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CLINICAL STUDY

Pediatric brain tumors in a low/middle income country: does it differ from that in developed world?

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Abstract Central nervous system (CNS) tumors are the most frequent solid tumors in children and adolescents. The epidemiology of these tumors differs in areas of the world. However, very little data is available in the low/middle income countries (LMIC). The aim of this study is to describe the characteristics of primary childhood brain tumors treated at a leading LMIC pediatric cancer hospital and its difference from that in other countries. One thousand one hundred fourteen children and adolescent having CNS tumors were treated in the largest pediatric cancer hospital in the Middle East during a period of 5½ years. They were diagnosed histopathologically in 80.2 %, through medical imaging in 19.4 % and via both tumor markers and imaging in the remaining 0.4 % of cases. Through epidemiological analysis was performed using all available patients' data revealed that 96 % of the patients had primary brain tumors, while only 4 % the primary lesion was in the spinal cord. The most common histological type was astrocytic tumor (30.0 %, pilocytic (GI) = 13.2 %, GII = 10.5 % and GIII + IV (high grade) = 6.3 %) followed by embryonal tumor (23.2 %, medulloblastoma = 18.7 %, PNET = 2.8 %, ATRT = 1.5 % and ependymoblastoma = 0.2 %) then ependymoma in 8.7 %, craniopharyngeoma in 5.3 %. The mean age at diagnosis was 7.1 ± 4.2 years which did not differ significantly by gender nor residency but it differed by the pathological subtype. The frequency of each pathological type was different among different age groups. Though the present study was a hospital-based analysis in a low/middle income country, yet it did not differ from the well-established population-based study reports in the high income countries.

Keywords CNS tumors · Brain · Spinal cord · Epidemiology · Children · Pediatric cancer

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Introduction

Central nervous system (CNS) tumors are the most frequent solid tumors in children and adolescents [1, 2]. It is well known that the pediatric and adolescent age groups are characterized by unique group of cancer that requires separate reporting. CNS tumors are the leading cause of cancer related deaths in childhood and adolescents. Furthermore, they may cause short and long term consequences due to the disease itself or its treatment. These sequelae cause survivors to suffer from a wide range of serious physical and neurological morbidities [3]. Childhood CNS tumors differ from those of adolescence and that of adulthood. Furthermore, they may even differ within the age range of the childhood. They include a wide range of

different histopathological subtypes, with significant variation in topographical distribution. Consequently this indicates different therapeutic strategies and results in varying out-come and prognosis. The diversity in time from onset of symptoms till patient presentation reflects the different biological behaviors of particular tumor entities [2, 4] Reported regional and global incidence of CNS tumors in children highlights a considerable variations among different regions and countries; According to the data from the American Cancer Society, National Cancer database (NCDB), Central Brain Tumor Registry of the United States (CBTRUS), the Surveillance, Epidemiology and End Results (SEER) as well as the EUROCARE study, the central nervous system tumors account for 27 % of pediatric malignancies in developed countries, representing the second most frequent neoplasm of childhood [4–6]. The CBTRUS estimated the average annual age-adjusted childhood CNS tumor incidence rate as 5.26 per 100,000 population [7]. Each year, approximately 30,000–40,000 new cases are diagnosed worldwide [8]. However, only scarce data is available about pediatric brain tumors in low/mid income countries (LMIC) [9]. Furthermore, on 2006 the coverage of patients by cancer registry was estimated to be 8 % in Asia, 11 % in Africa and 21 % in Latin America compared to 99 % of people in USA and 86 % in Canada [10]. This obviously reveal the difficult situation in low/middle income countries. The aim of this study is to describe the characteristics of primary childhood brain tumors treated at a leading comprehensive Egyptian pediatric cancer center and identification of any difference from that in high income countries.

