Research Article

Factors associated with diagnostic delay in children with Wilms' tumor

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Abstract

Background: In Wilms' tumor, the time elapsed between clinical diagnosis and the start of treatment is clearly associated with morbidity and mortality. As treatment delay can influence patient survival, identification of possible causes can mitigate the consequences arising from prolonged diagnostic uncertainty.

Objective: To ascertain whether an initial diagnosis of Wilms' tumor in the emergency department influences patient prognosis depending on the type of referral for definitive treatment.

Patients and methods: Retrospective chart review of 98 children receiving treatment for Wilms' tumor at the Brazilian National Cancer Institute (INCA) between April 2003 and December 2016. Patients were categorized into two groups: those referred directly from an emergency public department to INCA and those first transferred to another hospital before being referred to INCA.

Results: Of the 98 cases included in the study, 42.9% were direct referrals and 57.1% were indirect referrals. Presence of an abdominal mass was the most common presenting complaint, followed by abdominal pain. In cases with larger tumors, the mean tumor volume was greater than reported elsewhere in the literature, suggesting longer disease duration. Significantly higher tumor volumes were observed in patients with a palpable abdominal mass as compared to those with the second most frequent complaint (abdominal pain).

Conclusion: The findings of this study support the hypothesis that patients diagnosed with kidney masses in the emergency department are at greater risk of delayed diagnosis when they are referred first to a non-specialized outside hospital than when referred directly to a specialized cancer treatment unit.

Introduction

In childhood cancer, the time elapsed between clinical diagnosis and the start of treatment is clearly associated with morbidity and mortality [1,2]. As treatment delay can influence patient survival, identification of actionable causes for such delay can mitigate the consequences arising from prolonged diagnostic uncertainty [3].

One major cause of delay in definitive diagnosis of tumors is the time expended by patients on access to emergency services. This phenomenon, which has a major influence on the prognosis of neoplastic diseases [4], can be influenced by socioeconomic context and by disease-specific characteristics, and is particularly important in childhood cancers such as Wilms' tumor [5].

The peak incidence of Wilms' tumor occurs between 2 and 4 years of age, with 95% of children being diagnosed before age 10. This tumor accounts for 5 to 10% of all childhood cancers [6]. It usually presents as a well-defined, unilateral abdominal mass located on the flank, originating from the renal parenchyma [7].

Patients with Wilms' tumor often present first to the emergency department, and many cases go undiagnosed or misdiagnosed in this setting. Within this context, the objective of this study was to investigate whether the prognosis of

Wilms' tumor would be influenced by the type of referral from the emergency department to a definitive treatment facility.

Materials and methods

Retrospective, descriptive study carried out at the Brazilian National Cancer Institute (INCA), Rio de Janeiro, between April 2003 and December 2016. In a chart review design, the medical records of children admitted with a diagnosis of kidney tumor were selected for analysis.

Data on the patients' presenting complaints, socioeconomic status, and time elapsed between the first patient encounter and admission to INCA were collected and analyzed.

To characterize any possible diagnostic delay, patients were categorized into two groups: those referred directly (direct referrals, DR) and those referred indirectly (indirect referrals, IR) to INCA, according to the sequence of referral from the emergency public department (EPD) to a specialty oncology unit. Patients were categorized as DR when they were transferred directly from the EPD to a cancer center. Conversely, patients who were referred to another hospital before being referred or transferred to a cancer center were categorized as IR.

Signs and symptoms strongly suggestive of an abdominal tumor, such as a palpable abdominal mass, abdominal pain, hematuria, abdominal tenderness, and abdominal enlargement, were defined as major. Signs and symptoms nonspecific to neoplastic disease were classified as minor.

This study was approved as part of the cooperative protocol for the treatment of nephroblastoma – SIOP 2001 registered in the BRAZILIAN MINISTRY OF HEALTH - National Health Council - National Research Ethics Commission (CONEP) Registry No.: 9145, Filing No. 25000.101283/203-98.

Results

The study sample consisted of 98 children enrolled at INCA with a confirmed diagnosis of Wilms' tumor. The demographic profile of the patients is described in table 1.

