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# A Clinicopathological study of Wilms' tumor among Sudanese patients

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***Abstract***

***Background: Wilms' tumour is the commonest renal tumour in children, with unique pathogenesis and histology. Objectives: To determine the different tumour patterns and components, geographical distribution of the patient's tribes, and the relation of histopathology of the tumour to its clinical presentation and stage. Materials and Methods: We collected the data of 51 Wilms' tumor patients from January 2006 to December 2010 inclusive from Soba University Hospital, Radio Isotopes Centre Khartoum (RICK) and the National Health Laboratory (NHL) in Khartoum, Sudan. The data was collected from patient's files using a predesigned questionnaire. Formalin-fixed, paraffin-embedded blocks of processed histopathology specimens were***

***recut, stained and reviewed. SPSS and Microsoft Office Suite 2010 were used in data analysis. Results: The patients' ages ranged from 0.5 to 10 years with the mean age 3.4 years (SD = 2.1). The male-to-female ratio was 1.6:1.0. Forty two percent of patients were from Western Sudan (n=21). Abdominal mass was the presenting symptom in 50 patients. Duration of symptoms ranged from 3 days to 2 years. Eleven patients (21.6%) presented with metastasis, showing a statistically significant relationship with capsular invasion (P<0.03). Stage III, II, IV and I were diagnosed in 22, 17, 11 and 1 patient, respectively. Triphasic tumours were found in 82.2% of patients, with 61.9% showing mixed elements. Mesenchymal predominance was found in smaller tumours and blastemal predominance in larger tumours (P<0.44). The presence of muscle tissue in the stroma was found to correlate with less advanced stages of the disease (P<0.01). Anaplasia was related to age group 2-6 years (P<0.03), locally infiltrative tumour (P<0.05), and capsular invasion (P<0.02). We found that our results were comparable to other studies conducted in the same region and there is a significant relationship between the histology of the tumour, its size and clinical symptoms.***

***Key words:***

***Wilms' Tumor, Nephroblastoma, Anaplasia, Triphasic, Blastema***

**Introduction:**

Wilms' tumour or "nephroblastoma" is one of the most common solid extracranial malignancy in children (1 in 10,000 children, age 0-15 years) and is the commonest paediatric renal tumour [1]. It is a heterologous tumour with unique pathogenesis and histology as it can be tri, bi or mono phasic with different composition of its constituting elements. It is primarily seen in infants with 50% of cases occurring before the age of 3 years, 90% before the age of 6 years, rarely in adults and can be congenital. Some studies show a slight female predominance. The incidence is highest among Africans followed by European and Asian populations. [1]

The incidence rates of Wilms tumor worldwide are not uniform and there is great variation in the incidence between developed and the developing countries (Table 1). Children residing in sub-saharan Africa experience high incidence and a dismal outcome. Tumors in this region harbor wild type mutations and show biologically more aggressive disease [2]. Clues to the origin of Wilms tumor are more likely to come from genetic as opposed to environmental epidemiology. [3,4]

**Table1: Country wise incidence of wilms tumor ( ASR/million) [5]**

| **High Income** | | **Upper middle income** | | **Lower middle income** | | **Low income** | |
|---|---|---|---|---|---|---|---|
| Country | Incidence | Country | Incidence | Country | Incidence | Country | Incidence |
| USA | 9.1 | Libya | 3.3 | Egypt | 6 | Kenya | 9.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Germany | 9.7 | South Africa | 6.1 | Iran | 3.5 | Mali | 21.2 |
| Japan | 3.5 | Turkey | 5.4 | Algeria | 7.9 | India | 4.4 |
| Malta | 13.9 | Botswana | 4.3 | Tunisia | 7.6 | Uganda | 10.5 |

As the pathogenesis of Wilms' tumor relies mainly on genetics, its' clear ethnic variation is understandable. Literature studying different ethnic groups stated that U.S. blacks and Africans from Ibadan Nigeria had the highest incidence.[6] Before the segregation of the Sudan, when the data for this study was collected, ethnic diversity was at its maximum. Sudan was and still is an ethnic melting pot with variation of races greater than most countries.

