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Clinical Features and Treatment Strategies of Wilms' Tumor: A Setup in the Last Decade of the Millennia and Possible Inclusion of Advance Researches to Improve the Clinical Management

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This is a study of 20 cases of Wilms' tumor studied over a period of 3 years covering different hospitals of Karnataka in India. Although the study was concluded in the year 2000, it was found worthwhile to demonstrate that inclusion of the results of advance researches can improve the management of Wilms' tumor. This is to highlight the bitter realities that the little patients succumb to harsh disease just because the facilities of research developments do not reach the hospitals. The presentation of our study would show if the modern researches on (i) expression of genes and receptors (ii) immunological assays (iii) microarray technology would have been available, there would have been reduction in mortality. In this study during the last three years of 2000, the patients were studied in detail by taking history and clinical examination. Specific investigations like ultrasound of the abdomen, FNAC, CT scan, in addition to routine investigations were carried out. Treatment modalities included surgical treatment like nephrectomy, partial nephrectomy, chemotherapy and radiotherapy depending on the staging. The results of this study showed that (i) the stage I and II cases have good prognosis if detected early and managed aggressively (ii) that CT scan did not show any superiority over ultrasound evaluation except for the fact that it delineated internal characters of the tumor better (iii) Surgery could be performed successfully in all patients without any morbidity and mortality and (iv) Wilms' tumor responds very well to combination chemotherapy. However; recurrence, toxicity and mortality were difficult to be avoided. It is suggested that World Health Authorities may take a decision to implement the developments in researches for clinical management of Wilms'tumor to farthest hospitals in any country.

Key words: Wilms' tumor, combined chemotherapy, surgery, radiation, research development

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INTRODUCTION

The majority of renal tumors in children are Wilms' tumors and these occur predominantly in the toddler and preschool age group (1 to 4 years of age). These are the most common tumors associated with various congenital anomalies, such as sporadic aniridia, hemi hypertrophy and genitourinary anomalies (Huang *et al*., 2004; Glick *et al*., 2004). Within the last decades, striking improvement in terms of survival could be achieved in the treatment with a multi-disciplinary management. Whereas survival was 30% in the 1930s, now in all children with Wilms' tumor, survival rate reaches more than 90% in the SIOP/GPOH study group. The striking improvement in the management of Wilms' tumor has become a paradigm for successful cancer therapy (Kalapurakal *et al*., 2004). Now that overall good outcomes have been achieved, the primary objective of clinical trials on Wilms' tumor has shifted towards refinement of therapy for children with low-risk tumors, so that they can be spared from modalities resulting in improvement of excellent cure rates. Despite this fact, several issues remain of concern and ongoing discussion. About 80% of the world's children with this disease have much poorer chances of survival because of limited access to appropriate specialist care. Furthermore, the relapsing chances of nephroblastoma and metastatic disease have increased (Pritchard-Jones and Pritchard, 2004). The present study was an attempt to adopt varied approach of diagnosis and multi modal treatment to improve the clinical outcome and the survival rate in the millennium and a probable impact of the modern scientific developments (i) expression of genes and receptors (ii) immunological assays (iii) micro array technology on reduction of mortality, morbidity and recurrence of the disease.

MATERIALS AND METHODS

Twenty cases of Wilms' tumor were studied over a period of 3 years (1997 to 2000) covering different hospitals in Mangalore and Karnataka, India (mainly from Government Wenlock Hospital, TMA Pai Rotary Hospital Bejai and KMC Attavar Hospital). These patients were studied in detail by taking history and clinical examination. Specific investigations like ultrasound of the abdomen, FNAC (in some cases), CT scan (in some cases) in addition to routine investigations were carried out on every patient. Treatment modalities included surgical treatment like radical nephrectomy and partial nephrectomy, chemotherapy and radiotherapy, depending on the staging. Patients were called for regular follow up initially after 1 month and then once in 3 months apart from their chemotherapy appointments. During their visits, a detailed history and physical examination was conducted and an ultrasound abdomen done to look for recurrences and secondary deposits in suspected cases.

