

CHILDHOOD NEUROBLASTOMA IN THE UNIVERSITY HOSPITAL, KUALA LUMPUR: A STUDY INTO FEATURES OF PROGNOSTIC VALUE

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Summary

In the 15 year period between 1970 and 1984, 37 cases of histologically proven neural crest tumours (neuroblastoma, ganglioneuroblastoma and ganglioneuroma) were seen at the University Hospital, Kuala Lumpur. The ages of the patients ranged from 24 days to 11 years. More than 85% of cases were less than 5 years of age. There was no sex predilection. 17 were Chinese, 12 Malays and 8 Indians. About 68% of the tumours were abdominal and 30% were mediastinal in location. Approximately 14% of the tumours were undifferentiated neuroblastomas, 54% were differentiated neuroblastomas and 30% were ganglioneuroblastomas. Urinary vanillylmandelic acid was detected in 86% of cases for which screening was performed. At the time of biopsy, more than 80% of cases had metastatic disease. Of those with bone marrow examination, about 65% had evidence of tumour infiltration. The stage of disease appeared to be of prime importance in determining outcome. Because of the high prevalence of advanced disease, prognosis was generally poor in this study. An exception was Stage IVS disease which tended to have a good prognosis. Other factors of possible prognostic value were differentiation of the tumour and age of the patient.

Keywords: Neuroblastoma, ganglioneuroblastoma, ganglioneuroma, prognostic factors.

INTRODUCTION

Neuroblastoma is one of the commonest solid tumours of infancy and childhood. However, it remains as one of the least predictable in terms of biological behaviour and response to therapy. Recent reviews^{1,2} have commented on this enigmatic nature of the tumour and pointed out that it may be related to the ability of the tumour to differentiate into its more mature neural crest variants (ganglioneuroblastoma and ganglioneuroma). Prognosis has also been variously correlated to age of the patient, stage of the disease and location of the tumour. Published information on this tumour in the South East Asian region is scanty. In this paper, we report on our experience of childhood neural crest tumours seen at the University Hospital, Kuala Lumpur, with particular reference to features which may be of prognostic significance.

MATERIALS AND METHODS

During the 15 year period between 1970 and 1984, a histological diagnosis of neural crest tumour (including neuroblastoma, ganglioneuroblastoma and ganglioneuroma) was made in 37 paediatric patients of the University Hospital, Kuala Lumpur based on biopsies received in the Department of Pathology, Faculty of Medicine, University of Malaya.

The biopsy material was fixed in 10% buffered formalin and 4 µm thick sections stained with haematoxylin and eosin for light microscopy.

All histological sections were reviewed and tumours classified according to differentiation and maturation. **Undifferentiated neuroblastomas** appeared as sheets or compact nests of small, dark, round cells with hyperchromatic nuclei but no nucleoli. Rosette formation and the appearance of a fibrillary matrix were noted as early signs of differentiation. Nuclear enlargement, the presence of nucleoli and a distinct rim of eosinophilic cytoplasm indicated further maturation. **Ganglioneuroblastomas** exhibited ganglionic differentiation and were classified into two subtypes. **Diffuse ganglioneuroblastomas** showed a uniform population of differentiating neuroblasts and ganglion cells whereas **composite ganglioneuroblastomas** contained distinct foci of undifferentiated neuroblasts scattered in a maturing tumour. Ganglioneuromas were composed solely of mature ganglion cells, Schwann cells and neurite bundles.

Where available, bone marrow smears of the patients were reviewed for the presence of metastatic tumour. Case records of the patients were studied with particular reference to stage

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and presentation of the tumour at the time of biopsy and the outcome of the disease.