Patients and methods

All records of patients with primary CNS tumors diagnosed at the Children's Cancer Hospital Egypt 57357(CCHE) between July 7th 2007 (Date of Hospital Inauguration) and December 31st 2013 were reviewed. Cases enrolled were either pathologically proven primary intracranial (or intraspinal) tumors, through unequivocal radiological confirmation or medical imaging with increased tumor markers. Cases were classified according to the most recent 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System and the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3). The topographic codes of all registered patients during this period was thoroughly revised. All codes for CNS tumors were reported including C71.0–C71.9 (brain), C70.0–C70.9 (meninges) and C72.0–C72.9 (spinal cord, cauda equine, cranial nerves and undetermined parts of CNS) with the exclusion of metastatic lesions.

The most common tumors were Astrocytic tumor [30.0 %, pilocytic (GI) = 13.2 %, GII = 10.5 % and high grade (GIII + IV) = 6.3 %] followed by embryonal tumor (23.2 %, medulloblastoma = 18.7 %, PNET = 2.8 %, ATRT = 1.5 % and eendymoblastoma = 0.2 %) then BrainStem Lesions (BSL) in 16.0 %, ependymoma in 8.7 %, craniopharyngeoma in 5.3 %.

The less common types were Neuronal & Mixed Neuronal-Glial Tumors (4.2 %), Germ Cell Tumors (GCTs) (3.1 %) and Choroid Plexus Tumors (1.6 %).

Data abstracted from the patients' clinical records included age at the time of presentation, gender, histological diagnosis, and tumor locations. Categorical data were described in terms of frequencies and percentages, while quantitative data were described in terms of mean and standard deviation (SD) or median and inter quartile range (IQR). *T* test was used to compare means between two groups, while one way ANOVA was used to compare means of more than two groups. Chi square test was used to compare categorical data. Fisher's Exact test was used instead, if number of expected cases in 25 % or more of the cells is less than five. P values equal or less than 0.05 were considered significant. Statistical analysis was performed using the statistical package IBM-SPSS version 20.

Results

Retrospectively reviewing of 1114 patients' hospital records having the diagnosis of primary malignant tumors of the CNS was performed. The patients were admitted at the CCHE between July 2007 and December 2013. These patients represented 14.3 % of the total number of patients (below the age of 18 years) treated at CCHE during this period. All pituitary lesions were not included as the hospital policy is to refer these patients to general pediatric hospitals for their management. Out of these 1114 cases, 893 (80.2 %) patients were diagnosed histologically either through biopsy or resection specimens. Magnetic resonance imaging together with other medical imaging tools were the basis of diagnosis in 216 (19.4 %) patients. These were diagnosed as Brain Stem lesions (BSL) in 178, optic pathway glioma in 18 children while the remaining 20 patients include other diagnoses. Most (79.8 %) of the brain stem lesions were diagnosed as diffuse intrinsic pontine glioma (DIPG), while the remaining 20.2 % had the diagnosis of focal brain stem glioma (cervico-medullary, dorsal exophytic and intrinsic focal). Five cases (0.4 %) were diagnosed by elevated CSF markers beta-human chorionic gonadotropin (βHCG) and Alpha-feto-protein (AFP), in addition to radiology (3 Pineal, and 2 Suprasellar lesions).

Table 1 Pathological and Radiological sub-classification of cases

Mode of diagnosis	CNS subtypes	No.	Percent from each mode of diagnosis (%)	Percent from total (%)
Pathology	Astrocytic tumors	334	37.4	30.0
	Embryonal	258	28.9	23.2
	BSL	0	0.0	0.0
	Ependymomas	97	10.9	8.7
	Craniopharyngioma	59	6.6	5.3
	Neuronal and mixed neuronal-glial tumors	47	5.3	4.2
	Germ cell tumors	34	3.8	3.1
	Choroid plexus tumors	18	2.0	1.6
	Tumors of the pineal region	17	1.9	1.5
	Other Pathology	29	3.2	2.6
	Total	893	100.0	80.2
Radiology	BSL	178	82.4	16.0
	Other diagnosis	38	17.6	3.4
	Total	216	100.0	19.4
Radiology and tumour marker	Other diagnosis	5	100.0	0.4
	Total	5	100.0	0.4

Table 1 shows the different tumor subtypes including different, pathologically and radiologically diagnosed categories. Table 2 shows the gender distribution among the different subgroups. There is an overall predominance in males, (55.57 % n = 619) over females (44.43 % n = 495). Furthermore, a male predominance was noticed in mostly all subtypes. The male/female ratio ranged from 1.83 and 1.77 (Germ cell tumor and Ependymomas) to 0.97 (brain stem lesions).

