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NEUROBLASTOMA IN MALAYSIAN CHILDREN

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INTRODUCTION

NEUROBLASTOMA, one of the commonest tumours in childhood accounts for 11 to 14 per cent of all malignant solid tumours in children in the USA, UK and Australia (Dargeon, 1962; Bodian, 1959; Jones and Campbell, 1976). The overall 2 year survival rate has remained the same despite the use of chemotherapy (Leiken *et al.*, 1974).

Previous studies have mainly been in Caucasian children and information is not available on the epidemiology, clinical features, response to treatment and clinical vagaries such as the tendency to undergo spontaneous maturation and regression (Evans *et al.*, 1976) in Malaysian children with neuroblastoma.

This study reviews (1) the epidemiological and clinical features (2) the pathological staging and (3) the response to treatment and outcome in children with neuroblastoma seen at the University Hospital, Kuala Lumpur over a 10 year period.

MATERIALS AND METHODS

All children with neuroblastoma admitted to the Paediatric Unit, during the period 1968 through 1977 were reviewed. The diagnosis was based on biopsy findings or a combination of radiological, biochemical and bone marrow abnormalities in the absence of tissue confirmation in patients with widespread disease. Since 1973, combination chemotherapy which includes vincristine, adriamycin and cyclophosphamide, has been used together with the other modalities of treatment in the management of patients with advanced disease. Details of the illness, physical findings, results of investigations, pathological staging and response to treatment and subsequent outcome were documented and compared with other series.

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RESULTS

Epidemiology

During the index period, 16 children with neuroblastoma were admitted to the Unit. The total number of paediatric hospital admissions during this period was 24,532 cases. Neuroblastoma accounts for 0.65 per 1000 hospital paediatric admissions and 13.4 per cent of all malignant solid tumours in childhood.

Ethnic Distribution

The 16 children comprised 8 Chinese, 4 Malays, 3 Indians and 1 Orang Asli (aborigine). Chi-square analysis revealed no significant association between race and incidence of neuroblastoma among inpatients as seen in Table I.

Sex

In our series there were 10 males and 6 females. Chi-square analysis revealed no significant association between sex and the incidence of neuroblastoma among inpatients ($X^2=0.0274$, $df=1$ $P>0.5$).

Age at diagnosis

The mean age at diagnosis was 41.6 ± 33.2 months, SD; the youngest patient was 2 months

Table I

Ethnic Distribution of Neuroblastoma

Race	No. of Cases	No. of admissions 1068 - 1977
Chinese	8	12,040
Non-Chinese	8	12,492
Total	16	24,532

$X^2 = 0.006$,
df = 1,
$0.95 > p > 0.90$

old and the oldest 11 years respectively. Approximately 70 per cent of cases occurred by age of 4 years as in other series (Evans *et al.*, 1969).

Clinical Features

The average duration of symptoms prior to diagnosis was 4.5 weeks and ranged from 2 weeks to 3 months.

The commonest symptoms were fever, abdominal distension, anorexia and weight loss; the commonest signs were hepato-splenomegaly, proptosis, abdominal mass and fever as seen in Table II.

Table II

Presenting Symptoms and Signs in 16 patients with Neuroblastoma

Symptoms	No. of cases
Fever	11
Abdominal distension	8
Anorexia	7
Weight loss	6
Abdominal pain	3
Abdominal mass	3
Swelling of eye/face	3
Neck swelling	2
Blindness, mass at front of chest, loin pains, maxillary swelling, diarrhoea arthralgia, scalp mass	single cases

There was no association with hypertension or opsoclonus

Investigations

The mean haemoglobin level was 9.5 gdl $\pm$3.5 g/dl, SD and ranged from 2.3 g/dl to 19.0 g/dl; it was less than 10 g/dl in 9 of the 16 children. The mean white cell count was 10,306.25 $\pm$ 2,466.7 per cumm and ranged from 7000-14,200 per cumm. The platelet count was normal except in 2 patients with levels of 21 x 10^9/1 and 56 x 10^9/1 respectively. The ESR was elevated in 4 of 8 children and ranged from 82-126 mm/HR. Urine examination was generally normal except in 4 patients who had white cell counts ranging from 20-125 cells/mm^2 but viable counts were not significant. The urinary VMA screening test was positive in 13 of 14 cases and negative in 1 patient with a highly undifferenciated metastatic neuroblastoma. Blood urea was elevated in 1 of 12 cases.

