

Neuroblastoma with Orbital Secondaries

Ramesh Venkatesh*, HL Trivedi**

Abstract

A 10 mth old male child born of a non consanguineous marriage came to our OPD with swelling in the abdomen since 5 mths, swelling in the face which was gradually progressive and h/o of change in the voice and increased sweating and rashes all over the body. On ophthalmic examination, the patient had bilateral periorbital chemosis and the rest of the ophthalmic examination was normal. Patient was referred to paediatrics. He expired the next day.

Introduction

Neuroblastoma is the most common extracranial solid tumour in infancy. It is an embryonal malignancy of the sympathetic nervous system arising from neuroblasts (pluripotent sympathetic cells). Age, stage, and some molecular defects encountered in tumour cells are important prognostic factors and are used for risk stratification and treatment assignment.

Pathophysiology

Histology

The undifferentiated neuroblastomas histologically present as small, round, blue cell tumours with dense nests of cells in a fibrovascular matrix and Homer-Wright pseudorosettes. These pseudorosettes, which are observed in 15-50% of tumour samples, can be described as neuroblasts surrounding eosinophilic neuritic processes. In contrast, the completely benign ganglioneuroma is typically composed of mature ganglion cells, Schwann cells, and neuritic processes, whereas ganglioneuroblastomas include the whole spectrum of differentiation between pure ganglioneuromas and neuroblastomas.

*Resident; **Associate Professor, Department of Ophthalmology, TNMC and BYL Nair Hospital, Mumbai 400 008.

Shimada histopathologic classification system

- Favourable histology group
 - Patients of any age with stroma-rich tumours without a nodular pattern
 - Patients younger than 18 months with stroma-poor tumours, an MKI of less than 200/5000 (200 karyorrhectic cells per 5000 cells scanned), and differentiated or undifferentiated neuroblasts
 - Patients younger than 60 months with stroma-poor tumours, an MKI of less than 100/5000, and well-differentiated tumour cells
- Unfavourable histology group
 - Patients of any age with stroma-rich tumours and a nodular pattern
 - Patients of any age with stroma-poor tumours, undifferentiated or differentiated neuroblasts, and an MKI more than 200/5000
 - Patients older than 18 months with stroma-poor tumours, undifferentiated neuroblasts, and an MKI more than 100/5000
 - Patients older than 18 months with stroma-poor tumours, differentiated neuroblasts, and an MKI of 100-200/

5000

- Patients older than 60 months stroma-poor, differentiated neuroblasts, and an MKI less than 100/5000

Joshi histopathologic classification system

Favourable histology group

- A low mitotic rate (?10 mitoses per 10 high-power fields) and calcification present in any age group
- Either a low mitotic rate or calcification present in any patient younger than 1 year

Unfavourable histology group

- Either a low mitotic rate or calcification present in any patient older than 1 year
- A high mitotic rate and no calcification in any age group

Frequency

Neuroblastoma accounts for approximately 7.8% of childhood cancers in the United States and in the other international countries.

Mortality/Morbidity

According to the SEER data, the overall 5-year survival rate for children with neuroblastoma has improved from 24% in 1960-1963 to 55% in 1985-1994.⁴ In part, this increase in survival rate may be due to better detection of low-risk tumours in infants.

Race

Incidence of neuroblastoma is higher in white children than in black children. However, race does not appear to have any effect on outcome.

Sex

Males have a slightly higher incidence of

neuroblastoma than females, with a male-to-female ratio of 1.2:1.

Age

Age distribution is as follows: 40% of patients are younger than 1 year when diagnosed, 35% are aged 1-2 years, and 25% are older than 2 years when diagnosed

Clinical

History

A 10 mth old male child born of a non consanguineous marriage came to our OPD with swelling in the abdomen since 5 mths, swelling in the face which was gradually progressive and h/o change in the voice and increased sweating and rashes all over the body. On ophthalmic examination, the patient had bilateral periorbital chemosis and the rest of the ophthalmic examination was normal. Patient was referred to paediatrics. USG B scan showed enlarged lateral rectus muscle. Abdominal sonography showed a mass in the flanks 5 cm in diameter, soft in consistency. Investigations showed RBC-3.2 million/cu.mm, Hb- 9.2 gm%, PCV- 28.4%, MCV-94.3 fl, MCH- 30.5, MCHC- 32.3, WBC- 6500, polymorphous- 6%, lymphocytes- 94%, Platelet count-3,25,000, BUN-10, Sr Alk PO₄ – 524 and SGOT- 106, both of which were increased. He expired the next day (Fig. 1).