Although Astrocytic tumors are the most common subtype in both males and females yet, it represents 29.9 % of all subtypes among male while it accounts for 30.1 % among females. Moreover, Ependymoma subtype represents 10.0 % of males versus 7.1 % of females.

We classified the patients into 5 age groups (Table 2), less than 1, from 1 to <5, 5 to <10, 10 to <15 and 15 or more years old. More than one third of the patients were between 5 and 10 years old. Only 4.2 % (n = 47) of brain tumors occurred in children less than 1 year of age (Graph 1).

The mean age of the patients at diagnosis was 7.1 years (SD = 4.2), with a median of 6.5 years, and a range of 0.1–18 years. The mean age did not significantly differ by gender. The distribution of tumor subtypes varied among different age groups; for example GCT represented 2.1 % among patients less than 1 year versus 4.9 % in the age group 10 to <15 years. Embryonal tumors represented 27.7 % in patients 1–5 years compared to 14.7 % in patients 10 to <15 years. Astrocytic tumors were the most common category in patients <1 year (38.3 %), while Embryonal tumors (27.7 %) were the most common in patients 1–5 years old.

Most patients residence was Cairo Metropolitan (38.4 %) or Delta (31.6 %) areas. The geographical distribution of patients is illustrated in Table 3. It has been noticed that the distribution of different subtypes varied among the region of residence. While Embryonal tumors represent 21.3 % in Cairo Metropolitan region, it presents 37.8 % among North Coast residence.

According to ICD-O-3 coding, benign (0), borderline (1) and malignant tumors (3) constituted 2.96, 24.35 and 72.69 %, respectively. Benign tumors included: Choroid plexus papilloma, Dysembryoplastic neuroepithelial tumor, Gangliocytoma, Schwannoma and Neurofibroma. Borderline tumors included Pilocytic astrocytoma, Subependymoma, Myxopapillary ependymoma, Pineocytoma and some subtypes of Neuronal and mixed neuronal-glial tumors.

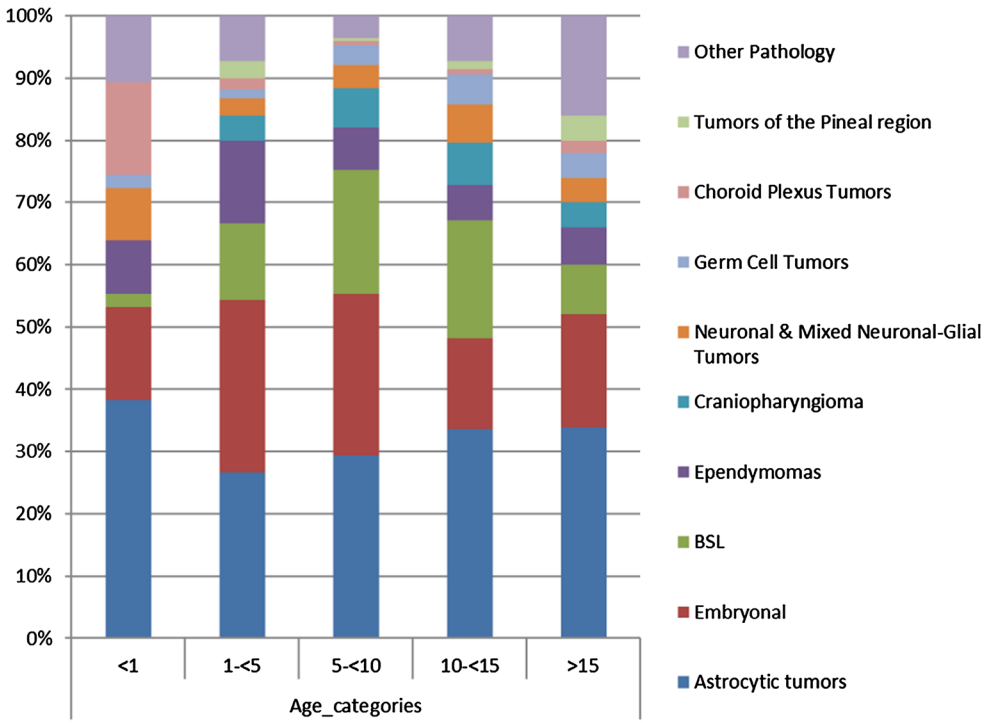
Anatomically; 96 % of all CNS tumors were located in the brain while 4 % were in the spinal cord. Astrocytic tumors, together with Embryonal and Ependymal tumors accounted for 79.5 % of all spinal cord tumors (data not shown).