Treatment consisted of surgery, chemotherapy and radiotherapy in various combinations. Whenever feasible, as much of the tumour as possible was removed. Resection of the primary tumour was achieved in 19 patients. Most patients had some form of chemotherapy consisting of vincristine, **adriamycin** and cyclophosphamide regime. In some patients with bulky tumours, chemotherapy was started preoperatively to render the tumour more resectable and was continued postoperatively. Radiotherapy was also given to patients with advanced disease in whom residual tumour remained postoperatively and sometimes as palliative therapy.

RESULTS

General

Table 1 shows the age distribution of the cases studied. The ages ranged from 24 days to 11 years. About 89% of patients were aged 5 years and younger. There was no sex predilection with a **male:female** ratio of 1.1. 17 (45.9%) were Chinese, 12 (32.4%) Malays and 8 (21.6%) Indians.

Presentation

The majority of the patients presented with abdominal mass (Table 2). The other common presentations were fever, metastatic disease, pallor and **paraplegia/paraparesis**. The duration of symptoms prior to admission ranged from 1 week to 12 months, with a mean of 2 months.

Location

25 (68%) of the tumours were abdominal and 11 (30%) were thoracic (mediastinal) in location. Abdominal tumours were more often encountered on the right side (52%) than the **left (36%)**, but this was not statistically significant.

Histological differentiation

14% of the tumours were undifferentiated **neuroblastomas**, 54% were differentiated **neuroblastoma** and 30% were ganglioneuroblastomas (Fig. 1) of which about equal numbers were of the composite and diffuse types (Table 3). Only one case of ganglioneuroma was encountered.

VMA and Differentiation .

Screening for urinary vanillylmandelic acid (VMA) was performed for 29 patients and was detected in 86% of screened **cases**. No significant correlation was observed between tumour differentiation and VMA positivity (Table 4).

Stage

The staging system employed in this study was the widely employed one of **Evans**.³ Information on stage of the disease at **presen-**

TABLE 1
AGE DISTRIBUTION OF 37 CHILDREN
WITH NEURAL CREST TUMOURS

Age group	No.	(%)
0 – 11 mths	6	(16.2)
1 – 2 yr	11	(29.7)
3 – 5 yr	16	(43.2)
6 – 10 yr	3	(8.1)
11 – 12 yr	1	(2.7)
Total	37	(100)

TABLE 2
PRESENTATION OF 37 CHILDREN WITH
NEURAL CREST TUMOURS

Complaints	No.	(%)
1. Abdominal mass	20	(54.1)
2. Fever	15	(40.5)
3. Metastasis	11	(28.2)
4. Pallor	4	(10.8)
5. Paraplegia/paraparesis	4	(10.8)

