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Evaluation of Renal Function in Pediatric Patients After Treatment for Wilms' Tumor

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. Wilms' tumor is the most common kidney cancer in children. Treatment consists of pre- and post-operative chemotherapy, surgery and in some cases radiotherapy. The treatment of nephroblastomas is very effective. Hence, the population of adult patients cured of this cancer in their childhood is steadily growing, generating a need for long-term health assessment, including renal function, due to the specifications of the therapy and the location of the tumor.

Objectives. The aim of the study was to evaluate nephrological complications after treatment for nephroblastoma. **Material and Methods.** The study group consisted of 50 children treated in the Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation at Wrocław Medical University (Poland) from 2002 to 2012. An analysis of the patients' medical histories was carried out. The glomerular filtration rate estimated by the Schwartz formula (GFR by Schwartz), serum creatinine levels, urea and electrolyte concentrations; the results of urinalysis and blood pressure were assessed. Each of these analyses was performed at the time of diagnosis, at the end of therapy, as well as 6 months, one year and two years after its completion.

Results. The study showed that, in most cases, implemented therapy had no significant impact on the deterioration of renal parameters in the two-year period following treatment for Wilms' tumor. However, the group of patients treated with cyclophosphamide and carboplatin required more careful monitoring, due to a higher risk of renal function deterioration.

Conclusions. The study shows that the problem of nephrotoxicity after treatment for Wilms' tumor is more frequent than indicated in other studies; however, the deterioration of kidney function in most cases is not serious. Additional attention should be paid to patients treated with cyclophosphamide and carboplatin. Assessment of the early and late effects of the treatment is a key element in improving the quality of the patients' life (*Adv Clin Exp Med* 2015, 24, 3, 497–504).

Key words: Wilms' tumor, renal tubular dysfunction, renal glomerulus dysfunction, GFR by Schwartz.

Wilms' tumor (nephroblastoma) is a kidney cancer occurring most commonly in childhood, with an incidence of seven cases per 1 million children. Nephroblastoma constitutes about 6–14% of all childhood cancers, making it, after central nervous system tumors and neuroblastoma, the third most frequent solid tumor [1, 2]. The majority of Wilms tumors are diagnosed in the first decade of life. According to the 2001 International Society of Pediatric Oncology (SIOP) protocol, treatment usually consists of preoperative chemotherapy, aimed at reducing the tumor's mass, followed by surgery, postoperative chemotherapy and, in

certain cases, radiotherapy. The chemotherapeutic drugs administered, as well as the duration of the therapy, depend on the clinical stage. At each stage of the disease, vincristine and actinomycin are the basis of the treatment. At the higher stages of clinical progression – particularly in patients with unfavorable histopathology – doxorubicin, cyclophosphamide, etoposide and carboplatin are additionally administered. Due to combined therapy, remission is achieved in approximately 85% of patients [3]. The quality of life of convalescents remains an important issue, which mainly depends on adverse events and toxicity of prior treatment.

Objectives

The aim of the study was to evaluate nephrological complications after treatment for nephroblastoma in relation to the specifications of the therapy and the location of the tumor.

