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ORIGINAL ARTICLE

To Demonstrate Challenges in Treating Infratentorial Brain Tumors in Pediatrics at the Children's Hospital and Institute of Child Health, Lahore

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ABSTRACT

Objective: To demonstrate challenges in treating infratentorial Brain tumors in pediatrics at The Children's Hospital and Institute of Child Health, Lahore

Methodology: This Descriptive observational study was done at the Department of Pediatric Hematology & Oncology at CH&UCH Lahore from August 2021 to February 2022. Sixty-four newly diagnosed patients of infra-tentorial tumors were enrolled by using non-probability, consecutive sampling technique. Main variables of study were age, parents education, socioeconomic status, traveling distance, TLS, stagging workup, Histopathology, Treatment, and Outcome . SPSS version 23.1 was used for data analysis. Test of significance was applied taking p value ≤0.05 as significant value.

Results: In this study, the mean age of children was 7.14 ± 3.76 years. Out of 64 children, 35 (54.7%) were males and 29 (45.3%) females Forty three (67%) patients belong to rural area and 21 (32%) from urban area. In our study population, Father of 24 (37.5%) patients and mother of 38 (59.37%) patients never attended school. Fifty six (87.5%) patients belong to low income socioeconomic status while 8(12.5%) patients from middle income status. Thirty four (53.12%) patients had a travelled for more than 200KM. Lag time 1 (patient interval) was <2 weeks in 43 (67.2%) cases, and 2-4 weeks in 20 (31.3%) cases. Lag time 2 (referred interval) was noted as <1 Month in 19 (29.7%) cases, and <2 Months in 26 (40.6%) cases. Lag time 3 (treatment interval) was noted in <1 Month in 2 (3.1%) cases, and <2 Months in 6 (9.4%) cases, but in 48 (75.0%) cases lag time 3 was not applicable. Out of 64 cases, cure with Gross Total Resection was noted in 5 (7.8%) cases, residual tumor in 21 (32.8%) and palliation in 37 (57.8%) cases.

Practical implication: The aim was to demonstrate all the challenges in treating Infratentorial tumors and start awareness in the doctor community specially GPs for proper and timely reffral,aware families about the danger signs and symptoms that could be brain tumor.

Conclusion: Advanced disease presentation is common, infra tentorial brain tumors are always challenging and has the least favorable outcomes amongst all pediatric tumors. Delayed diagnosis due to cultural and financial barriers and lack of care at primary health care level and poor referral to oncology units owing to deficient health care system are the major contributory challenges for management and poor outcomes.

Keywords: lag time, infra-tentorial tumors, challenges, Pediatrics

INTRODUCTION

Tumors in central nervous system (CNS) are second most common kind of solid malignancy in pediatric population.[1, 2] Every year, between 30,000 and 40,000 new instances of CNS malignancies are reported worldwide.[3] An estimated 88,190 new cases of malignant and non-malignant brain and other CNS tumors were expected to be diagnosed in the US population in 2021.[4] Over the last few decades, advances in diagnostic and therapeutic approaches have improved overall survival in underdeveloped countries. Malignant and non-malignant CNS tumors had a 5-year relative survival rate of 23.5 percent and 82.4 percent, respectively, in the United States.[4, 5] Despite this, due to a lack of access to neuroimaging and neurosurgery facilities, they are the primary cause of deaths in cancer patients aged 1 to 19 years in low and middle income nations.[6, 7]Infra-tentorial tumors account for more than 60% of pediatric brain tumors. Surgical resection is the first-line therapy for most infra-tentorial tumors in children, with the goal of gross-total excision, alleviation of symptoms and hydrocephalus, and improved survival.[8, 9] Such tumors appear with a variety of vague symptoms that mislead treating clinicians, resulting in a significant delay in diagnosis and treatment (lag time). Increased lag time can result in disease progression, insufficient tumor resection, or surgical morbidity, all of which can lead to long-term endocrine or neurocognitive consequences.[10-12]

There is paucity of data available about the epidemiology of CNS tumors in our institutions so this study is aimed to measure the challenges in treating infratentorial brain tumors and the time interval between onset of symptoms and initiation of treatment and its impact on the survival outcome. That can further pave way to start awareness campaign amongst primary health care professionals.

MATERIALS AND METHODS

This descriptive observational study was conducted in the Department of Pediatric Hematology & Oncology children hospital and , University of Child health science Lahore for about 6 months i.e., 01-08-2021 to 28-2-2022. Sample of 64 cases was estimated by keeping the confidence level at 95%, the margin of error at 12% and percentage of infra-tentorial tumors i.e., 60% in pediatric brain tumors.