Like most cancers, Wilms tumor is characterized by alterations in genes that regulate cell growth, differentiation, and proliferative potential; however, its genetics are more complex than the original Knudson & Strong's two hit theory.[7,8] Its biology illustrates several important aspects of childhood neoplasms: the relationship between malformations and neoplasia, the histologic similarities between organogenesis and oncogenesis, and the role of premalignant lesions.[9] It was found to occur in three settings: sporadically, in association with genetic syndromes, or familial. The sporadic cases form the majority ofpatients, [10 ]10% only are associated with specific medical syndromes, and familia1 disease is rare. [9]

Several gene mutations are associated with the pathogenesis of Wilms' tumor. The most important is WT1 which is located at chromosome 11p13. Mutations in only 1 allele is enough to promote changes that may lead to the formation of nephroblastoma. [10] Other genes implicated are WT2 (11p15), β-catenin signaling pathway, FWT1 and FWT2 and others[7] Associated syndromes are WAGR, Denys- Drash Syndrome and Beckwith-Weidemann syndrome. The association of Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation has led to the acronym WAGR syndrome.[11,12] Denys-Drash syndrome (DDS), which is a combination of intersex disorder and renal nephropathy, is an extremely rare association of Wilms' tumor.[13] The Beckwith-Weidemann syndrome (BWS) is characterized by umbilical hernia, macroglossia, neonatal hypoglycemia, gigantism, and increased risk for development of certain childhood cancers.[14]

Wilms tumor is one of the success stories of pediatric oncology with long term survival approaching 90% in localized disease and over 70% for metastatic disease. [15,16] There are different treatment schedules adopted by two large cooperative study groups, the National Wilms' Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP). Their recommendations differ on the timing of surgery with regards to preoperative chemotherapy. The protocols are a forthright, surgery-based system developed by NWTSG and a delayed surgery-based system developed by the

SIOP.[15] Never the less, radical nephrectomy is the standard of care for these patients with resectable tumors.[17] Prognosis depends mainly on the tumor stage at diagnosis, patient age and histological features (favorable vs. unfavorable depending on presence of diffuse anaplasia).[18] Anaplasia, which is threefold nuclear enlargement, hyperchromasia, and atypical mitotic figures, is the most valued histological prognostic parameter in all the literature.[19]

Cancer in children is an important cause of pediatric morbidity and mortality in Sudan. [20] Limited studies about nephroblastoma in Sudan are available. This study was conducted to investigate the clinical presentation of Wilms' tumor among Sudanese children, its' different geographical distribution, histopathological patterns and their relation to clinical presentation. It was done in the hope of understanding the disease for better management and outcome of the patients. It also reviews the findings of similar work in the region and around the world.

## Materials and Methods

This is a descriptive case series based study, carried out in Soba Teaching Hospital, the National Health Laboratory (NHL) and the Pediatric Oncology Department at the Radio Isotope Center Khartoum (RICK).The study sample is comprised of pediatric patients diagnosed with Wilms' tumor in the study area during the period from January, 2006 to December, 2010 inclusive (n=51). Only pediatric cases diagnosed as Wilms' tumor with complete histopathology material are included in this study. Patients with incomplete histopathology material and those older than 16 years old were excluded from this study.

Demographic and clinical data was collected from patient records in the laboratory, patient's files at pediatric surgery department archives and the main archive at Soba University Hospital (SUH). Patients who had their surgery in SUH and histopathology analysis at NHL were also included. Patient records at the pediatric oncology archives at RICK were reviewed for more clinical data including information regarding chemotherapy and geographical distribution of the patients' tribes. Patients with valid phone numbers were contacted for some of the missing data in the records.

Formalin-fixed, paraffin-embedded blocks of all processed histopathology specimens were recut and stained with hematoxylin and eosin for review. The information was collected into a predesigned questionnaire. The detailed personal, clinical and pathological data was analyzed using Statistical Package for Social Science Software (SPSS 15, IBM Corporation, Armonk, New York, USA) and Microsoft Office Suite 2010 (Microsoft Corporation, Redmond, Washington, USA). A p value $<0.05$ was considered significant in Pearson's chi-square ($\chi 2$) test.

Staging and histopathological classification was done as per the National Wilms Tumor Study Group (NWTSG).

Photomicrographs were taken using Olympus BX 51 microscope and attached camera and software at histopathology lab,SUH.

Permission for access of patients' files and histopathology material was obtained from SUH, NHL and RICK administrations respectively. Confidentiality of patients' personal information and clinical data was strictly maintained and handled with utmost discretion.

**Results**

The study included 51 patients who were diagnosed as Wilms' tumor in a five-year period from January 2006 to December 2010: (Figure 1)