Signs and symptoms of disease vary with site of presentation. Generally, symptoms include abdominal pain, emesis, weight loss, anorexia, fatigue, bone pain, and chronic diarrhoea. Hypertension is an uncommon sign of the disease and generally is caused by renal artery compression, not catecholamine excess.

- Because more than 50% of patients present with advanced-stage disease, usually to the bone and bone marrow, the most common presentation includes bone pain and a limp. However, patients may



Fig. 1 : Swelling of face with bilateral periorbital, Chemosis.

also present with unexplained fever, weight loss, irritability, and periorbital ecchymosis secondary to metastatic disease to the orbits. The presence of bone metastases can lead to pathologic fractures.

- Approximately two thirds of patients with neuroblastoma have abdominal primaries. In these circumstances, patients can present with an asymptomatic abdominal mass that usually is discovered by the parents or a caregiver.
- Symptoms produced by the presence of the mass depend on its proximity to vital structures and usually progress over time.
 - Tumours that arise from the paraspinal sympathetic ganglia can grow through the spinal foramina into the spinal canal and impinge on the spinal cord. This may result in the presence of neurologic symptoms, including weakness, limping, paralysis, and even bladder and bowel dysfunction.
 - Thoracic neuroblastomas (posterior mediastinum) may be asymptomatic and are usually diagnosed by imaging studies obtained for other reasons.

Presenting signs or symptoms may be insignificant and involve mild airway obstruction or chronic cough, leading to chest radiography.

- Thoracic tumours extending to the neck can produce Horner syndrome. Primary cervical neuroblastoma is rare but should be considered in the differential diagnosis of masses of the neck, especially in infants younger than 1 year with feeding or respiratory difficulties.
- In a small proportion of infants younger than 6 months, neuroblastoma presents with a small primary tumour and metastatic disease confined to the liver, skin, and bone marrow (stage 4S). If this type of tumour develops in neonates, skin lesions may be confused with congenital rubella, and, if the patient has severe skin involvement, the term “blueberry muffin baby” may be used.
- Approximately 2% of patients present with opsoclonus and myoclonus a paraneoplastic syndrome characterized by the presence of myoclonic jerking and random eye movements. These patients often have localized disease and a good long-term prognosis. Unfortunately, the neurologic abnormalities can persist or progress and can be devastating.
- Finally, intractable diarrhoea is a rare paraneoplastic symptom and is associated with more differentiated tumours and a good prognosis.

Physical

- Children are usually referred to a paediatric oncologist by primary care providers who have identified a persistent unexplained symptom or sign, either upon physical examination or based on screening test findings.

- In patients with suspected neuroblastoma, performing a thorough examination with careful attention to vital signs (e.g., blood pressure), neck, chest, abdomen, skin, and nervous system is essential.
- Metastatic lesions of the skin are common in infants younger than 6 months and may represent stage 4S disease.
- Examination of the abdomen may reveal an abdominal mass, leading to the appropriate workup.
- Neurologic examination may reveal Horner syndrome. In the case of dumbbell tumours, compression of the spinal cord may produce lower extremity weakness or paraplegia. Patients with neurologic involvement by tumour should be treated emergently, secondary to the risk of permanent neurologic sequelae.

Lab Studies

- Any child with a presumed diagnosis of neuroblastoma or any other childhood cancer should be referred to a paediatric cancer centre for proper care and evaluation. Laboratory studies should include the following:
 - Serum LDH (useful as biologic marker)
 - Ferritin (useful as biologic marker)
 - CBC count and differential (Anaemia or other cytopenias suggest bone marrow involvement.)
 - Urine collection for catecholamines (VMA/HVA)
 - The spot test for VMA/HVA is highly inaccurate. Centres usually send samples to a specialty laboratory and/or perform a timed collection of urine.

- A urinary catecholamine level is considered to be elevated if it is 3 standard deviations higher than the age-related reference range levels.

- Serum creatinine
- Liver function tests
 - Alanine aminotransferase (ALT)
 - Aspartate aminotransferase (AST)
 - Total bilirubin
 - Alkaline phosphatase
 - Total protein
 - Albumin
 - Prothrombin time (PT)/activated prothrombin time (aPTT)
- Electrolytes
- Calcium
- Magnesium
- Uric acid

Imaging Studies

- Obtain chest and abdominal radiographs to evaluate the presence of a posterior mediastinal mass or calcifications.
- A CT scan of the primary site is essential to determine tumour extent. The main body of the tumour is usually indistinguishable from nodal masses.
- In cases of paraspinal masses, MRI aids in determining the presence of intraspinal tumour and cord compression.
- I123/131-methyl iodobenzylguanidine (MIBG) accumulates in catecholaminergic cells and provides a specific way of identifying primary and metastatic disease if present. Increasing number of institutions have access to MIBG scanning.
- A technetium-99 bone scan can also be used to evaluate bone metastases.

