Neuroblastoma: A Clinico-Epidemiological Study in AL-Khadhimyia Teaching Hospital

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ABSTRACT:

BACKGROUND:

Neuroblastoma is the third most common childhood cancer, after leukemia and brain tumors, and is the most common solid extra cranial tumor in children. The term neuroblastoma is commonly used to refer to a spectrum of neuroblastic tumors (including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas) that arise from primitive sympathetic ganglion cells.

OBJECTIVE:

The aim of this research is to study the epidemiological and clinical feature of neuroblastoma in a group of Iraqi infants and children who were admitted to the pediatric ward of Al-Khadhimyia Teaching Hospital .

PATIENTS AND METHOD:

The study was done over a period of three months from 1st of Feb. 2010 to the end of Apr. 2010.In reviewing all files, 18 cases were collected from the Pediatric Hemato-Oncology Consultation Clinic in Al-Khadhimyia Teaching Hospital, they were diagnosed and treated consequently in the pediatric ward / hemato-oncology unit over a period of 9 years (2002-2010). Data regarding age, sex, residence, site of primary disease and clinical presentation were taken from the recording files in the pediatrics Hemato-Oncology Clinic. Methods used to diagnose our patients includes, fine needle aspiration of tumor mass, Bone marrow aspiration & biopsy of different sites. Chemotherapy was the main line of treatment.

RESULTS:

The total number of studied cases was eighteen cases. The median age was 15 months with male to female ratio of (0.63:1), 9 cases (50%) were below 1 year. Abdominal mass was the commonest site of tumor 12 cases (67%), weight loss was the most common symptom 18 cases (100%) followed by abdominal distention 14 cases(78%), abdominal mass represent the most common sign in 12 cases(67%). Stage IV was noticed in 9 cases (50%), 10 cases (56%) were a high risk group, 7 cases (38.8%) had bone marrow metastases, 6 cases (34%) finished treatment and survive, 4 cases(22%) relapsed, 2 cases(11%) died.

CONCLUSION:

The majority of cases were recognized during the first two years of age .Female were involved more than male. The outcome of treated cases was good and accepted. Abdominal mass is the commonest site , weight loss is the commonest symptoms

KEY WORD: neuroblastoma , childhood, manifestation, treatment.

INTRODUCTION:

The term neuroblastoma is commonly used to refer to a spectrum of neuroblastic tumors (including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas) that arise from primitive sympathetic ganglion cells. The neuroectodermal cells that comprise neuroblastic tumors originate from the neural crest during fetal development, and are destined for the adrenal medulla and sympathetic nervous system [(1)]. By contrast, pheochromocytomas and paragangliomas arise from a different type of cell, the chromaffin cell that also migrates from the neural crest to the adrenal gland. Together, both types of cells make up the adrenal medulla, a component of the sympathetic nervous system. [(2)] Neuroblastomas, which accounts for 97 percent of all neuroblastic tumors, are heterogeneous, varying in terms of location, histopathological appearance, and biologic characteristics [(2)]. They are most remarkable for

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their broad spectrum of clinical behavior, which can range from spontaneous regression, to maturation to a benign ganglioneuroma, or aggressive disease with metastatic dissemination leading to death. Clinical diversity correlates closely with numerous clinical and biological factors (including patient age, tumor stage and histology, genetic and chromosomal abnormalities), although it's molecular basis remains largely unknown. [3]

AIM OF THE STUDY:

The aim of this research is to study the epidemiological and clinical feature of neuroblastoma in a group of Iraqi infants and children who were admitted to the pediatric ward of Al-Khadhimyia Teaching Hospital .

PATIENTS AND METHOD:

A study was done over a period of three months from 1st of Feb. 2010 to the end of Apr. 2010.In reviewing all files, 18 cases were collected from the Pediatric Heamato- Oncology Consultation Clinic in Al-Khadhimyia Teaching Hospital they were diagnosed and treated consequently in the pediatric ward/ hemato-oncology unit over a period of 9 years (2002-2010). Data regarding age, sex, residence, site of primary disease ,metastases ,signs and symptoms ,staging according to the INSS(international neuroblastoma study group) ,risk group (depending on age and staging at diagnosis) , response to treatment (chemotherapy), outcome and follow up results were taken from the recording files in the Hemato-Oncology Clinic .Methods used to diagnose our patients includes:

1-laboratory studies: complete blood picture, renal and liver function test, serum (calcium, phosphorus, uric acid, LDH, ferritin).
2- Imaging studies: CT scan, MRI, abdominal ultrasound, standard skeletal survey.
3- Fine needle aspiration (FNA) and pathological exam of the mass in 9 cases.
4- Bone marrow aspirate from the posterior superior iliac crest in 4 cases.
5- Biopsy and histopathological examination of the following:
A- Excisional biopsy of the mass at presentation in 2 cases.
B- Excisional biopsy of lymph node in one case.
C- Skin nodule biopsy in one case.
6- Ascetic fluid and cytological study in one case.
Response to treatment (chemotherapy) was determined according to the international criteria for response and it was categorized into (complete response, partial response, mixed response, no response, progressive disease). Simple statistical analysis was done using Microsoft Excel program, mean +/-standard deviation & median as well as percentage were estimated.

RESULTS:

1. Neuroblastoma in relation to other tumors:-

From a period (2002-2010), 89 cases with malignant neoplasms , neuroblastoma represent the 2nd most neoplasm admitted to the pediatric ward / hemato-onclogy unit of Al-Khadhimyia teaching hospital and represents 18 cases (20%) of total cases as shown in fig-1-

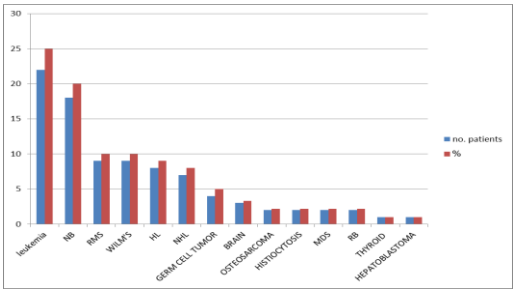

Fig 1: Shows relation of neuroblastoma with other tumor.

2. Age and sex distribution:

Among the overall 18 neuroblastoma cases the range of age was from (15 day to 15 year), mean age (31.4 +/- 1.5) months , median age was15 months. 9 cases (50%) (<1 year), 8cases (44.4%) (1-5 years) & 1 cases (5.6%) (>5 years) as it is shown in (table-1-). Number of males were 7cases (39%), no. of females were 11cases (61%). Male to female 0.63:1

Table 1: Shows the age distribution of the studied group.

Age (year)	No.	%
< 1	9	50
1-5	8	44.4
> 5	1	5.6
Total	18	100

4. Site of origin:

Most common site of presentation was abdominal mass which represents 12 cases (67%) followed by pelvic masses 2 cases (11%) , Thoracic mass 1 case (5.5%) , Lumbosacral mass 1case (5.5%) and unknown primary site 2 cases (11%) as it is shown in (table -2-)

Table 2: Shows primary site of the tumor.

Site of origin	No.	%
Abdominal mass	12	67
Pelvic mass	2	11
Thoracic mass	1	5.5
Lumbosacral mass	1	5.5
Unknown	2	11
Total	18	100

5. Clinical presentation:

Symptoms and Physical Signs:-

Weight loss was evaluated in all of the patients (100%) followed by abdominal distention which is evaluated in (78%), other symptoms are shown in (table -3-). The main physical findings was abdominal mass, (67%) followed by pallor (38.8%) as it is shown in (table -4-).

Table 3: Shows symptoms of the patients.

Symptoms	No.	%
Weight loss	18	100
Abdominal distension	14	78
Fever	4	22
Bone pain	4	22
Diarrhea	3	16.6
Paralysis of the lower limbs	2	11
Cough and shortness of breath	2	11
Urine retention	1	5.5

Note: Some patients had more than one symptom

Signs	No.	%
Abdominal mass	12	66.6
Pallor	7	38.8
Ecchymosis and Petechiae	4	22.2
Hepatomegaly	3	16.6
Emaciation	2	11
Pelvic mass	2	11
Raccoon eye	2	11

Note: Some patients had more than one sign

6. Mode of diagnosis:-

In this study some cases were diagnosed by fine needle aspirate (Abdominal, pelvic) in 9cases (50%), 4 cases (22%) by bone marrow exam, 2 cases (10%) by mass resection and histopathological examination ,1cases (5.5%) for each of the following, excisional biopsy of supraclavicular lymph node, skin nodule biopsy, ascetic fluid analysis as it is shown in (table -5-).

Table 5: Shows diagnostic procedures.

Diagnostic procedure	No.	%
Fine needle aspirate: Abdominal ,pelvic mass	9	50
Bone marrow exam	4	22
Mass resection	2	10
Excisional : supraclavicular lymph node	1	6
Ascetic fluid analysis	1	6
Skin nodule biopsy	1	6
Total	18	100

7. Staging:

According to the INSS, 9 cases (50%) were stage IV ,8 cases (44%) stage III ,one case (6%) stage II, no case in stage I and stage IVS as it is shown is(table-6-)

Table 6: Shows the staging of studied group.