RESULTS

Patient data: A total 20 patients were diagnosed of nephroblastoma. The age at diagnosis for these patients was 9 months to 12 years. Peak incidence of tumor was between 2-4 years. There were 4 cases in the age group between 0-2 (3 male and 1 female), 7 cases in age group 2-4 (4 male and 3 female), 6 cases in the age group 4 -6 (0 male and 6 female), one case each in the age group of 6-8 (male), 8-10 (female) and 12-14 (male). The overall incidence of Wilms' tumor was found to be 9 in male and 11 in female children (Table 1). Most of the patients studied were from South Kanara and Kasargod Districts. About 80% of the cases were from low socioeconomic status and 20% were from middle class. There was no relation to any significant past history. No other sibling suffered from similar illness in the family. Only one of the 20 patients had Aniridia. There were no other malformations like genitourinary malformations, mental retardation, hemi hypertrophy or macroglossia in the same patient.

Presenting symptoms: Mass per abdomen was the major presenting complaint in 18 out of 20 cases constituting 90% of all cases studied. Other patients presented with loss of appetite, fever and loss of weight. Thirteen patients presented with loss of weight among the other complaints. The other general complaints were fever (6 patients), abdominal pain (5 patients), hematuria (2 patients) and gastrointestinal complaints in 2 patients (Table 2).

Clinical examination: A detailed clinical examination was done to screen the patients and to evaluate the primary malignancy as well as to rule out secondaries. General physical examination was done on all patients. Six of the

Table 1: Age and sex-wise distribution of the different of Wilm's tumor cases

Age group (years)	Total No. of patients	Male patients	Female patients
0-2	4	3	1
2-4	7	4	3
4-6	6	0	6
6-8	1	1	0
8-10	1	0	1
10-12	0	0	0
12-14	1	1	0
Total	20	9	11

Table 2: Data showing presenting symptoms of the different cases of Wilms' tumor

Presenting symptoms	No. of patients	Percentage
Mass abdomen	18	90
Fever	6	30
Abdominal pain	5	25
Loss of apetite	13	65
Loss of weight	12	60
Haematuria	2	10
Symptoms pertaining to thoracic involvement	0	0
Symptoms pertaining to GI involvement	2	10
Neurological symptoms	0	0

patients had fever and 1 case had hypertension and hematuria as the initial complaint. Thirteen of the patients had pallor which constituted 65% of the study group. Abdominal examination detected mass in all the 20 cases. The masses were moving minimally on respiration and were firm to hard in consistency and non-tender. The masses were of variable sizes, site was predominantly in hypochondriac and lumbar region on the right and left depending on the respective sites. The surface of the masses was smooth to nodular and margins were ill defined. There was no continuation of the masses with other swellings. The masses were palpable and blotted. There was no free fluid detected clinically in the cardiovascular and respiratory systems. These systems were normal in all cases. Rectal examination was also normal in all the cases.

Duration of predominant symptom of abdominal mass: At the case presentation, none of patients had the abdominal mass symptom for more than a year. One had the symptom for 1 year. Three had the symptom for 2 months, while more three had the symptom for 3-6 months. Seven and six patients had the symptom for 1 month and 15 days, respectively (Table 3).

Investigation and diagnostic evaluation:

Routine investigations: Routine investigations revealed anemia in 13 cases. The peripheral smear study was within normal limits. Urea and creatinine were also within the normal limits. Microscopic hematuria was detected in 60% of the cases.

Specific investigation:

Ultrasound and CT scan: Ultrasound examination was done in all the cases. This was very useful in detection of Wilms' tumor. Out of 20 cases, 7 were right sided renal tumors, 12 were left sided and 1 was bilateral. Twelve of the tumors were located in the upper pole, 3 in middle pole and 1 in lower pole, while 4 occupied all three poles. In the right sided tumors, 5 were located in upper pole and only 1 tumor was located in the mid segment and 1 in the lower pole. Among left sided tumors, 6 of them were located in upper pole, 2 in mid segment and 4 tumors were present in all quadrants (Table 4).

