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### **Original Research Article**

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# Epidemiological analysis of central nervous system tumors in pediatric patients from a tertiary care centre in India

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#### **ABSTRACT**

**Background:** Tumors of the nervous system are the second most common childhood cancer after leukemia. The diagnosis of CNS tumors is challenging due to non-specific symptoms in children which mimic other less serious illness.

**Methods:** This was a retrospective analysis of case records of patients from 0-18 years of age, who were diagnosed with CNS tumors for a period of 7 years.

**Results:** Out of total 64 patients included in this study, 32 were females and 24 were males. The mean age was 13.2 years. The most common clinical presentation in patients with brain tumors was headache (92.3%) followed by visual symptoms in the form of blurring or loss of vision (42.3%) and swaying while walking (32.6%). The overall mean symptom interval for all patients was 274.8 days (approx. 9 months) ranging from 7-1820 days. In the present study out of total 64 patients, 54 were brain tumors (35 supratentorial and 19 infratentorial) and 10 were spinal tumors. The most common tumor location was cerebellum (21.8%) followed by cerebral cortex, spine and sellar area. Based on histopathology the most common tumor type in our study was astrocytoma. There was no significant correlation of symptom interval with age and gender but was significantly associated with location and tumor grade.

**Conclusions:** Early referral to centers with appropriate facilities will help, as many pediatric CNS tumors are low grade with better survival.

Keywords: Headache, Infratentorial, Supratentorial, Tumor grade, Paediatric brain tumors

#### INTRODUCTION

Tumors of the nervous system are the second most common childhood cancer after leukemia. The diagnosis of CNS tumors is challenging due to non-specific symptoms in children which mimic other less serious illnesses. Moreover, neuroimaging of young children often requires anesthesia and may therefore not be readily available especially in poor resource countries. The prognosis for children with intracranial tumors is dependent on the age at which the

diagnosis is made-the older the child the greater his chance of survival.<sup>2</sup> While some brain tumors are diagnosed rapidly, the majority of studies report a mean symptom interval of at least 14 weeks. This is in striking contrast to mean symptom intervals of 4.5 and 2.8 weeks for leukemia and Wilms' tumor, respectively.<sup>3</sup> The aim of present study was to study the clinic pathological profile of pediatric central nervous system tumors and to find the average time from symptom onset to diagnosis (symptom interval). We also aim to find

out the association of symptom interval with various factors which might be associated with diagnostic delay.

#### **METHODS**

Study design was retrospective analysis. Patients from 0-18 years of age, who were diagnosed with CNS tumors (both brain tumors and spinal tumors), admitted in pediatric and neurosurgery department for a period of 7 years (from January 2012 to December 2018).

#### Inclusion criteria

 Pediatric patients who are newly diagnosed with confirmed histopathological diagnosis of CNS tumors.

#### Exclusion criteria

 Already diagnosed or treated cases, patients who came for the first time to our institute with recurrence and those who came only for radiotherapy or chemotherapy were excluded.

#### Methodology

Case records of these patients were studied and details of age, gender, clinical presentation including duration of each symptom, investigations, management and outcomes were recorded. Symptom interval is defined as the time taken for onset of symptom to diagnosis. Histopathological reports of all patients were noted which was based on WHO 2007 Classification of CNS tumors as per institutional records. Institutional ethical committee approval was taken.

#### Statistical analysis

Statistical analysis was done using SPSS software, version 20.0 The correlation of symptom interval with age, gender, location of tumor and tumor grade was noted using chi square test and Pearson's correlation coefficient. The survival was found using kaplan meier survival curves.

