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Delays in diagnosis for children with newly diagnosed central nervous system tumors

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Abstract

Background. United States studies documenting time interval from symptom onset to definitive diagnosis for childhood central nervous system (CNS) tumors are more than a quarter-century old. The purpose of this study is to establish an accurate and contemporary Ohio baseline of the diagnostic interval for children with newly diagnosed CNS tumors.

Methods. Medical records were retrospectively reviewed for 301 children with newly diagnosed CNS tumors from January 2004 to August 2015 at Nationwide Children's Hospital. We obtained comprehensive data on 171 patients (56.8%). Records were reviewed for age, gender, tumor type, presenting symptoms, number of health care visits prior to diagnosis, time interval (in months) from onset of symptoms to definitive diagnosis, and any associated genetic syndromes.

Results. Of the 171 patients with newly diagnosed CNS tumors, 25 children (14.6%) had a known cancer predisposition syndrome (all with neurofibromatosis type 1). Among the remaining 146 children, the median and mean time intervals from symptom onset to definitive diagnosis were 42 days and 138 days (range < 1 to 2190 days), respectively.

Conclusions. We have documented and quantified the contemporary delays in diagnosis of childhood brain tumors in central Ohio to serve as a benchmark for our future planned interventions to reduce the time interval from symptom onset to diagnosis through adaptation of the United Kingdom HeadSmart program throughout the state of Ohio and ultimately throughout the United States.

Key words

childhood | CNS tumors | delayed diagnosis

Central nervous system (CNS) tumors are the second-most-common cancers in children between 1 and 19 years of age. Additionally, CNS tumors are the leading disease-related cause of death in children under 19 years of age in the United States.[1,2] Over the past few decades, the overall survival for patients with childhood CNS cancer has improved from 20% to around 74%.[3,4] Despite the advances in diagnostic modalities and treatment methods, children with CNS tumors continue to experience a broad array of nonspecific clinical features that may contribute to significant delays in diagnosis, evident in the time interval from the onset of symptoms to definitive diagnosis. These symptoms may vary by age, tumor type, and tumor location. Therefore, delays in diagnosis remain a significant concern, impacting morbidity, mortality, and quality of life.

Delays in diagnosis of childhood CNS tumors, not limited to any certain subtype, have only been evaluated in a few studies in the United States,[5,6] in the United Kingdom,[7] Canada,[8] and Israel.[9,10] The United States studies were published more than 25 years ago, with more recent studies in the few countries mentioned above. These studies reinforced the variety of presenting symptoms that contribute to the difficulties

with diagnosing brain cancer in children. Additionally, these studies demonstrated that children with lower grade tumors are at the greatest risk for delays in diagnosis.

The present study was undertaken to document the presenting clinical features of children with CNS tumors and to update the baseline time frame from symptom onset to definitive diagnosis in the state of Ohio. This time interval will become the basis for adaptation and implementation of a program called "HeadSmart," designed in the United Kingdom with the principal objective of enhancing awareness of signs and symptoms of children with brain cancer throughout both primary care and specialty care providers, as well as the broader lay public.

Methods

The medical records of 301 children diagnosed with primary brain tumors from 2004 to 2015 at Nationwide Children's Hospital in Columbus, Ohio, were reviewed. Medical records were reviewed to determine the presenting symptoms, age at diagnosis, sex, race, postal code, tumor type, tumor location, total number of health care visits reported prior to diagnosis, time interval, and any associated genetic cancer predisposition syndromes (neurofibromatosis type 1 [NF1], neurofibromatosis type 2 [NF2], or tuberous sclerosis). The admitting history and physical, oncology consultation note, or neurosurgical documentation were often sufficient to obtain the pertinent details. Definitive diagnosis was defined by radiographic evidence of the CNS tumor; the time interval was defined from the onset of symptoms to definitive diagnosis. Symptoms were characterized into 10 separate categories: headache, nausea and/or vomiting, abnormal gait and coordination (ataxia), hemiplegia, visual disturbances, seizure, fatigue and/or lethargy, behavioral changes, irritability, and weight loss. Health care visits were based upon parents' report and confirmed with the medical record when visits occurred within our medical system. Prior to data collection, the study was submitted to the Nationwide Children's Hospital Institutional Review Board and withdrawn with exempt status. Lastly, we considered the implications of a retrospective study that could be subjected to recall bias.[11] This study was approved with exempt status by the Institutional Review Board.

