



Original Research Article

Neuroblastoma: A study of the clinicopathologic characteristics and prognosis based on Mitotic Karyorrhectic Index

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ABSTRACT

Introduction: This retrospective study conducted at the Department of Pathology, Government Medical College, Thiruvananthapuram, Kerala, India, included all cases of Neuroblastomas received during the 5 year period- January 2004 to December 2008.

Materials and Methods: Resected specimens and Incisional biopsy specimen's/ lymph nodes of size more than 2x2 cm were included as per International Neuroblastoma Pathology Committee (I.N.P.C) criteria. The specimens were then classified into Undifferentiated (confirmed by Immunohistochemistry), Poorly Differentiated and Differentiating. Patient details and 3 year Follow up were obtained by communication with treating doctors and reviewing hospital records.

Results: During the 5 year period we received 38 specimens of Neuroblastomas, one specimen was rejected as it was less than 2x2 cms. The study was hence carried forth on 37 cases- 27 post-chemotherapy and 10 pre-chemotherapy. The Clinicopathologic features studied included Age, Sex, Clinical presentation, Tumor location, Preoperative Chemotherapy and the Gross and Microscopic features. Mitotic Karyorrhectic Index (M.K.I) was determined in the ten pre-chemotherapy cases.

Conclusion: The Ten Pre-chemotherapy Neuroblastomas were subclassified into Favorable and Unfavorable histology based on three parameters- Age, Histological Differentiation and M.K.I. Five cases belonged to Favorable group and Five to the Unfavorable group. One case was lost to follow up from both the groups respectively. The remaining 4 Favorable cases are doing well on follow up. In the Unfavorable group 3 cases expired and 1 is doing well. As M.K.I could not be determined, the 27 post -chemotherapy cases were followed up with age and histologic differentiation alone.

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1. Introduction

Neuroblastoma is the second most common solid malignancy of childhood after brain tumors accounting for 7-10% of all pediatric neoplasms, and as many as 50% of malignancies diagnosed in infancy.¹ Young and co-workers² estimate the prevalence at about 1 case per 8000-10,000 live births. The overall male: female ratio is about 1.2:1 in combined series.^{3,4} Over 80% of these tumors are detected in children under 4 years of age with exceptional but typical occurrence in adult age group.⁵ Clinical presentation is diverse- may present as enlarging

mass, metastasis or as paraneoplastic syndromes.³

Both familial and sporadic forms have been described with reports of autosomal dominant pattern of inheritance in the former.⁶ Recent Studies points to mutations of Anaplastic Lymphoma Kinase (ALK) gene as cause in Familial and some Sporadic cases and this has encouraged studies with ALK inhibitors as treatment.⁷ From a genomic standpoint, neuroblastoma occurs in the setting of chromosomal losses and gains, associated with good and bad prognosis.⁸ Most common are amplification of MYCN oncogene, gain of chromosome 17q and deletions of 11q and 1p.⁹

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The tumors are notoriously heterogeneous in their clinical behavior¹⁰ which can range from spontaneous regression, maturation to a benign disease, or being a highly aggressive metastatic disease with relapse and death.¹¹ It accounts for approximately 15% of all cancer-related deaths in the pediatric population.³ The histopathologic appearance mirrors its clinical heterogeneity which is evident by the numerous classifications that have been in use for these tumors. The latest accepted pathologic classification is that based on the recommendations of the International Neuroblastoma Pathology Committee (I.N.P.C), 1999 and partly revised in 2003.^{12,13} This system takes into account the degree of cell differentiation, Mitotic Karyorrhectic Index (M.K.I), and the age.¹³ Based on these parameters the tumors are classified into a Favorable prognosis group and an Unfavorable group.

2. Materials and Methods

All cases diagnosed as Neuroblastoma during the period January 2004 to December 2008 in the Department of Pathology, Government Medical College, Thiruvananthapuram were included in the study. For biopsy specimen and resection specimen from the same patient, the biopsy was included, as resection specimens were post-chemotherapy. Patient details and three year follow up were obtained by communication with treating doctors and reviewing hospital records.