Discussion

The pattern of primary brain tumors in children and adolescents has not been previously reported in Egypt and scarcely in other developing low and middle income

Table 2 Pathologically and radiologically diagnosed types of brain tumors by gender and age groups

CNS subtypes	Age categories												
	<1		1– <5		5– <10		10– <15		>15		Male: Female ratio	Total	
	No.	%	No.	%	No.	%	No.	%	No.	%		No.	%
Astrocytic tumors	18	38.3	94	26.6	123	29.4	82	33.5	17	34.0	1.24	334	30.0
Embryonal	7	14.9	98	27.7	108	25.8	36	14.7	9	18.0	1.43	258	23.2
BSL	1	2.1	44	12.4	83	19.9	46	18.8	4	8.0	0.97	178	16.0
Ependymomas	4	8.5	47	13.3	29	6.9	14	5.7	3	6.0	1.77	97	8.7
Craniopharyngioma	0	0.0	14	4.0	26	6.2	17	6.9	2	4.0	1.19	59	5.3
Neuronal and mixed neuronal-glial tumors	4	8.5	10	2.8	16	3.8	15	6.1	2	4.0	1.24	47	4.2
Germ cell tumors	1	2.1	5	1.4	14	3.3	12	4.9	2	4.0	1.83	34	3.1
Choroid plexus tumors	7	14.9	6	1.7	2	0.5	2	0.8	1	2.0	1.25	18	1.6
Tumors of the pineal region	0	0.0	10	2.8	2	0.5	3	1.2	2	4.0	1.13	17	1.5
Other pathology	5	10.6	26	7.3	15	3.6	18	7.3	8	16.0	0.85	72	6.5
Total	47	100.0	354	100.0	418	100.0	245	100.0	50	100.0	1.25	1114	100.0



Graph 1 Distribution of CNS tumors subtypes among different age groups

countries. The etiology remains largely unknown. The present study attempted to provide a descriptive overview of primary malignant CNS tumors among the pediatric population at CCHE, using hospital based cancer registry data, electronic medical records and the research department's database.

Our results showed, collectively and separately, disease predominance in males over females. We described the variation of the ratio of the two sexes in these series of tumors. Certain tumor types show a prediction for certain age groups in the present study population. The largest percentage of patients (37.5 %) was in the age group 5 to

Table 3 Distribution of Brain tumor cases according to geographic location

CNS subtypes	Metropolitan		Delta		Upper Egypt		North Coast		Canal and Sinai		Outside Egypt	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Astrocytic tumors	135	31.5	108	30.7	56	25.8	12	32.4	13	24.1	10	38.5
Embryonal	91	21.3	71	20.2	63	29.0	14	37.8	14	25.9	5	19.2
BSL	64	15.0	62	17.6	34	15.7	4	10.8	8	14.8	6	23.1
Ependymmas	40	9.3	34	9.7	15	6.9	3	8.1	4	7.4	1	3.8
Craniopharyngioma	25	5.8	15	4.3	10	4.6	2	5.4	6	11.1	1	3.8
Neuronal and mixed Neuronal-glial tumors	18	4.2	16	4.5	8	3.7	1	2.7	2	3.7	2	7.7
Germ cell tumors	14	3.3	12	3.4	6	2.8	0	0.0	2	3.7	0	0.0
Choroid plexus tumors	5	1.2	9	2.6	4	1.8	0	0.0	0	0.0	0	0.0
Tumors of the pineal region	6	1.4	4	1.1	6	2.8	0	0.0	1	1.9	0	0.0
Other pathology	30	7.0	21	6.0	15	6.9	1	2.7	4	7.4	1	3.8
Total	428	100.0	352	100.0	217	100.0	37	100.0	54	100.0	26	100.0

