictors of the degree of changes, as well as consequences of unilateral nephrectomy in an individual patient were the inspiration for studies presented in these groups of patients.

In the present study we tried to answer the following questions:

1. Does nephrectomy of an unilateral multicystic dysplastic or nonfunctioning hydronephrotic kidney respectively influence biomarkers of renal injury of the solitary kidney and

2. To what extent are duration after nephrectomy and kind of renal pathology pathogenic factors that may impair function of the solitary kidney.

MATERIAL AND METHODS

The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All parents and their children gave their informed consent prior to inclusion in the study. 27 children at the mean age of 10.7 years (3-18 years) were examined. The reason for nephrectomy was unilateral multicystic dysplasia (16 patients) or congenital nonfunctioning hydronephrotic kidney (11 patients) respectively. None of the children had additional urinary tract abnormalities diagnosed. The decision for nephrectomy was made when the participation of the kidney in renal clearance was smaller than 10% and recurrent infections were present. The time after nephrectomy ranged from 1-11 years (mean 5.3 years). In all patients the following parameters were analyzed:

- body mass index (BMI)
- mean arterial pressure (MAP)

Table 1. Estimated parameters in children with multicystic dysplasia and congenital hydronephrosis.

	Diagnosis	Dysplasia	Hydronephrosis	Statistical significance (p value)
Age (years)	Mean	9.3	13.09	0.08
	SD	5.23	5.3	
Time after nephrectomy (years)	Mean	5.75	4.9	0.48
	SD	2.72	2.3	
Creatinine (mg/dl)	Mean	0.71	0.81	0.12
	SD	0.23	0.17	
GFR (ml/min/1.73 m^2)	Mean	107.7	116.3	0.21
	SD	15.6	19.1	
Creatinine clearance (ml/min/1.73 m^2)	Mean	80.9	100.8	0.03
	SD	38.28	25.02	
Cystatin (mg/dl)	Mean	0.76	0.71	0.38
	SD	0.19	0.18	
Cystatin clearance (ml/min/1.73 m^2)	Mean	116.7	126.49	0.38
	SD	36.04	36.67	
Renal cortex thickness (cm)	Mean	1.29	1.56	0.005
	SD	0.2	0.3	
Albuminuria (mg/l)	Mean	27.2	41.55	0.06
	SD	86.3	65.33	
Kidney length (cm)	Mean	10.21	11.1	0.26
	SD	1.94	1.59	
MAP (mean arterial pressure)	Mean	79.3	87.7	0.1
	SD	13.5	12.16	
BMI (body mass index)	Mean	17.97	19.1	0.33
	SD	3.08	3.9	

- plasma creatinine (Jaffe method) and estimated GFR (glomerular filtration rate) (Schwartz method)
- creatinine clearance
- plasma cystatin C level (nephelometric method)
- renal cystatin clearance (Larsson formula)
- renal cortex thickness (by ultrasonography)
- daily albuminuria (mg/dl)
- daily urinary excretion of

- Transferrin (upper normal value 2.2 mg/24 h)
- IgG (upper normal value 3.8 µg/ml)
- α1 microglobulin (upper normal value 5 µg/ml)
- α2 macroglobulin (upper normal value 2.56 µg/ml/
- β2 microglobulin (upper normal value 0.216 µg/ml).

All the above biochemical parameters were estimated by routine laboratory methods (if not especially specified).

Statistical evaluation of results was performed using the U-Mann-Whitney test for two independent variables and Chi-square test respectively as appropriate.

RESULTS

As shown in table 1 children with unilateral multicystic dysplasia did not differ from those with congenital hydronephrosis by age, duration after nephrectomy, mean arterial blood pressure, body mass index (BMI), plasma creatinine, cystatin C level, or cystatin C clearance. In contrast renal creatinine clearance and albuminuria was higher (significantly for creatinine clearance and borderline significance for albuminuria) in congenital hydronephrotic than in multicystic dysplasia children. Urinary excretion of transferrin, IgG, α1-microglobulin, α2-macroglobulin and β2-microglobulin were of comparable magnitude in both pathogenic groups of children. As shown in table 1 hydronephrotic children showed a significantly greater thickness of the renal cortex as compared to children with multicystic dysplasia. The majority of children with multicystic dysplasia and congenital hydronephrosis respectively showed an enlarged length of the solitary kidney as compared with normal values for age (Figs. 1 and 2). Only in children with multicystic dysplasia a significant positive correlation was noticed between albuminuria and duration after nephrectomy ($p < 0.02$) (Fig. 3). There was no significant correlation between GFR and MAP and the time after nephrectomy respectively in both examined groups of patients (GFR/time after nephrectomy in kidney dysplasia and hydronephrotic patients, $p = 0.63$ and $p = 0.81$ respectively; MAP/time after nephrectomy in kidney dysplasia and hydronephrotic patients, $p = 0.40$ and $p = 0.73$ respectively). We found a positive and statistically significant correlation between MAP and BMI (Fig. 4) and also between renal cortex thickness and kidney length (Fig. 5) for both aforesaid groups.