Table 3: Duration of predominant abdominal mass at first presentation of the different cases of Wilms' tumor

Duration (days) of predominant abdominal mass at first presentation	No. of patients	Percentage
15 days	6	30
1 month	7	35
2 months	3	15
3-6 months	3	15
1 year	1	5
More than 1 year	-	-

Table 4: Site related incidence of Wilms' tumor as detected by ultrasound

Position of kidney	No. of Tumors	Upper pole	Middle pole	Lower pole	All the three poles
Right	7	5	1	1	-
Left	12	6	2	-	4
Bilateral	1	1	-	-	-
Total tumors	20	12	3	1	4

Table 5: Ultrasound classification of different stages of Wilms' tumor

Diagnosed stage	No. of patients	Percentage
Stage I	10	50
Stage II	4	20
Stage III	4	20
Stage IV	1	5
Stage V	1	5

The ultrasound evaluation on classification of different stages revealed that ten were in stage I, four cases (stage II), four cases (stage III), one case (stage IV) and another case (stage V). CT scan was done in 8 cases to compare ultrasound evaluation, preoperative findings and histopathological examination. One case diagnosed as stage I by CT scan and USG was found to be stage II on HPE and another stage II per operatively and HPE. Chest x ray was routinely done in all 20 cases and no lung metastasis was found in any of them on initial admission. The staging was arrived at after USG examination and in some cases CT evaluation and was modified after surgery and histopathological evaluation (Table 5).

Histopathology: Histopathological findings revealed 18 cases to be of favorable histology and 2 were of unfavorable histology. Nineteen cases had triphasic components while 1 case had biphasic component. None of the cases had monophasic component. Eighteen of the cases were of mixed tumor type, blastemal predominant (1), stromal predominant (1), epithelial predominant (0) (Table 6).

Treatment strategies: Treatment was given as per National Wilms' Tumor Study-4 (NWTS-4) regimen which was a combination of surgery, chemotherapy and radiotherapy depending on stage of the tumor. Out of the 20 patients, 19 underwent radical nephrectomy, 1 patient (stage IV) was inoperable. The patient in stage V was given preoperative chemotherapy with vincristine and actinomycin for 8 weeks and then reassessed following

Table 6: Histopathological findings in different cases of Wilms' tumor

Tumor	No. of cases	Percentage
Tumor type		
Triphasic	19	95
Biphasic	1	5
Monophasic	0	0
Tumor type		
Mixed type	18	90
Blastemal predominant	1	5
Stromal predominant	1	5
Epithelial predominant	0	0
Tumor type		
Favorable histology	18	90
Unfavorable histology	2	10

this. She underwent radical nephrectomy on the right side with a biopsy on the other side. This was followed by chemotherapy with vincristine, actinomycin and doxorubicin for 8 weeks following which she underwent partial nephrectomy on the left side. She again underwent chemotherapy for 10 weeks with radiotherapy to the abdomen (150cGY) for 10 days.

Out of 10 patients with stage I, 5 are disease free after a maximum of 24 months, 2 patients came with local recurrences/residual tumor. One of these patients had developed recurrence of the tumor and he also developed secondaries in the lung. He was given chemotherapy. Radiotherapy of the abdomen was also given and good response was observed. One patient came with hepatic and peritoneal secondaries and later developed ascites. This patient was on irregular treatment and could not be saved. One of the patients with stage I unfavorable histology had recurrence of the tumor and is lost to follow up. Three patients with stage I were also lost to follow up. Out of the 4 patients with stage II disease, 3 are disease free after chemotherapy and one patient was lost to follow up. Out of the 4 patients with stage III disease, one developed secondaries in chest and was given chemotherapy and responded well to chest radiotherapy was subsequently given chemotherapy. One developed peritoneal secondaries with local recurrence and died of cancer cachexia. One patient developed a thrombus in IVC with local recurrence/residual tumor. The thrombus was initially at level of ® renal vein and extended just above the level of the diaphragm. At the level of hepatic veins, IVC was partially occluded with hepatic veins showing flow towards IVC. The thrombus went on to lodge in the atrium and child died of cardiac failure. One patient was on the follow up and doing well. The patient with stage IV disease died 1 week after chemotherapy was started. This was due to internal bleeding and shock. The patient with stage V survived and there were no untoward events.

DISCUSSION

The age incidence in this study was observed to be 6 years for 17 out of 20 patients. The majority of cases (7) were between 2-4 years. This observation is supported by data of NWTS and Blair and Birch, (1994). The sex ratio for the incidence showed slight female preponderance with the male: female ratio observed was 0.81. The sex ratio observed in the present study is in agreement with the data recorded by Stiller and Parkin (1990).

