CLINICOPATHOLOGICAL ANALYSIS AND CLASSIFICATION OF NEUROBLASTIC TUMOURS - EXPERIENCE OF PAEDIATRIC HOSPITAL

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ABSTRACT: BACKGROUND: Neuroblastomas are the most common extracranial solid tumors in infancy and childhood. They are biologically distinctive and interesting paediatric tumors. Neuroblastoma is an embryonal malignancy of sympathetic nervous system arising from neuroblasts. **AIMS AND OBJECTIVES:** The objective of the present study is to study the spectrum, morphological features of neuroblastic tumors and to classify the tumors applying the International Neuroblastoma Pathology Classification (INPC). **MATERIAL AND METHODS:** This is a 4.5 year retrospective study undertaken at Department of pathology, Paediatric Referral Hospital, Hyderabad. A total of 41 cases of neuroblastic tumors were included in our study from January 2004 to June 2009. The Haematoxylin and eosin stained slides were evaluated for histopathological features including differentiation, presence or absence of Schwannian stroma and Mitotic-Karyorrhectic index (MKI). They were clinically staged using International Neuroblastoma staging System (INSS) and graded according to International Neuroblastoma Pathology Classification (INPC). **OBSERVATIONS AND RESULTS:** The commonest age group was found to be less than 1.5 years and more common in boys. The most common presenting site was adrenal gland (36.5%) followed by retroperitoneum (31.7%). Most of the patients presented in advanced clinical stage (Stage 4) with mass abdomen as the presenting symptom (41.4%). Of the 41 cases, 14 were observed as favourable histology (FH) subgroup while 27 as unfavourable histology (UH) subgroup.

CONCLUSION: INPC has formulated the classification of neuroblastic tumors based on grade of neuroblastic differentiation and MKI value linked with age at presentation. Histopathologic prognostication permits early identification of the patient at risk of relapse or fatal outcome.

KEYWORDS: Neuroblastoma, Mitotic Karyorrhectic Index, International Neuroblastoma staging System (INSS), International Neuroblastoma Pathology Classification (INPC).

INTRODUCTION: Neuroblastomas are the most common extracranial solid tumours accounting for 8% to 10% of all paediatric cancers^[1]. They come under the biologically distinct and interesting paediatric small round cell tumours.

The historical evidence of Neuroblastoma as a malignant disease of childhood dates back to 1864 when German physician Sir Rudolf Virchow for the first time described its histological appearance^[2].

Many clinical manifestations of Neuroblastoma are related to the tumour site, metastatic disease and its metabolic tumour byproduct. The most common site of neuroblastoma is abdomen arising in the adrenal gland followed by thorax, pelvis and rarely neck and head^[1]. Neuroblastoma is one of the unusual human malignancies known to display spontaneous regression from undifferentiated to a completely benign cellular form^[3].

International criteria for a common neuroblastoma staging system were first described in 1988 and consequently revised in 1993. The International Neuroblastoma Staging System (INSS) is based on clinical and pathological criteria used in staging of the disease and to stratify treatment protocols^[4].

With some modifications, the International neuroblastoma pathological committee in 1999 has accepted, the classification system for neuroblastic tumours suggested by Shimada et al. in 1984. The International Neuroblastoma Pathological Classification (INPC) was again revised in 2003^[5]. It is the most accepted classification for neuroblastic tumours recognized for its prognostic value.

The INPC distinguishes a favorable histology group from an unfavorable histology group of Neuroblastic tumours by applying the concept of age dependent normal ranges of morphologic features, such as Schwannian stromal development, grade of neuroblastic differentiation, and mitosis karyorrhexis index.

According to INPC, Neuroblastic tumours were morphologically classified into Neuroblastoma, undifferentiated; poorly differentiated and differentiating subtypes, ganglioneuroblastoma intermixed, Ganglioneuroblastoma nodular and Ganglioneuroma^[5].

The most significant clinical variables that predict patient outcome include stage of disease (INSS), patient's age at diagnosis and the site of the primary tumour. Patients with early stages (1, 2 and 4S) have better outcomes, while those with advanced stages (3 and 4) have poor survival. Infants below the age of 1 year have significantly better outcome than older patients with the same stage of disease. Patients with adrenal gland as the location of their primary tumours have poorer outcome than patients with tumours arising at other sites^[3].

In the present study, the spectrum, morphological features of neuroblastic tumours were studied and the tumours were categorised applying the International Neuroblastoma Pathology Classification (INPC).

