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ORIGINAL PAPER

Childhood central nervous system tumors at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran, Iran

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Abstract
Purpose As central nervous system (CNS) tumors account for second most common childhood malignancies and the first cause of mortality in children with cancer, improving treatment modalities can lead to increase the health care of patients. In this study, we examined the prevalence of childhood brain tumors in patients who referred to MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC) for treatment.
Methods A retrospective review of all children less than 15 years old with a CNS histologically proven tumor, who presented to MPCTRC from April 2007 to April 2010, was performed. Data was analyzed by SPSS version 19 with Kolmogorov–Smirnov and Chi-square tests.
Results There were 198 (124 boys) children eligible for the study. The majority of the tumors were infratentorial (n=134), and the rest were supratentorial (n=60) and spinal (n=4) cases. The median age was 6.11±3.65 years old. Medulloblastoma (n=66), low-grade glioma (n=52), and high-grade glioma (n=40) were the most common tumors. The mean duration of follow-up was 21 months. At the time of this analysis, there were 105 (53 %) children alive, 82 (41.4 %) deaths, and 11 (5.6 %) lost for follow-up. The survival rate was 51.68±5.22 %.
Conclusions In contrast of high rate of death in this study, other general characteristics can serve as benchmark for improving our care for children with brain tumors in Iran.

Keywords Brain tumor · CNS tumors · Children · Iran

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Introduction

The second most common childhood malignancies after leukemia are central nervous system (CNS) tumors [3, 19]. These tumors comprise nearly 15–20 % of all childhood neoplasms [23]. Annually, childhood CNS tumors account for approximately 2,000 cases less than 20 years old in the USA [6, 21]. In 2007, there were 20,500 individuals (11,170 males and 9,330 females) with CNS tumor in the USA [12, 18].

The worldwide age-standardized incidence of CNS tumor in all ages is 3.7 for males and 2.6 for females per 100,000 people annually [9]. Age-standardized incidence rate of childhood CNS tumor in England are 6.5–7.7 per 100,000 males and 4.5–4.9 per 100,000 females [7]. Embryonal tumors account for 33 % of cases in children less than 3 years old [8, 14]. Medulloblastoma, glioma, and ependymoma are the most common types of childhood brain tumors [5, 10, 17, 22].

Approximately 3–5 % of children with medulloblastoma may suffer systemic metastases [15].

As the childhood neoplasms are the second most common cause of death beyond the neonatal age group [4, 16], and CNS tumors are the leading cause of morbidity and mortality in children with cancer [20, 21], improving in diagnosis and managing of pediatric CNS tumors can increase long-term survivors and quality of life [4]. Global age incidence for mortality of CNS tumor is 2.8 for males and 2 for females per 100,000 [4, 7]. Treatment patterns can be a powerful prognostic factor in improving the outcome of childhood CNS tumors in developing countries [1, 2].

The objective of this study is to evaluate the prevalence of childhood CNS tumors in patients who referred to MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC) for treatment and follow-up. By evaluating the prevalence of enrolled patients, we can use the data as benchmark information for cancer registry system of childhood brain tumors in Iran [11, 13]. In this way, there should be more investigations about the incidence of childhood central nervous system tumors in Iran, as this is a hospital-based study.

Patients and methods

A retrospective review of all children less than 15 years old with a CNS tumor, who referred to MPCTRC from April 2007 to April 2010, was performed. Only patients with histologic confirmation were included in the study. We collected demographic, clinical, pathologic, treatment, family history, and survival data for each patient.

Epidemiological evaluation

A data capture sheet has been assigned for each individual that included epidemiological information about sex, age at diagnosis, signs and symptoms, tumor location, prior malignancy, family history of cancer in the parents, and consanguinity. All patients categorized according to their age at diagnosis into four groups: <1, 1–5, 5–10, and 10–15 years old. Patients received multimodality treatments according to the pathology of their tumor. MPCTRC provides financial supports for all of the admitted Iranian and non-Iranian patients who are accepted for treatment at our center. According to data compiled at welfare services in this center, we could evaluate the socioeconomic status of patients.

