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Incidence and Outcomes of Neuroblastoma: A Prospective Study at a Tertiary Care Centre in Western Rajasthan

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ABSTRACT
Neuroblastoma is a common childhood cancer with poor prognosis. Neuroblastoma most commonly affects children age 5 or younger, though it may rarely occur in older children. To present our experience with neuroblastic tumours and their outcome in the patients treated at our centre. This is prospective study done at the Department of Paediatric Surgery at SMS Medical College, Jaipur, Rajasthan, India between May 2021 to April 2022 done on Infants and children with neuroblastic tumours treated in the Department of Paediatric Surgery at SMS Medical College, Jaipur, Rajasthan, India between May 2021 to April 2022. 12 patients were included with mean age of 61.87±47.56 months. Male predominance seen in the patients, majority patients were in stage 2. Post treatment, 1 patient presented with recurrence and a total of 2 patients died. Since significant number of patients still relapse and eventually die of the disease and hence it becomes vital for investigators to first better understand the origins of this disease and then develop novel treatment strategies for those who are diagnosed with it.

INTRODUCTION

Neuroblastoma is the most common solid extracranial tumour in infants and children. It represents approximately 7% of all cases of childhood cancer and results in about 15% of cancer deaths in children[1]. The annual incidence of the disease is 10.5 per one million children. It can occur anywhere along the sympathetic nervous system, including the superior cervical, paraspinal and celiac ganglia; the majority arises in the adrenal glands[1]. Due to the high variability in its presentation, clinical signs and symptoms at presentation can range from a benign palpable mass with distension to major illness from substantial tumor spread. Neuroblastic tumours are heterogeneous group of embryonic tumours derived from neural crest cells. It represents a spectrum of disease from undifferentiated, aggressive to differentiated and largely quiescent tumours. Chromosomal copy number changes are the most common genetic event in neuroblastoma. The best-characterized copy number alteration associated with poor prognosis is the amplification of the *MYCN* oncogene[1].

Malignant peripheral neuroblastic tumours (PNTs), account for the most of PNTs, with nearly 50% of patients have a high risk phenotype. It is characterised by widespread disease dissemination and poor long-term survival. PNTs are responsible for 12% of deaths associated with cancer in children younger than 15 years of age. Some tumours undergo spontaneous involution without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy[1].

One of the main features of Neuroblastoma is the various ways it presents itself, which depends on numerous factors, such as patient's age, the location of the tumor, the stage, the presence of metastases and paraneoplastic syndromes. The main signs and symptoms, which are usually delayed in appearing, are often non-specific and similar to other childhood diseases, making early diagnosis difficult. Signs of the disease vary from a painless mass that is detected accidentally, to a rapidly growing progressive tumor. Classical symptoms such as fever, pain, weight loss and irritability are associated with metastatic neuroblastoma. Proptosis and periorbital bruising are frequent and result from the way the tumor infiltrates the periorbital bones[5].

There is a paucity of literature on the outcome of children with neuroblastic tumours from a developing country like India. Lack of awareness, illiteracy, low socioeconomic status and relatively less referral centres are associated with late presentation, poor outcome and high dropout rate.

Aim: To present our experience with neuroblastic tumours and their outcome in the patients treated at our centre.

MATERIALS AND METHODS

This is prospective study done at the Department of Paediatric Surgery at SMS Medical College, Jaipur, Rajasthan, India between May 2021 to April 2022 done on Infants and children with neuroblastic tumours treated in the Department of Paediatric Surgery at SMS Medical College, Jaipur, Rajasthan, India between May 2021 to April 2022.

Inclusion criteria: All patients with diagnosis of Neuroblastic tumours who were treated in our institute from May 2021 to April 2022.

Exclusion criteria

Patients with inadequate records: Who discontinued treatment or died before diagnosis were excluded from the study.

Data analysed were pertaining to the age, sex, clinical presentation, site, stage, diagnostic evaluation performed, management (surgery/chemotherapy/ radiotherapy), post-operative problems and follow-up results. Diagnoses were made either on the basis of histopathological examination of the tumour tissues taken through biopsy (open/trucut) or by fine-needle aspiration samples with or without immunohistochemistry. All patients were evaluated by contrast enhanced computed tomography (CT) scan, skeletal survey, bone scans along with complete haematology, liver and renal function tests, coagulation profile, etc.,

I131 MIBG scan, DOTONAC PET CT-scan and MYCN evaluation were not available at our centre. Patients were categorised on the basis of 'age of the patients (<12 months and >12 months); 'sites' of the tumour (abdominal [adrenal, non-adrenal, pelvic] and extra-abdominal [thoracic, thoraco-abdominal, cervical, cervico-thoracic]) and 'stage' of the tumour as described by International Neuroblastoma Risk Group (INRG). Treatment varied on the basis of clinical presentation and stage of the disease. All patients having Stage L-1 were primarily operated, while Stage L-2, M and MS patients were received neoadjuvant chemotherapy followed by surgery when possible. Surgical resection was attempted only when radiological findings suggested resectability without image-defined risk factors (IDRFs). During surgery, resection of tumour was tried as complete as possible, but it was not possible in many patients. In such cases, Gross Total Resection (GTR) was performed which was defined as removal of more than 90% of tumour mass. Children with no response (NR) or progressive disease (PD) were referred to higher centres or for palliative care. MIBG therapy, Myeloablative therapy and autologous stem cell transplantation (ASCT) facility is not available in our institute. The final outcomes were assessed as complete response (CR), Partial response