Staging	No.	%
Stage I	0	0
Stage II	1	6
Stage III	8	44
Stage IV	9	50
Stage IVS	0	0
Total	18	100

8. Risk group:-

The risk group classification of the patients depending on the age and staging at diagnosis, was as follow 2 cases (11%) low risk, 6 cases (33%) intermediate risk and 10 cases (56%) high risk .

9. Site of metastases:-

Bone morrow metastases represent 7 cases (38.8%) ,long bone 4 (22.2 %) cases ,skull 3 (16.6%) cases ,liver involvement 3 (16.6%) cases , followed by 1(5.5%) case for each of pelvic bone ,vertebra, skin and distant lymph nodes , as shown in (table-7-)

Table 7: Shows the Site of metastases.

Metastasis	No.	%
Bone marrow	7	38.8
Long bone	4	22.2
Skull	3	16.6
Liver	3	16.6
Vertebrae	1	5.5
Pelvic bone	1	5.5
Skin	1	5.5
Distant lymph nodes	1	5.5

10. Treatment:
Chemotherapy was the main line of treatment in all patients (100%) despite the fact that drugs was not always available but courses were given regularly , non-available drugs were bought
11. Outcome of patients: Of the total 18 patients who received chemotherapy the outcome was as following ,7 cases (39%) were off treatment ,survive and on regular follow up ,4 (22%) cases fromoutside hospital by the families although they are very expensive. There was problem of poor surgical cooperation. Radiotherapy was not given even when required because the instrument is outdated and the appointment was too late. relapse after finishing treatment and refuse retreatment ,4 (22%) cases showed no response to treatment, 3 (17%) cases died as it is shown in(table -8-).

Table 8: Shows Outcome of patients.

Outcome of treatment	No.	%
Off treatment and survive	6	34
Relapse after finishing chemotherapy	4	22
No response	4	22
Lost	2	11
Died	2	11
Total	18	100

DISCUSSION:

The current therapy of neuroblastoma is the result of co- operation efforts of surgeon, radiotherapy and clinical pediatric oncologist which is the main obstacle in this study. In this study neuroblastoma represent (20%) of the total neoplasm admitted to our unit second most common tumor after acute lymphoblastic leukemia, compared to Abboud study 2008(Child's Central Teaching Hospital/ Baghdad) (4.2%) [4] , AL-Sheyyab study(Jordan) 2003 (6%) [5] , Sebastian O.Ekenze et al(Nigeria) (2009) (8.6%) [6],this can be explained by referral of cases and the drainage of patients to our hospital.
The range of age was (15day -15 yr) which is similar to AL- soodany study (45day-146 months) [7] and to TPOG at Oct.2006 (0.3-210) months. [8] but different from Abboud study 2008 (8-72) months [4]
The median age was 15 months which is lower than Abboud study (32 months) [4], Sebastian O.Ekenze et al , median age is (5 yr) [6]. AL-Mulhim study (Saudia Arabia) 1998 (22 months) [9], & (36 months) in London et al (U.S.A) 2005[10] .
Fifty percent of cases occur below 1 year of age which is similar to AL-Sheyyab study (86%) of cases occur in (0-4yr.) [5] and different from Abboud study (75%) of cases occur in (1-5yr.) age group [4] and Sebastian O.Ekenze et al (53.3%) of cases occur in (5-9) yr [6] as well as London et al (64%) of cases above 1 year [10], in H-Shroeder et al (Denmark) 2009 (36.2%) occur in (24-59) months [11] . Male to female ratio equal to 0.63:1, in AL-Sheyyab study 1.77:1 [5] , AL-Mulhim study 1.5:1 [9] , in TPOG study ratio was 1.01:1 [10], this difference may be due to pooling of patients to our hospital.
The common site of origin is abdominal mass (67%) which is similar to AL-soodany study (68.9%) [7] , In Abboud Study it represents (97.7%) [4], Sebastian O.Ekenze et al (66.6%) [6], AL-Mulhim study (70%) [9] ,TPOG study (59%)[10], H-Shroeder et al (80.6%) [11].
Weight loss is the most common symptom present in our study (100%) which is higher than AL-Mulhim study , weight loss found in (35%) [9] .Abdominal distention found in (78%) of cases which is higher than reported elsewhere, (64%) [4] , (20 %) [7] , (55 %)[9] respectively .Fever present in (22%) of cases which is approximately similar to Abboud Study (20.5%) [4] & lower than AL-soodany study (52%) [7] , AL-Mulhim study it represents in (40%) of cases [9]. Diarrhea found in (16.6 %) of cases which is higher than AL-Mulhim study (1%)[9].This mean that Para neoplastic syndrome is more in our patients. Pallor found in (38.8 %) of cases which is higher than Abboud Study (14.9 %) [4] and AL-Mulhim study (25 %) [9] , this means that our patients may have more bone marrow involvement or the tumor aggravated the already existing anemia. Hepatomegaly found in (16.6%) of cases which is approximately similar to Abboud Study (12.8%)[4] and lower than AL-soodany study (38 %)[7].Eye involvement (raccoon eye and