Analysis

Data analyzed by SPSS version 19, with confidence intervals of 95 %. Kolmogorov–Smirnov test had been used for consideration the distribution of normal or abnormal patterns in variables, Chi-square for parametric and Spearman method for non-parametric data respectively. Also for comparing two means, we used *t* test.

Results

The total number of patients admitted to our center during the study period was 1,517 children. Out of admitted patients, 198 (13.1 %) had CNS tumors. There were 45 cases who presented initially for second opinion but were found to be eligible for therapy at our center and were treated and followed by our team.

The majority of enrolled patients were boys (124, 62.6 %). The ratio of male/female was 1.67/1. The tumor location was supratentorial (n=60, 30.3 %), infratentorial (n=134, 67.7 %), and spinal (n=4, 2 %). Table 1 shows location and gender for each age group.

The median age was 6.11±3.65 years (range 1 to 14 years). Table 2 provides details about pathology of tumors per location. Table 3 shows tumor histology and gender for each age group.

According to our study, 100 (50.5 %) patients had different signs and symptoms for 1 to 6 months prior to diagnosis and others were asymptomatic. The most common clinical presentations according to frequency were vomiting (n=106, 53.5 %), headache (n=102, 51.5 %), disturbance of balance (n=51, 25.7 %), disturbance of sight (n=104, 52.5 %), papilledema (n=15, 7.6 %), and vertigo (n=14, 7.1 %).

The family history of cancer in distant relatives was positive in 50 (25.25 %) cases. In 19 children (38 %), the family history was positive for CNS malignancies, and in 31 cases (62 %) as non-CNS cancers including leukemia (n=13), gastrointestinal cancers (n=10), breast cancer (n=4), sarcoma (n=2), and lymphoma (n=2). Four children had neurofibromatosis type1 and one patient had tuberous sclerosis. The parental marriage of patients was 38.9 % (n=77). Half of the enrolled patients had low socioeconomic status (n=102, 51.5 %) according to data compiled at welfare services in MPCTRC.

There were 31 patients (15.7 %) with documented relapse in their medical records. This included medulloblastoma (n=10), high-grade glioma (n=6), low-grade glioma (n=5), ependymoma (n=5), supratentorial primitive neuroectodermal tumor (sPNET, n=3), and spinal (n=2). The median time of relapse in enrolled patients was 1.9±2.38 years.

Eighty-two (41.4 %) cases died during or after the treatment, which included high-grade glioma (n=24), medulloblastoma (n=22), low-grade glioma (n=20), ependymoma (n=7), sPNET (n=4), ATRT (n=2), germ cell tumor (n=1), primary CNS lymphoma (n=1), and optic pathway glioma (n=1). The cause of death in our cohort was not well documented and it was due to tumor progression. The mean duration of follow-up was 21 months. In this study, 11

Table 1 Distribution of sex and age per tumor location

Age	<1 year			1–5 years			5–10 years			10–15 years			Total of sex groups
Tumor location	Supratentorial	Infratentorial	Spinal	Supratentorial	Infratentorial	Spinal	Supratentorial	Infratentorial	Spinal	Supratentorial	Infratentorial	Spinal	
Male	3 (60 %)	2 (40 %)	0	10 (62.5 %)	29 (63 %)	1 (100 %)	15 (62.5 %)	40 (67.8 %)	1 (100 %)	7 (46.7 %)	15 (62.5 %)	2 (100 %)	125 (63.1 %)
Female	2 (40 %)	3 (60 %)	0	6 (37.5 %)	17 (37 %)	0	9 (37.5 %)	19 (32.2 %)	0	8 (53.3 %)	9 (37.5 %)	0	73 (36.9 %)
Total of age group	10 (5.1 %)			63 (31.8 %)			84 (42.4 %)			41 (20.7 %)			198 (100 %)

(5.6 %) of patients were lost for follow-up. The survival rate of childhood central nervous system tumors in this study was 51.68±5.22 %.

Table 4 shows the summary treatment modalities per tumor histology.