(PR); NR and PD according to international criteria for response to treatment. CR was defined as absence of tumour at the primary and metastatic sites as confirmed by radiological studies with or without histopathology of the resected specimen. Overall survival (OS) was calculated from the date of diagnosis to date of last follow-up and event for OS was death.

RESULTS

In the study, 12 patients were included with mean and median age of 61.87±47.56 months and 60 months (range of 2-180 months). About 75% (n = 8) of patients were males (Fig. 1).

Out of total, n = 1, n = 7 and n = 4 patients were in Stage L-1, L-2 and 4, respectively (Fig. 2).

Most common presentation was fever (>80%) followed by lump/pain/discomfort (>69%), bone pain (>30%), lower limb paresis (>6%), diarrhoea (>2%) and proptosis (>2%).

Chemotherapy was given to all patients with malignant histology according to the risk group.

Out of total 12 patients, surgery was performed in 58% (n = 7), but gross total excision (GTR) was achieved in only 71.4% (5) patients. Only biopsy could be done in 8.3% (1) patient as he showed matured histology (Fig. 3).

33.33% (n = 4) of patients were referred to other higher centres based on the parent/patient request during their course of chemotherapy (Table 1).

Out of total 12 patients, 50% (n = 6) of patients showed CR, 33.3% (n = 4) of patients had PR, whereas 16.6% (n = 2) had NR or had PD. (n = 1) of patients reported recurrence.

About 16.6% (n = 2) patients died during the course of follow-up (event). Kaplan-Meier method was used to compute the mean and median event (death)-free survival time of the treated patients. Out of the total 12 patients, 2 (16.6%) achieved events (deaths), whereas rest 10 (83.33%) were censored. Out of the survivors, Seven (58.33%) patients are under regular follow-up and out of them one patient has active disease (Fig. 4).

In this cohort, out of the available patients' demographic characteristics (age and gender) and clinical findings (stages, type of interventions), age ($p = 0.047$) and stage ($p = 0.003$) were found as statistically significant, whereas gender ($p = 0.114$) and site ($p = 0.700$) of tumour were statistically insignificant (each $p>0.05$) for OS. In multivariate analysis, both the significant variables have been included. Results showed that only stage was statistically significant ($p = 0.008$) and independent predictor of the mortality after adjusting age that was not statistically significant ($p = 0.381$). There was an insignificant difference in survival probability of the cancer patients between Stages L-1 and L-2 and the result was found to be statistically insignificant.

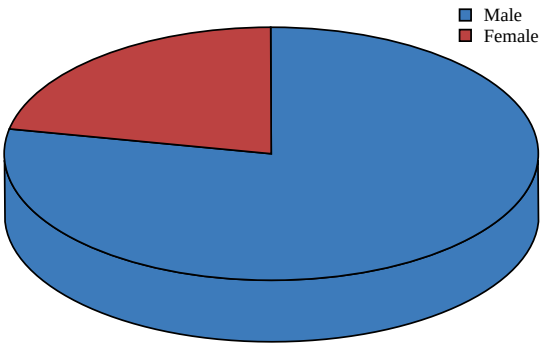

Fig. 1: Distribution according to gender

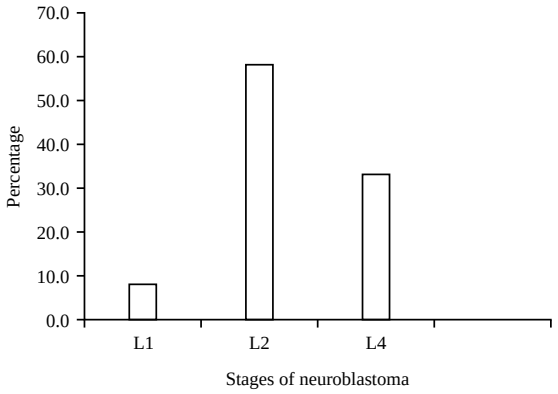

Fig. 2: Distribution according to stage

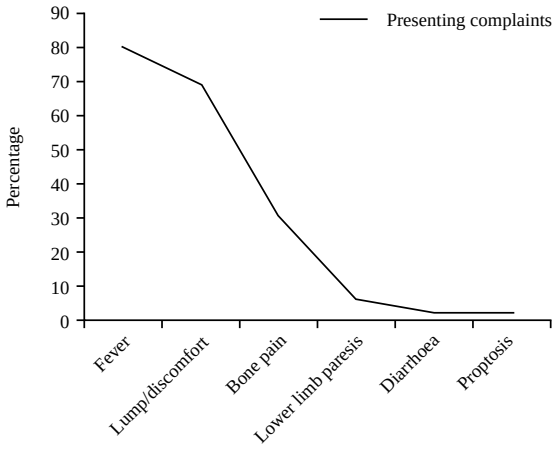

Fig. 3: According to presenting complaints

Table 1: Type of management

Type of management	No. of patients
Surgical management	7
Biopsy alone	1
Referred to higher centre	4