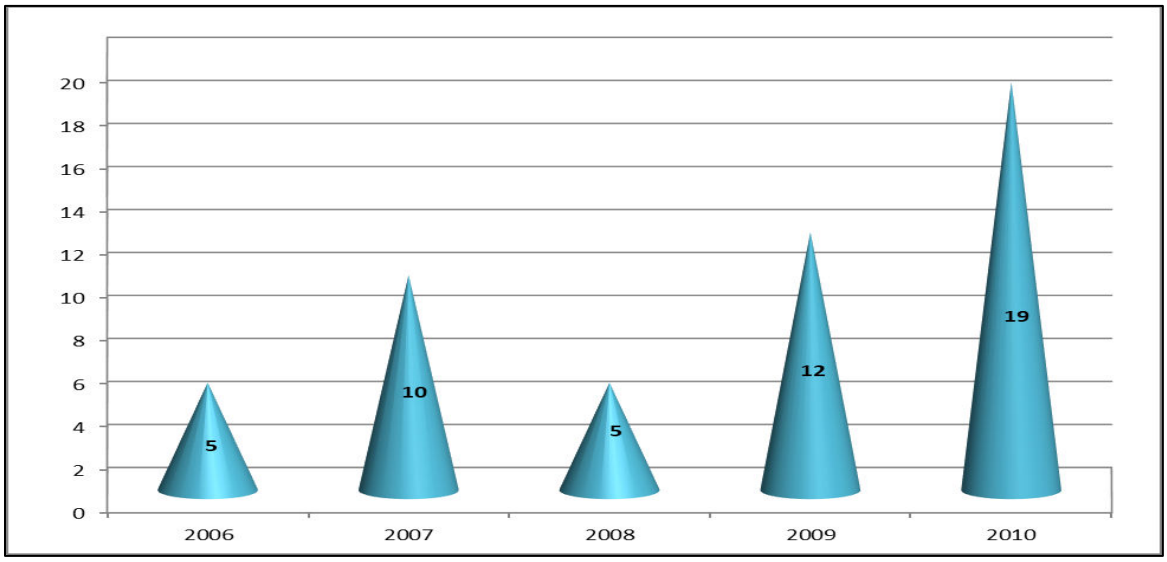


Figure 1: Distribution of Patients among the five year interval of the study.

The age ranged from 0.5 years to 10 years, with the mean age of 3.4 years (SD ± 2.1) (Table. 2).

**Table2 : Distribution of Wilms tumors**

| Age ( years) | Right kidney | Left kidney | Unknown | Total |
|---|---|---|---|---|
| 0-2 | 9 | 10 | 0 | 19 |
| 3-6 | 18 | 8 | 0 | 26 |
| >6 | 3 | 2 | 1 | 6 |
| Total | 30 | 20 | 1 | 51 |

Age group 3-6 years displayed a statistical significance of right kidney involvement by the tumor (P<0.42). Most patients were males, with male-to-female ratio of 1.55:1.Preoperative chemotherapy was not received by any of the patients. Patients' tribes coming from Western Sudan were 21 patients, 18 patients from tribes of Central Sudan, 7 patients from tribes of Northern Sudan. Only 4 patients came from Southern Sudanese tribes "now the Republic of South Sudan". In one patient the tribe was unknown. The Southern tribes showed a statistical correlation with inoperable tumor (P<0.016) but not with metastasis; however, lung metastasis was strongly related to patients from Western tribes (P<0.024) (figure 2 and table 3).

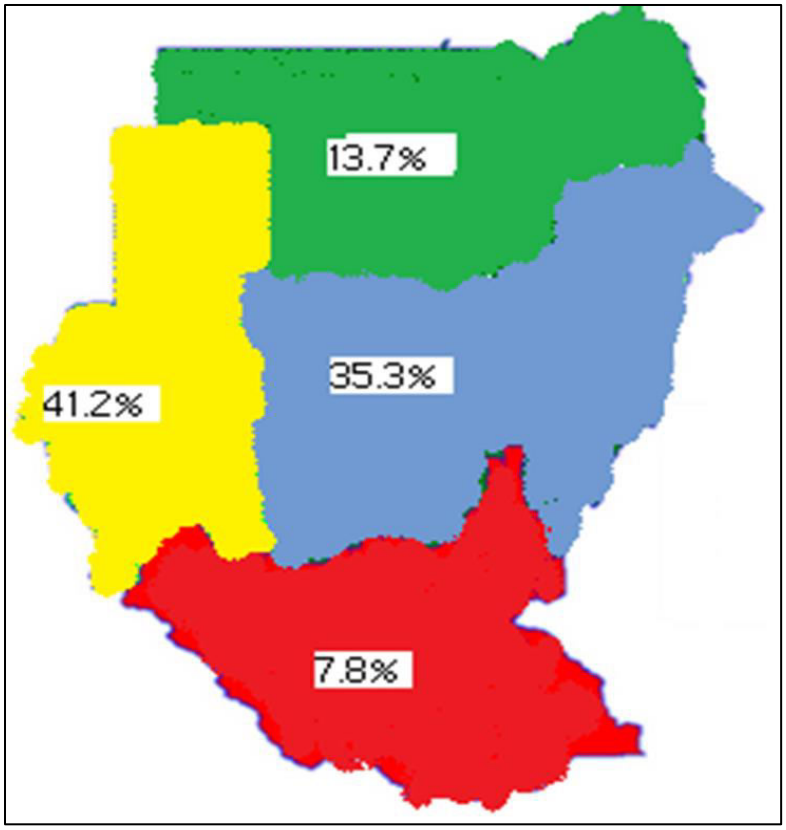


Figure 2: Map of Sudan showing the geographical distribution of patients' tribes who were diagnosed with Wilm's tumor (2006-2010) as apercentage. (Map 'Not to Scale')