Discussion

The aim of this research is to evaluate the status of pediatric CNS tumors at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC) located in Tehran, Iran. MPCTRC is a non-government organization to support children suffering from cancer that has commenced its activity in early 1991 and has been expanding since then. It also provides financial, social support, and housing support for pediatric hematology and oncology departments in academic centers in Tehran [3].

Useful measures of the health care regarding childhood cancers will provide by epidemiological studies [1]. This may guide to disease etiology and planning cancer registry system [1]. The epidemiologic profile of childhood brain tumors living in different geographic regions (Korea, Iran, Brazil, and Morocco) have been examined by several other groups [10]. Different reported reports in Iran show that this study is one of the complete researches on epidemiologic profile of childhood central nervous system tumors in Iran [13]. As MPCTRC is one of the main referral childhood malignancies' centers in the capital city of Iran, the data compiled by this research can be useful for managing health care system of childhood brain tumors.

Central nervous system tumors are the second most frequent malignancy in most part of the world [5] with a prevalence of 15–20 % of all childhood malignancies [21]. At MPCTRC, the number of eligible patients with childhood CNS tumors is lower than expected (198 out of 1,517 patients; 13.05 %). There are different potential reasons for this low prevalence of childhood CNS tumors in our center. One explanation is the high referral of other pediatric cancers (such as leukemia, bone tumors, and sarcomas) to our center. Another possible explanation is the low referral rate of pediatric CNS tumors as many neurosurgeons may not feel the need to refer some tumors such as low-grade gliomas (the second most common pediatric CNS tumor) for chemotherapy, and many radiation oncologists may not refer some malignancies for chemotherapy post-radiation. A third possibility is that tumors without histologic confirmation such as diffuse pontine glioma were excluded. A comprehensive national review or cancer registry may help in answering this question.

Different reports as a research by Karkouri in Morocco demonstrated predominant male incidence in childhood CNS tumors [2, 10, 18, 21, 23]. According to the present study, males comprised 63.1 % and females 36.9 % of CNS

Table 2 Pathology of tumors in study cohort

Tumor histology	Tumor location			Total
	Supratentorial	Infratentorial	Spinal	
Medulloblastoma	–	66 (49.26 %)	–	66 (33.33 %)
Low-grade glioma	21 (34.97 %)	31 (23.16 %)	1 (25 %)	53 (26.77 %)
High-grade glioma	19 (31.6 %)	21 (15.65 %)	–	40 (20.20)
Ependymoma	6 (10.09 %)	14 (10.43 %)	2 (50 %)	22 (11.11 %)
PNET	8 (13.33 %)	–	1 (25 %)	9(4.54 %)
AT/RT (atypical teratoid rhabdoid tumor)	2 (3.33 %)	1 (0.75 %)	–	3 (1.51 %)
Germ cell tumor	1 (1.67 %)	1 (0.75 %)	–	2 (1.01 %)
Craniopharyngioma	1 (1.67 %)	–	–	1 (0.51 %)
Primary CNS malignant lymphoma	1 (1.67 %)	–	–	1 (0.51 %)
Histiocytosis	1 (1.67 %)	–	–	1 (0.51 %)
Total	60(100 %)	134 (100 %)	4 (100 %)	198 (100 %)

tumors, with respectively 1.7-fold higher incidence in males than females. However, patients younger than 1 year had the same sex distribution. In our cohort, the median age was 6.11±3.65 years, which is in concordance with other reports [2, 12, 21]. In our study, the median age at diagnosis was similar to the mean age at diagnosis reported in a study by Mehrazin on pediatric brain tumors in Iran [13].

In this hospital base study, the commonest types of CNS tumors were medulloblastoma (34.02 %), low-grade glioma (26.83 %), high-grade glioma (20.61 %), and ependymoma (10.31 %), respectively. Consistent with findings of other published studies on pediatric brain tumors, the data of this study is similar to other reports [2, 15, 18]. We also found that ependymoma was the fourth most common histological tumor type in all considered patients. This finding is as same as study group by Karkouri in Morocco.

