

Building a Neuro-Oncology Program and Epidemiological Profiling of Pediatric Brain Tumors in a Tertiary Cancer Care Center in India

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Abstract

Background: Treatment of childhood brain tumours requires coordinated efforts by multiple specialities - neurosurgery, neuroradiology, neuropathology, oncology, and radiotherapy. The outcome is worse in developing countries compared to developed countries because of deficiencies in proper registry, failure of timely diagnosis, lack of availability and co-ordination of multiple specialists required for comprehensive management and high abandonment rates.

Method: The pediatric neuro-oncology program was initiated in collaboration with the neighbouring neurosurgery institution as a step towards improving care for pediatric brain tumor patients in our hospital. Epidemiology, treatment and follow-up of brain tumours in children aged 1-14 years attending the pediatric oncology department were studied. Patients received multimodality treatment with surgery, radiotherapy and chemotherapy by specialists in both centres. The study period was from January 2008 to December 2012.

Results: There were 375 pediatric brain tumour patients during the study period. 166 patients (44.2%) had supratentorial tumors and 209 (55.73%) had infratentorial tumors. 42.6% of tumours were high-grade and 53.6% were low grade. The commonest histopathological tumour type was astrocytoma (48.8%) followed by medulloblastoma (24.5%). 287 (76.5%) patients underwent surgery, 216 (57.6%) patients received radiotherapy, 97 (25.8%) patients received chemotherapy and 94 (25%) required follow-up only. Patient follow-up rates improved from 37.2% to 82.6% and treatment abandonment decreased from 35.8% to 14.8% over these years.

Conclusions: Impact of the pediatric neuro-oncology program in our hospital has made it possible to provide comprehensive multidisciplinary treatment in a co-ordinated manner, describe the epidemiology of pediatric brain tumors, reduce treatment abandonment, and improve the follow-up of pediatric brain tumour patients.

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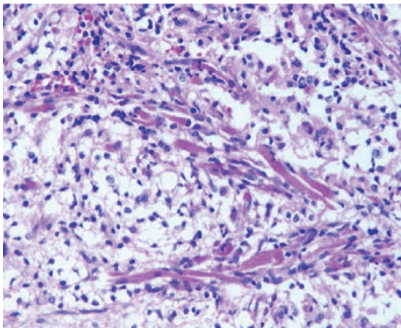
Introduction

Brain tumors are the most common pediatric solid malignancy, second in overall cancer incidence only to leukemias, and represent between 16% and 23% of all pediatric malignancies.¹ Their treatment is challenging and technically demanding; however, improvements in diagnosis and therapy have increased worldwide survival. Cure rates in children with brain tumors are lower in low and middle income countries due to under-diagnosis, incorrect clinical assessment, and lack of availability of appropriate radiological, neurosurgical, and radiotherapy services.² In developing countries like India, complete registration of brain tumors and reliable data collection rarely occurs due to monetary constraints; hence, the exact burden of this disease is unnoticed.³ Management of childhood brain

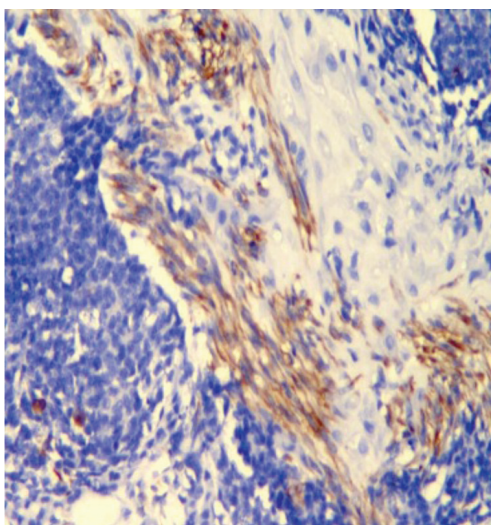
tumors requires the coordinated efforts of specialists in neurosurgery, neuroradiology, neuropathology, radiation oncology, pediatric oncology, neurology, rehabilitation, endocrinology, and psychology.^{4,5} Often, these specialist departments are not available in one location, which presents considerable difficulty for clinicians and patients.