All newly diagnosed cases of infratentorial tumors who presented to our center aged less than 18 years were included while patients with incomplete data or relapsed cases of CNS tumors were excluded from the study. All patients who fulfilled the above selection criteria were enrolled in the study by applying "non-probability, consecutive sampling. Informed consent was obtained from parents to use their information for research purpose. Demographics like age, sex, clinical presentation, labs, treatment details, etc. were obtained. The lag time between the onset of symptoms and initiation of treatment was noted, defined as pretreatment interval:

- Lag 1: Parental delay or patient interval (the time taken from recognition of the first sign or symptom to presentation to Primary health professional)
- Lag 2: Primary health professional delay or referral interval (the time from first consultation with Primary health professional to the first consultation with a neurosurgeon)
- Lag 3: Treatment interval (the time from the neurosurgeon to the oncologist).

Data of 64 patients were collected regarding age, gender, education of parents, socioeconomic status demographic distribution, the lag time, travelling distance to the hospital, tumor location, metastatic workup, histopathology findings, csf for cytospin, Radiological findings, MRI of the spine and outcome.

In our study , income status was defined as low income (<50000), middle income(>50000), education status as uneducated (never attended school), under matric (education < 10 class), undergraduate (having bachelor study), graduate (having master study),

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RESULTS

In this study, the mean age of children was 7.14 ± 3.76 years. Out of 64 children, 35 (54.7%) were males and 29 (45.3%) were females. Headache 9 (14.01%), vomiting 6 (9.34%) and fits 6 (9.34%) were among the most common presenting complaints. In the majority of cases the duration of symptoms was 1-2 months [28 (43.8%)] Table 1

Forty three (67%) patients belong to rural area and 21 (32%) from urban area. In our study population, Father of 24 (37.5%) patients and mother of 38 (59.37%) patients never attended school. Fifty six (87.5%) patients belong to low income socioeconomic status while 8(12.5%) patients from middle income status. Thirty four (53.12%) patients had a travelled for more than 200KM. Table 2.

The parental delay was shorter (< 2weeks in 67.2 % cases) compared to diagnostic lag time (<2 Months in 40.6% cases). Treatment was also delayed for >1month in majority of cases (14 out of 16 applicable cases) but in 48 (75.0%) cases lag time 3 was not applicable due to palliation. Table 3

Table 1: Baseline features of children enrolled in the study

Feature	Frequency(%), mean ± SD
N	64
Age	7.14 ± 3.76
sex	
Male	35 (54.7%)
Female	29 (45.3%)
Weight (kg)	20.90 ± 9.57
Year of enrollment	
2021	42 (65.6%)
2022	22 (34.4%)
Presenting complaints / symptoms	
Headache	9 (14.01%)
Vomiting	6 (9.34%)
Fits	6 (9.34%)
Visual disturbance	5 (7.8%)
Altered Consciousness	5 (7.8%)
Gait abnormality, difficulty in walking or unable to walk	6 (9.4%)
Cranial Palsies	1 (1.6%)
Most of mentioned above	48 (75.0%)
Others	3 (4.7%)
Duration of symptoms	
< 1 Month	14 (21.9%)
1-2 Months	28 (43.8%)
2-6 Months	17 (26.6%)
>6 Months	5 (7.8%)

Among 64 patients enrolled in the study, the most common site of tumor was the posterior fossa [51 (79.7%], followed by the Brain stem [11 (17.18%)], and Spinal [2 (3.11%)]. Radiological evaluation was done for the brain in 63 (98.4%) cases while 32 (50%) cases had CT / MRI of the spine. CSF findings were negative in 5 (7.8%) cases but in 59 (92.2%) cases, CSF was not evaluated. Histopathological examination was done in 34 (53.1%) cases in which 27 (79.41%) cases were having medulloblastoma, 4 (11.76%) cases were having ependymoma, and 3 (8.81%) cases were having high grade glioma. Table 4

Shunting followed by gross total resection was done in 22 (34.4%) cases. Surgery was followed by Chemotherapy in 16 (25.0%) cases and Radiotherapy in 8(12.5%). Whereas 18 (28.1%) cases had subtotal resection followed by palliation therapy. Out of 64 cases, 5(7.8%) cases were cured, 21(32.8%) had residual tumor and 37 (57.8%) cases were advised palliation therapy. Out of 64 children, 53 (82.8%) have completed their follow-up after treatment. Table 4