Stevenson attended that inherited genetic conditions and some especially diseases as neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome could be account as known risk factors in suffering childhood CNS tumors. In addition, Singhal reported that nearly 5 % of patients with optic nerve glioma had neurofibromatosis type 1 as underlying disease. In our cohort five children had genetic condition (four NF1 and one tuberous sclerosis) known to predispose for CNS tumors.

Dearlove et al. offered that there is a significant relation between incidence of familial history of cancer and the rate of occurring childhood brain tumors [8]. Ostorm et al. in 2012 suggested that there could be an association between benign brain tumors and family history of cancer their literature review also demonstrated the relation between familial history of cancer and gliomas [17]. In our study, family history of cancer was positive in 50 children (25.3 %).

Parental marriage in Iran is as high as in other Middle Eastern countries with mean frequency of 30 % in urban and up to 64 % in rural areas. Considering parental marriage should be considered as a critical public health issue in terms of other inheritable malignant and non-malignant disorders that impact negatively on the social welfare of Iranian population. Out of 198 patients, 38.9 % were the product of parental mating. Certainly, there should be more investigation to conclude that these parameters (parental marriage and family history of cancer) could consider as high risk factors of CNS tumors. These results imply the need for surveillance of family members of cancer victims in Iran. Regarding linkage analysis of the family history of brain tumors with parental marriage for drawing a conclusion, there should be enough data.

African-Americans showed 13–40 % high risk of death for malignant brain tumors [7]. In this study, the mortality rate of CNS tumor in children was 41.4 % (n=82 out of 198) which higher that the developed world, this may be due to several reasons including different histology, ages, and follow-up. Unfortunately, the cause of death was not well documented to make any conclusion. However, this study demonstrated the need to improve documentation of mortality causes. Such documentation will help us identify potential aspects to improve our clinical care. One explanation for high rates of death during or after treatment is welfare status of patients. Most of the patients were from rural areas in Iran that confronted with financial and residential problems during their child's treatment. In spite of supporting by MPCTRC, they had to leave the therapy for discussed matter, in this way; the death rate will interestingly become high.

Our study creates a more comprehensive picture of pediatric brain tumors in Iran because in spite of being single center analysis, it includes histopathological analysis that provides more information about childhood brain tumors than previous studies.

These data imply the attention that in Iran, establishing cancer registry is needed to fully follow-up the epidemiologic distribution of pediatric central nervous system tumors. The establishment of cancer registry source in Iran would suggest of the pediatric tumor burden which will be useful for standard diagnostic and therapy protocols in referred patients.

Table 3 Distribution of sex and age per tumor histology

TH	MB		LGG[a]		HGG[b]		Ependymoma		PNET		AT/RT		Others[c]	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
<1	–	1 (100 %)	4 (66.7 %)	2 (33.3 %)	1 (33.3 %)	2 (66.7 %)	–	–	–	–	–	–	–	–
1–5	14 (60.9 %)	9 (39.1 %)	6 (42.8 %)	8 (57.2 %)	9 (90 %)	1 (10 %)	7 (63.6 %)	4 (36.4 %)	2 (100 %)	–	1 (100 %)	–	1 (100 %)	–
5–10	25 (75.8 %)	8 (24.2 %)	10 (47.6 %)	11 (52.4 %)	11 (57.9 %)	8 (42.1 %)	5 (100 %)	–	2 (100 %)	–	–	1 (100 %)	2 (100 %)	–
10–15	7 (77.8 %)	2 (22.2 %)	6 (54.5 %)	5 (45.5 %)	1 (12.5 %)	7 (87.5 %)	4 (100 %)	–	3 (75 %)	1 (25 %)	1 (100 %)	–	1 (100 %)	–

Abbreviations: *TH* tumor histology, *M* male, *F* female, *MB* medulloblastoma, *PNET* peripheral neuroectodermal tumors, *ATRT* atypical rhabdoid teratoid tumor, *LGG* low-grade glioma, *HGG* high-grade glioma