DISCUSSION

The fact that the solitary kidney assures maintenance of systemic homeostasis is not controversial. Only few reports prove that unilateral nephrectomy predisposes to albuminuria and focal hyalinization of glomeruli, and consequently to the development of chronic impairment of the solitary kidney [3, 4].

The decision for nephrectomy also has to be made carefully because of the fact that it has been proven that together with the removed renal tissue, the hormonal and enzymatic activity of the

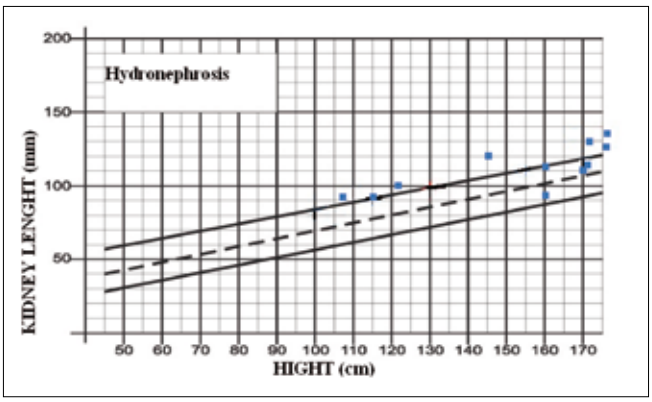

Fig. 1. Relationship between kidney length and child height in patients with hydronephrosis. Parallel lines indicate the parameters in the general population.

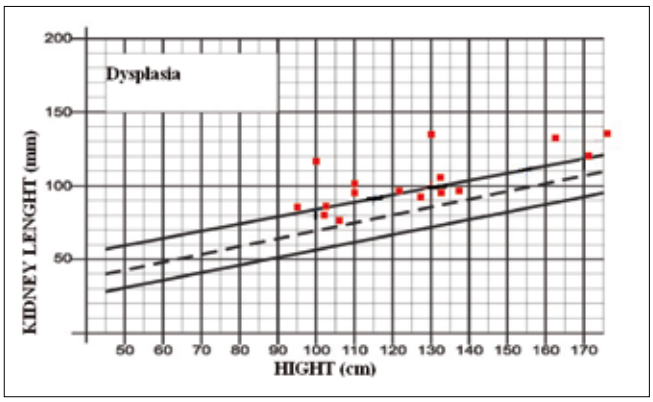

Fig. 2. Relationship between kidney length and child height in patients with kidney dysplasia. Parallel lines indicate the parameters in the general population.

kidney is lost as well, which causes not fully recognized pathophysiological consequences. Kidneys, apart from their excretory function, are the source of many hormones, biologically active peptides, and enzymes participating in maintaining systemic homeostasis. About 30 particularly biologically active substances synthesized by renal tissue have been identified, among which the most known and studied are: erythropoietin, active vitamin D derivatives, renalase, and components of the renin-angiotensin-aldosterone system [6].

Reduction of the number of active nephrons leads to hyperfiltration and compensatory hypertrophy of the remaining kidney parenchyma. The pathophysiology of compensatory hypertrophy is relatively well known [7, 8]. It is connected with the hypertrophy of individual nephrons and not with the growth of their number. It is accompanied by glomerular hyperfiltration in the remaining nephrons [9]. The process of hyperfiltration is actually considered as the primary cause of the remote consequences of nephrectomy