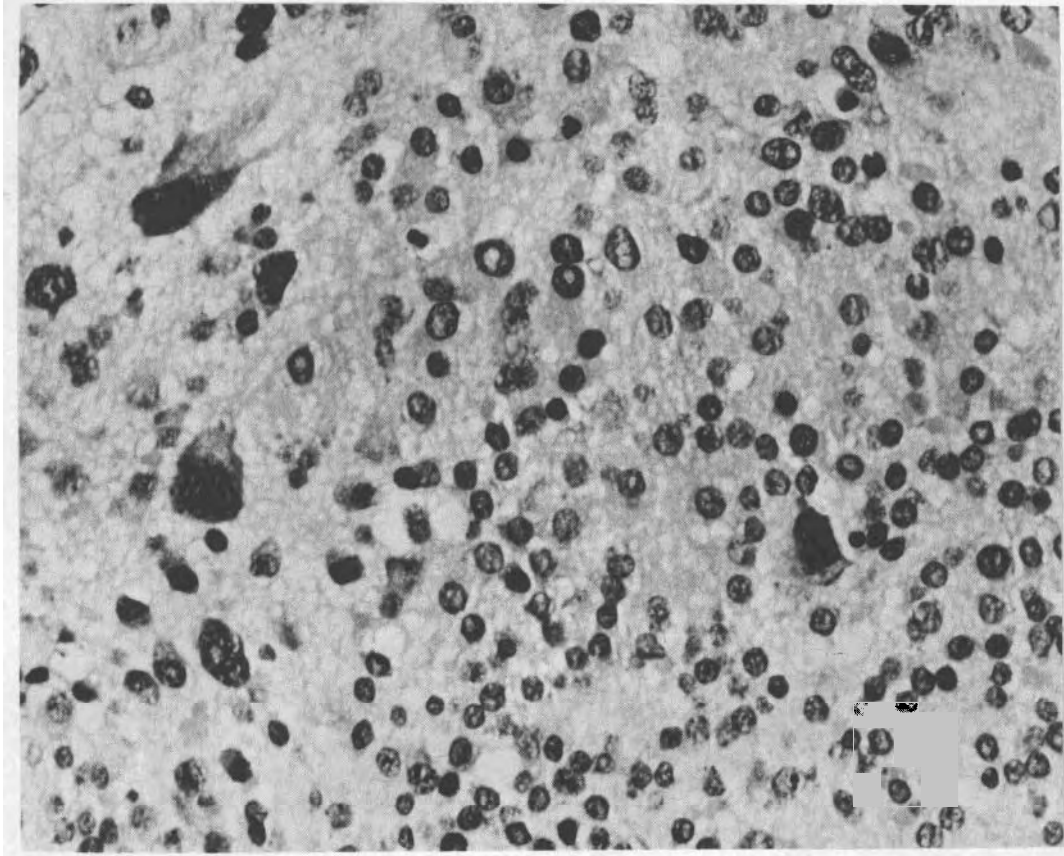


FIG. 1 : Diffuse ganglioneuroblastoma showing large ganglion cells scattered in a background of differentiating neuroblasts with vacuolated cytoplasm and fibrillary matrix. H & E X 700.

TABLE 3

HISTOLOGICAL DIFFERENTIATION OF CHILDHOOD NEURAL CREST TUMOURS

Differentiation	No.	(%)
1. Undifferentiated neuroblastoma	5	(13.5)
2. Differentiated neuroblastoma	20	(54.1)
3. Ganglioneuroblastoma		
- composite type	6	(16.2)
- diffuse type	5	(13.5)
4. Ganglioneuroma	1	(2.7)
Total	37	(100)

TABLE 4
COMPARISON OF TUMOUR DIFFERENTIATION WITH VMA POSITIVITY

Differentiation	No. screened	No. positive	% positive
Undifferentiated neuroblastoma	4	3	75
Differentiated neuroblastoma	14	12	86
Ganglioneuroblastoma	10	9	90
Ganglioneuroma	1	1	100
Total	29	25	86

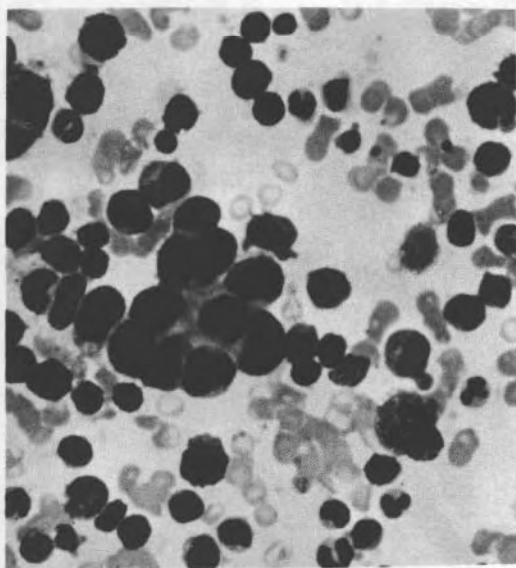


FIG. 2 : Bone marrow aspirate showing a clump of neuroblasts amidst normal marrow cells. MGG X 850.

tation was available in 33 patients. The majority of patients presented late. There were no patients in Stage I. 1 (3%) and 3 (9%) patients presented in Stages II and III respectively. 24 (73%) patients were seen in Stage IV while 5 (15%) presented in Stage IVS. Of the 31 patients with bone marrow examination, 20 (65%) had marrow involvement (Fig. 2). 40% of patients had lymph node metastasis while liver metastases was noted in 11%.