[a] Includes low-grade glioma, pilocytic astrocytoma, fibrillary astrocytoma

[b] Includes high-grade glioma, anaplastic astrocytoma, glioblastoma multiforme

[c] Includes germ cell tumors (n=2), CNS lymphoma (n=1), craniopharyngioma (n=1), histiocytosis (n=1)

Table 4 The characteristics of patients and treatment modalities according to tumor histology

Tumor	Mean Age	M/F	RT (%)	CT	SU N (%)			Mean F/U duration (month)	Dead *N* (%)	Lost F/U *N* (%)
					BIO	PR	TR			
MB	5.83±3.1	2.3/1	77.2 %	CCNU+Vcr+Dexa	25 (41.7 %)	10 (16.6 %)	25 (41.7 %)	22	22 (33.3 %)	5 (7.6 %)
PNET	8.75±4.6	7/1	75 %	8 in 1	1 (12.5 %)	3 (37.5 %)	4 (50 %)	15	4 (50 %)	0
ATRT	6.67±4.5	2/1	66.7 %	8 in 1	2 (66.7 %)	1 (33.3 %)	–	9	2 (66.7 %)	1 (33.3 %)
LGG[a]	6.27±3.8	0.92/1	50 %	Carbo+Vcr	22 (61.2 %)	4 (11.1 %)	10 (27.7 %)	22	20 (41.7 %)	3 (6.3 %)
HGG[b]	6.10±3.4	1.2/1	72.5 %	Carbo+Vcr	20 (60.7 %)	5 (15.1 %)	8 (24.2 %)	20	24 (60 %)	0
Ependymoma	5.75±3.5	4/1	80 %	Carbo+Vcr	3 (15.8 %)	6 (31.6 %)	10 (52.6 %)	16	7 (35 %)	2 (10 %)
OPG	1.00±0.0	3/1	0 %	Carbo+Vcr	1 (100 %)	–	–	39	1 (25 %)	0
Others[c]	7.78±4.7	2/1	55.6 %	CCNU+Vcr+Cis	3 (75 %)	–	1 (25 %)	29	2 (22.2 %)	0

[a] Includes low-grade glioma, pilocytic astrocytoma, fibrillary astrocytoma

[b] Includes high-grade glioma, anaplastic astrocytoma, glioblastoma multiforme

[c] Includes germ cell tumors (n=2), CNS lymphoma (n=1), craniopharyngioma (n=1), histiocytosis (n=1)

Abbreviations: *M* male, *F* female, *RT* radiation therapy, *CT* chemotherapy, *SU* surgery, *N* number, *Bio* biopsy, *PR* partial resection, *TR* total resection, *F/U* follow-up, *MB* medulloblastoma, *PNET* peripheral neuroectodermal tumors, *ATRT* atypical rhabdoid teratoid tumor, *LGG* low-grade glioma, *HGG* high-grade glioma, *OPG* optic pathway glioma, *Cis* cisplatin, *Vcr* vincristine, *CCNU* lomustine, *8 in 1* (eight drugs in 1 day) cisplatin+procarbazin+CCNU+vincristine+cyclophosphamide+prednisolone+hydroxyurea+Ara-C

Like other researches, our study had different limitations too. One limitation was the inability to follow-up by location of patient residence which limited our ability to calculate the incidence rate of mortality. The pathologic reports were the next limitation as some cases referred to MPCTRC did not have their pathology report with them. Another limitation of this study was the fact that some cases were treated by private neurosurgeons in other cities than Tehran that made us unable to contact for gathering further information.

Conclusion

This study demonstrated the need to improve cancer registry system through mortality and morbidity for our patients with CNS tumors and for better understanding of the real incidence of these malignancies in Iranian children. We found that medulloblastoma like other previous studies is the most common pediatric brain tumor in Iran. In addition, in concluding that parental marriage and family history of cancer are risk factors of childhood brain tumors, further studies on this issue are required. These data can be a benchmark for increasing our understanding of childhood CNS tumors in Iran so it can have the potential to trigger further researches as multi-center studies in Iran and specially in developed countries.

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Conflict of interest The authors taking part in evaluation and writing the manuscript have not any conflict of interest for this report.

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