Table 2:

Number	Percentage	
Father education		
Uneducated	24	37.5
Matric	23	35.93
Under Graduation	11	17.18
Graduation	6	9.3
Mother Education		
Uneducated	38	59.37
Matric	16	20.0
Under Graduation	9	25.0
Graduation	1	1.5
Socioeconomic status (thousand)		
<25	51	79.68
25-50	9	14.0
>50	4	6.25
Traveling distance (kilometer)		
<200	30	46.87
>200	34	53.12

Table 3: Lag time from symptoms to final diagnosis (n = 64)

		Frequency
Lag time 1	<2 Week	43 (67.2%)
	2-4 Weeks	20 (31.3%)
	> 4 weeks	1 (1.6%)
Lag time 2	<1 Month	19 (29.7%)
	<2 Months	26 (40.6%)
	<3 Months	5 (7.8%)
	<4 Months	3 (4.7%)
	>4 months	11 (17.2%)
Lag time 3	<1 Month	2 (3.1%)
	<2 Months	6 (9.4%)
	<3 Months	2 (3.1%)
	<4 Months	1 (1.6%)
	<5 Months	1 (1.6%)
	>5 months	4 (6.3%)
	Not Applicable	48 (75.0%)

Table 4: Diagnosis and treatment given in a tertiary care hospital (n = 64)

		F (%)
Site of tumor	Posterior Fossa	51 (79.7%)
	Brain stem	13 (20.3%)
Radiological findings (CT / MRI)	Brain	63 (98.4%)
	Spine	32 (50%)
Laboratory findings (CSF)	Negative	5 (7.8%)
	Not done	59 (92.2%)
Histopathology / Biopsy	Done	34 (53.1%)
	Not done	30 (46.9%)
Treatment given	Shunting + Resection	22 (34.4%)
	Chemotherapy	16 (25.0%)
	Radiotherapy	8 (12.5%)
	Resection followed by palliation	18 (28.1%)
Outcome	Cured	5 (7.8%)
	Not cured	59 (92.2%)
	Residual	21 (32.8%)
	Need Palliation therapy	37 (57.8%)
	Other	1 (1.6%)
Follow-up	Yes	53 (82.8%)
	No	11 (17.2%)

Parental delay did not show any significant effect on the outcome of patients (p-value >0.05). however, shorter diagnostic and treatment delays were associated with a better outcome. (p<0.05). Table 4

Table 5: Effect of lag time on outcome

		Outcome		Total (n=64)	P-value
		Cured (n=5)	Not cured (n=59)		
Lag Time 1	<2 Week	5	38	43	0.2660
	2-4 Weeks	0	20	20	
	> 4 weeks	0	1	1	
Lag Time 2	<1 Month	5	14	19	0.012
	<2 Months	0	26	26	
	<3 Months	0	5	5	
	<4 Months	0	3	3	
	>4 months	0	11	11	
Lag Time 3	<1 Month	1	1	2	0.042
	<2 Months	0	6	6	
	<3 Months	1	1	2	
	<4 Months	0	1	1	
	<5 Months	0	1	1	
	>5months	1	3	4	
	Not Applicable	2	46	48	

DISCUSSION

Our aim was to identify and understand the importance of patient, doctor and treatment related lag times in outcome of primary brain tumors in a developing country. In our study, parental lag time had no significant association with outcome. Although pre-diagnosis symptom interval has a significant impact on tumor grade and disease progression, however outcome is not affected[13] Arnautovic et al and colleagues studied on consequences of delayed diagnosis of low-grade gliomas on patient outcome in a 10-year-old retrospective study. They observed that children having grade I tumors had a significantly longer pre diagnosis symptom interval than did children with higher grade tumors but survival was not affected. In fact, in other studies[14,15] shorter parental lag times are associated with poorer outcome. This is explained by the fact that aggressive tumors tend to present earlier than those with insidious onset who are of low grade. Hence, outcome of parental delay should be studied separately in individual types of brain tumors rather than grouping them together.

Majority (67%) of patients in our study presented with parental delay (lag time 1) of < 2 weeks. This is shorter parental interval compared to other published series.[16] This can be explained by the fact that medulloblastoma constituted a major chunk (78%) of our diagnosis, which due to aggressive nature tends to present early.[16] Secondly, in our study, younger children (<4years) had shorter parental delays(..) compared to older children because parents generally are quite sensitive to nonspecific signs/symptoms that occur in toddlers and infants. In addition, brain tumors in young children usually localized to posterior cranial fossa are often aggressive.