Specimens were categorized as Resection specimens and Incisional Biopsy specimens / Lymph nodes. Biopsy specimens of less than 2x2cm size were not included in the study as per the I.N.P.C guidelines. For prognostic categorization only pre-therapy tissue samples were included. All the specimens received were fixed in 10% formalin.

Gross features like weight of specimen in grams, size in centimeters, necrosis, hemorrhage, calcification, cystic change, nodularity and lymph nodes (adherent/ non-adherent to capsule) were noted.

For resected specimens, sections were taken from grossly heterogeneous areas, any normal tissue if present, and from lymph nodes. For biopsy specimens the tissue was all embedded. The tissues were processed, paraffin embedding was done and sections were stained with Haematoxylin and Eosin. Multiple serial sections were also taken and studied. Based on the size of the specimen, the number of slides studied varied from One (with 2-3 sections per slide) in cases of incisional biopsy to Ten (with 2-3 sections per slide) in case of resection specimens.

Neuroblastomas (NB) were classified as per I.N.P.C criteria^{12,13} into three subgroups-NB Undifferentiated, NB Poorly differentiated and NB Differentiating. The diagnosis of Undifferentiated neuroblastoma was confirmed by a panel of immunohistochemical markers that included Neuron Specific Enolase, Desmin and Leucocyte Common

Antigen.

The Mitosis Karyorrhexis Index (M.K.I)¹⁴ was determined for pre-treatment cases of Neuroblastomas by actual counting under high power (400X) field. The cell density and average number of tumor cells was first determined in different high power fields. Areas of necrosis, poor preservation, hemorrhage and crush artifact were avoided. On an average areas of sparse, moderate and dense cellularity contain 200, 400, 800 cells / high power field respectively. Total of 5000 cells were counted. The number of cells showing mitosis and karyorrhexis (Crescentic, lobulated, neutrophil-like, punctuate, do-nut shaped or star shaped fragmented nuclei) were then determined. Lymphocyte-like condensed nuclei can represent both apoptosis and necrosis and were hence not included.

M.K.I was then expressed as percentage of cells with mitosis and karyorrhexis to the total number of cells. The Neuroblastoma cases were then assigned one of 3 MKI classes, i.e., Low-MKI (<100/5000 cells or <2%), Intermediate-MKI (100– 200/5000 cells or 2-4%), or High-MKI (>200/ 5000 cells or >4%), after the number of mitotic and karyorrhectic cells per 5000 denominator cells was calculated.

The cases were then classified into a Favorable and Unfavorable prognostic category as per the I.N.P.C guidelines based on three parameters, 1. Age, 2. Histologic Differentiation, and 3.M.K.I. (Table 1)

The next step was assessment of 3year prognosis, which was obtained from hospital records and discussing with treating doctors.

3. Results

During the 5 year study period we received 38 cases of Neuroblastomas- of which 27 were resection specimens and 11 were biopsies. One biopsy was less than 2x2cms and was hence not included. Hence the study was carried forth on 37 cases.

The clinicopathologic features analyzed are as follows.

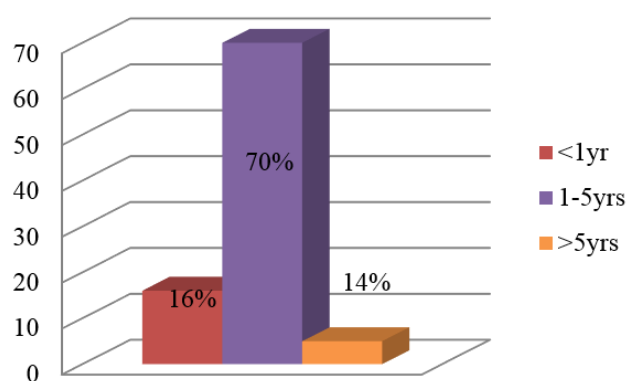


Fig. 1: Age

Table 1: Prognostic categories of neuroblastoma as per INPC criteria^{12,13}

Age	Differentiation	M.K.I	Prognostic Category
<1.5yr	Undifferentiated	Any	Unfavorable Histology
<1.5yr	Poorly Differentiated or Differentiating	Low or Intermediate	Favorable Histology
<1.5yr	Any	High	Unfavorable Histology
1.5-5yr	Undifferentiated or Poorly Differentiated	Any	Unfavorable Histology
1.5-5yr	Differentiating	Low	Favorable Histology
1.5-5yr	Differentiating	Intermediate or High	Unfavorable Histology
>5yr	Any	Any	Unfavorable Histology