The Pediatric Oncology Division (POD) of our institution sees approximately 80 pediatric cases of primary central nervous system (CNS) tumors per year, which comprises 15% of the total pediatric cancers. The Radiotherapy and Pediatric Oncology departments are independently functioning. Most brain tumor cases are referred to us from the Sree Chitra Thirunal Institute for Medical Science and Technology (SCTIMST), which is a National Institution par excellence with an efficient neurosurgery team. Pediatric

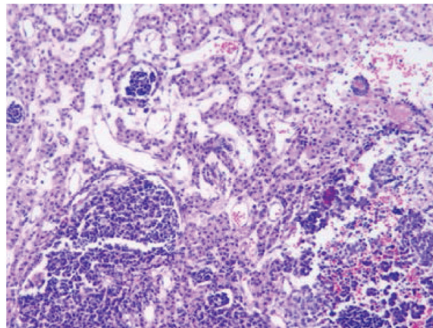
Myogenic differentiation



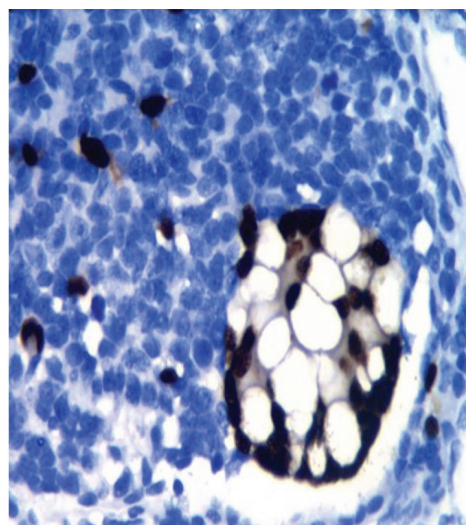
Desmin



Epithelial differentiation



Myogenin



Melanotic differentiation

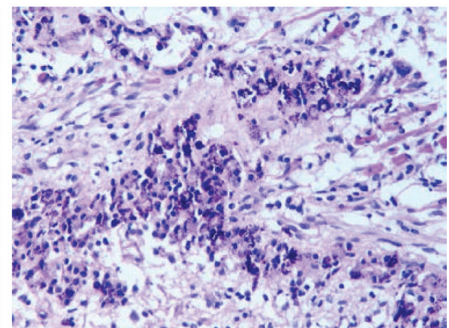


Figure 1. (a) Medulloblastoma showing myogenic (200 \times), epithelial (100 \times) and melanotic (200 \times) differentiation (hematoxylin and eosin staining). (b) Immunohistochemistry staining of medulloblastoma with melanotic (myogenin, 400 \times) and myogenic (desmin, 200 \times) differentiation.

Table 1. Histopathologic break-down of the pediatric brain tumors.

Tumor type	Patients (N)	Percentage
Medulloblastoma	89	24.5
Astrocytoma	163	43.5
Glioblastoma multiforme	12	3.3
Ependymoma	26	7.14
Craniopharyngioma	22	6.04
Supratentorial PNET	16	4.4
Oligodendroglioma	3	0.8
Choroid plexus neoplasms	5	1.3
Atypical teratoid/rhabdoid tumor	6	1.65
Germ cell tumor	7	1.9
Optic pathway glioma	7	1.9
Rare histology	8	2.1
Unverified/unclassified	11	2.9

PNET: Primitive neuroectodermal tumor

brain tumor patients have been largely managed by surgery and radiation. The pediatric oncologist's role was limited to providing certain chemotherapy regimens and supportive care for a few patients - mostly those less than 3 years of age. As a result, the exact number, treatment details, and follow-up or outcome of these patients was not known. Because of various reasons, a large number of patients did not begin treatment or were lost to follow-up after initiation of treatment. For those who continued with treatment, considerable inconvenience was caused because of multiple parallel doctor appointments and therapy sessions in various departments. Lack of collaboration was most evident in challenging cases and uncommon tumors that lacked uniformity in decision-making. An increased need existed for interaction and co-ordination between the treating specialists, especially to improve overall quality of service.

The Neuro-Oncology Program was conceived as part of the Quality Improvement Program in the POD. Its aim was to deliver comprehensive treatment to pediatric brain tumor patients by a coordinated multidisciplinary approach. This program provided the platform for all concerned specialists to convene and paved the way for interaction, constructive discussion, and combined decision making for all aspects of CNS tumor management. This program aimed to address challenges such as delays in scheduling surgery and radiation appointments, maintenance of a

brain tumor registry, and tracking patients to reduce treatment abandonment and improve follow-up. This program was proposed as an academic forum for post-graduate trainees and other doctors.