The three most common presenting symptoms were headache (14.01%), vomiting (9.34%), and cerebellar symptoms (9.34%), which are consistent with literature review[13,14,15,16] concerning infratentorial brain tumors. Sanchez et al observed cerebellar syndrome in 21 patients (65.6 %) with infratentorial tumor compared with six (31.5 %) with supratentorial tumor17.

In our study, short doctor lag times were associated with better outcome (p value<0.05). In our study, pretreatment time interval (interval between diagnosis and treatment) was inversely correlated with prognosis (p value <0.05). This is in contrast to Mexico based Multivariate Survival Analysis that showed patients who had treatment delay >13 days (n = 62) exhibited no difference in prognosis (p = 0.963) in comparison to those treated <=13d. These contradictory findings can be reasoned by the fact that our pretreatment interval spanned over months while the Mexican research in discussion had a delay of few days only. Such delay times can be attributed to poor referral system, health infrastructure and scarce pediatric neurosurgical and oncological facilities. However, literature concerning effect of pretreatment time interval on outcome of pediatric brain tumors is scarce

In our study we observed that the doctor lag time (diagnostic interval) in most cases was less than 2 months. In a study done on time to diagnosis of pediatric brain tumors in Japan by Hirata et al. and colleagues, they observed median interval from first presentation to diagnosis was less than 2 weeks.18 This can be explained by the fact that we live in a resource restricted setting where tertiary care hospitals /advanced neuroimaging facilities are limited. Pediatricians and pediatric neurologists are not well known of; hence people resort to general practitioners, who are not qualified enough to make the right diagnosis and confuse the symptoms with URTIs, labyrinthitis, acute cerebellar ataxia and acute gastroenteritis. Secondly, the non-affording class of patients have to resort to the government setups for specialized workup where they have to wait in long queues. Thirdly, parents have a poor educational status due to which they lose follow up after first consultation and resort to quacks and home remedies for symptomatic relief. This fact is backed up by several studies in literature[19,20] that poor socioeconomic status combined with illiteracy contributes to longer diagnostic delay.

In our study, short doctor lag times were associated with better outcome (p value). This is similar to what Hirata et al. concluded from retrospective study that shorter diagnostic delays are correlated with better patient treatment and quality of life.[18]

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This is the first research of its kind in Pakistan that studies the effect of all three lag times (parental, doctor and treatment) on survival outcome in pediatric brain tumor patients. Unfortunately, our lag-times tend to be longer in duration as compared to developed countries like Japan[18.] This leads to increased morbidity, mortality, increased financial and parental psychological stress. In developed countries like UK, pre symptom diagnostic intervals have been significantly reduced to 4 weeks or less by initiatives like Head Smart Programme[21,22] which do so by promoting mass awareness through symptom and clinical guideline cards plus conduction of training modules for health care professionals. Programs such as National Polio Eradication[23]and National TB control Programme[24] have been quite successful in Pakistan in reducing diagnostic delays. Similar initiatives taken at grass root level are the need of the hour in underdeveloped countries like Pakistan. Therefore, we propose:

1. Clinical diagnostic algorithms provided to primary care physicians for early referral to specialists
2. Mass education to raise public awareness and reduce ignorance
3. Improvement in health care infrastructures
4. Prioritizing patient for neuroimaging for suspected brain tumours in government setups.
5. Widening the horizon of paediatric neuro-oncology as a supra-specialization.

Since our analysis was based on small sample size and heterogenous cases, further high-powered studies are needed to confirm our findings.

CONCLUSION

Advanced disease presentation is common, infra tentorial brain tumors are quite challenging and has one of the least favorable outcomes amongst cancers. Late diagnosis due to cultural and socioeconomic barriers and lack of treatment at primary care level and poor referral to cancer units owing to deficient health care system are the major challenges for management and poor outcomes.