less than 10 years, while only 4.2 % of brain tumors patients had less than one year of age. These results are consistent with most available data describing the pediatric CNS tumors, both in developed and developing countries (LMIC). The distribution of brain tumors by histology followed the same pattern reported in the international literature: [11–15]. Astrocytic tumors represents (30.0 %), embryonal tumors (23.2 %), brain stem glioma (16.0 %), and ependymal tumors (8.7 %) were the most common histology across all age groups.

Although the present study rely on hospital based data, with its limitation yet, CCHE is the largest referral pediatric cancer center not only in Egypt but also in the Middle East. Furthermore, the relative frequencies of the different histological subtypes are consistent with the findings published in most population based registries in North America [16] and Middle East, in which the most common histology was astrocytic tumors which accounted for slightly less than half of the whole tumors (42.4 %). It was followed by embryonal tumors (29.7 %), ependymal tumors (7.9 %), oligodendroglial tumors (3.5 %), and germ cell tumors (1.2 %) [17]. In another hospital based study in Iran, the commonest types of CNS tumors were medulloblastoma (34.02 %), low-grade glioma (26.83 %), high-grade glioma (20.61 %), and ependymoma (10.31 %) [18].

The Egyptian national population-based cancer registry program estimated the number of CNS cancer patients, in all ages, to be 6004 in 2013, 8740 in 2025 and 16888 in 2050. This report relay the increasing numbers on both the population growth and population structure changes in favor of younger population [19]. The Gharbiah cancer registry, the more established population-based cancer registry in Egypt, showed a considerable discrepancies from our findings and from that of the international publications. In Gharbiah cancer registry the most common histology was medulloblastomas followed by astrocytomas and the male to female ratio was 0.7:1 [20]. However, our findings are consistent with other Egyptian hospital based findings [9]. Discrepancies in the relative frequencies and gender distribution between the hospital based findings and population based findings in Egypt might be understood in view of the very small frequency of cases identified in Gharbiah cancer registry (50 cases).

Despite concordance with international results, the reported geographical distribution in our study is not fully representative to the actual incidence of brain tumors in Egypt, since the majority of cases may be referred by nearby centers. The percentage distribution of pediatric brain tumors reflects the relative distribution of the population in different areas of Egypt. However, it is yet to be determined, whether our results reflect the true regional pattern of brain tumors distribution among the Middle East.

Our results might pave the way and set a baseline for further evaluation. There is a need for thorough ongoing assessment of geographical and other demographic variables, demanding more nation-wide cooperation and networking between medical staff and cancer registries. Clearly, future regional studies of incidence patterns and up-to-date epidemiological assessment are warranted.

Gender is not a risk factor for developing CNS tumors in children, except for medulloblastoma, which has a clear predilection for males [21]. It is worth noting that there are no pure distinct ethnic group among the Egyptian population, therefor this issue cannot be accurately tested in this study.

In conclusion, this study revealed that CNS cases presented to CCHE had consistent frequency and distribution of tumors (age, gender and subtypes) with those reported

by most of the relevant studies in the Western and Middle East countries [9, 16, 21–24]. The results of our study present an important epidemiological understanding of patients with brain tumors and emphasizing the great need of prospective more detailed epidemiological population-based studies.