**Table 3: Region-wise and Stage-wise distribution of tumors.**

| | | CENTRAL | NORTH | WEST | SOUTH | UNKNOWN | Total |
|---|---|---|---|---|---|---|---|
| STAGE | I | 1 | 0 | 0 | 0 | 0 | 1 |
| | II | 5 | 3 | 8 | 1 | 0 | 17 |
| | III | 10 | 3 | 9 | 0 | 0 | 22 |
| | IV | 2 | 1 | 4 | 3 | 1 | 11 |
| Total | | 18 | 7 | 21 | 4 | 1 | 51 |

Abdominal mass was the commonest presenting symptom seen in 50 patients (98%) and the major cause for seeking medical treatment or consultation. Only one patient sought medical advice due to epistaxis and coincidentally was found to have an abdominal swelling during routine clinical examination. Other presenting symptoms were loss of appetite , weightloss, fever, pain, hematuria and epistaxis (Table 4).

**Table 4: Stage-wise clinical presentation**

| | | ABDOMINAL MASS | PAIN | HEMATURIA | FEVER | WEIGHT LOSS | EPISTAXIS | OTHER ANOMALIES | Total |
|---|---|---|---|---|---|---|---|---|---|
| STAGE | I | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 3 |
| | II | 16 | 4 | 2 | 7 | 5 | 1 | 2 | 37 |
| | III | 22 | 6 | 1 | 6 | 10 | 1 | 2 | 48 |
| | IV | 11 | 2 | 1 | 5 | 6 | 0 | 1 | 26 |
| Total | | 50 | 12 | 5 | 18 | 22 | 2 | 5 | 114 |

**Table 5: Region-wise cases and their clinical presentation**

| | | Abdominalmass | Pain | Hematu-ria | Fever | Weight loss | Epistaxis | Other anomalies | Total |
|---|---|---|---|---|---|---|---|---|---|
| Region | Central | 18 | 5 | 1 | 6 | 7 | 0 | 1 | 38 |
| | North | 6 | 3 | 2 | 2 | 4 | 0 | 2 | 19 |
| | West | 21 | 3 | 2 | 7 | 10 | 2 | 2 | 47 |
| | South | 4 | 1 | 0 | 2 | 1 | 0 | 0 | 8 |
| | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| Total | | 50 | 12 | 5 | 18 | 22 | 2 | 5 | 114 |

Epistaxis was statistically correlated with an earlier presentation (P<0.011).Hematuria is significantly correlated with smaller mass sizes (P<0.040) and an earlier stage of the disease (P<0.019).

The right kidney was involved by the tumor in 30 patients (58.8%), and the left kidney was involved in 20 patients (39.2%). In one case the involved kidney was not stated in the records. None of the patients were found to have bilateral involvement of the kidneys.

Symptoms duration ranged from 3 days to 2 years, commonly 2 months, accounting for 25.5% of patients.

Congenital anomalies were found in 5 patients (9.8%), bilateral undescended testis in 3(one had congenital glaucoma),back deformity in one and delayed speech in one patient. None of the patients had congenital syndrome (WAGR, Beckwith-Weidemann, or Denys-Drash syndromes). Absence of lymph node metastasis in patients with congenital anomalies showed a statistical significance (P<0.045).

Tumor size measured by radiology ranged from 7 to 23 cm in their greatest diameter. The mean size was 14 cm. Metastasis at presentation was found in 13 patients (21.6%): lung and liver metastasis in 5 patients (9.8%) respectively and adrenal, peritoneum and bone

involvement in 1 patient each (1.96%). Patients with liver and bone metastasis took a longer time to seek medical help. The site of metastasis was significantly correlated with the duration of symptoms (P<0.010). Distant metastasis at presentation was also correlated with capsular invasion (P<0.027).

According to the NWTS staging system, 22 patients (43.14 %) presented at stage III, 17 (33.33%) at stage II, 11 at stage IV (21.57%), and one patient (1.96%) at stage I. Information regarding neoadjuvant therapy was available in two thirds of the patients.