Table 2: Classification and follow up

Age	Differentiation	M.K.I	Category	3 year Follow up
<1yr	Differentiating	<2%	Favorable	Doing well
<1yr	Differentiating	2-4%	Favorable	Doing well
<1yr	Differentiating	2-4%	Favorable	Lost to follow up
1-5yrs	Differentiating	<2%	Favorable	Doing well
1-5yrs	Differentiating	<2%	Favorable	Doing well
1-5yrs	Differentiating	2-4%	Unfavorable	Expired
1-5yrs	Differentiating	>4%	Unfavorable	Lost to follow up
>5yrs	Differentiating	2-4%	Unfavorable	Expired
<1yr	Undifferentiated	<2%	Unfavorable	Doing well
1-5yrs	Undifferentiated	<2%	Unfavorable	Expired

Table 3: Age [p value = 0.1284 - Not Significant]

Age	Doing well	Relapse / Expired
≤1yr	5	0
>1yr	14	12

Table 4: Differentiation [p value = 0.7054 – Not Significant]

Differentiation	Doing well	Relapse / Expired
Differentiating	13	7
Poorly Differentiated / Undifferentiated	6	5

Table 5: M.K.I [p value = 0.4643 – Not Significant]

M.K.I	Doing well	Relapse / Expired
≤2% <2%	4	1
>2%	1	2

None of the p values calculated were significant due to less number of cases in the study.

3.1. Age

The age range varied from 4months to 9years with one case in the adult age group, 34 years. The most common group was between 1–5 years accounting for 26 cases [70%], 6 cases were in the <1yr group (16%), 5 belonged to the >5

yr group (14%) [Figure 1]

3.2. Sex

There was a male predominance with 23 males (62%) compared to females (23%) [M:F = 1.6 :1]

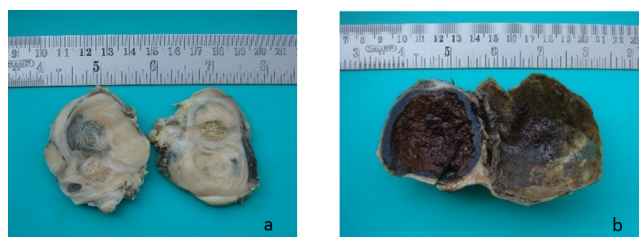


Fig. 2: Cut surface of Neuroblastomas. **a):** Well circumscribed solid cut surface with specks of calcification (Histology- Neuroblastoma Differentiating) **b):** Predominantly cystic with hemorrhage (Histology- Neuroblastoma Poorly Differentiated)

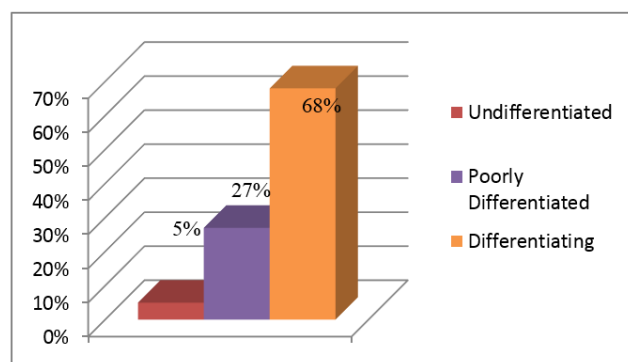


Fig. 3: Neuroblastoma subtypes

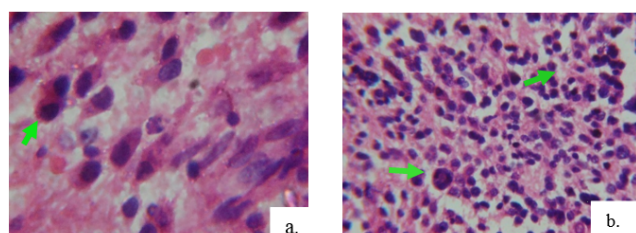


Fig. 4: Photomicrographs showing; **a):** Mitosis (100x); **b):** Karyorrhexis (40x)