Statistical Analysis

Statistical analysis was primarily descriptive. Data were summarized with frequencies and percentages for categorical variables and medians and ranges for continuous variables. Any statistical comparisons were completed using nonparametric methods. Analyses were performed in SAS software, version 9.4 (SAS Institute, Cary, NC, USA) or the R statistical language (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 301 children identified with a primary brain tumor during the study period, 171 patients were available for analysis. The implementation of our electronic medical record system (August 2006) along with incomplete data and unclear time intervals reduced the total patients included in the final analysis. The median age at diagnosis among the complete cohort was 8 years (range, 1 to 28 years). Our hospital serves the adolescent and young adult population and 2 such cases (25 years, 28 years) were included in the final analysis. The male-to-female ratio was 1.41:1 (100 males, 71 females). Additionally, 27 patients had a preceding diagnosis prior to their presentation with a brain tumor: 1 patient with von Willebrand disease, 1 patient with trisomy 21, and 25 patients with NF1. The 25 NF1 patients were excluded from the primary analysis, leaving 146 patients (Table 1). The median time interval from symptom onset to definitive diagnosis for the NF1 cohort was 0 days, confirming earlier diagnosis secondary to surveillance methods that are necessary given these patients' known predisposition to CNS tumors.

Table 1 Demographics of patient cohort

Variable	
Total patients	146
Age, median (range)	8 years (<1 to 28)
Male, *n (%)*	83 (56.8%) -1.32:1
Race, *n (%)*	
White	111 (76.0%)
Black	14 (9.6%)
Asian	4 (2.7%)
Other	12 (6.2%)
Unknown	8 (5.5%)
Tumor type, *n*	
Low-grade gliomas	64
Medulloblastoma	24
DIPG	16
High-grade gliomas	12
Ependymoma	9
Other CNS PNET	6
CNS ATRT	5
Choroid plexus carcinoma	4
Primary CNS germ cell tumor	4
Meningioma	2

Abbreviations: ATRT, atypical teratoid/rhabdoid tumor; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; PNET, primitive neuroectodermal tumor

Symptoms

Symptom categories were established prior to the study based upon previously published data.[7] Symptoms with strong overlap were grouped together due to their similarities. Headache was the most frequent symptom reported, present in 56% of patients, followed by nausea and vomiting (50%), abnormal gait (32%), visual disturbances (31%), and seizures (12%). Less frequent symptoms exhibited by patients included lethargy, behavioral changes, irritability, and weight loss. Symptom categories were divided for children greater than 4 years and less than 4 years based upon the 2007 Wilne et al systematic review and meta-analysis published in *Lancet Oncology*.[12] Among 111 children 4 years of age or older at diagnosis, headache continued to be the most common symptom, followed by nausea and vomiting, visual disturbances, abnormal gait, and seizures. The remaining symptoms described at presentation are represented in Table 2.

Of the 35 patients who were under the age of 4 years at diagnosis, headache was less likely to be a reported symptom present at the time of diagnosis (23%). The most common symptoms present in this age group were nausea and vomiting, followed closely by abnormal gait. The remaining symptoms occurred far less in children less than 4 years of age at diagnosis.

Tumor Type

Low-grade gliomas were the most commonly represented tumor type in our cohort (45%). Overall, gliomas represented 56% of the pediatric brain tumors in our study, similar to previously published data.[2] Embryonal tumors were the next-most-common tumor type in our study (24%), including 24 medulloblastomas, 5 atypical teratoid/rhabdoid tumors (AT/RT), and 6 other CNS embryonal tumors (formerly known as primitive neuroectodermal tumors or PNET). Other tumor types represented in our study included diffuse intrinsic pontine glioma (DIPG), ependymoma, choroid plexus carcinoma, primary CNS germ cell tumor, and meningioma. Additionally, there were 77 patients with supratentorial tumors (52.7%) and 69 patients with infratentorial tumors (47.3%). Tumor types are represented in Table 3, with corresponding median time intervals from symptom onset to definitive diagnosis.

Table 2 The most common presenting symptoms by age

Symptom, *n (%)*	Age <4 years	Age ≥4 years
Headache	8 (23)	74 (67)
Nausea/vomiting	19 (54)	54 (49)
Abnormal gait	18 (51)	29 (26)
Visual disturbances	5 (14)	40 (36)
Seizures	1 (3)	17 (15)
Lethargy	4 (11)	12 (11)
Behavioral changes	2 (6)	9 (8)
Irritability	2 (6)	4 (4)
Weight loss	2 (6)	6 (5)
Papilledema	0 (0)	4 (4)