Stage and survival

Adequate information on survival was available for 23 patients. Table 5 presents a comparison of the stage of disease and survival. Of the 5 patients who survived beyond 2 years, 3 were in Stage IVS and 1 each in Stages II and III. There were no survivors among Stage IV patients.

Age and survival

A comparison of the patients' age and survival is shown in Table 6. 4 out of 8 children aged 1 year or younger survived beyond 2 years. 3 of them were in Stage IVS. In contrast, only 1 out of 15 patients older than 1 year survived longer than 2 years. Thus, the younger age group appeared to survive longer than older patients, but this difference may be due to the presence of Stage IVS disease in the younger age group.

Sex and survival

Table 7 showed that males appeared to do better than females, but this was not statistically significant.

Differentiation and survival

Although there was a suggestion that patients with ganglioneuroblastomas survived longer than those with less mature tumours (Table 8), the true contribution of tumour differentiation to survival was difficult to assess. No patient with undifferentiated neuroblastoma survived beyond 2 years. Of the 2 patients each with differentiated neuroblastoma and ganglioneuroblastoma who survived for more

TABLE 5
COMPARISON OF STAGE OF TUMOUR AND SURVIVAL

Stage	No. assessed	Survival: No. (%)			No. not assessed	Total
		< 2 yr	2-5 yr	> 5 yr		
I	—	—	—	—	—	—
II	1	0	1(100)	0	0	1
III	3	2(67)	0	1(33)	0	3
IV	15	15(100)	0	0	9	24
IVS	4	1(25)	0	3(75)	1	5
Total	23	18(78)	1(4)	4(17)	10	33

TABLE 6
COMPARISON OF AGE OF PATIENT WITH SURVIVAL

Age	No. assessed	Survival: No. (%)			No. not assessed	Total
		< 2 yr	2-5 yr	> 5 yr		
< 1 yr	8	* 4(50)	1(13)	+3(38)	3	11
2-4 yr	11	10(91)	0	1(9)	9	20
> 5 yr	4	4(100)	0	0	2	6
Total	23	18(78)	1(4)	4(17)	14	37

* = 1 in Stage IVS

+ = All in Stage IVS

TABLE 7
COMPARISON OF SEX OF PATIENT WITH SURVIVAL

Sex	No. assessed	Survival: No.:(%)			No. not assessed	Total
		< 2 yr	2-5 yr	> 5 yr		
Male	10	7(70)	0	3(30)	9	19
Female	13	11(85)	1(8)	1(8)	5	18
Total	23	18(78)	1(4)	4(17)	14	37

TABLE 8
COMPARISON OF TUMOUR DIFFERENTIATION AND SURVIVAL

Differentiation	No. assessed	Survival: No. (%)			No. not assessed	Total
		< 2 yr	2-5 yr	> 5 yr		
Undifferentiated neuroblastoma	5	* 5(100)	0	0	0	5
Differentiated neuroblastoma	10	8(80)	0	*2(20)	10	20
Ganglioneuroblastoma	7	4(57)	1(14)	+2(29)	4	11
Gangioneuroma	1	1(100)	0	0	0	1
Total	23	18(78)	1(4)	4(17)	14	37

* = 1 in Stage IVS

+ = Both in Stage IVS

TABLE 9
COMPARISON OF TUMOUR LOCATION WITH SURVIVAL

Location	No. assessed	Survival: No. (%)			No. not assessed	Total
		< 2 yr	2-5 yr	> 5 yr		
1. Abdominal	15	11(73)	0	4(27)	10	25
2. Thoracic	8	7(87)	1(13)	0	3	11
3. Undetermined	—	—	—	—	1	1
Total	23	18(78)	1(4)	4(17)	14	37

than 5 years, 3 had Stage IVS disease which could itself have contributed to a better survival. It is noteworthy that the one patient with Stage IVS disease who did not survive beyond 2 years had an undifferentiated tumour.