Especially in patients with negative MIBG study findings.

- Skeletal surveys may also be useful, especially in patients with multiple metastatic lesions.
- Positron emission tomography (PET) scan are under evaluation.

Other Tests

- Obtain the following as baseline studies before therapy with anthracyclines:
 - ECG
 - Echocardiogram or resting radionuclide ejection fraction scan
- Baseline hearing tests are recommended before cisplatin therapy.
- Baseline creatinine clearance should be measured, especially if serum creatinine is abnormal.

Staging

- International neuroblastoma staging system
 - Stage 1
 - Localized tumour with complete gross excision, microscopic residual disease, or both
 - Ipsilateral lymph nodes negative for tumour (Nodes attached to the primary tumour may be positive for tumour.)
 - Stage 2A
 - Localized tumour with incomplete gross resection
 - Representative ipsilateral nonadherent lymph nodes microscopically negative for tumour
 - Stage 2B
 - Localized tumour, complete gross excision, or both with ipsilateral

nonadherent lymph nodes positive for tumour

- Enlarged contralateral lymph nodes, which are negative for tumour microscopically
- Stage 3
 - Unresectable unilateral tumour infiltrating across the midline, regional lymph node involvement, or both
 - Alternately, localized unilateral tumour with contralateral regional lymph node involvement
- Stage 4 - Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
- Stage 4S
 - Localized primary tumour (as defined for stages 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow (< 10% involvement)
 - Limited to infants

Medical Care

Care of children with cancer is provided by a multidisciplinary team involving paediatric oncology, radiation oncologists, surgeons, and anaesthesiologists, as well as nurse practitioners, nurses, pharmacists, psychologists, and physical and occupational therapists dedicated to the special needs of these children.

Cooperative group treatment strategies

- Low-risk group treatment strategy
 - Patients with localized resectable neuroblastoma (stage 1) have excellent EFS with surgical excision

- of tumour alone.
- Similar therapy is offered to patients with stage 2A/2B disease who are presently being assigned to a low-risk category if they are younger than 1 year, regardless of *MYCN* status or histology. Additionally, patients with stage 2B/2C disease who are older than 1 year are considered low-risk if they have non-*MYCN*-amplified or amplified tumours with favourable histology.
 - Patients with 4S disease (i.e., non-*MYCN*-amplified tumours, favourable histology, hyperdiploid tumours) are also considered to be in the low-risk group and are offered resection of the primary tumour, followed by observation. Chemotherapy may be used to control life-threatening situations.
 - Intermediate-risk group treatment strategy
 - These patients receive multimodality therapy, including surgery, chemotherapy, and, in selected situations, radiation therapy.
 - Intermediate-risk patients include children younger than 1 year with stage 3/4/4S disease and favourable biology (non-*MYCN*-amplified tumours, regardless of histology and DNA index).
 - Patients are considered to be in the intermediate-risk group if they are older than 1 year with stage 3 non-*MYCN* and favourable histology tumours. These patients are offered therapy with 4 of the most active drugs against neuroblastoma (i.e., cyclophosphamide, doxorubicin, carboplatin, etoposide) for either 4 or 8 cycles, depending on histology and DNA index. In these patients, surgery can be performed either at time of diagnosis or following multiagent chemotherapy. If residual disease is present after chemotherapy and surgery, radiation therapy could be considered.
 - High-risk group treatment strategy
 - Patients with high-risk disease include those with stage 2A/2B disease who are older than 1 year and have *MYCN*-amplified unfavourable histology tumours.
 - Infants with stage 3/4/4S and with *MYCN*-amplified tumours or children older than 1 year with stage 3, *MYCN*-amplified or non-*MYCN*-amplified tumours, and unfavourable histology tumours are also considered high-risk.
 - All patients older than 1 year with stage 4 tumours are considered to be in the high-risk group, regardless of *MYCN* status or histology. These patients seem to require treatment with multiagent chemotherapy, surgery, and radiotherapy, followed by consolidation with high-dose chemotherapy and peripheral blood stem cell rescue. In the future, some patients older than 1 year with favourable biologic characteristics may be downgraded to the intermediate-risk group.
 - Risk of relapse from minimal residual disease after consolidation may be decreased with cis-retinoic acid treatment.

Surgical Care

Surgical resection plays an important role in the treatment of patients with

neuroblastoma.

- For patients with localized disease, surgical resection is curative.
- For patients with regional or metastatic disease, surgery to establish a diagnosis and obtain adequate samples for biologic studies is essential. Typically, second-look surgery postchemotherapy is used to attempt a complete resection. The emphasis in the second-look procedure is as complete a debulking as possible without sacrificing major organ function.
- Patients with residual disease postchemotherapy and surgery may benefit from the use of radiotherapy.