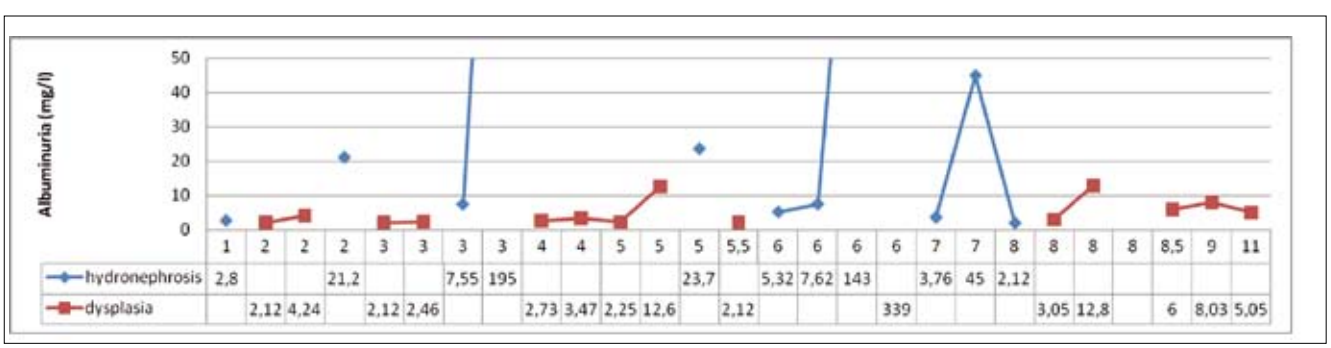

Fig. 3. The relationship between albuminuria and the time after nephrectomy (years) in a group of patients with dysplasia and hydronephrosis. Spearman correlation for dysplasia R = 0.56 (p = 0.02). No correlation for hydronephrosis (p = 0.6).

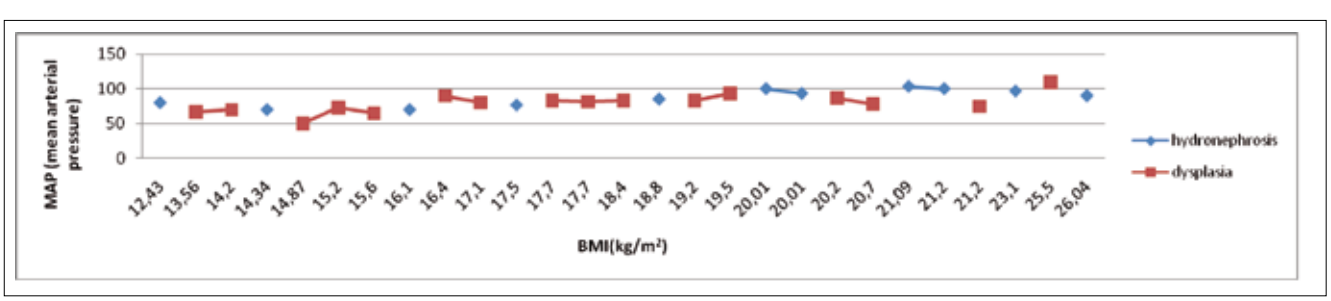

Fig. 4. The relationship between mean arterial pressure (MAP) and body mass index (BMI) in a group of patients with dysplasia and hydronephrosis. Spearman correlation for dysplasia R = 0.65 (p = 0.006) and for hydronephrosis R = 0.72 (p = 0.01).

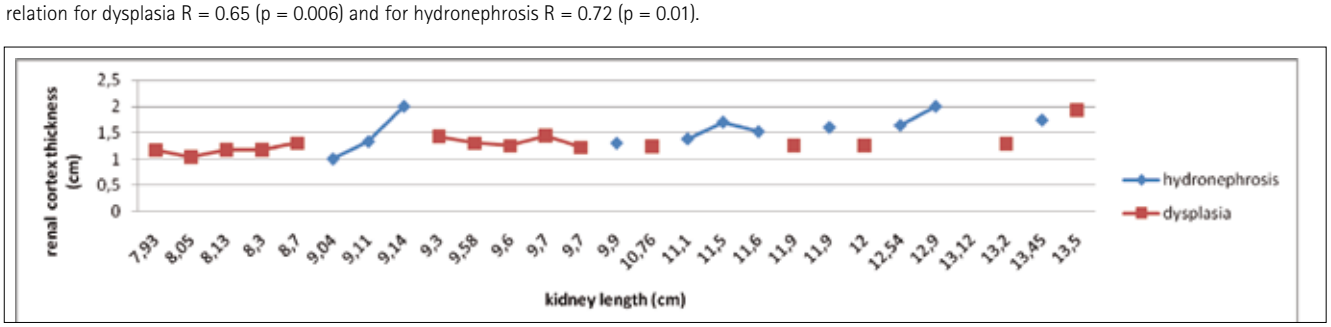

Fig. 5. The relationship between kidney length and renal cortex thickness. Spearman correlation for dysplasia R = 0.58 (p = 0.02) and for hydronephrosis R = 0.63 (p = 0.04).

induced by altered hemodynamics in glomeruli, increased load of dissolved substances undergoing filtration, increased reabsorbing function of proximal tubules, and increased activity of hypothetic renothropic, endocrine, and growth factors such as IGF-1, IGFBP-3, VEGF, and MMP-9 [10]. Particularly interesting is the fact that some of the above mentioned factors are supposed to participate in the processes of fibrosis and hyalinization of the solitary kidney [10].