References

1. Arora RS, Alston RD, Eden TOB et al (2009) Age-incidence patterns of primary CNS tumors in children, adolescents, and adults in England. Neuro Oncol 11:403–413. doi:10.1215/15228517-2008-097
2. Orkin S (2009) Oncology of infancy and childhood. Saunders Elsevier, Philadelphia
3. Strother DR, Pollack IF, Fisher PG, Hunter JV, Woo SY, Pomeroy SL et al (2002) Tumors of the central nervous system. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 4th edn. Lippincott Williams and Wilkins, New York, NY, pp 751–824
4. Rickert CH, Paulus W (2001) Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 17:503–511
5. American Cancer Society (2012) Cancer facts and figures. American Cancer Society, Atlanta
6. Magnani C, Aareleid T, Viscomi S et al (2001) Variation in survival of children with central nervous system (CNS) malignancies diagnosed in Europe between 1978 and 1992: the EUROCARE study. Eur J Cancer 37:711–721
7. Dolecek T a, Propp JM, Stroup NE, Kruchko C (2012) NEURO-ONCOLOGY CBTRUS Statistical Report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009
8. Bleyer WA (1999) Epidemiologic impact of children with brain tumors. Child's Nerv Syst 15:758–763. doi:10.1007/s003810050467
9. El-Gaidi MA (2011) Descriptive epidemiology of pediatric intracranial neoplasms in Egypt. Pediatr Neurosurg 47:385–395. doi:10.1159/000337872
10. Parkin DM (2006) The evolution of the population-based cancer registry. Nat Rev Cancer 6:603–612
11. Gjerris F, Agerlin N, Børgesen SE et al (1998) Epidemiology and prognosis in children treated for intracranial tumours in Denmark 1960–1984. Childs Nerv Syst 14:302–311
12. Bauchet L, Rigau V, Mathieu-Daudé H et al (2009) Clinical epidemiology for childhood primary central nervous system tumors. J Neurooncol 92:87–98. doi:10.1007/s11060-008-9740-0
13. Kadri H, Mawla AA, Murad L (2005) Incidence of childhood brain tumors in Syria (1993–2002). Pediatr Neurosurg 41:173–177. doi:10.1159/000086557
14. Harmouch A, Taleb M, Lasseini A et al (2012) Epidemiology of pediatric primary tumors of the nervous system: a retrospective study of 633 cases from a single Moroccan institution. Neurochirurgie 58:14–18. doi:10.1016/j.neuchi.2012.01.005
15. De la Torre Mondragón L, Ridaura Sanz C, Reyes Mujica M, Rueda Franco F (1993) Central nervous system tumors in Mexican children. Childs Nerv Syst 9:260–265
16. Kohler BA, Ward E, McCarthy BJ et al (2011) Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 103:714–736. doi:10.1093/jnci/djr077
17. Beygi S, Saadat S, Jazayeri SB, Rahimi-Movaghar V (2013) Epidemiology of pediatric primary malignant central nervous system tumors in Iran: a 10 year report of National Cancer Registry. Cancer Epidemiol. doi:10.1016/j.canep.2013.03.002
18. Mehrvar A, Faranoush M, Hedayati Asl AA et al (2014) Childhood central nervous system tumors at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran. Iran. Childs Nerv Syst 30:491–496. doi:10.1007/s00381-013-2256-8
19. Ibrahim AS, Khaled HM, Mikhail NNH et al (2014) Cancer incidence in Egypt : results of the population-based cancer. Regist Prog Egypt 2014:1–17
20. Abdelbar I, Ismail K, Hablas A et al (2007) Cancer in Egypt, Gharbiah Triennial Report of 200–2002, Gharbiah
21. Ferlay J, Shin HR, Bray F, Forman D MC and PD Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. In: GLOBOCAN 2008 v2.0 - Lyon, Fr. Int. Agency Res. Cancer; 2010. Available from http//globocan.iarc.fr, accessed 13/8/2013
22. Fast Stats: an interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats. Accessed 13 Aug 2013
23. Mehrazin M, Rahmat H, Yavari P (2006) Epidemiology of primary intracranial tumors in Iran, 1978–2003. Asian Pac J Cancer Prev 7:283–288
24. Katchy KC, Alexander S, Al-Nashmi NM, Al-Ramadan A (2013) Epidemiology of primary brain tumors in childhood and adolescence in Kuwait. Springerplus 2:58. doi:10.1186/2193-1801-2-58