#### **RESULTS**

#### Patient characteristics and clinical presentation

Out of total 64 patients included in this study, 32 were females and 24 were males with M: F ratio as 0.7:1. The mean age was 13.2 years. Total 47(73.4%) patients were in 11-18 years of age group, 9 patients (14.1%) were 6-10yrs of age group and 8(12.5%) patients were 0-5 years of age group (Figure 1). The most common clinical presentation in patients with brain tumors was headache (92.3%) followed by visual symptoms in the form of blurring or loss of vision (42.3%) and swaying while

walking (32.6%), as shown in Table 1. In patients with spinal tumors the most common complaint was neurological deficit followed by sensory symptoms, limb pain and swelling (Table 1). The overall mean symptom interval for all patients was 274.8 days (approx. 9 months) ranging from 7-1820 days, for brain tumors average symptom interval was 254.8 days (approx. 8.5months), ranging from 7-1820 days and for spinal tumors it was 369.5 days (approx. 1 year) ranging from 15-1440 days (Figure 2, Figure 3).

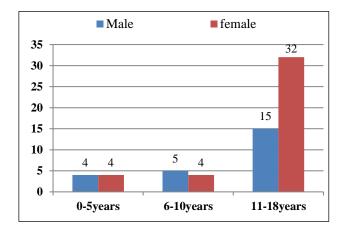


Figure 1: Age and gender distribution.

Table 1: Clinical presentation and symptom interval in patients with CNS tumors.

Symptoms of brain tumors	Total pts (%)	Symptom interval Range (days)	Mean of symptom interval (days)
Headache	48(92.3)	7-1080	146.22
Vomiting	12(23.1)	3-90	30.75
Swaying while walking	17(32.6)	15-720	123.5
Neurological deficit	15(28.8)	4-150	56.3
Seizures	6(11.5)	5-1080	444.2
Behavioural com- laints	3(5.7)	10-210	83.3
Visual symptoms	22(42.3)	4-1080	104.3
Hearing deficits	2(3.8)	360-720	540
Urinary incontinence	2(3.8)	4-7	5.5
Growth and pubertySymptoms	4(7.6)	360-1820	630
Altered sensorium	3(5.7)	2-10	5.3
Symptom of spinal t	umors		
Neurological deficit	10(90.9)	15-720	151.5
Limb pain	7(63.6)	10-1440	284.3
Swelling	2(18.2)	20-1440	780
Sensory symptoms	4(36.3)	10-1080	467.5

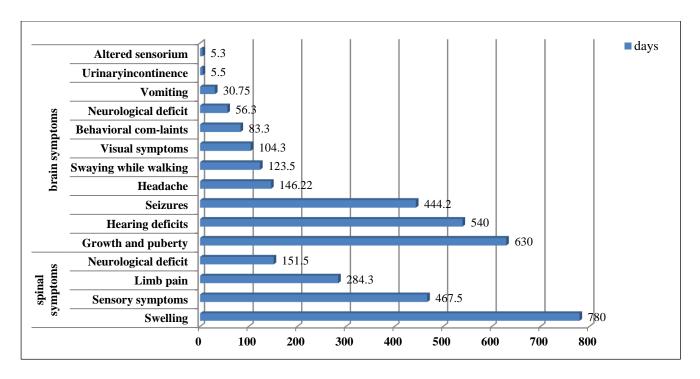


Figure 2: Mean symptom interval for CNS tumors.

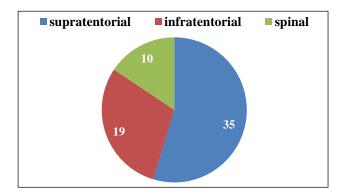


Figure 3: Distribution of tumor location.

Table 2: Age wise distribution of CNS tumors.

Age group	Supratentorial	Infratentorial	Spinal
0-5 years	3	4	1
6-10 years	4	5	0
11-18 years	28	10	9
Total	35	19	10

#### Tumor distribution and types

In the present study out of total 64 patients, 54 were brain tumors (35 supratentorial and 19 infratentorial) and 10 were spinal tumors (Figure 3). In children <10 years age infratentorial tumors were more common and in 11-18 years age group supratentorial tumors were more common (Table 2). The most common tumor location was cerebellum (21.8%) followed by cerebral cortex, spine and sellar area (Figure 4). Cerebellum, ventricles

and sellar region were equally the most common locations of CNS tumors in 0-5 years of age group.