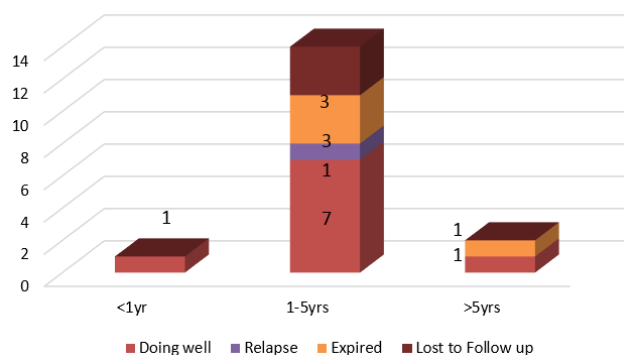


Fig. 5: 3 year follow up of differentiating neuroblastoma

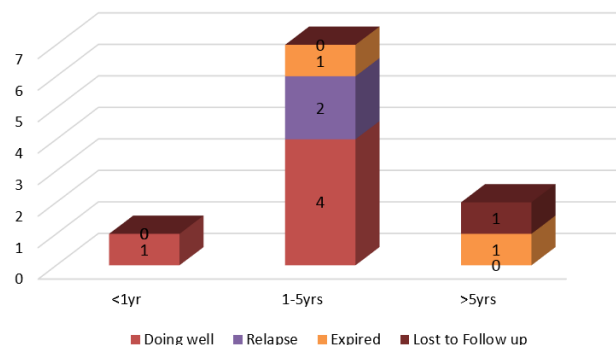


Fig. 6: 3 year follow up of poorly differentiated neuroblastoma

3.3. Clinical presentation

The most common presenting complaint was as an abdominal mass, 30 cases [81%] of whom 5 cases subsequently developed metastasis in - liver (3 cases), lymph nodes (1 case) and bone marrow (1 case). Of the remaining 7 cases of neuroblastoma, the presenting complaint was lymph node metastasis in 2 [5%] and ataxia/opsoclonus in 5 cases [14%]. No syndromes were identified in any of the cases.

3.4. Tumor location

The adrenal gland was the commonest location of neuroblastomas (81%), the rest were located in the mediastinal (11%) and paravertebral (8%) regions.

3.5. Preoperative chemotherapy

All the resection specimens of neuroblastomas- 27 (77%) received had history of pre-operative chemotherapy. The remaining 10 cases (23%) of incision biopsy specimens had no chemotherapy.

3.6. Gross features

The weight of the resection specimens ranged from 10gms to 300gms with majority (10 cases) having weights between 20-40gms. The sizes of the specimens ranged from 15cms in greatest diameter to 5cms. Among Incision biopsies, only those that measured > 2x2cms were included.

All but one specimen were well circumscribed with the typical appearance of grey-white lobulated growth with variable calcification, cystic change, hemorrhage and necrosis. [Figure 2] The other showed infiltration into adjacent fat. The most common features seen on gross examination were hemorrhage (26 cases) and necrosis (17 cases). None of the cases had adherent lymph nodes. Eleven cases had associated non-adherent lymph node enlargement of which seven cases showed metastases. The post chemotherapy cases showed extensive areas of fibrosis

and hyalinization. Areas of necrosis were also noted.