Type of specimens were 37 nephrectomies and 14 biopsies. Preoperative chemotherapy was not given to any of the patients. Triphasic tumors were found in 42 patients (82.2 %), out of which 12 had blastemal predominance and 2 had epithelial and mesenchymal predominance. The size of the mass is correlated to the type of histological predominance in triphasic tumors; Mesenchymal predominance was found in smaller tumors and blastemal predominance was found in larger tumors.Fever is statistically correlated to triphasic tumors with mixed elements (P<0.038). Spindle cell stroma was found in the majorty of cases (96.1%). Other components were muscle in 13 cases (25.5%), adipose tissue in 8 cases (15.7%), and squamous or mucinous epithelium in 4 cases (7.8%). Cartilage, bone, neurogenic tissue, and rhabdomyosarcomatouselements had not been detected in any of the cases in this study (Table 6). The presence of muscle in the stroma was found to be correlated with less advanced stages of the disease (P<0.016), and with the absence of weight loss in the presenting symptoms (P<0.019). The presence of adipose tissue was correlated to tumors that were not confined to the kidney (P<0.008). Anaplasia was found in 4 patients in the study group, accounting for 7.8%. It was statistically significant with older age groups (P<0.030), tumor not confined to the kidney (P<.050) and presence of capsular invasion (P<0.021). Although all anaplastic tumors were stage III, there was no statistically significant correlation. Capsular invasion was detected in 11 patients (29.7%) . Short duration of symptoms correlated to the absence of capsular invasion (P<0.001). All the tables from table 7 to table 18 shows the various case related data in our study. Out of the 37 nephrectomies, lympho-vascular/renal sinus invasion was detected in 10 patients and only 5 had lymph node metastasis (13.5%). Lymph node metastasis was found to be closely related to capsular invasion (P<0.047). Necrosis was evident in 42 cases (82.4%), 5 of which displayed massive post chemotherapy necrosis (9.8%). The inoperable tumors showed no necrosis in their histology (P<0.002). (Figures 3,4,5and 6).

**Table 6: Histological features in different stages of Wilms tumors**

| | | I | II | III | IV | Total |
|---|---|---|---|---|---|---|
| Histology | ANAPLASIA | 0 | 0 | 4 | 0 | 4 |
| | SPINDLE | 1 | 17 | 20 | 11 | 49 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | MUSCLE | 0 | 9 | 3 | 1 | 13 |
| | SQUAMOUS/MUCINOUS EPITHELIUM | 0 | 2 | 2 | 0 | 4 |
| | ADIPOSE TISSUE | 0 | 2 | 4 | 2 | 8 |
| | CASULAR INVASION | 0 | 2 | 7 | 2 | 11 |
| | NECROSIS | 0 | 14 | 19 | 9 | 42 |
| | EXTENSIVE NECROSIS | 0 | 3 | 1 | 1 | 5 |
| | LYMPHOVASCULAR INVASION | 0 | 3 | 4 | 3 | 10 |

**Table 7: Predominant component**

| Component | Blastemal | Epithelial | Mesenchymal | Mixed |
|---|---|---|---|---|
| Number of cases | 12 | 2 | 2 | 26 |

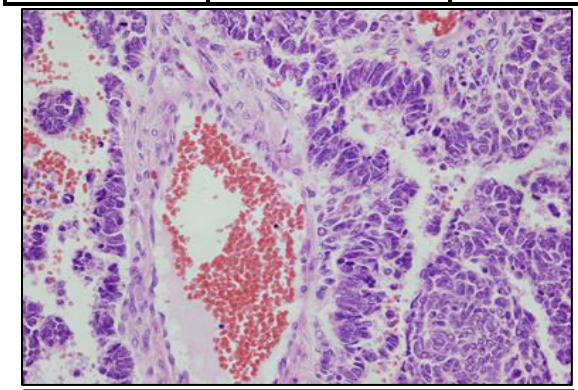

Figure: 3: Wilms' tumor with blastemal cells that show anaplasia "large hyperchromatic nuclei with bizarre

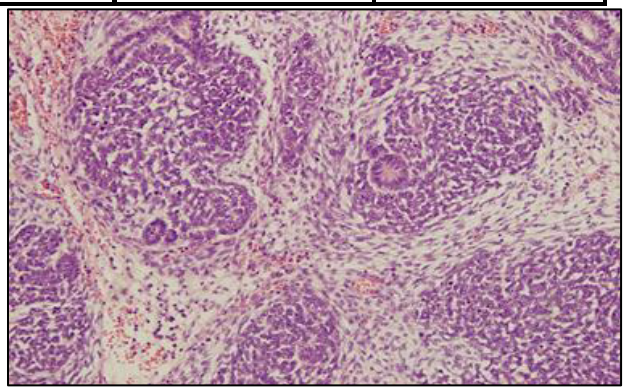

Figure 4: Wilms' tumor showing the classical triphasic pattern of blastemal cells, aborted tubules and spindle cell stroma

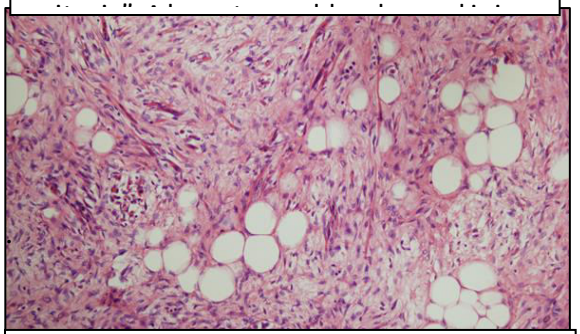

Figure 5: Wilms' tumor showing blastemal cells and stroma composed of spindle cells, muscle fibers and clusters of adipocytes.