Table 3: Age wise distribution of location of CNS tumor.

Location	0-5 yrs.	6-10 yrs.	11-18 yrs.	Total
Spine	1	0	9	10
cerebellum	2	5	7	14
cortex	0	2	11	13
Ventricles	2	0	0	2
Choroid plexus	0	0	1	1
Nerves	0	1	2	3
Sella	2	1	7	10
pituitary	0	0	3	3
Pineal gland	0	0	1	1
thalamus	1	0	1	2
Midbrain	0	0	2	2
Brainstem	0	0	2	2
Optic chaisma	0	0	1	1
Total	8	9	47	64

However, in age group 6-10 years cerebellum was most common and in 11-18 years age group cerebral cortex was the most common location of CNS tumors (Table 3). Based on histopathology the most common tumor type in our study was astrocytoma which was seen in 19 patients. In 0-5 years, age group medulloblastoma and astrocytoma common, in 6-10 year age group medulloblastoma were most common and in 10-18 year age group astrocytoma was most common tumor type (Table 4).

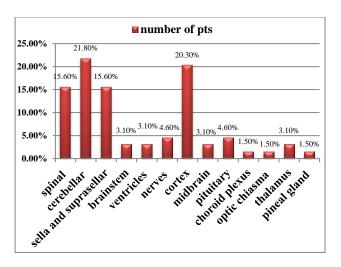


Figure 4: Distribution of CNS tumor location.

#### Factors affecting symptom interval

The symptom interval had significant correlation with tumor location. For infratentorial tumors the mean symptom interval was 99.7 days (Approx. 3 months) and for supratentorial tumors it was 330.1 days (Approx. 11 months) and the difference was found to be significant with p value 0.018. The symptom interval had no significant correlation

with gender (p value 0.213). On an average male patient took 325.5 days (10.8 months) and female patients took 243.59 days (8.1 months) before diagnosis. There was no significant correlation of symptom interval with age as Pearson correlation r equals  $0.2277 (r^2=0.0518)$  and p value 0.0726 (Not significant for p<0.5). The symptom interval had significant correlation with grade of tumor based on histopathology. Out of 64 patients, 20(31.2%) had high grade tumors and the mean symptom interval in these patients was 56.32 days (1.8 months), however 44(68.75%) patients had low grade tumors and the mean symptom interval was 369.14 days (12.3 months). The difference was found to be significant (p value is 0.001545). Only 17 patients out of 64(26.5%) were diagnosed within 30 days from symptom onset which included 5 male and 12 female patients (Table 5).

#### Operative characteristics

Hydrocephalus was present in 33(51.5%) patients at the time of diagnosis. CSF diversion procedures were done in 23 patients (table 6). Depending on site and characteristics of tumor, CSF diversion procedure along with biopsy only was done for 9 patients, who were later operated by definitive surgery in the form of either total resection subtotal resection.

0-5 years 6-10 years Sr. No. Histopathology 11-18 years

DI. 110.	Histopathology	0-5 years	0-10 years	11-10 years	Total	
1.	Astrocytoma	2	1	16		
	Low grade	2	0	11	19	
	High grade	0	1	5		
2	Embryonal tumors					
	Medulloblastoma	2	3	1	0	
	PNET			1	8	
	Atypical teratoid /rhbdiod	1				
3	Craniopharyngioma	1	1	6	8	
4	Ependymal tumors					
	Ependymoma			4	5	
	Anaplastic ependymoma		1			
5	Oligodendroglioma		2	3	5	
6	Germ cell tumors			2	2	
7	Choroid plexus			1	1	
8	Nerves					
	Schwanomma		1	3	6	
	MPNST			1		
	Neurofibroma	1				
9	Mesenchymal					
	Chondroma			1		
	Ewings sarcoma			1	5	
	Hemangioblastoma	1		1		
	Undifferentiated pleomorphic sarcoma			1		
10	Meningioma			2	2	
11	Pituitary					
	Microadenoma			2	3	
	Macroadenoma			1		
	Total	8	9	47	64	

Table 4: Age wise distribution of histopathology of CNS tumors.

