NEUROBLASTOMA IN CHILDREN*

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Neuroblastoma is one of the most common malignant neoplasms of infancy and childhood between birth and three years of age; ranking with Wilm's tumor and teratoma. Between the ages of four and twelve years, tumors of the central nervous system, leukemia and lymphomas, predominate. Kidney and adrenal tumors, however, occupy the third rank after leukemias and brain tumors.[1,2]

The improvement in anesthesia and surgical techniques and the progress in cancer chemotherapy have had a great influence on the prolongation of the life of the cancer patient in the past decade. In recent months, several reports have appeared in pediatric literature concerning the survival rate and prognosis in neuroblastoma.[3, 4, 5, 6]

We have seen 11 cases of neuroblastoma at the Hacettepe Children's Hospital in the past three and one-half years. In age they

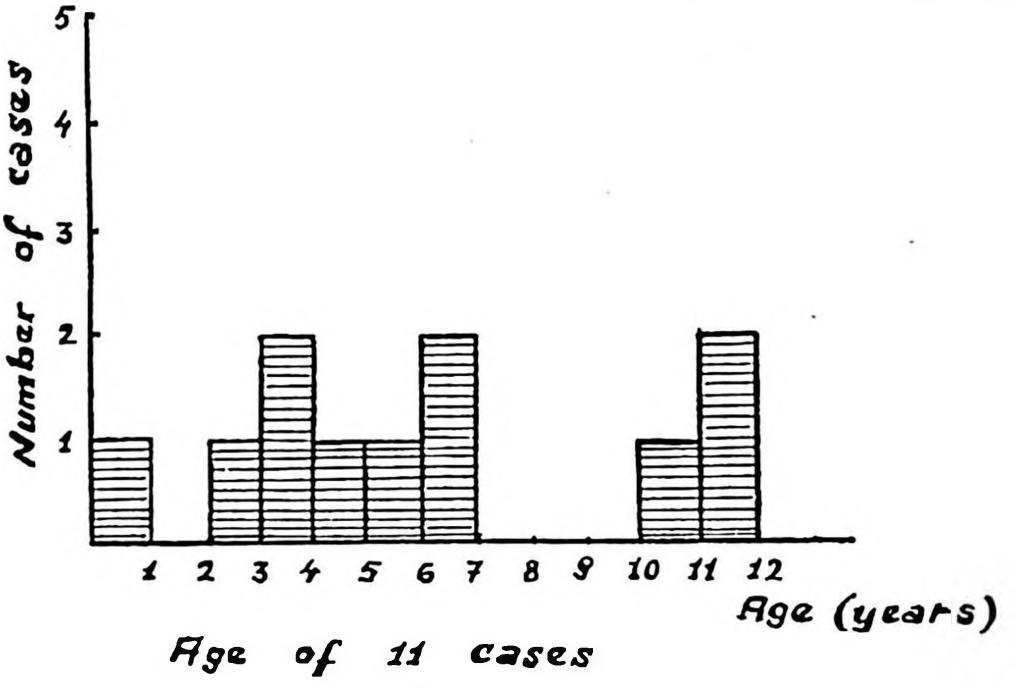

Figure 1.

ranged between 5 months and 11 years. The youngest was a female with a neuroblastoma arising from the abdomen with metastasis to the

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liver. The two oldest patients were 11 years old, male and female, with tumors arising from the abdomen and right kidney with general bony metastasis. The average age was 5 years and 9 months. (Fig. 1). There was no sex preponderance in the incidence of neuroblastoma in the reported cases in the literature.[1, 3, 7, 8, 9] In our small group there were 8 males and 3 females.

Neuroblastomas are the tumors which originate from tissues which give rise to the adrenal medulla or other portions of the sympathetic system, e. g. the retroperitoneum, posterior mediastinum or cervical ganglia, abdominal pelvic sympathetic chains and associated main ganglia—the celiac and mesenteric ganglia.

Microscopically, the neuroblastoma is cellular, composed of dark cells resembling lymphocytes. It has the characteristic feature of a circular grouping or pseudorosette formation around a fibrillar network. It differs from the sympathicogonioma only in its somewhat greater maturity and some differentiated ganglion or pheochrome cells may be present. The cells tend to be larger, irregular and oval in shape and some may have elongated cytoplasmic processes. The medulloblastoma of the mid-brain and retinoblastoma of the eye arise from undifferentiated neural elements, have a similar histologic structure and occur in childhood.[10]

Childhood neuroblastomas have been divided into two groups on the basis of the distribution of the metastasis.