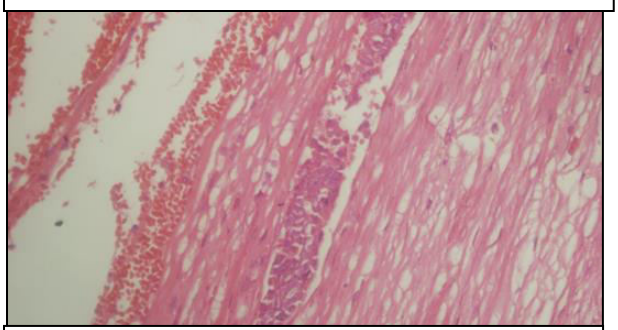

Figure: 6: Wilms' tumor showing infiltration of a blood vessel with blastemal cells

| Table8: Tumor extension and anaplasia in relation to stage | | | | | | |
|---|---|---|---|---|---|---|
| STAGE | Tumor confirmed to kidney | | Attached to adjacent structures | | Anaplasia | |
| | Yes | No | Yes | No | Yes | No |
| I | 1 | 0 | 0 | 1 | 0 | 1 |
| II | 14 | 2 | 2 | 14 | 0 | 17 |
| III | 5 | 10 | 11 | 4 | 4 | 18 |
| IV | 0 | 5 | 5 | 0 | 0 | 11 |

| Table9: Anaplasia and Necrosis in tumors | | | | |
|---|---|---|---|---|
| | **Anaplasia** | | **Necrosis** | |
| | Present | Absent | Present | Absent |
| Tumor confined to kidney | 0 | 20 | 15 | 5 |
| Tumor extending beyond kidney | 4 | 14 | 17 | 0 |

| Table 10: Capsular invasion in relation to lymphovascular invasion and metastasis | | | | |
|---|---|---|---|---|
| Capsular invasion | Lymphovascular invasion | | Distant metastasis | |
| | Yes | No | Yes | No |
| Present | 6 | 5 | 2 | 9 |
| Absent | 4 | 21 | 2 | 23 |
| Unknown | 0 | 1 | 1 | 0 |

| Table 11: Anaplasia and Capsular invasion | | |
|---|---|---|
| Anaplasia | Capsular invasion | |
| | Yes | No |
| Yes | 3 | 0 |
| No | 8 | 25 |

**Discussion**

A significant increase of cancer incidence in Sudan has been witnessed in the last decade. [20] The exact incidence of Wilms' tumor in Sudan is unknown. That is attributed to the quality of cancer registry and hospital records. The poor registration of medical data was one of the biggest obstacles for this study.

In the 5 year (2006-2010) of this study, 5 children were diagnosed in 2006 and 19 children in 2010. This is almost four-fold increase in the number of diagnosed cases and can partially be explained by the urbanization of the Sudanese population and the expanded workload this has inflicted on Soba University Hospital. The advances in radiographic imaging, histopathology and referral policies may have also contributed to this increase in number.

The mean age at presentation in this study is 3.4 years, maximum age 10 years and minimum age 0.5 years. This correlates well with a similar study in Alexandria Egypt in a 20 year retrospective study, where they found the age of patients ranging between 0.3 and 11.8 years with a mean of 3.5years.[21] Also in a study by Breslow et al (2006) of 7,455 patients, from the National Wilms' Tumor Studies 3,4 and 5, the mean ages for males and females were 3.5 ±2.8 years and 4 ±2.9 years, respectively.[22] However, they found strong association between age and gender and none was found in this study, probably due to the smaller study sample size. In a study from Tehran Iran, the median age was found to be 3.16 years, slightly lower than our findings. [22]

The male-to-female ratio in this study is 1.55:1 agreeing with the male predominance found in the studies from Tehran and Alexandria (1.2:1).[21,22 ] On the other hand NWTS and SIOP studies show a slight female predominance with a male-to-female ratio of 0.89:1.[23, 24]Although the study by Breslow et al(1993) showed a younger age at presentation for males and called for more laboratory studies to explain the differences between males and females in ages-at-onset [3], in this study we could not statistically prove an association of age at presentation and gender.

As the pathogenesis of Wilms' tumor relies mainly on genetics, its' clear ethnic variation is understandable. A lot of work has been done on the incidence in different ethnic groups in the literature. U.S. blacks and Africans from Ibadan Nigeria had the highest incidence. [6]Sudan is an ethnic melting pot with diversity of races greater than most countries. The percentage of Wilms' tumor in this study shows a marked increase in western tribes in Sudan. Such variation as does exist is more closely associated with race than geography. [3] These patients present with a more aggressive disease and lung metastasis ($P<0.024$). On the other hand, patients from Southern tribes of the Sudan presented with inoperable masses ($P<0.016$), yet no metastasis.