Table 5: Distribution of symptom duration with age group.

Symptom interval	0-5 years	5-10 years	10-18 years	Total
1-30 days	1(12.5%)	4(44.4%)	12(25.5%)	17
>30 days	7(87.5%)	5(55.5%)	35(74.4%)	47
Total	8	9	47	64

p value 0.314, non-significant

Table 6: CSF diversion procedures.

CSF diversion procedure	No of patients
Endoscopic ventriculostomy	5
Extra ventricular drain	2
VP shunt	13
Ommaya reservoir	3

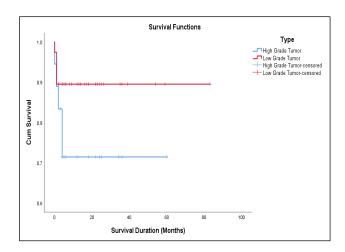


Figure 5: Kaplan Meier survival curves for CNS tumor cases.

Table 7: Comparison of various Indian studies on pediatric CNS tumors.

Characteristics	Present study (Tirupati)	Madhvan R <sup>4</sup> et al, (Chennai)	Suresh SG <sup>4</sup> et al, (Chennai)	Shah HC <sup>5</sup> et al, (Gujrat)	Sangita RM <sup>6</sup> et al, (Mumbai)	Jain <sup>14</sup> et al, (AIIMS Delhi)
No of patients	64	250	52	76	239	819
Duration of study	2012-2018	2006-2011	2012-2016	2012-2013	2001-2015	2002-2007
Mean Age	13.2 yrs. (0-18yrs.)	NA (0-18yrs.)	4yrs.	10.69yrs. (0-19yrs.)	NA (0-18yrs.)	NA (0-18yrs.)
Gender	M=24 F=40	M=111 F=139	M=37 F=17	M=42 F=34	M=131 F-101	NA
Common Tumor type						
Astrocytoma	19(29.6%)	52%	28.8%	40.8%	46.8%	33.7%
Medulloblastoma and PNET	7(10.9%)	21.6%	34.6%	29%	18.4%	16.8%
Craniopharyngioma	8(12.5%)	3.6%	NA	11.8%	9.2%	12.7%
Oligodendroglioma	5(7.85)	6%	NA	NA	10%	0.7%
Ependymoma	4(6.2%)	10.4%	9.6%	6.6%	12.5%	8.5%
Germ cell tumor	2(3.1%)	1.6%	9.6%	NA	1.3%	2.2%

#### Outcome

Out of total 64 patients 7 patients died, 15 patients lost to follow up, 4 are still on treatment and 44 patients completed treatment and are on regular follow up. The overall mean survival time was 69.6 months (95%CI: 61.6-77.6). In case of high grade tumors the mean survival was 43.5 months (CI: 31.2 - 55.7) and in low grade tumors the mean survival was 74.3 months (CI: 66.3 - 82.4) (Figure 5). No significant difference was found by Long rank test between high grade and low grade tumors with respect to survival (p = 0.119).

#### **DISCUSSION**

For better understanding of pediatric CNS tumors, the clinical and epidemiological data from different centers

of world must be reported and this is one such attempt. The mean age in present study was 13.2 yrs which was higher than other studies reported in India. Females were more than males in the present study which is similar to Madhvan r et al, but not with other Indian studies (Table 7).<sup>4</sup> CNS tumors are more common in boys than girls as per reports worldwide.<sup>3,5,6</sup>

In western population, it was found that astrocytomas and medulloblastomas are the two most common brain tumors in children. However Ependymomas were the third most common childhood brain tumor in various Western studies from Germany, Canada, Sweden, and Morocco.<sup>7-10</sup> On the contrary, craniopharyngioma was the third most common tumor in various Asian studies from Korea, Beijing, Japan, and India which is consistent with our study.<sup>11-14</sup> Most common type of tumor in present

study was astrocytoma and second most common was embryonal tumors. Craniopharyngiomas were third most common tumor type which is consistent with many other studies.<sup>4,15-17</sup> (Table 7).