Diet

- Nutrition plays an important role in therapy.
- Children need adequate caloric intake to attain normal growth and development, and to recover from the adverse effects of therapy.
- Nutritionists typically help to provide adequate supportive care during therapy.
- Supplemental nutrition is often required during therapy. This should occur via the enteral route (nasogastric or gastric tube). The parenteral route should be used only after failure to supplement adequately using enteral feedings.

Activity

No specific restrictions are placed on activity.

- Patients who are thrombocytopenic should avoid strenuous activity and contact sports.
- Patients should avoid ill contacts, especially if neutropenic.

Prognosis

- Determinants of response and outcome

- Stage, age, and several biologic characteristics of the tumour determine outcome.
- Similarly, the patient may also have genetic polymorphism characteristics that influence drug absorption, distribution, metabolism, and excretion.
- Several treatment strategies are available to treat patients with recurrent neuroblastoma.
 - A local recurrence in a patient with low-stage disease generally has a good prognosis, and patients usually receive standard chemotherapy, surgery, and/or radiation as necessary.
 - Patients with disseminated disease at presentation have a high recurrence rate and a poor outcome.
 - For patients with recurrent disease in this setting, various phase I/II agents are generally available.
- Response criteria are used to evaluate the efficacy of therapy.
 - Complete clinical response - More than 90% decrease (sum of the products of the greatest perpendicular diameters) of the primary tumour and metastatic disease (if any), no new lesions, healing of bone lesions
 - Partial clinical response - A decrease of 50% or less (sum of the products of the greatest perpendicular diameters) of the primary tumour and metastatic disease (if any), no new lesions, healing of bone lesions
 - Minor response - More than 25% and less than 50% decrease (sum of the products of the greatest perpendicular diameters) of primary tumour and metastatic disease (if any), no new

- lesions, healing of bone lesions
- No response - Less than 25% decrease (sum of the products of the greatest perpendicular diameters) of primary tumour or metastatic disease (if any), no new lesions
- Progressive disease - More than 25% increase (sum of the products of the greatest perpendicular diameters) of the primary tumour or all metastatic lesions (if any), appearance of new lesions

Patient Education

For compliance and good medical care, patients and families must understand the importance of treatment and adverse effects of medications used. In addition, they should learn to recognize and identify signs and symptoms of complications that require urgent medical care.

Medical/Legal Pitfalls

- **Diagnostic workup:** Cancer is rare in children; therefore, if neuroblastoma is suspected, prompt referral to a paediatric oncology centre for multidisciplinary evaluation and appropriate care is essential. Most patients initially present for evaluation to either the primary care providers or a general surgeon. A surgeon without expertise in the management of paediatric tumours may attempt to biopsy or resect a mass without the availability of the necessary resources to obtain and process tumour samples for biologic studies. This intervention can lead to difficulty in risk-assignment and in administration of appropriate therapy.
- **Informed consent:** Paediatric oncology has benefited from the high level of participation of children in clinical trials. The paediatric oncologist must be an

effective communicator in providing informed consent to patients and families; a thorough discussion of the potential benefits and risks is warranted. Without compromising the enthusiasm and desire by the subspecialist to achieve a cure for the patient, families must be made aware that complications during cancer treatment can result in death or long-term morbidities.

References

1. Shimada H, Chatten J, Newton WA Jr, *et al.* Histopathologic prognostic factors in neuroblastic tumors: definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastomas. *J Natl Cancer Inst* 1984;73 (2) : 405-16.
2. Joshi VV, Rao PV, Cantor AB, *et al.* Modified histologic grading of neuroblastomas by replacement of mitotic rate with mitosis karyorrhexis index. A clinicopathologic study of 223 cases from the Pediatric Oncology Group. *Cancer* 1996; 77 (8) : 1582-8.
3. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet* 2007; 369 (9579) : 2106-20.
4. London WB, Castleberry RP, Matthay KK, *et al.* Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol* 2005; 23 (27) : 6459-65.
5. Acharya S, Jayabose S, Kogan SJ, *et al.* Prenatally diagnosed neuroblastoma. *Cancer* 1997; 80 (2) : 304-10.
6. Altman AJ. Management of malignant solid tumors. In: *Hematology of Infancy and Childhood*. 1993.
7. Attiyeh EF, London WB, Mosse YP, *et al.* Chromosome 1p and 11q deletions and outcome in neuroblastoma. *N Engl J Med* 2005; 353 (21) : 2243-53.
8. Bagatell R, Rumcheva P, London WB, *et al.* Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. *J Clin Oncol* 2005; 23 (34) : 8819-27.