In the Pepper group (1901) there is early and extensive metastasis to the liver which results in abdominal distention. Hutchinson, in 1907 described primary adrenal tumors with metastases to the skull, orbit, dura, long bones and sometimes lungs.[10] It has been claimed that the Pepper type usually arises from the right adrenal and the Hutchinson type from the left. This has not been found to be true, and it appears that the position of the metastasis is not determined by the site of the primary tumor. Also the distribution of the metastases bears no relationship to the cytologic character or anatomical site of the primary growth.[10, 11, 12]

Location. Neuroblastomas can arise from sympathetic tissue anywhere in the body. They can appear from the chains in the neck, the thorax, abdomen, brain, adrenal medulla or retroperitoneum.[6, 10, 13, 14, 15] In our 11 cases, 5 originated from the abdominal cavity, 2 from the right kidney, 1 from the left kidney and 2 from the cervical ganglion. In one case the primary site was undetermined. (Fig. 2).

Symptoms and Physical Findings. Neuroblastoma may present different symptoms because of the variability in origin of the primary tumor and metastases. Involvement of the different systems is manifested by varieties of related symptoms and physical indications. The most common are:

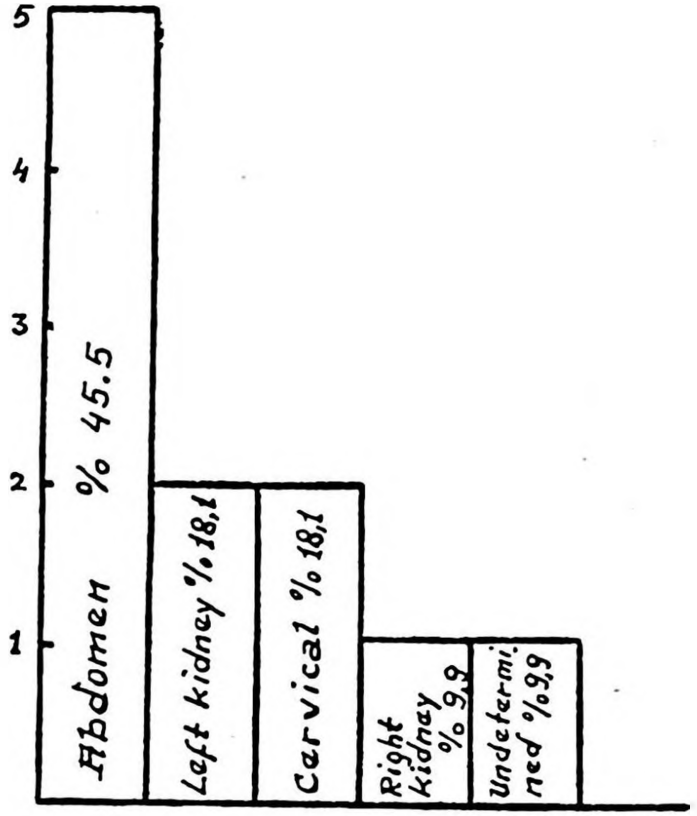

Fig. 2 — Location of 11 Cases

1. Growth – generally a non-tender abdominal mass, cervical mass or a mediastinal growth.
2. Pain – depending on the localization and metastases manifested as abdominal, chest or bone pain etc.
3. Progressive weight loss, fatigue and anorexia.
4. Pallor and anemia.
5. Fever – gencrally unexplained until other symptoms appear.
6. Miscellaneous – cough, dyspnea, irritability, headache, proptosis (exophthalmos), emesis, hematuria, paralysis or other compression symptoms.

The symptoms of our cases are shown in table 1.

Diagnosis is made by microscopic examination of removed tumor tissue, biopsy material or postmortem examination. Nine cases were proved by positive biopsy; the bone marrow showed evidence of neuroblastoma cells in two cases.

Metastasis takes place by way of the blood stream and lymphatic invasion; also by local extension to the regional lymphnodes.[5,9,14,16,17]

Metastasis may be localized or generalized; disseminated to the kidney, intestines, lungs, diaphragm, pancreas, liver and other organs; brain, orbits, vertebrae, skull and other bones. The bone marrow may be replaced before roentgenographic changes are seen in skeletal films.