Material and Methods

The Study Group

The study group consisted of 50 children treated for Wilms' tumor in the Department of Bone Marrow Transplantation, Oncology and Hematology of Wrocław Medical University (Poland) in the years 2002–2012. The qualitative data on the patients are presented as frequencies and percentages, and the quantitative data as mean, median and standard deviations. The data were calculated using Microsoft Office Excel 10.0 (Microsoft, Redmond, WA, USA). The age of the patients at the time of the nephroblastoma diagnosis ranged from two months to 12 years (median 3.1 years). Boys accounted for 44% of the patients and girls for 56% of them. Clinical stage I was confirmed in 58% ($n = 29$) patients, stage II in 26% ($n = 13$), stage III in 8% ($n = 4$), and clinical stage IV in 4% ($n = 2$). Bilateral Wilms' tumor – the 5th clinical stage – was diagnosed in 4% ($n = 2$) children. The right kidney was affected in 38% of children ($n = 19$), the left in 58% ($n = 29$). A histologically high risk (HR) was found in 8 patients (16%), intermediate risk (INT) in 33 patients and low risk (LOW) in 9 (18%) patients. The treatment was performed according to the SIOP 2001 protocol, accepted by the Polish Pediatric Solid Tumors Group. Preoperative chemotherapy was recommended in 92% of the children. Total nephrectomy was performed in 82% of the patients ($n = 41$) and nephron sparing surgery (NSS, partial nephrectomy) in 18% ($n = 9$). Postoperative chemotherapy was implemented in all the patients. During the course of treatment the following cytostatic drugs were administered: vincristine ($n = 50$), actinomycin ($n = 48$), doxorubicin ($n = 18$), etoposide ($n = 5$), carboplatin ($n = 5$) and cyclophosphamide ($n = 5$). Local radiotherapy was implemented in 12% of the children ($n = 6$), while irradiation of the lungs was administered in 6% of the patients ($n = 3$). Relapse was diagnosed in four patients: one case of isolated relapse in the central nervous system (CNS) and three in the lungs. One patient with pulmonary relapse had progression within the CNS during treatment and therapy failed.

Methods

The parameters of renal function and blood pressure were assessed both at the beginning and

at the end of the treatment as well as 6 months, 1 year and 2 years after its completion.

In the assessment of renal function the following parameters were analyzed: glomerular filtration rate (GFR), serum creatinine level, serum urea level, urinalysis results with particular attention to the occurrence of hematuria or microalbuminuria, blood pressure and serum levels of sodium, potassium and phosphorus. GFR assessment was based on the child's height and concentrations of serum creatinine, and the eGFR ratio was calculated using the Schwartz formula: $eGFR = [K \times \text{height (cm)}] / \text{serum creatinine level (mg/dL)}$, the value of K being respectively: 0.45: infants with normal birth weight, 0.55: children aged 2–12 years, 0.55: girls over 12 years old and 0.7: boys over 12 years old [4]. GFR was analyzed according to the age of the child, and evaluated as correct when over 39 mL/min/1.73 m² of body surface area in children 1 to 6 months old, over 49 mL/min/1.73 m² in children 6–12 months old, over 62 mL/min/1.73 m² in children 12–23 months old and over 90 mL/min/1.73 m² in children over 2 years old [5].

The maximum serum creatinine level varied in different age groups, and was assessed as follows: 7 weeks to 3 years: 0.4 mg/dL, 4 to 7 years: 0.5 mg/dL, 8 to 10 years: 0.8 mg/dL, 10 to 13 years: 0.9 mg/dL [5]. As regards the concentration of urea in the blood serum, values above 40 mg/dL were considered to be raised, regardless of the age of the child [2].

The function of proximal tubules was evaluated based on the level of 3 electrolytes – sodium, potassium and phosphorus – in the blood serum. The accepted reference values for serum electrolyte levels were as follows: sodium 138–144 mEq/L, potassium 3.4–4.7 mEq/L and phosphorus 4.49–5.51 mEq/L.

In each case, blood pressure was assessed during a physical examination, according to centile charts for the weight and height of the children based the results of the OLAF Project setting standards for blood pressure of children and young people in Poland [6]. The results were presented in percentiles, and abnormally high blood pressure was defined as values exceeding the 95 percentile.

Results

Creatinine, GFR by Schwartz

Reduced GFR was observed in 10% of the children at the beginning of the therapy ($n = 5$), in 28% of the patients at the end of the treatment ($n = 14$), in 42% 6 months after completion of the treatment ($n = 21$), 38% a year after the end of the treatment ($n = 19$) and 24% two years after the end of the therapy ($n = 12$). Figure 1 presents the results of

GFR by Schwartz for all age groups at each of these points in time.

The health check-ups at the end of the therapy showed no decrease in GFR by Schwartz in patients under one year old. At this stage, abnormal GFR rates were reported in six children aged 12–23 months and in 17 patients > 2 years old. Post-treatment follow-ups 6 months after completing the treatment revealed a reduced GFR in two patients aged 12–23 months and in 17 patients aged > 2 years. One year after the therapy, reduced creatinine clearance according to Schwarz was observed in one patient aged 12–23 months and in 20 patients aged > 2 years. Two years after completing the therapy, GFR was reduced in 7 patients aged > 2 years.