3.7. Microscopy

The classification of the tumors was done as per the I.N.P.C criteria.^{12,13} The Neuroblastoma cases that we received belonged predominantly to the differentiating category [68%] with 5-50% of the neuroblasts showing ganglionic differentiation in a background of neuropil and most showing areas of calcification. The poorly differentiated cases showed only <5% differentiation towards ganglion cells. Background showed neuropil. Areas of calcification were seen in some. One case also showed bizarre cells. The undifferentiated group showed sheets of small round cells with frequent mitosis and apoptotic bodies. No neural differentiation was seen light microscopically. Confirmation was by immunohistochemistry using Neuron Specific Enolase, Desmin and Leucocyte Common Antigen. In both pre and post chemotherapy cases the predominant group was Differentiating Neuroblastoma [Figure 3]. M.K.I [Figure 4] was determined in all the ten cases of neuroblastoma that were pre-chemotherapy biopsies as per I.N.P.C criteria.^{12,13}

The neuroblastomas were further sub classified into Favorable and Unfavorable groups based on three parameters- Age, Histological Differentiation and M.K.I. All cases were followed up for three years. Table 2 shows the classification and 3 year follow up. A multivariate analysis was not possible due to less number of cases for which analysis of all three parameters was possible.

For the 27 post chemotherapy resections M.K.I could not be assessed. Hence prognostic classification could not be done, but the 3 year follow up was obtained. There were 10 cases of Poorly differentiated subtype and 17 cases of Differentiating Neuroblastoma. No Undifferentiated subtype was identified. Figure 5 shows follow up in Differentiating group and Figure 6 in Poorly Differentiated.

An independent association of prognosis with each of the three parameters included in INPC guidelines i.e Age, Differentiation and MKI was analyzed. As 6 cases were lost to follow up, analysis was possible only in 31 cases for Age and Differentiation [Tables 3 and 4]. For M.K.I the number was reduced to 8, as 2 cases were lost to follow up [Table 5]. Statistical analysis using a 2 tailed Fisher exact test was done for each of the three prognostic factors separately, by combining groups due to less number of cases.

4. Discussion

During the study period of five years we received 38 cases of neuroblastoma, 1 was excluded due to small size of biopsy. Of these 10 were pre-chemotherapy biopsies and 27 were post-chemotherapy resections. The various clinicopathological features studied and the 3 year follow up is given below.

4.1. Age

In the present study the most common age of presentation of neuroblastomas accounting for 70% of the cases was in the 1-5years subgroup. The youngest was 4months of age and the oldest case was in a 34year old female who presented as an abdominal mass. This was comparable with studies by Allan S.G et al⁵ (1-4 years, 80%), Koop C.E et al¹⁵ (1-5 years, 75%), Grosfeld J. L et al¹⁶ (0-8 years, 90%) and Rosen E.M et al¹⁷ (0-4 years, 85%).

4.2. Sex

Our study showed a male predominance in neuroblastomas, M:F ratio being 1.6:1. This was also comparable with various studies like Koop C.E et al¹⁵ (M:F = 1.2:1), Grosfeld J.L et al¹⁶ (M:F = 1.2:1) and Black C.T et al⁴ (M:F = 1.4:1)

4.3. Clinical presentation

The most common clinical presentation of neuroblastomas in our study was as an abdominal mass, accounting for 80% of the cases. The present study is comparable with the studies by Grosfeld J.L et al¹⁶ (75%) and Voute P.A et al¹⁸ (75%). The study by Koop et al¹⁵ showed presentation as abdominal mass in only 50%.

4.4. Tumor location

In our study the commonest location of Neuroblastomas was the adrenal gland (81%). 70% cases were also in the adrenal gland in the study by Suzuki H et al,¹⁹ whereas in the study by Kelly D.R et al¹ only 40% were in adrenal gland.

4.5. Gross Features

All the resection specimens of Neuroblastoma received were post-Chemotherapy cases. The commonest features seen were Hemorrhage (96.3%) and Necrosis (63%). The other features were Lobulation (40.7%), Calcification (29.6%) and Cystic change (14.8%). This is classically described as the gross feature of Neuroblastomas. Fibrosis was another post chemotherapy change noted.²⁰

4.6. Microscopy

68% of the Neuroblastoma cases that we received were of the Differentiating type followed by Poorly differentiated in 27% and Undifferentiated in 5% of the cases. In the study by Hiroyuki Shimada et al²¹ Neuroblastomas were Poorly differentiated in 85%, Differentiating in 13% and Undifferentiated in 2%. The study by Samuel Navarro et al²² also showed a preponderance of the Poorly differentiated subtype in 97% the remainder being Differentiating. Undifferentiated cases were not analyzed.