Infratentorial tumors were more common in children <10 yrs of age and supratentorial in 11-18 yrs of age, However overall supratentorial was common location followed by infratentorial and spinal in present study which is consistent with many other studies. <sup>18-19</sup> Cerebellum was most common tumor location (21.8%) followed by cortex (20.8%) which is also consistent with many other studies. <sup>20,21</sup>

We have observed that the presenting symptoms were consistent with other studies but in our patients symptoms like headache, visual disturbance, neurological deficits, swaying while walking, limb pain, growth and pubertal delay had long symptom interval, which could be due multiple factors like parental neglect or delay by clinician in deciding the need for imaging or lack of availability of facilities for neuroimaging, or all of them.<sup>4,14,22</sup>

As per study done by Flores LE et al, interval from the onset of symptoms to the diagnosis in 79 children with primary brain tumors was compared with that in 45 children with Wilms' tumor and 123 children with acute leukemia.<sup>22</sup> The patients with brain tumors had a significant delay from symptom onset to diagnosis. Only 38% of primary brain tumors were diagnosed within the first month after the onset of symptoms. In contrast, 84% of Wilms' tumors and 80% of cases of acute leukemia were diagnosed within one month of the onset of symptoms. In the present study only 17 patients (26.5%) were diagnosed in < 30 days after onset of symptom. In a similar study done by Edgeworth J et al23 duration of clinical history ranged from less than one week to 130 weeks. One month after symptom onset 68% children were not correctly diagnosed and after six months 20% were still not diagnosed.

The mean symptom interval was more for spinal tumors than cranial tumors. In a study done by M. Dobrovoljac et al.<sup>24</sup> The median Presymptomatic Symptom Interval (PSI) of all patients was 60 days (range 0-3010 days) and only 81 (32%) of the 252 brain tumours were diagnosed within 30 days after onset of signs/symptoms. They also observed that age had a statistically significant correlation with PSI (Pearson's correlation r=0.32, P<0.0001) with shorter PSI for younger children. However there was no correlation of symptom duration with age in the present study. In another study done by Mehta V et al, the mean time to diagnosis was 7.3 months, and only 41% of cases were correctly diagnosed within three visits to various physicians.<sup>25</sup>

In a study done by S.H. wilne et al, the symptom interval, documented in 175 patients, varied from 1 day to 120 months with a median value of 2.5 months and children

aged 3 years or less had a significantly shorter median symptom interval than older children (1.0 v 3.0 months).<sup>26</sup>

In a study done by Bettina C. Reulecke et al, patient's age and gender both had no statistically significant influence on the interval between symptom onset and diagnosis, but there was a significantly shorter interval between symptom onset and diagnosis in high-grade tumors. This study also had similar findings.<sup>27</sup>

The overall mean survival time in present study was 69.6 months. In case of high-grade tumors, the mean survival was 43.5 months and in low grade tumors the mean survival was 74.3 months. A study done by Lachi Pavan Kumar et al, has reported a median overall survival of 36 months in age <14 years for medulloblastomas.<sup>28</sup>

Limitations of this study were short study duration and retrospective data. More prospective studies with large sample size are needed for better understanding the epidemiology and survival of children with CNS tumors.

#### **CONCLUSION**

CNS tumors in children have varied presentations with long duration of symptoms before they are diagnosed. The patients with symptoms that mimic CNS tumor symptoms should be kept under close follow up. Choosing patients who are in need of neuroimaging is challenging. Early referral to centres with appropriate facilities will help, as many paediatric CNS tumors are low grade with better survival.

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Institutional Ethics Committee.

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