MATERIALS AND METHODS: In the present study, we evaluated 41 cases of Neuroblastic tumours at the department of Pathology, Paediatric Referral Hospital, Hyderabad, for a period of 4.5 years from January 2004 to June 2009. Detailed history of the patient including age, chief complaints, present, past, family history were documented. The clinical examination, with relevant investigations was done. Radiological and histopathological examinations were carried out and bone marrow aspiration was performed in some cases. Immunohistochemistry was performed using chromogranin A (DAKO-Polyclonal rabbit anti Chromogranin antibody) to differentiate undifferentiated neuroblastoma subtype from other small round cell tumours.

For the assessment of the Mitotic - Karyorrhectic Index, we used the method published by Joshie et al. (1996)^[6]. Average number of mitotic and karyorrhectic cells were counted in 10 or more randomly chosen suitable fields of approximately 5000 tumour cells and the MKI assessed. The denominator for MKI is 5000 neuroblastic cells.

One of 3 MKI classes is documented:

- 1) Low MKI with, 2% mitotic and karyorrhectic cells,
- 2) Intermediate MKI with 2–4% mitotic and karyorrhectic cells, and
- 3) High MKI with 4% mitotic and karyorrhectic cells.

The patients were classified into Favourable histology (FH) and Unfavourable histology (UH) subgroups based on INPC and clinically staged using INSS.

RESULTS: In the present study the age wise incidence showed age group ranging from neonate to 13 years. Majority of the patients were aged below 1.5 years (51.2%) (Table 1). Of 41 cases, 30 were male children and 11 were female. Male to female ratio was 3:1.1 with male preponderance.

In our study, majority of the cases 17/41(41.4%) presented with mass abdomen(Figure 1A,1B) . 9/41 (21.9%) cases presented with secondary deposits at various sites like bone marrow (4cases), lymph nodes (3 cases), multiple skeletal metastasis (2 cases), scalp(Figure 1A)and orbital metastasis one case each. In one case paraplegia was observed which was due to paraspinal region involvement.(Table 2) In about 4/41 cases the bone marrow aspiration smears showed tumour deposits (Figure 11).

Among 41 cases of neuroblastoma studied, the most common primary location was adrenal gland comprising of 15/41(36.5%)(Figure 2). Next common site was retroperitoneum 13/41 (31.7%)(Figure 3). Mediastinum was the site of primary tumour in 04/41 (9.7%) of cases (Figure 4). In 03/41 (7.3%) of cases pelvis was the primary site of tumour origin patients presented with retention of urine and difficulty in defecation. Other primary sites encountered in this study were isolated case of head and neck swelling presenting with a neck mass.

Clinical staging according to INSS, majority of the cases presented in advanced stage (Stage 3&4) 58.4%. (Table 3)

The most common gross morphological feature was hemorrhagic areas (20/41). Areas of calcification were observed as chalky white areas and gritty to cut, these were seen in 10/41(24.3%) of cases (Figure 2).

In our series majority were Neuroblastoma, undifferentiated subtype (Figure 5), 20/41 (48.7%) and all were confirmed by Immunohistochemistry using Chromogranin A(Figure 7).Among these cases majority were in the age group below 5years18/20 (90%). Among poorly differentiated subtype (Figure 8) majority of the cases 9/16 (56%) occurred below the age group of 1.5 years.2

cases of differentiating subtype(Figure 9)and 2 cases of Ganglioneuroblastoma intermixed(Figure 10)affected the patients in the age group of 1.5 years.(Table 4)

Among the undifferentiated tumours majority had the high MKI value of 12/20 (60%)(Figure 6), and only 3/20 (15%) had low MKI value. Poorly differentiated tumours showed high MKI value in 2/16(12.5%). In both differentiating and ganglioneuroblastoma, MKI value was low. (Table 5)

International Neuroblastoma Pathology Classification of neuroblastic tumours was done for grading. Of the 41 cases, 14 were under favourable histology (FH) subgroup while 27 under unfavourable histology (UH). All the undifferentiated tumours were categorized into unfavourable histology, MKI was high in about 12/20 (60%). Among the poorly differentiated type 9/16 are favourable, 7/16 are unfavourable subtype. All the cases of differentiating and ganglioneuroblastoma were classified into favourable subtype, showing low MKI. (Table 6)

DISCUSSION: Neuroblastoma remains the third most common malignancy of the childhood and constitutes about 15 percent of cancer related deaths in children. Despite the usage of increasingly aggressive combined modality treatments which have improved the remission rate and duration, the long term survival for stage 4 disease has persisted to not more than 15 percent. Neuroblastoma has been associated with molecular genetics and other biologic differences, which may lead us to a better understanding of the pathophysiology and precise treatment [7].

