

Post-operative hypertension in children undergoing surgical treatment for Wilms tumor

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ABSTRACT

Introduction: Wilms tumor (WT) is the most common form of childhood kidney cancer. Hypertension (HT) is noted in children with WT either at the time of initial presentation or in the post-operative follow-up period. Increased renin secretion could be the probable reason in most of the cases. **Objective:** The objective of this study was to assess the severity of HT and response to the treatment. **Materials and Methods:** We retrospectively reviewed all the children who had been treated for WT and presented with HT in the follow-up period. All the children below the age of 18 years with histologically confirmed WT, diagnosed between January 2000 and December 2018 at our hospital, were included in the study. Only patients with a documented diagnosis of HT that required treatment with antihypertensive therapy were included in the hypertensive group. **Results:** A total of 3 patients (8.57%) developed age-related HT in the follow-up period, needing medications. Amlodipine (calcium channel blocker) was a drug used in all children to control HT. **Conclusion:** HT is known to occur in children treated for WT at the time of initial diagnosis or during follow-up. Children can be properly managed with the use of medications.

Key words: Hypertension, Nephron-sparing surgery, Wilms tumor

Wilms tumor (WT) is the most common form of childhood kidney cancer. It accounts for 6% of all pediatric cancers and represents more than 95% of the kidney tumors in children and is commonly seen in children younger than 5 years [1,2]. Considerable progress has been made in the treatment of WT over the past few decades. At present, the 5-year overall survival (OS) exceeds 90% [3,4].

Hypertension (HT) is commonly noted in children presenting with WT. It could be due to increased renin secretion in response to renal ischemia produced by the pressure of the tumor on the hilar or intrarenal vessel. Moreover, the tumor itself could directly be responsible for HT by producing renin itself. In addition, as the Brenner–Barker hypothesis noted, there is a significant reduction of nephrons with the development of renal HT and progressive renal failure [5,6]. Approximately 20–55% of children with WT reportedly present with HT at diagnosis [7-9].

Cozzi *et al.* [10] reported that there is an inverse relationship between the number of nephrons and blood pressure (BP), irrespective of whether nephron number is reduced congenitally or in postnatal life [11]. Vahid-Hosseini *et al.* found that patients who had undergone bilateral partial nephrectomy (PN) demonstrated less HT than those who underwent unilateral partial

plus contralateral total nephrectomy [12]. Hubertus *et al.* reported that 66.7% of their patients had HT after unilateral partial plus contralateral total nephrectomy and 20% after bilateral PN [13]. We retrospectively reviewed our series of children who had been treated for WT and presented later with HT.

MATERIALS AND METHODS

We retrospectively included all children below the age of 18 years with histologically confirmed WT, diagnosed between January 2000 and December 2018 at our hospital. This was a single-center study with clearance obtained from the Institutional Ethical Committee. All the patients signed informed consent before the commencement of the study. Data on demographics, BP at diagnosis, histopathology, stage (I, II, III, IV, or V), chemotherapy, radiotherapy, complications, and treatment outcomes were collected. Only patients with a documented diagnosis of HT that required treatment with antihypertensive therapy were included in the hypertensive group.

Patients with incomplete data were excluded from the study. HT was diagnosed based on the published standard definition of systolic and/or diastolic BP $\geq 95^{\text{th}}$ percentile for age, gender, and height [14]. Documented BP was used to classify children

into normotensive and hypertensive groups. Descriptive statistics were used to summarize patient demographics and clinical information.

RESULTS

During the study, a total of 35 children underwent surgery for WT. Thirteen of these children underwent unilateral radical nephrectomy, 15 underwent unilateral nephron-sparing surgery, one child with bilateral WT underwent bilateral nephron-sparing surgery, and the remaining six underwent simple/cytoreductive nephrectomy/palliative nephrectomy. The mean age of the children was 39.6 months (range – 12–72 months). There were 21 males and 14 females. None of the children had high BP at presentation.

Twenty-eight children with unilateral operable WT (Stages I and II) who underwent either unilateral radical nephrectomy or nephron-sparing surgery had a mean follow-up of 53.68±23.82 months. Children (n=13) undergoing unilateral ablative/radical nephrectomy had significantly higher mean systolic and diastolic BP at the end of 12 months after surgery when compared to children (n=15) undergoing unilateral nephron-sparing surgery (Table 1). However, only two children undergoing unilateral radical nephrectomy had age-related HT needing treatment with medications.