Due to the risk of severe toxicity after the administration of carboplatin and cyclophosphamide, a comparison of complications in 2 groups was performed: patients treated with cyclophosphamide and carboplatin (n = 5) vs. the group not treated with cyclophosphamide and carboplatin (n = 45). No evidence of these drugs having

a detrimental effect on glomerular filtration function was observed. The results are shown in Fig. 2.

An analysis was carried out of GFR in relation to the type of surgery performed on the patient. There was no significant difference in the results obtained in the group treated with nephron sparing surgery (NSS, n = 9) vs. the group treated with total nephrectomy (n = 41). The results are shown in Fig. 3.

In the study group, raised levels of serum creatinine were observed in 60% of the patients (n = 30) at the beginning of the treatment, in 64% (n = 32) at the end of therapy, in 64% (n = 32) 6 months after the treatment ended, 48% (n = 24) one year after and 26% (n = 13) two years after the completion of the therapy. The results are shown in Table 1 and Fig. 4.

Serum Levels of Urea and Electrolytes

No increase was observed in the serum level of urea either at the beginning nor at the end of the treatment. However, a rise did occur 6 months

Fig. 3. Comparison of mean GFR results in patients undergoing total nephrectomy (n = 41) and nephron sparing surgery (NSS) (n = 9) at each stage of monitoring

Table 1. Evaluation of mean, median and standard deviation of serum creatinine level in all patients at each stage of monitoring

	Mean	Median	Standard deviation
Beginning of treatment	0.53	0.54	0.15
End of the therapy	0.55	0.56	0.15
0.5 years after therapy	0.59	0.61	0.12
1 year after therapy	0.58	0.60	0.16
2 years after therapy	0.58	0.61	0.13

and 1 year after completing the therapy in 4% (n = 2) of the patients. There were no significant disturbances in electrolyte levels (sodium, potassium and phosphorus) at any time during the examinations. The data are presented in Table 2.

Urinalysis

At the beginning of the treatment hematuria was observed in 28% of the patients (n = 14), while 18% of the children (n = 9) had microalbuminuria.

After the completion of the therapy, hematuria was detected in 4% of the patients (n = 2) and microalbuminuria in 2% (n = 1). Six months after finishing the therapy, hematuria was found in 0% and microalbuminuria in 0% of the patients; after 1 year, hematuria was found in 4% (n = 2) and microalbuminuria in 4% (n = 2); after 2 years the frequency of the 2 conditions remained 4% (n = 2) and 4% (n = 2).

Blood Pressure

Blood pressure above the 95th percentile was observed in 15 patients at the moment of diagnosis, in eight patients at the end of the treatment, in 4 patients 6 months after completing the therapy, in 5 patients one year after completing the treatment, and in 4 patients 2 years after completing the therapy. The data are presented in Fig. 5.

Discussion

Therapeutic protocols for the treatment of Wilms' tumor include a variety of cytostatic drugs, such as vincristine, actinomycin, doxorubicin and

Fig. 4. Level of creatinine in all patients at each stage of monitoring

Table 2. Electrolyte levels in all patients at each stage of monitoring

Sodium	Decreased ↓	Normal ↔	Increased ↑
Beginning of treatment	39% of patients	61% of patients	0% of patients
End of the therapy	17% of patients	83% of patients	0% of patients
0.5 years after therapy	21% of patients	79% of patients	0% of patients
1 year after therapy	6% of patients	92% of patients	2% of patients
2 years after therapy	0% of patients	100% of patients	0% of patients
Potassium	↓	↔	↑
Beginning of treatment	4% of patients	84% of patients	12% of patients
End of the therapy	2% of patients	94% of patients	4% of patients
0.5 years after therapy	0% of patients	81% of patients	19% of patients
1 year after therapy	0% of patients	75% of patients	25% of patients
2 years after therapy	3% of patients	85% of patients	12% of patients
Phosphorus	↓	↔	↑
Beginning of treatment	46% of patients	42% of patients	12% of patients
End of the therapy	27% of patients	41% of patients	32% of patients
0.5 years after therapy	57% of patients	29% of patients	14% of patients
1 year after therapy	18% of patients	55% of patients	27% of patients
2 years after therapy	22% of patients	56% of patients	22% of patients

in certain cases etoposide, carboplatin and cyclophosphamide. Each of these drugs can cause serious complications during treatment or after its completion. What is more, the toxicity of radiotherapy used on the tumor bed, the entire abdominal cavity or in some cases the pulmonary fields cannot be ignored.