proptosis) found in (22%) of cases which is similar to AL-soodany study (23 %) [7] and higher than Abboud Study (12.8%) [4] and AL-Mulhim study (10 %)[9], this indicates more distant metastatic infiltration in our patients. Opsclonosmyoclonos found in (5.5 %) of cases which is similar to AL-Mulhim study (5%) [9] .

In this study diagnosis was established by fine needle aspirate in (50%) of cases while in TPOG study the most common method of diagnosis is by mass resection and histopathological examination in (85%) [8], in this study fine needle aspirate is done either because the mass is feasible as in (scalp nodule), or the mass is very large (abdominal) and operation is very difficult as the patient need preoperative debulking in addition to poor surgical cooperation.

The most common stage at presentation was stage IV (50%) followed by stage III (44%), this is similar to Abboud study in which stage IV represents (45%) and stage III (32.5 %) [4] , Sebastian O. Ekenze et al stage IV (40%) stage III(46.7%) [6], TPOG study stage IV(43%) [8] , Al-Mulhim study stage IV (35%) stage III (30%) [9] , London et al stage IV (44%) [10] , H-Shroeder et al stage IV(52.5%) and stage III (16.9%) [11], David L.Baker et al stage IV (37%) stage III (56.3%) [12] ,this mean that the common stage of neuroblastoma in our country and surrounding and abroad is stage IV and stage III and both of these are late stages which indicates that the early presentation is passed unnoticed by the patient until the disease become advanced .

High risk group is the common risk group in our study (56%) which is similar to TPOG study (59%) of cases occur in high risk group [8] .This is also related to the late presentation and delay diagnosis. The outlook in patients with stage III& II with intermediate risk is better than those with advanced stage IV& III

Bone metastases is found in (49.8 %) of cases which is higher than Abboud study (30%) [4],AL-soodany study (24%) [7] , TPOG study (8%) [8] AL-Mulhim study (25%) [9] while Bone marrow involvement at time of diagnosis notice in (38.8%) of cases which is approximately similar to Abboud study (35%) [4] and Seo-Jin Park et al (30%) [13] and higher than TPOG study (6%) [8] and AL - Mulhim study (15%) [9]. Liver involvement found in (16.6 %) of cases which lower than Abboud study (30%) [4] and similar to AL-Mulhim study (15%) [9] .

Regarding the outcome of patients four patients (22%) relapsed compared to TPOG study (13.2%) had relapsed [8] . Seven patients (39%) survive the condition and on follow up which is higher than Sebastian O.Ekenze et al (14 %) [6]. Three patients died (17%) one not related to disease , it's due to congestive heart failure and other due to disease progression which may be explained by resistant to chemotherapy and the third one was lost to follow up. In Sebastian O. Ekenze et al (57.7%) of cases died because of chemotherapy toxicity [6] , in TPOG study (5%)of cases died [8] , AL -Mulhim study (40%) of cases died [9] , H-Shroeder et al (56.9%) of cases died [11] ,in David L. Baker et al study (4.2%) died, the primary cause the disease itself [12] .

Delayed presentation was a hindrance in the management of our patients and this may be due to delay in referral from the peripheral hospital, ignorance of the problems by the parents and sometimes poverty may play role in our society. It is also evident from this study that a substantial number of children did not comply with the treatment protocol. Common reasons adduced for non-compliance was inability to afford to buy some of the chemotherapeutic drugs that were not available in our center

CONCLUSION:

The majority of cases were recognized during the first two years of age, female were involved more than male. The main presentation was abdominal mass. The commonest symptoms is weight loss .Fifty percent of cases had advanced diseases stage IV. The majority of cases occurred in high risk group despite that the outcome of treated cases was good and accepted.

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