Materials and Methods

The Neuro-Oncology Program involved active participation of specialists from departments of interest in two neighboring institutions that were situated on the same campus. Neurosurgeons from the neighboring institute in addition to pediatric oncology and radiation oncology clinicians from our institute formed part of the program. Neuroradiology and neuropathology specialists were available in both centers. Sessions were convened once or twice each month to discuss difficult cases that presented to both institutes. Emphasis was given for discussing patients who needed well-coordinated care plans, those that sparked interest such as atypical clinical presentations, interesting imaging or histological features, conflicts of a radiological nature, histopathological behavior of tumors or discrepancies in histopathological diagnosis obtained from both institutions, and rare tumors. In addition, our neuropathologist coordinated with the National Institute of Mental Health and Neurosciences (NIMHANS), one of the best institutions for this specialty in India and the Mayo Clinic (USA) for expert pathology opinions when needed. A registry was maintained to enroll

Table 2. Year-wise follow-up statistics of pediatric patients with brain tumors.

Year	Total patients	Did not report back for starting treatment (N)	Discontinued treatment after starting (N)	Treatment abandonment (%)	Follow-up (%)
2008	56	Not known	Not known	Not known	37.2
2009	81	19	10	35.8	76.4
2010	88	10	4	15.9	81.5
2011	76	12	4	21.05	83.2
2012	74	8	3	14.8	82.6

all pediatric brain tumor cases, their personal and clinical data, diagnosis, treatment plan, and follow-up. Patients who missed their appointments or abandoned treatment were tracked by telephone calls, given proper counseling, and encouraged to return for treatment.

Epidemiology of pediatric brain tumors was compiled with the help of the brain tumor registry. We collected data from the medical records of children with brain tumors registered between January 2008 and December 2012. Clinical history, radiographic studies and histopathology slide reviews were required to establish a diagnosis. Patients received multimodality treatment with surgery, radiotherapy and chemotherapy based on age, histopathology, and staging. Follow-up data was collected from the brain tumor registry. Descriptive epidemiology methods were used for statistical analysis.

Results

In the 5-year period between January 2008 to December 2012, POD treated 375 new pediatric brain tumor patients, which constituted 15% of

total malignancies diagnosed in children <14 years of age.

Age and gender

There were 213 (56.8%) boys and 162 (43.2%) girls with a male:female ratio of 1.3:1. A total of 49 (13%) patients were <3 years of age, 231 (61.6%) were 3-10 years of age, and 95 (25.3%) were >10 years of age. There were 286 (76.4%) patients referred to us from the neighboring neurosurgery institute which was our partner in the Neuro-Oncology Program.

Location and grade of tumors

There were 166 (44.2%) supratentorial tumors and 209 (55.73%) infratentorial tumors. Tumor grade was determined by radiologic imaging or histopathology analysis. High grade tumors comprised 42.6% of cases, 53.6% were low grade, and grade was not determined in a minority of cases.

Histopathology

Astrocytomas comprised the largest histopathological type (48.8%). The majority were low grade astrocytomas. Other histopathological types

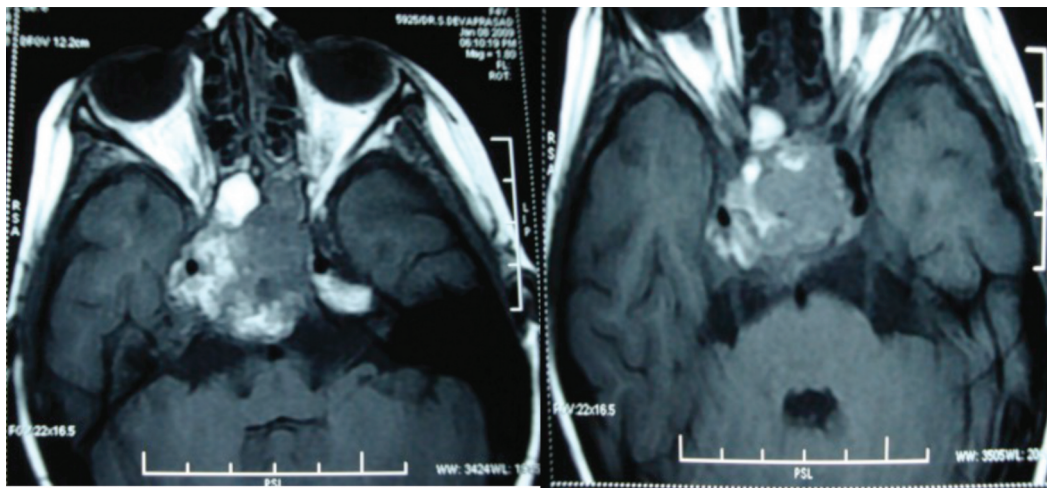


Figure 2. MRI images of clival chordoma.