The adaptive response in the remaining kidney depends on the age at which the operation was performed. In case of complete lack of excretory function of the removed kidney, the process of compensatory hypertrophy may begin as early as in the prenatal period and continues in the subsequent years of the child's life [11].

Most authors stress the fact that reduction in GFR, indicating impairment of the solitary kidney, may appear merely 15-25 years after nephrectomy. There are reports stating that nephrectomy in infancy leads to hyalinization of glomeruli as late as in adult life [12]. Canadian studies proved that after 23 years the average value of GFR in a group of patients with solitary kidney was equal to 74% of the average value of GFR in a control group of patients with both kidneys [1].

In recent years many authors have become interested in the function of the solitary kidney after donation for transplantation but their observations comprise only few patients and short time periods after nephrectomy [13, 14]. Reports concerning the function of the solitary kidney after surgical treatment of Wilms' tumors in children are much more common [15,16]. In these reports the importance of oncological vigilance and monitoring renal adverse effects of chemotherapy are emphasized.

It is not clear why, after unilateral nephrectomy, some patients develop proteinuria and renal insufficiency, while other patients do not experience such changes. Some authors suggest that the reason of this phenomenon is obesity or a low number of nephrons in the solitary kidney [17]. This concept seems very attractive. Taking into account pathophysiological data stating that the number of nephrons in one human kidney can range from 300,000 to more than 1,000,000, it seems likely that morphological functional changes can be of different intensity in individual patients and their consequences (at albuminuria and glomerulosclerosis) do not necessarily concern all patients to the same extent. What is crucial is the early identification of patients in whom functional impairment of the solitary kidney in the follow-up may be expected.

Albuminuria and the reduction of GFR are indicators of kidney damage. Albumin excretion is substantially statistically higher in adults with a solitary kidney and increases together with the extension of the follow-up [18]. This suggests that the glomerular capillary wall becomes more permeable to albumins during the process of compensatory hypertrophy, which begins already in childhood [18].

Studies performed on animals have shown that it is possible to prevent or alleviate adverse effects of glomerular hyperfiltration by the supply of a low protein, low phosphate diet or administration of lipid lowering drugs [19, 20]. However there are no appropriate reports on the effectiveness of such therapeutic maneuvers in men. Therefore direct transposition of results obtained in animals into human pathology may be inappropriate.

Most authors suggest that children after unilateral nephrectomy should be provided with special care throughout their lives as a chronic state of hyperfiltration may lead to progressive damage of the remaining nephrons [3, 4]. Others question the necessity of routine monitoring of GFR in patients after unilateral nephrectomy if they do not develop any additional risk factors [21]. The presence of developmental anomalies in the remaining kidney and infections of the urinary system obligates close surveillance and constant monitoring of its function.

As shown in this study in the majority of children of both examined groups the solitary kidney after removal of the multicystic dysplastic or congenital hydronephrotic one, was greater in size when compared with the upper normal value, regardless of the duration after surgical treatment. Additionally in some children biomarkers of kidney injury (increased albuminuria, urinary excretion of transferrin, IgG, α1-microglobulin, α2-macrogloblin, and β2-microglobulin respectively) were present. Finally, only in children with a multicystic dysplastic kidney, a positive correlation was found between albuminuria and duration after surgical removal of the pathologically altered kidney. From our results it follows that neither kind of pathology of the diseased kidney nor duration after surgical removal are reliable predictors of development of pathological alterations in the remaining solitary kidney. Our observations are of limited value as the time passed after nephrectomy was restricted up to 11 years, while kidney injury caused by hyperperfusion of the solitary kidney may be found not sooner than after 20-30 years, if at all, after nephrectomy of the diseased kidney. In addition until now it is not clear why biomarkers of renal injury appear only in a certain percentage of patients after unilateral nephrectomy. This fact proves the pathogenic complexity of compensatory hypertrophy of the solitary kidney after nephrectomy of the dysplastic or hydronephrotic one. Our results suggest that children after nephrectomy of a unilateral dysplastic or hydronephrotic kidney and a presumably „normal" solitary kidney are at increased risk for development of renal hyperperfusion injury. Therefore these patients need prolonged and careful follow-up in order to detect and treat injury to the solitary kidney as early as possible.

CONCLUSIONS

1. In the majority of children after nephrectomy of a unilaterally multicystic dysplastic or congenital hydronephrotic kidney, compensatory overgrowth of the solitary „normal" kidney was found.

2. In contrast to children with unilateral congenital hydronephrosis, in children with a multicystic dysplastic kidney the duration after nephrectomy of the diseased kidney seems to be a potential promoter of albuminuria.

3. As presence of renal injury biomarkers of the solitary kidney may be present in some children after 1-11 years following nephrectomy, prolonged and careful follow-up of these children is mandatory.

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