Ninety-eight percent of this study's patients presented with abdominal mass, in contrast to the United Kingdom Children's Cancer Study Group (UKCCSG) who reported this rate to be 74% [25], and in Johannesburg South Africa where they reported it to be 76% [26]. Our figure is closer to other developing countries, e.g. Alexandria 86.6% [21], and Iran 90.9%. [22] Early detection in developed countries could be explained by the availability of health services and increased awareness of the society. However, our percentage of patients presenting with fever and weight loss are more than triple the figures from these countries. This could be due to similar symptoms manifested by other

endemic infectious diseases in Sudan that might lead patients' families and rural health workers to relate the symptoms to these diseases.

**Table12: Country-Wise data of Clinical presentation and histology of Wilms tumor cases.**

| **Signs/symptoms** | **Sudan (Present study)** | **Kenya**[27] | **South Africa**[28] | **Egypt**[29] | **Iran**[30] | **Nigeria** [31] | **Jordan**[32] |
|---|---|---|---|---|---|---|---|
| Abdominal mass | 50% | 97.7% | 77% | 65% | 90.9% | - | - |
| Abdominal pain | 12% | - | 25.5% | 3.5% | 10.9% | 32% | - |
| Hematuria | 5% | 6.8% | 9.6% | 5% | 14.5% | 16% | - |
| Weight loss | 22% | 34.5% | 20.7% | 1.5% | 1.8% | 56% | - |
| Fever | 18% | 16.5% | - | - | 5.5% | | - |
| Vomiting | - | 10.5% | - | 3% | - | - | - |
| Epistaxis | 2% | - | - | - | - | - | - |
| Others | 5% | 33.1% | 13% | 19% | 1.8% | - | - |
| **Histology:*Favourable*** | 92.15 % | - | 87.27% | 32.6% | - | 96.7 % | 86.9% |
| **Histology:*Unfavourable*** | 7.85% | - | 12.8% | 65.2% | - | 3.3% | 15.1% |

**Table13:Presentation of Wilms tumor as reported in different studies in other countries**[5,33,29, 32,28,27]

| **Country** | **M:F** | **Median Age at diagnosis(Y)** | **Stage at diagnosis** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **I** | **II** | **III** | **IV** | **V** | **Unknown** |
| **Sudan (Present study)** | 1.5:1 | 3.4 | 1.96 % | 33.33 % | 43.14 % | 21.57 % | - | - |
| **Sudan** | 0.9:1 | 4.1 | 3% | 19% | 68% | 11% | - | - |
| **Iran** | 1:1 | 3.8 | 23% | 35% | 32% | 5% | 4% | - |
| **Egypt** | 1:1 | 3.8 | 23.3 % | 35.4% | 32.4% | 5.1% | 3.8 % | - |
| **Jordan** | 1.17:1 | 3.3 | 27.9 % | 34.4% | 16.4% | 11.5% | 9.8 % | - |
| **SouthAfrica** | 0.8:1 | 3.8 | 37% | 18% | 24% | 21% | - | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **SouthAfrica** | 2:3 | 3.25 | 57% | 33% | 60% | 38% | - | - |
| **Kenya** | 1.14:1 | - | 3.2% | 42.4% | 36% | 16.8% | 1.6% | - |
| **Malawi** | 1:1 | 3.5 | 24% | 39% | 37% | - | - | - |
| **United kingdom** | 1.1:1 | 2.8 | 60% | 19% | 20% | - | - | 1% |
| **Germany** | 1.1:1 | 3.4 | 58% | 11% | 8% | 20% | 3% | - |

In our study, the majority of patients presented in the stage II and III, and it is similar to another study reported in Sudan.[5] (Table 12& 13). Earlier presentations has been reported from developed countries(table 20).Patients with epistaxis presented early, and those with hematuria had smaller tumors and stage II disease. Von Willebrand factor(VWF) testing was not done in our case who presented with epistaxis. Early presentation by patients with epistaxis can be explained by the fact that bleeding is a more alarming symptom. The cause is most likely to be acquired Von Willebrand's syndrome (AVWS) type III according to a French study on the causes of AVWS. [34]

Patients with aniridia, anomalies of the male genitalia, and the Beckwith-Weidemann syndrome tend to have substantially younger ages at diagnosis.[3] An association between age at presentation and congenital anomalies was not statistically proven in our study. However, the absence of lymph node metastasis was statistically significant in those patients ($P<0.045$) implying a better outcome. That could be due to a milder disease form in those patients, or more logically, their families sought medical help sooner than those patients who seemed normal to their families.