Nearly 70% of patients, irrespective of age, present with metastatic disease. Spread is common to bone marrow, bone, liver, lymph nodes, and skin. Clinical symptoms at presentation are directly related to the site of tumour involvement. Patients presenting with abdominal disease can have symptoms of distension, swelling, pain, and bowel obstruction.

Metastatic disease chiefly presents with symptoms related to various sites of involvement, including localized pain, painful gait, and periorbital swelling and ecchymoses. Neuroblastoma spread to the skin is usually seen in infants INSS, Stage 4S disease with skin lesions showing bluish discoloration. Rarely Opsoclonus-myooclonus syndrome may occur with disconjugate eye movements, muscle jerking, and unsteadiness and has more favorable disease outcome [1].

Jereb et al. (1984)[8]reported the age range of neuroblastic tumours to be 0 to 23 months; Nyari et al. (2006) [9]1 day to 14 years; while Stephen et al. (2012)[10]stated the age range to be 2 to 8 years. Our results are consistent with studies done by Nyari et al., Jereb et al. and Stephen et al.

Ladenstein et al. (1995)[11]evaluated 117 patients with neuroblastoma. The male to female ratio was 1.18:1, with slight male preponderance. Studies by El-Sayed et al.(2010)[12] and Shuangshoti et al. (2012)[13]similarly documented male preponderance. Our results are consistent with the available literature.

In a study done by Kusuma kumary et al. (1998)[14] adrenal gland was the most common site of origin (54.9%) for neuroblastic tumours followed by Retroperitoneum (19.8%). Mag et al. (1999)[15] similarly reported adrenal gland to be the most common primary site (88%). The adrenal gland(50%)was the most common location according to Stephen et al. (2012)[10]. Our studies confirm the findings by Mag et al., Kusuma kumary et al., Joshi et al. and Stephen et al.

In a series reported by Takeuchi et al. (1995)[16]35.4% of cases presented with INSS Stage 4; Ibrahim et al. (1998)[17]documented 35% of the cases presenting with Stage 4, while Goto et al. (2001) [18]reported 39.6%with Stage 4, Matthias et al. (2002)[19] stated that there were 34.1% of

cases with clinical stage 4. The present study shows 36.5% cases presenting with INSS stage 4 as reported by other authors. Most of the cases (55.6 %) in our study presented with advanced stages which included stage 3 and 4. Studies by Goto et al., Kusuma kumary et al. revealed similar results with neuroblastic tumours presenting in advanced stages (Table 7).

Among the morphological patterns, poorly differentiated subtype, Neuroblastoma was predominant in the study by Shimada et al. (1999)^[20] with 69.1%, Hideki et al. (2006)^[21] with 71.9%, and Samuel et al. (2006)^[22] with 67%. In our present series undifferentiated neuroblastoma was predominant comprising 48.7% of cases which was in contrast with other studies (Table 8).

Shimada et al. (1999)^[20] reviewed 227 neuroblastic tumours. Among these cases, 196 were available for study of age distribution and clinical stage by the International Neuroblastoma Pathology Classification. Favourable histology was seen in 103 cases and Unfavourable in 93 cases. 76.6% of the cases with age < 1 year showed favourable histology. In patients with age ≥ 1 year, Unfavourable histology was seen in 69.6% whereas. Patients with Low risk and less advanced stages (Stage 1, 2 and 4S) at presentation had favourable histology in 78.5%. In patients with advanced stages (Stage 3, 4), unfavourable histology was seen in 70.9%.

In this present study we reviewed 41 neuroblastic tumours for study of age distribution and clinical stage by the INPC. Favourable histology was seen in 14 cases and Unfavorable in 27 cases. 72.7% of the cases with age < 1 year showed favourable histology and 18.6% showed unfavorable histology. In patients with age ≥ 1 year, Unfavourable histology was seen in 81.4% whereas, 27.3% of the cases showed favourable histology. Patients with less advanced stages (Stage 1, 2 and 4S) at presentation had favourable histology in 81.8% while unfavorable in 18.6% of the cases. In patients with advanced stages (Stage 3, 4), unfavourable histology was seen in 81.4% and favourable histology in 18.2% of the cases. Our findings were similar to that reported by Shimada et al. (1999) (Table 9).