REFERENCES

1. Coven SL, Stanek JR, Hollingsworth E, Finlay JL. Delays in diagnosis for children with newly diagnosed central nervous system tumors. Neurooncol Pract. 2018;5(4):227-33.
2. Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, et al. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomarkers Prev. 2014;23(12):2716-36.
3. Elhassan MMA, Mohamedani AA, Osman HHM, Yousif NO, Elhaj NM, Qaddoumi I. Patterns, treatments, and outcomes of pediatric central nervous system tumors in Sudan: a single institution experience. Childs Nerv Syst. 2019;35(3):437-44.
4. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017. Neuro Oncol. 2020;22(12 Suppl 2):iv1-iv96.
5. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer. 2009;45(6):992-1005.
6. Maaz AUR, Yousif T, Saleh A, Pople I, Al-Kharazi K, Al-Rayahi J, et al. Presenting symptoms and time to diagnosis for Pediatric Central Nervous System Tumors in Qatar: a report from Pediatric Neuro-Oncology Service in Qatar. Childs Nerv Syst. 2021;37(2):465-74.
7. Joaquim AF, Ghizoni E, Tedeschi H, Ferreira MAT. Fundamentals of Neurosurgery: Springer; 2019.
8. Wells EM, Packer RJ. Pediatric brain tumors. Continuum (Minneap Minn). 2015;21(2 Neuro-oncology):373-96.
9. Moussalem C, Ftouni L, Mrad ZA, Amine A, Hamideh D, Baassiri W, et al. Pediatric posterior fossa tumors outcomes: Experience in a tertiary care center in the Middle East. Clin Neurol Neurosurg. 2020;197:106170.
10. Lassaletta A, Bouffet E, Mabbott D, Kulkarni AV. Functional and neuropsychological late outcomes in posterior fossa tumors in children. Childs Nerv Syst. 2015;31(10):1877-90.
11. Yule SM, Hide TA, Cranney M, Simpson E, Barrett A. Low grade astrocytomas in the West of Scotland 1987-96: treatment, outcome, and cognitive functioning. Arch Dis Child. 2001;84(1):61-4.
12. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur J Paediatr Neurol. 2010;14(4):298-303.
13. Reulecke BC, Erker CG, Fiedler BJ, Niederstadt T-U, Kurlemann G. Brain Tumors in Children: Initial Symptoms and Their Influence on the Time Span Between Symptom Onset and Diagnosis. Journal of Child Neurology. 2008;23(2):178-83.
14. Sánchez Fernández I, Loddenkemper T. Seizures caused by brain tumors in children. Seizure. 2017;44:98-107.
15. Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. Neuro-oncology. 2016;18(suppl_5):v1-v75.
16. Molineus A, Boxberger N, Redlich A, Vorwerk P. Time to diagnosis of brain tumors in children: a single-centre experience. Pediatrics international : official journal of the Japan Pediatric Society. 2013;55(3):305-9.
17. Mehta V, Chapman A, McNeely PD, Walling S, Howes WJ. Latency between symptom onset and diagnosis of pediatric brain tumors: an Eastern Canadian geographic study. Neurosurgery. 2002;51(2):365-73.
18. Wilne SH, Ferris RC, Nathwani A, Kennedy CR. The presenting features of brain tumours: a review of 200 cases. Archives of disease in childhood. 2006;91(6):502-6.
19. Haimi M, Nahum MP, Arush MWB. Delay in diagnosis of children with cancer: a retrospective study of 315 children. Pediatric hematology and oncology. 2004;21(1):37-48.
20. Shay V, Fattal-Valevski A, Beni-Adani L, Constantini S. Diagnostic delay of pediatric brain tumors in Israel: a retrospective risk factor analysis. Child's Nervous System. 2012;28(1):93-100.
21. Barr RD. "Delays" in diagnosis: a misleading concept, yet providing opportunities for advancing clinical care. Journal of Pediatric Hematology/Oncology. 2014;36(3):169-72.
22. Bourkiza R, Cumberland P, Fabian ID, Abeysekera H, Parulekar M, Sagoo MS, et al. Role of ethnicity and socioeconomic status (SES) in the presentation of retinoblastoma: Findings from the UK. BMJ open ophthalmology. 2020;5(1):e000415.
23. Kaliki S, Ji X, Zou Y, Rashid R, Sultana S, Taju Sherief S, et al. Lag Time between Onset of First Symptom and Treatment of Retinoblastoma: An International Collaborative Study of 692 Patients from 10 Countries. Cancers (Basel). 2021;13(8):1956.
24. Posner M, Jaulim A, Vasalaki M, Rantell K, Sagoo MS, Reddy MA. Lag time for retinoblastoma in the UK revisited: a retrospective analysis. BMJ open. 2017;7(7):e015625.
25. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences. Pediatrics. 2002;109(3):e45-e.
26. Coven SL, Stanek JR, Hollingsworth E, Finlay JL. Delays in diagnosis for children with newly diagnosed central nervous system tumors. Neuro-oncology practice. 2018;5(4):227-33.