Lung and liver metastasis were the most common sites. The site of metastasis correlated with the duration of symptoms ($P<0.010$). Patients with liver and bone metastasis took a longer time to seek medical help. Breslow et al (1986) for the NWTS, found that distant metastasis at presentation correlated to capsular invasion, as did the author ($P<0.027$). In that study, they found that all the indicators of regional spread of the disease within the abdomen were strongly associated with the presence of metastases. Patients with overt disease in the abdominal cavity or with microscopic tumor in the surgical margin were more than twice as likely to have distant metastases, than were those whose tumor was apparently confined to the kidney. If there was microscopic evidence of lymph node involvement or invasion of the renal vasculature, whether inside the kidney or outside, the finding of concomitant metastasis was increased at least threefold.[35]

The type of histological predominance in triphasic tumors correlated to the size of the mass: mesenchymal predominance in smaller sizes and blastemal predominance in larger tumors. A study by Sidhom et al (2004) found that presence of blastemal predominance had an adverse effect on outcome. In this study we were unable to find statistical relation of blastemal predominance to other factors of poor outcome.[36]

Analyses of the histology of Wilms' tumors occurring in patients with sporadic tumors with WT1 mutation have shown that stromal differentiation, particularly along muscle lines, tends to predominate.[37] Pritchard-Jones suggests that the normal role of WT1 may be to suppress muscle differentiation in the primitive metanephric mesenchymal cells.[38] In our study the presence of muscle in the stroma (25.5%) was found to correlate with less advanced stages of the disease (P<0.016), and with the absence of weight loss in the presenting symptoms (P<0 .019). This is in concordance with the concept that the presence of relatively mature skeletal muscle "fetal rhabdomyomatous nephroblastoma" carries a favorable prognosis and should not be confused with rhabdomyosarcoma that has the opposite prognosis.[39]

On the other hand, presence of adipose tissue correlated to the tumor not being confined to the kidney (P<0 .008). This finding will need support by other larger studies to validate this relation.

Anaplasia "threefold nuclear enlargement, hyperchromasia, and atypical mitotic figures" [19] is the most valued prognostic parameter in all the literature. Anaplastic tumorswere detected in 7.8% of our study group. This was less than the NWTS 12%, [40] but is comparable to that found in Johannesburg. [26]In this study, anaplasia had statistically significant relationship with older age groups (P<0.030), tumor not confined to the kidney (P< .050) and presence of capsular invasion (P<0.021). Although all anaplastic tumors were stage III, in this study, no statistical significance was proved. As D'angio et al. stated in NWTS 3, the outlook has been poor for the children afflicted with the anaplastic form of Wilms' tumor. We can confer from these findings the correlation of anaplasia with poor outcome. However, its relationship with unresponsiveness to therapy, or lack of relations to aggressiveness will need larger studies with monitoring of response to therapy. [41, 42]

The NWTS revealed that lymph nodes or distant metastasis werethe most important poor prognostic indicators.[43] Invasion of the renal capsule, intrarenal vessels, or renal sinus and lack of a perirenal inflammatory reaction were designated as "microsub-staging" factors and are related to negligible relapse rates.[44]In this study, 5 patients had lymph node metastases. It was found to be closely related to capsular invasion (P<0.047). Capsular invasion was detected in 11 patients . Its absence was mostly seen in patients who presented after a short duration of symptoms (P<0 .001).Three out of the 4 patients with inoperable tumors showed no necrosis in their histology (P<0.002), and they have not received any preoperativechemotherapy .Boccob et al. demonstrated that post chemotherapy necrotic tumors have excellent outcome.[45] However, the cultural and socioeconomic status of our patients and lack of guidance delay their diagnosis and worsen their outcome.

One case of the rare teratoid Wilms' tumor was found in this series and requires special mention. As stated by Meyers et al. of a review of all the teratiod Wilms' tumors reported

online to that date, teratoid Wilms' tumors appear to present with a high stage, increased incidence of bilaterality and have a high mortality rate.[46]

**Conclusion:**

The mean age at presentation of Sudanese patients is in concordance with international studies; but to the contrary, it had no statistical correlation to gender. On the other hand, a male-to-female ratio shows a slight male preponderance, disagreeing with the findings of NWTS.

The disease was more prevalent in the west of Sudan, where they had aggressive disease presenting with lung and liver metastases.Abdominal mass was the major presenting symptom, followed by fever and weight loss, which was more than other reported in theliterature.. Capsular invasion "indicator of regional spread of the disease" was strongly associated with the presence of metastases.

Mesenchymal presence predominated in smaller tumor and blastemal component was predominant in larger tumors. There was a relationship between the histology of the tumor and clinical symptoms.A milder course of the disease was also related to tumors with rhabdomyomatous elements in the stroma. Anaplasia was related to older age at presentation, locally infiltrative tumors, presence of capsular invasion, and advanced clinical stage.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest.

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