Thus the infants under the age of 1 year, less advanced stages (Stage 1, 2 and 4S) and with favourable histology subtype had a better prognosis in contrast to the those patients aged above 1 year, advanced stages and unfavourable histology.

CONCLUSION: INPC has formulated the classification of neuroblastic tumours based on grade of neuroblastic differentiation and MKI value associated with age at presentation. Histopathological prognostication permits early identification of the patients at risk of relapse or fatal outcome. Majority of the patients in early clinical stage showed low MKI, while in advanced clinical stage high MKI was documented, showing that clinical behavior and morphological features of the tumours have better correlation. Thus it is possible on histopathology to predict the clinical behavior of the tumours. Neuroblastoma is a heterogeneous tumour that correlates significantly with the prognosis for recovery of the patient. Age, stage and biological features encountered in the tumour cells are important prognostic factors and are used for stratification of patients at risk and subsequently the preferred treatment.

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Table 1: Age wise incidence of Neuroblastoma in our study.

AGE (YEARS)	NO. OF CASES (41)	PERCENTAGE
<1.5	21	51.2%
1.5-5	16	39.0%
>5	04	09.7%

Table 2: Clinical Presentation of Neuroblastic tumours in our study.

PRESENTING SYMPTOM	NO. OF CASES (41)	PERCENTAGE
Mass abdomen only	17	41.4%
Mass abdomen and fever/weight loss/pallor/jaundice	07	17.0%
With metastatic deposits	09	21.9%
Shortness of breath	01	2.4%
Delayed milestones	01	2.4%
Difficulty in passing urine	01	2.4%
Jaundice	01	2.4%
Paraplegia and urinary retention	01	2.4%

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Table 3: Clinical Staging According To International Neuroblastoma Staging System (INSS) Of Neuroblastic Tumours in our Study.

CLINICAL STAGE	NO. OF CASES (41)	PERCENTAGE
1	02	4.8%
2	15	36.5%
3	09	21.9%
4	15	36.5%
4s	-	-

Table 4: Histopathological subtypes of neuroblastic tumours in different age groups in our study.

AGE YEARS	Undifferentiated neuroblastoma		Poorly differentiated neuroblastoma		Differentiating neuroblastoma		Ganglioneuroblastoma intermixed	
	No. Of cases(20)	%	No. Of cases(16)	%	No. Of cases(2)	%	No. Of cases(3)	%
<1.5	9	45%	9	56%	2	100%	2	66.6%
1.5-5	9	45%	5	31.2%	0	0%	0	0%
>5	2	10%	2	12.5%	0	0%	1	33.4%

Table5: MKI in Histopathological subtypes of Neuroblastic tumours in our study.

MKI	Undifferentiated neuroblastoma		Poorly differentiated neuroblastoma		Differentiating neuroblastoma		Ganglioneuroblastoma intermixed	
	No. of cases(20)	%	No. of cases(16)	%	No. of cases(2)	%	No. of cases(3)	%
Low	3	15%	11	68%	2	100%	3	100%
Inter mediate	5	25%	3	18.7%	0	0%	0	0%
High	12	60%	2	12.5%	0	0%	0	0%

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Table 6: International Neuroblastic Pathological Classification of Neuroblastic tumours in our study.

Histological variants	Age	MKI (41)			N=41	
		Low	Intermediate	High	FH	UH
Undifferentiated Neuroblastoma	<1.5y	0	4	5	0	9
	1.5-5y	2	1	6	0	9
	>5y	1	0	1	0	2
Poorly differentiated neuroblastoma	<1.5 y	6	3	0	9	0
	1.5-5y	4	1	1	0	6
	>5y	0	0	1	0	1
Differentiating neuroblastoma	<1.5y	2	0	0	2	0
Ganglioneuroblastoma intermixed	<1.5Y	1	0	0	1	0
	1.5-5y	1	0	0	1	0
	>5y	1	0	0	1	0
Total		18	9	14	14	27

Table 7: Comparison of clinical stage of presentation according to International Neuroblastoma Staging System among different studies.