Chest X-ray revealed either lung, hilar or mediastinal metastases in 6 patients and destruction of the sternum in 1 instance. Skeletal survey revealed abnormalities in 6 cases (3 also had chest X-ray abnormalities) which included dehiscence of cranial sutures by meningeal metastases, demineralisation of the sella turcica, erosion of the skull and roof of orbit, destruction of the nasal bones and metastases in the pelvis, long bones, maxilla, mandible and spine. Intravenous pyelogram disclosed downward displacement of the kidney in 11 cases calcification in 2 and hydronephrosis in 1 case respectively. Liver scan revealed cold areas in 4 of 5 cases studied. The bone marrow was infiltrated by tumour cells in 10 of 13 cases studied. The diagnosis was confirmed by biopsy in 9 cases and from a combination of radiological, biochemical and bone marrow abnormalities, without tissue confirmation in 7 patients. The pathological staging proposed by Evans et al. (1971) was adopted and of the 16 children reviewed 1 had stage III disease, 11 had stage IV disease and 4 had stage IV-S disease. The outcome of treatment in these patients is recorded in Table III.

The patient with stage III disease had inoperable tumour which responded well to chemotherapy and radiotherapy and no evidence of residual tumour was detected at surgery 3 months later. He was maintained on continuation chemotherapy but was subsequently lost to follow up after he developed metastases at 9 months.

Table III

Clinical staging and outcome of treatment in 16 cases of Neuroblastoma

Stage	No. of cases	Outcome
III	1	Metastases at 9 months, lost to follow up.
IV	11	4 died within 6 months; 6 lost to follow up. 1 alive and well at 9 months
IV-S	4	1 died of septicaemia while in remission. 1 refused treatment. 2 alive and well (2½) and 3 years later respectively).

Four of 11 patients with stage IV disease died within 6 months 2 within a few days; 6 patients were lost to follow up and 1 is alive and well on a vincristine, adriamycin, cyclophosphamide (VAC) regime 9 months after radiotherapy for a mediastinal neuroblastoma eroding the sternum.

2 of 4 patients with stage IV-S disease have survived 2½ years and 3 years respectively with minimal chemotherapy and radiotherapy. One patient refused treatment while another died of pseudomonas septicaemia at 3 months while on 2 weekly VAC regime following surgery and radiotherapy; autopsy revealed no evidence of tumour.

DISCUSSION

The present study reveals that neuroblastoma in Malaysian children behaves in much the same manner as in Caucasian children. The frequency of this tumour in relation to the other childhood malignancies and the epidemiological and clinical features appear to be similar to that of other series (Dargeon, 1962; Bodian, 1959; Jones and Campbell, 1976).

A significant proportion of our patients were anaemic at presentation but this was not related to bone marrow infiltration. The VMA screening test, positive in 93 per cent of our patients compares well with the positive rates reported in other series (77% McKendrick and Edwards; 96% Gitlow *et al.*, 1970; Voute *et al.*, 1975). The prognosis of patients without increased catecholamine excretion is poor and is associated with a highly undifferenciated form of neuroblastoma (Voute *et al.*, 1975) which usually arises in the midline such as the coeliac axis or pelvis area. Almost all our patients presented with metastases compared with two-thirds in other series (Evans *et al.*, 1978); none of our children had stage I or II disease. Metastases in the liver are mainly found in infants up to 6 months and skeletal metastases in older children (Wieberdink, 1957). Although papilloedema, scalp nodules,. dehiscence of sutures and erosion of orbit and skull have been observed in some cases metastases have not been found to invade the brain.