Therefore, assessment of the early and long-term effects of the treatment is a key element in improving the quality of life of the patients. In accordance with the SIOP 2001 protocol, monitoring patients after treatment is performed every

3 months through the first 2 years, and every 6 months after that. During the follow-up visits, the children underwent health examinations, which included blood pressure measurement and assessment of kidney function efficiency. To evaluate renal function, widely-used and well-known tests are used, such as the serum level of creatinine, urea, GFR and urinalysis. To assess the risk of Fanconi syndrome it is necessary to check for electrolyte disturbances. It is also necessary to check the height and weight of the child at least once a year.

Fig. 5. Hypertension in patients treated for Wilms' tumor at each stage of monitoring

According to the current therapeutic protocol, the most commonly performed operating procedure is total nephrectomy. In certain circumstances it is possible to perform partial nephrectomy (nephron sparing surgery, NSS) [7, 8]. Indications for this type of procedure are mainly tumors at low clinical stages, lesions localized peripherally (not in the middle), and small lesions in bilateral Wilms' tumor cases. The majority of patients still undergo a total nephrectomy – surgery removing the entire kidney along with the tumor, since they do not meet the criteria for NSS outlined above. Therefore, special attention and regular monitoring of the remaining kidney is vital. In the present study monitoring was performed at several intervals to obtain the most accurate evaluation of the risk of nephrotoxicity.

One of the most easily available and commonly performed tests of renal function is the GFR. In this study, a reduced GFR by Schwartz was observed in many cases. However, there was no significant difference in the GFR results between patients treated with the potentially nephrotoxic drugs, such as cyclophosphamide or carboplatin, and the patients who didn't require the use of these cytostatics. The satisfactory results in the cases of treatment with alkylating drugs should be interpreted cautiously, due to the small study group undergoing this treatment.

No significant differences were found in GFR depending on the type of surgery (total nephrectomy vs. NSS treatment). It should be emphasized that patients who underwent nephron sparing surgery were selected very carefully. They were children with tumors in low clinical stages, with favorable histologies, without distant metastases and with smaller tumors, which also meant that they received less toxic post-operative cytostatic treatment. Only one child who underwent nephron sparing surgery required intensified treatment with cyclophosphamide and carboplatin after receiving the histopathological examination results. None of the children who underwent NSS were treated with local radiotherapy.

Renal toxicity risk assessment after treatment for Wilms' tumor has also been carried out by other authors [9, 10]. Data reported in the literature indicate the need for special supervision of the remaining single kidney function. Bailey et al. [10] described a reduced GFR measured by ^{51}Cr -EDTA clearance in 22% of 40 patients tested. GFR evaluation was performed at different times after the end of the treatment (from 21 days to 27 years, mean: 10.7 years). There was no statistically significant reduction of GFR in patients who received local radiotherapy. Undoubtedly, one of the greatest advantages of the Bailey et al. study was the very long

follow-up period, which made it possible to detect long-term complications.

De Graaf et al. showed reduced GFR in 17% children ($n = 41$) after treatment for Wilms' tumor. The average monitoring period after the completion of therapy was 13 months [11]. GFR was determined by clearance of ^{125}I -iothalamate (excretion rate) and ^{131}I -hippurate. All the patients underwent total nephrectomy. Two groups of patients were compared; the first received chemotherapy alone ($n = 29$), the second also required local radiotherapy ($n = 12$). A statistically significant reduction in GFR was observed in patients undergoing chemotherapy combined with radiotherapy.