One child (2.85%) with bilateral WT, who had undergone bilateral nephron-sparing surgery with a follow-up period of 12 months, presented with HT 7 months after surgery. He presented with vomiting, confusion, and weakness. He needed admission, complete bed rest, and medications. Out of the remaining 6 children (17.14%) who underwent simple/cytoreductive nephrectomy/palliative nephrectomy were on chemoradiation therapy, three died due to disease at a mean follow-up of 49 months. The remaining two were alive at a mean follow-up of 38 months with neither of them having HT.

A total of 3 patients (8.57%) developed age-related HT needing medications. Amlodipine (calcium channel blocker) was the drug used in all children to control HT. An initial dose of 2.5 mg once a day was used and if required, it was increased to 2.5 mg twice daily. All the children were taking the drug and control of HT was found to be adequate.

DISCUSSION

HT is known to be associated with several childhood cancers at diagnoses, such as WT, neuroblastoma, brain tumors, and pheochromocytoma [7]. The etiology of HT in the children with cancer could be multifactorial. It could be due to renin secretion by the tumor or secondary to mechanical mass effect causing renal vascular compression or thrombosis. Hormonal secretion of glucocorticoids or catecholamines, cancer-related pain, treatment with steroid chemotherapy, and increased intracranial pressure could be other causes of HT [7-9].

In children with WT, HT results from increased renin production secondary to intrarenal vascular compression.

Table 1: Pre- and post-operative parameters of the study population

Number	Parameters	NSS (n=13)	SN/RN (n=15)	p-value
1	Pre-operative serum creatinine (mg %)	0.48±0.16	0.42±0.11	0.0001
	Post-operative serum creatinine (mg %)	0.56±0.08	0.88±0.06	
2	Pre-operative systolic BP (mmHg)	102.6±9.57	104.0±6.47	0.0012
	Post-operative systolic BP (mmHg)	109.4±5.57	110.6±7.63	
3	Pre-operative diastolic BP (mmHg)	65.3±6.18	64.3±6.04	0.0114
	Post-operative diastolic BP (mmHg)	74.5±5.19	82.1±8.78	

p<0.01 statistical significance. BP: Blood pressure

Alternatively, renin may also be produced by tumor cells [15]. Increased plasma renin concentration has been reported in approximately 80% of hypertensive WT children at diagnosis, and relapse was observed in three out of four patients with increased plasma prorenin/renin concentrations [8,16]. Renin production is controlled by the renin-angiotensin system, which plays a decisive role in maintaining BP homeostasis.

Vahid-Hosseini *et al.* [12] concluded that the decreased number of nephrons following surgery for WT is associated with a high risk of HT and also end-stage renal disease. They analyzed four children (eight kidneys) with bilateral WT and eight unilateral undergoing complete resections. The size of the kidney was measured using volumetric analysis computed tomography scan imaging. Total kidney volume was significantly larger after bilateral PN (98.1 cm³) versus unilateral partial plus total contralateral nephrectomy (60.9 cm³). The authors concluded that children with bilateral WT benefited from bilateral nephron-sparing surgery. HT was less common after bilateral PN.

At present, the International Society of Paediatric Oncology risk stratification is based on stage, histology, tumor volume, and the response of the tumor to pre-operative chemotherapy [17]. Although HT is reported in up to 55% of children with WT at diagnosis, its prognostic significance on survival outcome has never been studied [7-9]. Jastaniah *et al.* [18] retrospectively analyzed 85 children with WT diagnosed between January 2000 and August 2013 to determine the prognostic effect of HT at diagnosis on outcomes. The remission rates were 56% in the hypertensive group as compared to 82% in the normotensive group. The 5-year OS in the hypertensive group was 67% as compared to 89% in the normotensive group. The authors concluded that HT at diagnosis was a predictor of poor outcome.

Anesthetic management can be challenging in children with HT, diagnosed in the pre-operative period. HT could be severe enough to cause encephalopathy and cardiovascular compromise. Secondary hyperaldosteronism and hypokalemia could manifest itself as chronic HT [19]. Significant intraoperative bleeding could result from improperly controlled HT. Pre-operative recognition of HT and appropriate pre- and perioperative treatment is

mandatory for safe surgical treatment. Angiotensin-converting enzyme inhibitors are the drugs of choice. One could add a short-acting beta-antagonist to control HT in severe cases [19]. All the children with HT in our series were adequately managed with medications in the follow-up period.

CONCLUSION

HT is known to occur in children treated for WT at the time of initial diagnosis or during follow-up. Children can be properly managed with the use of medications.

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