TABLE 1

PRESENTING SYMPTOMS OF ELEVEN CASES

SYMPTOM	NUMBER OF CASES
Fever	7
Abdominal Mass	6
Weight Loss	3
Anorexia	3
Abdominal Pain	2
Edema in Eye or Exophthalmus	2
Cervical Mass	2
Edema in Legs	1
High B.P.	1
Oliguria	1
Fatigue	1
Incontinence (Urinary)	1
Hematuria	1

Sixty to seventy-five per cent of patients show evidence of metastasis at the time of first hospital admission.[1,3,8,14] Six of our 11 cases were free from metastasis but in 5 cases the tumor had already metastasized when the patients were first seen. Three cases had generalized bone metastases, one case had metastasis into the liver. *Therapy.* The attitude towards neuroblastomas has been changing in recent years. Increasing numbers of reported cures in the literature, encourage the physician to use a multiple attack (surgery, chemotherapy and radiation) in order to obtain a permanent cure or at least palliation and extension of life in reasonable comfort. Major surgery or complete extirpation of the tumor, if no metastasis is present,[3,5,11,18] is the treatment of choice with roentgen ray irradiation given over the operative site immediately after surgery.[5,11,14] In some cases, when complete removal of the tumor is impossible,

either a partial excision or a biopsy is done and radiation is given to the remaining tumor mass postoperatively.

Chemotherapy, (different agents have been used, including nitrogen mustard, chlorambucil, Actinomycin D, TEM, vitamin B12, steroids, Cooley's toxin, antifolics, etc.) and roentgen ray irradiation are used extensively on patients with generalized metastasis.

Two of our 11 patients had nephrectomy, one had excision of the cervical mass and the rest had biopsies. Six of them were given radiation therapy to the lesion area.

PROGNOSIS AND DISCUSSION

Several factors play an important role in survival rate and prognosis in neuroblastoma. There have been early and recent excellent reviews concerning prognosis[3, 7, 8, 9, 11, 12, 16] and many survival reports[10] following major surgical attack[3, 5, 18, 19] and spontaneous regression of the tumor.[20, 21, 22, 23] Also we see a number of survival reports with metastasis[4, 11, 20, 24, 25, 26] and some survivals for as long as fifteen years.[19, 26, 27]

Generally a fourteen month survival in children is accepted as equivalent to the five year period commonly used in evaluating the results of malignant tumors in adults.

Age. The age of the patient has a significant importance in relation to the survival rate. Chances of survival are definitely found to be good among those of the two years and younger age group because of the higher incidence of maturation or regression of the tumor in this age group.[3, 5, 7] Prognosis is considered to be poor in older children due to more frequent skeletal metastases.[3]

The Presence or Absence of Local or Distant Metastasis influences survival. There is found to be a significant decrease in the rate of 3 year survivals among those with demonstrable metastasis at the time of diagnosis as compared with the survival rate among those with no demonstrable metastatic lesions.[11]

Degree of Cytologic Differentiation. An analysis of the literature indicates that most of the 14 month survivors were found among those with relatively well differentiated tumors.[3, 12, 22] However, the occurrence of tumors of different cytologic characteristics is statistically unrelated to age.

Site of Primary Tumor. It was thought that cervical neuroblastomas had a better prognosis than those of other locations; this perhaps

is true because of chances of earlier detection, diagnosis and therapy in comparison with the other sites. However, statistical analysis again showed that the anatomical distribution of the primary site is irrespective of the age group and the incidence of 14 month survivors is not significantly related to the site of the primary tumor.[3]

Therapy. Many reports reviewed the effect of therapy on the final outcome[1, 3, 5, 8, 11, 18, 24, 28] and claimed that better prognosis or longer survival rates were obtained with total excision of the tumor with postoperative irradiation (88 %). However, chances for long term survival became less with partial excision and roentgen ray therapy (64 %) and biopsy of the tumor combined with radiation and chemotherapy (38 %).[5] But generally it is accepted that statistically there is no difference in survival rate among groups treated with surgery alone, or groups treated with radiotherapy alone, or groups treated with a combination of surgery and radiotherapy.

Six of our patients are dead at the time of publication of this report. In our series, the number of patients is small and the period for follow-up is not long enough to draw conclusions on the prognosis. The outcome has always been poor in those with bony metastases at the time of diagnosis and death occurred shortly after diagnosis. The form of therapy instituted did not show any influence on prognosis. However, cervical sympathetic chain involvement without metastases appears to have a better prognosis if a total excision is possible.

A review of the literature gives the impression that there are several factors that influence the prognosis in neuroblastoma in children and the treatment consists of total excision followed by local radiation if there is no demonstrable metastasis. If this is not possible, partial surgical removal followed by radiation and chemotherapy is advised. Patients with extensive metastases should be given roentgen ray therapy and chemotherapy. Every effort should be made for palliation and a comfortable prolongation of life.

Summary

Clinical summaries on 11 patients with neuroblastoma are presented. Literature, therapy and various other factors concerning prognosis are reviewed.

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