Site of tumour and survival

Table 9 compares the location of the primary tumour with survival. All 4 patients who survived for more than 5 years had abdominal tumours. There was no difference in the histological pattern between thoracic and abdominal tumours. It was felt that the better survival of patients with abdominal tumours may be related to the fact that more of them were in Stage IVS.

DISCUSSION

It has been increasingly recognised that the results of treatment of malignant neural crest tumours have been disappointing in spite of the advent of multimodal therapy. Neuroblastomas have not expressed the improved survival rates observed in other malignant childhood tumours such as nephroblastomas and rhabdomyosarcomas. In recent times, interest in this group of tumours has centred around features of prognostic significance, about which there is still considerable controversy.

In our study, the stage of the disease appears to be of prime prognostic importance, with Stage IV disease indicating a gloomy outcome. The exception to this rule was Stage IVS disease which tended to have a good prognosis. This is in agreement with the findings of other workers.⁴

The contribution of age and tumour differentiation to survival was less certain. All 5 patients with Stage IVS disease were 1 year old or

younger. 4 of these 5 patients showed evidence of tumour differentiation, 2 being differentiated neuroblastomas and 2 ganglioneuroblastomas. The 1 patient in Stage IVS who did not survive beyond 2 years had an undifferentiated tumour. Thus it appears that both age and tumour differentiation may have roles to play in determining outcome but these factors were interlinked with the stage of the disease particularly Stage IVS. Most workers regard age as an important factor. Some have attributed this to the observation that infants more often have localised resectable disease⁵ while others have observed a better prognosis in infants in spite of extensive disease.⁶ Why infants do better than older children remains a question. Various studies have shown that the better prognosis is not necessarily related to stage or differentiation.^{6,7} In addition, the metastatic pattern is different and a greater tendency towards spontaneous regression has been reported.^{8,9} Thus, it is probable that there is an intrinsic difference between tumours of older and younger children.

Neural crest tumours form a fascinating group of tumours because of the ability of its more malignant variant, the neuroblastoma, to mature towards ganglioneuroblastoma and ganglioneuroma. Among ganglioneuroblastomas, the diffuse type is thought to be less aggressive than the composite type.¹⁰ Our figures are too small for statistical analysis, but it is noteworthy that composite ganglioneuroblastomas were more often in Stage IV disease than the diffuse type. Because of their neural crest origin, secretion of a variety of catecholamine precursors and metabolites by these tumours has been suggested as a possible biochemical determinant of differentiation.¹¹ However,

our study indicated that most of the tumours secreted VMA irrespective of differentiation. Because of the high prevalence of VMA positivity, the diagnosis should always be carefully reviewed when a non-VMA secreting tumour is encountered.

Some workers have pointed out that thoracic neuroblastomas have a better prognosis than abdominal ones,¹² this being related to the higher prevalence of maturation in thoracic tumours.^{13,14} Neither a difference in prognosis nor maturation was observed in our present study.

Bone marrow involvement by tumour was a frequent occurrence. It is important to differentiate between tumour cells and lymphoblasts in the marrow as the latter has been reported to correlate with a good prognosis.¹⁵ Tumour cells tended to occur in clusters of 5 to 15 cells. Unlike lymphoblasts, neuroblasts do not have an affinity for vital stains such as PAS.

Unlike other studies, we have not observed a sex predilection in tumour prevalence.¹⁰ Although there have been some reports of better survival among females than males, our study did not reflect such a difference.

We conclude that the stage of the disease is the prime prognostic indicator in this group of tumours although the age of the patient and tumour differentiation may have contributory roles. In the local situation, prognosis is generally gloomy because of the high prevalence of Stage IV disease at presentation.

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