There was no enough data to substantiate environmental factors like consumption of tea, coffee by parents, use of oral contraceptives, dyes, vaginal infections, jaundice in neonate, as an etiology of Wilms' tumor. One patient had Aniridia with BL cataract and there were no other malformations in any of the patients. The incidence of Aniridia is found to be more (5%) in this study as compared to the observation of Miller *et al.* (1964) who found the incidence to be 0.6-0.7%. Ganguly *et al.* (1973) reported 25% of cases of Wilms' tumor presented with hypertension which was attributed to increase in rennin activity. This observation was contrary to our study, since only one case (5%) had presented with hypertension. Associated signs and symptoms were found to be 20-30% of the total cases including malaise, pain and hematuria in the study done by Green (1985). Present study showed 5 patients presenting with abdominal pain which corresponded to the study of Green (1985). However; 2 patients were presented with gross hematuria (10%) and 30% of cases had microscopic hematuria (Green, 1991).

Clinical examination detected abdominal mass in all 20 patients of Wilms' tumor in the present study. Twelve of the 20 patients had mass on the left side and 7 had mass on right side and one case had bilateral Wilms' tumor. The age of presentation for the bilateral tumor in the present study was 20 months. The incidence of bilateral tumor and the age of presentation, observed in present study contradicts the observation of Nachman *et al.* (1984), who showed 6% of the patients to have bilateral Wilms' tumor at a median age of 30 months.

Observations on USG examination were similar to studies done by Burger *et al.* (1985) and D'Angio *et al.* (1989). The ultrasound evaluated the size, site extent of tumor mass, capsular invasion, vascular invasion, vascular thrombi, par aortic lymphadeopathy, liver metastasis, free fluid and pleural effusion. This was compared with similar evaluation for Wilms' tumor by CT scan in some cases. In our study we did not find CT scan to be very superior to ultrasound evaluation for Wilms' tumor. Present analysis is supported by the observation of Ehrlich *et al.* (2006), who showed that the appropriate treatment of lesions identified only on CT is controversial. These authors documented a report from St. Jude's hospital, which concluded that the variability in interpretation of thoracic CT scans limits the predictive

utility of these studies. Only 2 cases which were staged as II during USG evaluation were diagnosed as stage III by CT scan picking up Para aortic nodes. The cases that were upstaged pre-operatively and HPE were missed by CT scan too.

During ultrasound examination, solid and cystic lesions and extra renal and intra renal masses were differentiated. Most of the masses were of mixed or of homogenous echo texture with area of hemorrhage, calcification and necrosis were able to pick up vascular thrombi in USG evaluation with a fair amount of accuracy, which corresponded to the study of Ramos *et al.* (1988). A little difficulty was experienced with large tumor pushing IVC/aorta. Two patients had IVC thrombus and 1 patient had thrombus in renal vein. CXR was routinely done in all 20 patients on initial presentation had no lung metastasis. However; 2 patients on follow up came up with lung secondaries, one of these patients developed pleural effusion as a complication.

The intraoperative findings revealed no death during the operation or in the immediate post operative period. This corresponded to the study done by Burger *et al.* (1985) who observed that surgery was the best therapeutic modality with minimal mortality. One out of 20 cases was found to be unrespectable intraoperatively. In 1 out of 20 cases, tumor tissue was left behind. This part was stuck to the left dome of the diaphragm. In all the cases a wide trans-abdominal incision was taken allowing adequate evaluation and biopsies of surrounding structures. Suspected to be involved and assessment of contra lateral kidney. One case of bilateral Wilms' tumor was given preoperative chemotherapy.

Results of histopathological examination showed 18 of the 20 cases to be of favorable histology, while 2 were unfavorable histology. Two out of 18 cases of favorable histology were initially diagnosed as mesoblastic nephroma, but on repeated smaller sections as proposed by Beckwith (1993), the tumor was found to be of favorable histology. Eighteen of the 20 cases showed mixed elements, 1 case had predominantly blastemal element. Nineteen of 20 cases were triphasic and 1 was biphasic. The 2 cases with unfavorable histology showed one to be of biphasic and the other was triphasic. One case which was diagnosed as stage III on CT scan due to enlargement of par aortic nodes was down staged to stage II as these nodes were due to reactive histiocytosis. Beckwith (1993) showed in his study that classic Wilms' tumor contains cells derived from stromal, blastemal, epithelial elements and that not all tumors are triphasic. Many Wilms' tumors exhibit biphasic, blastemal and stromal elements or may even show monophasic pattern. This was contrary to present study. The treatment modalities were based on the program of NWTS-4 regimen of combined approach.