included medulloblastomas (24.5%), ependymomas (7%), and craniopharyngiomas (6%). There were 6 patients diagnosed with atypical teratoid/rhabdoid tumors and 7 with intracranial germ cell tumors. In addition, 3 patients were diagnosed with oligodendroglioma, a rare tumor in the pediatric age group. Rare histologies reported (one case each) included clival chordoma, glial sarcoma, CNS neuroendocrine tumor, pituitary adenoma, primary CNS lymphoma, invasive meningioma, and microglioma (Table 1).

Patients received multidisciplinary treatment that included surgery, chemotherapy, and radiotherapy based on age and histopathology. A total of 287 (76.5%) patients underwent surgery. From these, gross total/subtotal excision was performed in 254 patients and only 33 patients had biopsies. The remainder of patients did not have surgery because of various reasons that included very young age, eloquent location of the tumor, poor general condition, metastatic status, and disease progression.

Chemotherapy was administered to 97 (25.8%) patients. Concurrent chemo-radiation with vincristine, followed by 6-8 cycles of vincristine, cisplatin, and lomustine per the standard protocol, was administered to patients >3 years of age who were diagnosed with medulloblastoma and a few cases of ependymoma/anaplastic astrocytoma who recurred after radiation. Patients with optico-chiasmatic tumors received Packer's low-grade glioma protocol with vincristine and carboplatin. Patients <3 years of age received the COG (Children's Oncology Group) Baby Brain Protocol chemotherapy and delayed radiation.

There were 216 (57.6%) patients who received radiotherapy and 94 (25%) required observation only. A total of 49 (13%) patients received no adjuvant treatment from our center due to various reasons – received treatment elsewhere, disease progression, death or treatment refusal and prematurely stopping treatment.

Follow-up

Table 2 shows the patient follow-up and treatment abandonment in successive years. There was no follow-up data for 36 patients. However,

follow-up rates have successively improved from 37.2% to 82.6% and, treatment abandonment has decreased from 35.8% to 14.8% over the years.

Discussion

Childhood brain tumors form about one-fifth of pediatric malignancies. These patients require multi-disciplinary management with coordinated efforts from specialists in various treatment modalities. Treatment of each child has to be optimized according to factors such as age, tumor type and location, extent and feasibility of surgical excision, expertise of available treatment modalities, patient affordability, and compliance.

With advances in technology and research, more specialities are involved in pediatric brain tumor management in the modern era. Multidisciplinary clinics have become standard of care in developed countries.⁶ In our institution, standard multidisciplinary treatment and supportive care are offered to all brain tumor patients. However, because treating departments from two different institutions were involved in managing these children, co-ordination between the different specialists, tracking the patients, and ensuring compliance was a major challenge. Because the brain tumor patients were dispersed between various departments, the exact disease burden and follow-up were not known to any of the departments concerned, which was another disadvantage.

Limited data is available regarding epidemiology of pediatric brain tumors in India.

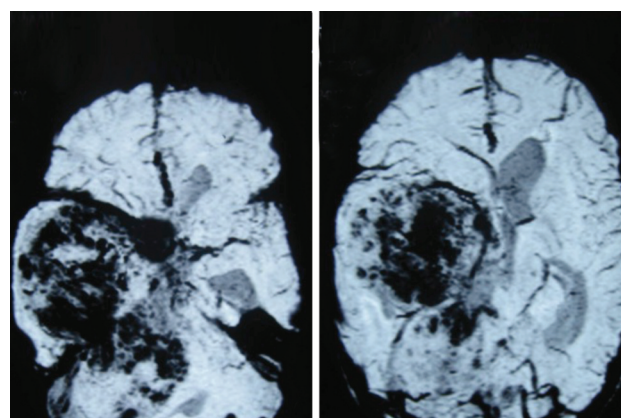


Figure 3. MRI images of mesenchymal chondrosarcoma.