Pediatricians were responsible for all EPD visits and referrals before admission to INCA.

Evaluation of referral flows showed that 42 cases (42.9%) were referred directly to INCA after imaging performed in the EPD was suspicious for a renal tumor. In the 56 remaining cases (57.1%), patients were evaluated at two or more outside facilities before being referred to INCA (Table 2).

The median time from onset of symptoms to onset of medical care was 3 weeks, ranging from 1 day to 8 weeks. In 66 patients (67.3% of cases), the time from symptom onset to first pediatric appointment was 30 days.

Regarding the presenting complaint (i.e., the chief complaint initially mentioned in the emergency department), 92 patients (93.9%) had major abdominal signs or symptoms. An abdominal mass was the presenting complaint in 53 cases

(54.1%); in 48 of these 53 (90.6%), the mass was identified by the patient's mother. Other major signs and symptoms included abdominal pain, hematuria, and abdominal enlargement. Nonspecific complaints, such as pallor and weight loss, were also reported (Table 3).

Table 3 also describes the most relevant clinical findings stratified by type of referral (direct or indirect).

Presence of an abdominal mass was the main driver of direct referral from the EPD to INCA, perhaps due to the large tumor volume in these patients (median 571 cm^3, range 65 to 2,502 cm^3). Patients in the indirect referral group had a median tumor volume of 545.5 cm^3.

Computed tomography was the diagnostic imaging method of choice in 48 cases (49%), followed by whole-abdomen ultrasound in 17 cases (17.3%). No reports of diagnostic imaging were found in the medical records of 33 cases (33.7%).

Renal tumor location features after referral to INCA are described in table 4.

Table 1: Major demographic characteristics of children with Wilms' tumor and their mothers.

Child age (years)	Mean: 3.5±2.8 Median: 3 Range: 4 months to 15 years		
		N	%
Sex	Male	54	55.1
	Female	44	44.9
Skin color	White	59	60.2
	Brown	28	28.6
	Black	11	11.2
Municipality of origin	Other municipalities	58	59.2
	Rio de Janeiro proper	37	37.2
	Other states	2	2.4
	Overseas (Angola)	1	1.2
Maternal educational level	Not reported	31	31.6
	Primary	48	49.0
	Secondary	14	14.3
	Higher	5	5.1

Table 2: Number of pediatric visits at outside facilities before patient registration at INCA.

No. Visits	N	%
One (DR)	42	42.9
Two or more (IR)	56	57.1
Total	98	100.0

Table 3: Presenting complaints among 98 children with Wilms' tumor, stratified by direct (DR) or indirect (IR) referral to INCA.

Presenting complaint	Overall (n, %)	DR (n, %)	IR (n, %)
Abdominal mass	53 (54.1)	34 (64.1)	19 (35.9)
Abdominal pain	20 (20.4)	4 (20)	16 (80)
Hematuria	11 (11.2)	1 (9.1)	10 (90.9)
Abdominal enlargement	8 (8.2)	3 (37.5)	5 (62.5)
Other complaints	6 (6.1)	0 (0)	6 (100)
Total	98 (100)	42	56

Table 4: Renal tumor location features in children referred to INCA

	n	DR (n, %)	IR (n, %)	p*
Localized disease	79	51 (64.6)	28 (35.4)	0.01
Local metastases	4	1 (25.0)	3 (75.0)	0.44
Remote metastases	15	3 (20)	12 (80.0)	0.05
Total	98 (100%)	56 (57.2)	42 (42.9)	

Discussion

Among the 98 cases of Wilms' tumor reviewed in this study, 72 (73.5%) presented between the ages of 1 and 4, which is consistent with the age range reported in the literature [6]. The association between the child's age and delayed diagnosis is also well described in studies of this neoplasm [5,7], especially when the tumor size is small. The diagnostic delay in younger patients was less than in older children, perhaps because younger children tend to be seen more frequently by their pediatrician than older children. In addition, parents are more concerned about the health status of younger children. The detection of symptomatic disease in older children is highly reliant on self-reporting, while younger children are more closely watched by their parents. Other issues also appear to be related to the delay in diagnosis, such as lower family educational attainment [8] and older parents [9], although the present study was not designed or powered to investigate either factor. One possible explanation is that younger parents tend to seek medical attention faster than older parents do.