The data on morbidity and mortality revealed; (i) five of the 10 patients with stage I were disease free after a maximum of 24 months; (ii) two patients came with local recurrence/residual tumor. One of these patients developed recurrence of the tumor and secondaries in the lung. He was to be given chemotherapy and radiotherapy. One of the patients with stage I unfavorable histology had recurrence of the tumor and is lost to follow up. (iii) One patient came with hepatic and peritoneal secondaries. She later developed ascites and could not be saved. (iv) three patients with stage 1 were lost to follow up (v) of the 4 patients with stage III disease, one developed secondaries in chest and responded well to chest radiotherapy and subsequently was on chemotherapy, one developed peritoneal secondaries with local recurrence and died of cancer cachexia; one patient had developed a thrombus in IVC with local recurrence. The thrombus was initially at level of right renal vein and was extending just above the level of diaphragm. At the level of hepatic veins IVC was partially occluded with hepatic veins showing flow towards IVC. The thrombus went on to lodge in the atrium and child died of cardiac failure. (v) The patient with stage IV disease died 1 week after chemotherapy was started. Cause of death was bleeding causing shock. This patient had secondaries in liver. (vi) All patients who underwent chemotherapy had alopecia from which they recovered 6-8 months after stopping the drugs. All patients had nausea and vomiting after starting chemotherapy. All the eight patients (stage II and III) who received doxorubicin had bone marrow depression and pancytopenia. This attained very low levels between 3-4 weeks and they picked up gradually. Three out of these patients had counts below 4000 and were given half the dose subsequently. None of the patients could afford colony stimulating factors. The patients who received radiotherapy had mild irritation (radiation dermatitis) of the abdominal skin.

The results of present study have highlighted the bitter realities that the little patients succumb to harsh disease just because the facilities of research developments do not reach the farthest away hospitals. Inclusion of the results of advance researches in the strategies can improve the management of Wilms' tumor. Researches on more specific molecular changes have been suggested as important predictors of adverse outcome in Wilms' tumor with favorable histology. These include gain or over expression of genes from 1 q (Hing *et al.*, 2001; Lu *et al.*, 2002), high expression of

the telomerase reverse transcriptase gene TERT (Dome *et al*., 1999) and expression of the neurotrophic tyrosine kinase receptor NTRK2 (TRKB) gene (Eggert *et al*., 2001). Immunological assays have linked adverse outcome with relative over expression of TP53 (Sredni *et al*., 2001), PCNA (Skotnicka-Klonowicz *et al*., 2002) and FASN proteins (Camassei *et al*., 2003) and with relative under expression of HSPA1A (HSP70) and ABCC1 (MRP1) (Efferth *et al*., 2001a, b). Microarray technology has been used to obtain prognostic ally significant expression profiles from a variety of tumors. Much of this research has focused on adult tumors. However, there is some work also on the clinical outcome prediction demonstrated in medulloblastoma, a pediatric malignancy (Pomeroy *et al*., 2002). There is also evidence for a clinical outcome (survival based classification of a limited number of Wilms' tumors (Takahashi *et al*., 2002; Li *et al*., 2002; Udtha *et al*., 2003).

RECOMMENDATIONS

- Early detection and referral from the peripheral centers with the help of governmental and social organizations.
- Aggressive therapy-chemotherapy, radiotherapy, surgery or a combination whenever indicated.
- Meticulous supportive care during treatment.
- Positive attitude in the care of cancer patient and perseverance to continue therapy.
- High cost of intensive chemotherapy or multi modal treatment for the patients with funds from government and social organizations.
- Inclusion of the results of advance researches (i) expression of genes and receptors (ii) immunological assays (iii) microarray technology can improve the management of Wilms' tumor.
- It is suggested that the world health authorities would take a decision to implement the developments in researches to farthest away hospitals managing Wilms' tumor in any country.

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