Di Tulio et al. [12] described reduced GFR, assessed by creatinine clearance, in only 1 of the 34 patients enrolled in the study (from 2.7 to 15.8 years, mean 8.6 years). Levitt et al. [13] observed a decreased GFR in 19% of the 53 patients in the study. GFR was measured using the clearance of ^{51}Cr -EDTA. The average follow-up time and the assessment of individual measurements was 13 years. A statistically higher risk of renal complications (reduced GFR, insufficient kidney growth) in children < 24 months at the diagnosis and in patients after local radiotherapy was proven.

The current study has shown that the problem of nephrotoxicity, manifested by decreased GFR, is more frequent than previously believed. This may be related to the more aggressive methods of treatment currently being used. However, it is possible that more and more cases of nephrotoxicity are being registered due to improved and more frequent monitoring of the patients. According to the present study, patients who underwent local radiotherapy and combined cyclophosphamide and carboplatin treatment are at higher risk of kidney complications. In this group, a reduction of creatinine clearance after therapy for Wilms' tumor was more frequently observed.

Urinalysis is a valuable and easily accessible test providing worthwhile information about kidney function. At the different stages of monitoring in the present study, there were no significant abnormalities manifesting as proteinuria or the presence of blood in urine. Only trace microalbuminuria or single red blood cells in the sample were found.

In the study by Bailey et al. [10], microalbuminuria was found in 5% of the patients ($n = 2$), and in a study by Levitt et al. [13] it was noted in 9% of the patients; in neither study did the patients show any other symptoms of renal dysfunction at the same time. In a study carried out by Di Tulio microalbuminuria was noticed in more patients: 35% of all those tested [12]. These values are higher than those obtained in the present study.

At the time of diagnosis, nephroblastoma patients quite often present hypertension. Most commonly this is a type of renal-vascular hypertension caused by compression of the renal artery by a large tumor mass. The effects of treatment for Wilms' tumor on blood pressure have also been analyzed by other authors [10, 12, 14]. In the 2002 study conducted by Bailey et al., [10] increased blood pressure was shown in 2% of the 40 patients during follow-up examinations after treatment for nephroblastoma. Despite hypertrophy of the remaining kidney noted in 90% of the patients ($n = 36$), in most of the patients' blood pressure remained normal. The average follow-up period was 10.7 years. It is possible that extension of the follow-up time in the present study would show similar results. The current results show a clear trend towards the normalization of blood pressure as time passes after the end of therapy. There are no other more recent studies assessing the risk of hypertension in children treated according to the SIOP 2001 protocol.

In a 1993 study conducted by Di Tulio et al., no cases of hypertension were noted in a group of 34 patients [12]. Finkelstein et al. observed high blood pressure in 7% of patients in a group of 2243 children, of whom 1528 patients had at least one blood pressure measurement performed [14]. That study was conducted 5 years after the completion of therapy. The authors pointed out the necessity of careful monitoring of young patients after treatment for Wilms' tumor. Undoubtedly, the great advantage of that study was the long period of observation and the large study group.

Janda et al. reported hypertension in 20% of the patients when assessing blood pressure in a group of 20 children [15]. Levitt et al. showed abnormally high blood pressure results in 11% of a group of 53 children evaluated from 7.8 to 19 years after completing treatment for nephroblastoma [13]. The children were at average age of 12.9 ± 3.0 years at the time of treatment; 4 children had hypertension above the 95th percentile, and 2 of them received antihypertensive medication.

Most authors agree that hypertension occurs relatively rarely as a complication of treatment of Wilms' tumor. The results of the present study confirm observation.

To summarize, the current study found no clear advantage to nephron sparing surgery over total nephrectomy in reducing the risk of renal complications, but due to the small number of cases, further observation should be undertaken [7, 8]. Special attention should be paid to patients treated with cyclophosphamide and carboplatin [16]. In these cases, it is necessary to monitor the late complications of treatment carefully. Although, this study and the majority of the cited literature show that treatment for Wilms' tumor has no significant effect on kidney function, there is a consensus that regular monitoring is needed. It should also be noted that during the 2-year follow-up period in this study some complications may not yet have been revealed. Good results do not eliminate the need for conducting periodic check-ups, or for a healthy lifestyle after recovering from cancer.

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Conflict of interest: None declared

Received: 25.10.2013

Revised: 6.01.2014

Accepted: 8.05.2015