After the inception of this Neuro-Oncology Program, we could profile pediatric brain tumor cases in our hospital with the help of the new registry. Astrocytomas were found to be the most common tumors, followed by medulloblastoma, ependymoma, and craniopharyngioma. Our results agreed with a previous multi-institutional study of Indian hospital-based prevalence of pediatric brain tumors by Jain et al.³ Another single-institution study from South India reported a greater incidence of medulloblastoma, but that study did not include children less than 5 years of age.⁷

This new program has enabled us to improve co-ordination between the surgeon, pathologist, radiation oncologist, and pediatric oncologist. Treatment of brain tumors is now a team effort. It is possible to prioritize patients based on the need for intervention and avoid delays in obtaining the dates for surgery and radiation. Surgeons are willing to attempt difficult surgeries and re-explorations as salvage therapy in patients where such procedures would make meaningful differences. The sessions have led to the formulation of treatment approaches in certain patients for whom there was difficulty in assigning a definite care plan at the onset, helped to discuss discrepancies in histopathology reports from both institutions, and make appropriate decisions for patient benefit. In cases where expert opinion was needed, specimens were sent to more advanced neuropathology centers in India or the Mayo Clinic in the United States.

Treatment abandonment is a major contributor to therapy failure in children with cancer in developing countries that leads to decreased survival. Studies from tertiary centers in India have reported abandonment rates from 17%-62% for pediatric cancers.⁸ Inadequate communication between the treating team and patient's parents, predetermined beliefs of the parents regarding the incurability of cancer, and lack of finances were identified as significant factors that led to treatment abandonment.⁸ These lacunae were filled to some extent by formation of the brain tumor registry, improvements in communication

with parents, tracking of patients who missed appointments and encouraging them to come back for treatment completion. As a result, it has been possible to improve brain tumor follow-up from approximately 37% to more than 80% over five years, along with a decrease in treatment abandonment from 35% to 14%.

Regular updating of pending results, information about new interventions, scrutiny of innovative treatments, revision of management decisions, and other patient issues were discussed in successive meetings to maintain a continuum. It was also possible to study rare tumors and familiarize ourselves with their management. Pediatric cases, as well as adult brain tumor cases have been discussed with enthusiastic participation of all specialists. High quality academic discussion and interaction is beneficial to all participants, especially postgraduate doctors in their training.

There was the exceptional case of a 2-year-old boy with medulloblastoma that had melanotic, epithelial and myogenic differentiation (Figure 1). Other interesting cases included a 4-year-old girl with clival chordoma (Figure 2) and another girl with mesenchymal chondrosarcoma of the brain (Figure 3) for whom management of treatment was challenging. The most notable singular case was that of a 5-year-old girl with a histiocytic lesion in her brain, which was reported as an extremely rare entity (microglioma) by the Mayo Clinic and other international experts (Figure 4). Microglia are resident tissue histiocytes of the CNS which may undergo neoplastic transformation. Microgliomas are considerably difficult to diagnose because of their complex immunohistochemistry characteristics.⁹

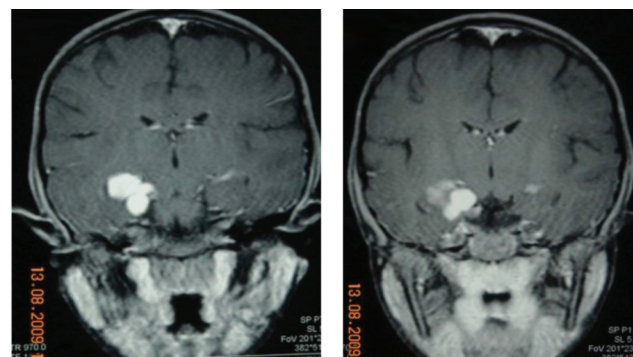


Figure 4. MRI images of microglioma.

The limitation of this study is that this may not reveal the exact disease burden in the community. Our hospital lacks an in-house neurosurgery department. Neurosurgeons that work in the periphery may be treating numerous pediatric brain tumors, and it is possible that many of these patients are not referred. Another limitation was that we have not performed molecular studies due to technical and logistic considerations. Currently, as advances in understanding the biology of brain tumors emerge, molecular information is rapidly being integrated into diagnostics and therapeutics of clinical protocols.¹⁰

Future plans include analyzing the 5-year survivals of this cohort, accruing facilities for molecular genetics for brain tumors, promotion of research for new and innovative therapies, mobilizing social and financial support for needy patients in order to assist them with treatment completion, and collaboration with other neuro-oncology centers in India and abroad for further improvements in service.

In conclusion, this study was an important, initial attempt towards improvisation of patient care with the available limited resources. Such coordinated programs might be possible to implement in other centers in developing countries where all specialities are not available in a single institution. This could be a key start to developing further strategies for better outcomes in these children.

Acknowledgment

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Conflict of interest

No conflict of interest is declared.

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