Prognosis appears to correlate with age and extent of disease. The outcome in our patients has been poor because of the advanced stage of their illness. Only one of our stage IV patients appears to be disease free at 9 months. The poor prognosis in stage IV patients has been observed in other centres (Evans *et al.*, 1978).

A favourable prognosis has been observed in Stage IV-S disease as in other series (Evans *et al.*, 1978). The reason for this is not clear but may be related to a unique interaction between the host and the tumour (Jones and Campbell, 1976) and as a rule these patients need little if any treatment as spontaneous regression usually ensues. In advanced cases a short course of chemotherapy and/or low dose radiation may initiate regression of disease. Significant bone marrow infiltration warrants chemotherapy such as delivered to patients with overt bone metastases but caution needs to be exercised in over zealous treatment as this may lead to myelosuppression or immunosuppression and increased mortality from infection.

One of the major problems encountered in the management of malignancies in Malaysia appears to be the problem of follow up. Eight of the 16 cases studied were lost to follow up and they were from the lower socio-economic group emphasising that social and economic factors are important considerations in cancer therapy programmes.

SUMMARY

A review of 10 years experience of neuroblastoma in the University Hospital, Kuala Lumpur

reveals no significant differences in either the epidemiological or clinical features between Malaysian and Caucasian children. The prognosis of patients with stage III and stage IV disease remains poor despite surgery, radiotherapy and chemotherapy. With limited treatment a favourable outcome is recorded in infants with stage IV-S disease.

REFERENCES

Bodian, M. (1959): Neuroblastoma. *Pediatr. Clin. North America,* **6:** 449-472.

Dargeon, H.W. (1962): Neuroblastoma. *J. Pediat.* **61:** 456-471.

Evans, A.E., D'Angio, G.J. and Randolph, J. (1971): A proposed staging for children with neuroblastoma. *Cancer,* **27:** 374-378.

Evans, A.E., D'Angio, G.J. and Koop, C.E. (1976): Diagnosis and treatment of neuroblastoma. *Pediatr. Clin. North America.* **23:1** 161-170.

Evans, A.E., Heyn, R.M., Newton, W.A., Leiken, S.L. (1969): Vincristine sulphate and cyclophosphamide in children with metastatic neuroblastoma. *J. Amer. Med. Assoc.* **207:** 1325-1327.

Gitlow, S.E., Bertani, L.M., Rausen, A., Gribetz, D., Dziedzic, S.W. (1970): Diagnosis of neuroblastoma by qualitative and quantitative determination of catecholamine metabolites in urine. *Cancer,* **25,** 1377-1383.

Jones, P.G. and Campbell, P.E. (1976): Tumours of Infancy and Childhood. Blackwell Scientific Publications. Oxford, London, Edinburgh, Melbourne pge 538-562.

Leiken, S.L., Evans, A.E., Heyn, R. *et al.* (1974): The impact of chemotherapy on advanced neuroblastoma. Survival of patients diagnosed in 1956, 1962 and 1966-68. *J. Pediat.* **84:** 131-134.

McKendrick, T. and Edwards, R.W.H. (1965): The excretion of 4-hydroxy-3 methoxy-mandelic acid by children. *Arch. Dis. Child.* **40,** 418-425.

Voute, P.A., Putten, N.J. and Burgers, J.M.V. (1975): Cancer in Childhood. Clinical management. Edited by Bloom H.J. G., Lemerle, J., Weidhardt, and Voute, P.A., Springer-verlag. Berlin Heidelberg. New York, 138-148.

Wieberdink, J. (1957): Foetal haemic metastasis. An explanation of the Pepper type of metastasis in adrenal neuroblastoma. *Brit. J. Cancer,* **11:** 378-383.