INSS Stage	Takeuchi ¹⁶ et al	Ibrahim ¹⁷ et al	Goto ¹⁸ et al	Matthias ¹⁹ et al	Kusuma kumari ¹⁴ et al	Present study
1	35.4%	0%	11.4%	09.9%	4.3%	4.8%
2	10.4%	30%	20.8%	13.0%	6.5%	36.5%
3	8.3%	30%	21.8%	25.4%	25%	21.9%
4	35.4%	35%	39.6%	34.1%	58.6%	36.5%
4S	10.4%	5%	6.8%	17.3%	4.3%	0

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Table 8: Comparative studies on histopathological variants of Neuroblastic tumours.

Histological variants	Shimada ²⁰ et al N=224	Hideki ²¹ et al N=746	Samuel ²² et al N=115	Present study N=41
Neuroblastoma-undifferentiated	2.6%	1.3%	0	48.7%
Neuroblastoma-poorly differentiated	69.1%	71.9%	67%	39.0%
Neuroblastoma – differentiating	6.6%	11.1%	02%	4.8%
Ganglioneuroblastoma – intermixed	2.2%	4.0%	13%	7.3%
Ganglioneuroma	0	1.3%	12%	0%
Ganglioneuroblastoma-nodular	8.4%	10%	0	0

Table 9: Comparative study of neuroblastoma with respect to INPC at different age groups and clinical stages.

	Shimada ²⁰ et al. n=193		Present study n=41	
	FH N=103	UH N=93	FH N=14	UH N=27
Age				
<1 year	69.9%	23.6%	72.7%	18.6%
>1year	30.1%	76.3%	27.3%	81.4%
CLINICAL STAGE				
1+2+4s	70.8%	21.5%	81.8%	18.6%
3+4	29.1	78.4%	18.2%	81.4%

FIGURES

Figure 1: A: 2 year male child presented with mass abdomen and scalp metastasis. B: 2 year female child presented with abdominal mass

Figure 2: Gross morphology of Neuroblastoma. A: Left Adrenal mass, well encapsulated globular soft tissue mass measuring 4x3.5x3 cm. B: Cut section: Grey brown to grey white, with areas of hemorrhages. At foci showing chalky white areas indicating calcification.

Figure 3: Gross morphology of Neuroblastoma. A: Retroperitoneal Mass, well encapsulated, globular mass measuring 4.5x3x2.5 cm B: Cut section: Loss of architecture of the kidney, cortex and medulla are not demarcated. Grey white to grey brown, with cystic areas

Figure 4: Gross morphology of Neuroblastoma. A: Mediastinal Tumour, Globular soft tissue mass measuring 4x4x3 cm. B: Cut section: grey white to grey brown with solid and cystic areas largest cyst measuring 2cm in diameter.

Figure 5: Microphotographs of Neuroblastic tumours. A: Undifferentiated neuroblastoma (Haematoxylin and Eosin 10x) B: Undifferentiated neuroblastoma. (Haematoxylin and Eosin 40x)

Figure 6: Microphotographs of Neuroblastic tumours.

A: Undifferentiated neuroblastoma cells showing karyorrhectic bodies (Haematoxylin and Eosin 100x)

B: Undifferentiated neuroblastoma cells showing high mitotic activity (Haematoxylin and Eosin 40x).

Figure 7: Microphotographs of Neuroblastic tumours. A: CHROMOGRANIN A cytoplasmic positivity for undifferentiated neuroblastoma (Haematoxylin and Eosin 10x) B: CHROMOGRANIN A cytoplasmic positivity for undifferentiated neuroblastoma. (Haematoxylin and Eosin 40x)

Figure 8: Microphotographs of Neuroblastic tumours. A: Poorly differentiated neuroblastoma (Haematoxylin and Eosin 10x) B: Poorly differentiated neuroblastoma with homer wright pseudo rosettes. (Haematoxylin and Eosin 40x)

Figure 9: Microphotographs of Neuroblastic tumours. A: Differentiating neuroblastoma (Haematoxylin and Eosin 10x) B: Differentiating neuroblastoma. (Haematoxylin and Eosin 40x)

Figure 10: Microphotographs of Neuroblastic tumours. A: Ganglioneuroblastoma showing both neuroblastic and ganglionic components (Haematoxylin and Eosin 10x) B: Ganglioneuroblastoma. (Haematoxylin and Eosin 40x)

Figure 11: Microphotographs of Neuroblastic tumours. A: Bone marrow smears showing tumour deposits, 10x. B: Bone marrow smears showing tumour deposits 40x.