In childhood cancer, the time elapsed between clinical diagnosis and the start of treatment is strongly associated with the subsequent course of the disease, particularly regarding family behavior, e.g., both its reaction and adaptation to the diagnosis of cancer in a child and to its consequent morbidity and mortality [10].

When a clinician is faced with the unexpected finding of an abdominal mass in a child presenting to the emergency department, reliable data on onset and clinical course are often unknown. This can lead to breakdowns in the diagnostic process and to a delay in definitive diagnosis, which is further influenced by several factors, including difficulty - both by the child's parents and by the attending physician - in realizing the true severity of the signs and symptoms presented by the patient. In a systematic review on delayed diagnosis of pediatric cancers, Brasme, et al. [11] found that the presence of the abdominal mass was a major red flag, and that greater tumor volume is indicative of greater disease burden, which may be related to a longer duration of illness and more advanced disease progression. This highlights the importance of accurate perception of the severity of signs and symptoms when patients first present to the emergency department. In 1992, Delahunt, et al. [12] noted that prolonged delay in the diagnosis of renal tumors significantly reduced the likelihood of survival, on both univariate and multivariate analysis. Nevertheless, a more in-depth assessment of the relationship between delayed diagnosis and adverse prognosis is needed, particularly when an abdominal mass is not the presenting complaint, as several factors —family-related, care-related, socioeconomic, or even tumor biology itself—can influence treatment outcomes.

In the present study, the criteria of interest related to clinical presentation and disease characteristics were presenting complaint, tumor volume, and initial staging. Presence of an abdominal mass (which relates directly to an increase in tumor volume) was the most common presenting complaint, followed by abdominal pain. In cases with larger tumors, the mean tumor volume was greater than reported elsewhere in the literature [13], suggesting longer disease duration.

The presence of an abdominal mass is an important predictor of malignant neoplasm and influences the time to diagnosis; as it is a major red flag, patients with this sign are likely to be referred sooner for specialized care [14]. Among the cases diagnosed with a presenting complaint of abdominal mass, only 34 were referred directly to a specialized cancer center; 19 were inadequately referred to other facilities before arriving at INCA. This certainly contributed to a longer duration of illness, which, in the specific case of Wilms' tumor, may lead to initiation of care only when remote metastases are already present, requiring intensification of therapy. The findings of this study support the hypothesis that patients diagnosed with kidney masses in the emergency department are at greater risk of delayed diagnosis when they are referred first to a non-specialized outside hospital than when referred directly to a specialized cancer treatment unit.

Histological characteristics and tumor staging are the two most significant prognostic factors for patients with renal neoplasms, as they are associated with an increased risk of recurrence [15]. Staging reflects the extent of the disease in its initial presentation, which, in turn, reflects the chronology of disease progression. The relationship between time to diagnosis and subsequent prognosis is complex and multifactorial; as noted above, aspects related to tumor biology, medical care, and family environment can all act as determinants of diagnostic delay [16].

The diagnosis of cancer in a child can be particularly challenging, given the rarity of the disease and the nonspecific nature of many initial signs and symptoms, which often overlap with those of more common childhood illnesses. Studies show that special attention should be given to the role of parents in reporting that "something is not right" with their child [10]. In the event of unexplained abnormal findings, specialist evaluation is always warranted. However, it is important to note that physicians who refer a child to many different specialists or who call a child back for repeated check-ups actually cause a greater delay in reaching the correct diagnosis [17].

We conclude that, even when care in the emergency department is provided by a pediatric specialist, the presence of nonspecific, less-common signs and symptoms in Wilms' tumor can cause diagnostic confusion, especially in the absence of abdominal enlargement caused by the tumor. This can be an important factor in preventing timely recognition of malignant disease and delaying referral to a specialist cancer

center, which, in turn, can have an adverse impact on the prognosis of children with Wilms' tumor.

Acknowleadgment

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