DISCUSSION

Presenting symptoms: In a study by Hero *et al*.[5], out of 46 patients who underwent chemotherapy, symptoms included existing or threatening transverse myelopathy (n 23), compression of the urinary tract (n 9), upper airways (n 6), or major vessels (n 3),

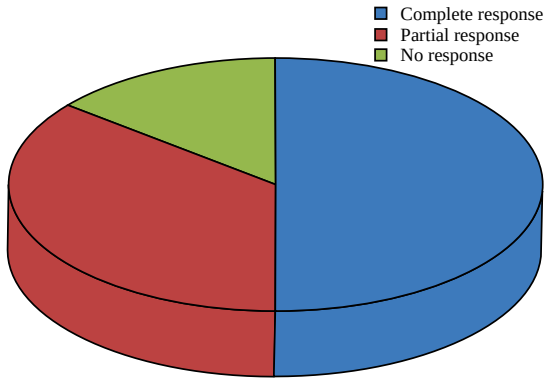

Fig. 4: Response to treatment

severely reduced general condition (n 4) and opsoclonusmyoclonus-syndrome (n 1), no symptoms in 11 patients.

Whereas in our study, fever (>80%) followed by lump/pain/discomfort (>69%) followed by bone pain (>30%) were the major presenting features.

Staging and grading: In a study by Hero *et al*.[5] 157 had stage 1, 113 stage 2 and 70 stage 3 disease.

In a study by Kerbl *et al*.[6] 16 of 46 patients were classified as stage 1, three as stage 2A, eight as stage 2B, 14 as stage 3, four as stage 4 and one as stage 4s.

In a study by Liu *et al*.[7], Grades I-II 15 (1.2) Grades III-IV 608 (49.7) were seen.

As per study done by Chang *et al*.[8], A total of 75 children with all stages of neuroblastoma were identified, of which 23 children in the low stage were enrolled. There were 12 (16.0%) patients in stage 1 and 11 (14.6%) patients in stage 2.

In our study, Stage 1 = 1, stage 2 = 7 and stage 3 = 4 cases were seen.

Treatment and outcome: In a study done by Atkins *et al*.[4], Complete Response was seen in 17%, Partial Response was seen in 9%, only BIOPSY was done in 63%.

In a study done by Hero *et al*.[5], Complete resection was achieved in 177 (stage 1, n 156, stage 2b, n 15, stage 3, n 6) and nearly complete resection in 13 patients (stage 2, n 11, stage 3, n 2).

In a study by Kerbl *et al*.[6] treatment consisted of surgical resection alone in 27 of 46 patients, chemotherapy alone (after bone marrow aspiration and biopsy) in one patient and combined operation and chemotherapy in 18 patients. At a median follow-up of 61 months, 44 of 46 patients (96%) diagnosed through the screening program were alive, 38 without evidence of disease, four with small tumor residuals demonstrable by imaging techniques and one with partial response. One patient with previous stage 2B disease developed disseminated relapse 7 months after incomplete resection of a tetraploid neuroblastoma. Following intensified treatment, the patient is alive 89 months after diagnosis although no complete remission could be achieved (stable disease). Two of 46 patients (4%) died of therapy-related complications.

In a study by Liu *et al*.[7], surgical resection was done in 76% and therapy/no treatment done in 23%.

In a study done by Chang *et al*.[8], all children with stage 1 were treated by surgery alone, There was 1 patient who suffered a relapse at 6.1 month of age. However, the patient received salvage chemotherapy and thereafter had long-term disease-free survival., There were 11 (14.6%) patients in stage 2, Five patients received initial open surgical biopsy, followed by chemotherapy. Six patients received up-front total or near-total excision, followed by adjuvant chemotherapy, which included carboplatin, etoposide, cyclophosphamide and doxorubicin. One patient had MYCN amplification and 2 patients had unfavorable Shimada histology. Seven patients (63.6%) in stage 2 received chemotherapy. There were 2 relapses, at 7.6 and 13.2 months after diagnosis, respectively.

In our study, of total 12 patients, surgery was performed in 58% (n = 7) but gross total excision was achieved in only 71.4% (5) patients. 6 patients showed CR, 4 patients had PR, whereas 2 had NR or had PD. 8.3% (n = 1) of patients reported recurrence.

CONCLUSION

Since significant number of patients still relapse and eventually die of the disease and hence it becomes vital for investigators to first better understand the origins of this disease and then develop novel treatment strategies for those who are diagnosed with it.

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