4.7. Follow up

Three year follow up was obtained for all the cases. This included 10 pre-chemotherapy biopsies and 27 post-chemotherapy resections. As M.K.I could be determined only in pre chemotherapy cases, the classification into Favorable and Unfavorable prognostic groups based on Age, Histologic Differentiation and M.K.I was limited to ten cases.

The three year follow up of the pre- chemotherapy cases saw two cases lost to follow up. Of the remaining, four belonged to the Favorable group and were doing well at end of three years. Three cases in the Unfavorable group expired and one case in same group is doing well on three year follow up. Due to less number of cases a multivariate analysis was not possible in our study.

In the study by Shimada H et al²¹ it is stated that the Favorable histology (FH) subgroup showed a 90.4% 5-year event free survival and the Unfavorable histology (UH) subgroup showed 26.9% event free survival. ($P < 0.0001$). In the study by Samuel Navarro et al²² a total of 115 of 120 patients were assessed. The 60-month survival rate was 97.7% in favorable patients compared with 73.8% in unfavorable patients ($P < 0.0002$). The study by Hideki Sano et al²³ also confirmed that the International Neuroblastoma Pathology Classification adds independent prognostic information beyond the prognostic contribution of age.

M.K.I was not determined in the 27 post chemotherapy cases and hence classification into Favorable/ Unfavorable group was not possible. Prognosis was plotted against the remaining two factors ie, Age and Histological Differentiation. Two cases were in the <1 year group, one of the differentiating type and the other poorly differentiated, both are doing well on follow up. In the 1-5 year subgroup, of the Differentiating histology, 7 cases are doing well, 1 relapsed, 3 expired and 3 were lost to follow up. In the Poorly differentiated histology, 4 are doing well, 2 relapsed and 1 expired. In the >5 year subgroup, 1 is doing well and 1 expired in the Differentiating histology and in Poorly differentiated histology, 1 case expired and 1 was lost to follow up.

A statistical analysis using a 2 tailed Fisher exact test for each of the prognostic factors (merging the ages of 1-5 and >5 years and also merging expired and relapsed cases) had p value of 0.1284 (Age), 0.7054 (Differentiation), 0.4643 (M.K.I). The values are not significant. This is due to the less number of cases.

5. Conclusion

This study which aimed at studying the clinicopathologic spectrum and prognosis of Neuroblastomas, was carried out on 37 cases that were received during a 5 year period at our center. All cases were followed up for three

years to assess prognosis on the basis of three parameters-Age, Histological differentiation and M.K.I as per I.N.P.C criteria.

Analysis of the clinicopathologic characteristics showed that our study was comparable to reference studies on the subject, with the commonest age group being 1-5 years, slight predilection in males, commonest presenting complaint being as an abdominal mass and adrenal being the most common location. Gross examination of specimens also collaborated with textbook definitions of the tumor. Contrary to other studies, on microscopy we had more number of Differentiating histology than Poorly Differentiated. But as most of our specimens were post chemotherapy, chemotherapy-effect should be considered.

Three year follow up based on three prognostic factors Age, Differentiation, M.K.I was carried out in 10 pre chemotherapy cases. Multivariate analysis was restricted by less number of cases. The significance of each variable was analyzed separately by 2 tailed Fischer exact test, but again due to less number of cases analyzed, significance could not be obtained in all three.

To conclude the clinicopathologic spectrum of Neuroblastomas at our centre is comparable to various studies on the tumor. But a prognostic analysis requires more number of cases, involving a longer study period. Analysis of genetic and molecular markers which were beyond the scope of this study can also be included for a more defined and therapy based prognostic classification.

6. Source of funding

None.

7. Conflict of interest

None.

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