Health Care Visits

Of the 146 remaining patients (without NF1), 32 patients (21.9%) had no reported health care visits and 9 patients (6.2%) had an unknown number of health care visits prior to definitive diagnosis. The remaining 105 patients (71.9%) had at least 1 documented contact with the health care system prior to their diagnosis, although 13 patients/families were unsure whom the patient had seen. These patients amassed 237 total visits, with the primary care physician and emergency department being the most frequent point of contact. More specifically, 88 patients had between 1 and 3 visits prior to diagnosis, 10 patients had 4 to 6 visits prior to diagnosis, and 7 patients had more than 7 visits prior to diagnosis (range, 1–10 visits). Patients in the cohort visited nearly all pediatric subspecialties for symptoms prior to diagnosis: Behavioral medicine, cardiology, diet/nutrition, endocrinology, otorhinolaryngology, gastroenterology, general surgery, hematology, infectious diseases, neurology, neurosurgery, ophthalmology, orthopedics, physical therapy, radiology, and rheumatology. Visits to their primary care physician or local urgent care/emergency department made up nearly 50% of all encounters to the health care system. Overall, neurology, ophthalmology, and gastroenterology were the most common pediatric subspecialties visited prior to diagnosis. Children less than 4 years of age (28 patients) visited their primary care provider or local urgent care/emergency department more often (69% vs 41%) prior to diagnosis than children greater than 4 years of age (77 patients).

Among children with 1 to 3 reported visits to the health care system, the median time interval from symptom onset to definitive diagnosis was 42 days (range, 0–2190 days).

Table 3 Tumor type with corresponding time interval from symptom onset to definitive diagnosis

Tumor Type	*n*	Median Interval in Days (Range)
Choroid plexus carcinoma	4	22 (1–95)
CNS ATRT	5	30 (14–365)
DIPG	16	30 (7–730)
Ependymoma	9	35 (8–137)
High-grade gliomas	12	17.5 (0–180)
Low-grade gliomas	64	60 (0–2190)
Medulloblastoma	24	30 (5–365)
Meningioma	2	135 (60–210)
Other CNS PNET	6	113.5 (0–365)
Primary CNS germ cell tumor	4	107 (14–150)

Abbreviations: ATRT, atypical teratoid/rhabdoid tumor; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; PNET, primitive neuroectodermal tumor

Additionally, children with 4 to 6 reported visits to the health care system experienced a median time interval from symptom onset to definitive diagnosis of 143.5 days (range, 7–365 days). Lastly, those patients with 7 to 10 reported health care visits experienced a median time interval from symptom onset to definitive diagnosis of 94 days.

Time Interval

The overall time interval from symptom onset to definitive diagnosis documented in our patient cohort varied from 0 to 2190 days, with a median interval of 42 days. Children less than 4 years of age at initial diagnosis had a shorter median time interval from symptom onset to diagnosis than those 4 years or older (30 days vs 60 days), but this was not statistically significant (P = .1064). Additionally, children with infratentorial tumors tended to have a shorter time interval from symptom onset to definitive diagnosis than those with supratentorial tumors (30 days vs 60 days) that was statistically significant (P = .0445). The median time interval for low-grade gliomas from symptom onset to definitive diagnosis was 60 days, nearly 2.5 weeks longer than the overall cohort median time interval (P = .0104). There were only a few patients (n = 14) with the diagnosis of CNS germ cell tumor, meningioma, PNET, or unclassified type, and the median time interval for patients with these diagnoses was greater than 100 days (range, 100–135 days). Lastly, the faster growing tumors such as high-grade gliomas, DIPG, and medulloblastomas all had median time intervals less than 30 days.

Discussion

This study of pediatric primary brain tumor patients of all tumor types is the most recent to focus on the time interval from symptom onset to definitive diagnosis in the United States. The presenting symptoms in our study (Table 2) are fairly similar to those documented in previous publications, although we found a higher number of cases with nausea and vomiting, abnormal gait, and visual disturbances.[7,10,12] Additionally, we documented that headache is not as common a symptom in children less than 4 years of age at diagnosis, suggesting thoughtful consideration for further evaluation for children in this age group.

The mean time interval from symptom onset to definitive diagnosis in our study was 4.5 months (19.4 weeks). Previous studies over several decades have demonstrated little improvement in the time interval for pediatric brain tumors in the United States. Flores et al[5] compared the mean time interval of pediatric brain tumor patients (6.5 months) to that of children with Wilms' tumor (2.8 weeks) and acute leukemia (1 month). As a part of our study, we also reviewed 182 cases of acute lymphoblastic leukemia diagnosed over the same time frame. The mean time interval from symptom onset to definite diagnosis of children with acute leukemia was 14 days; therefore, our study compared with the 1986 study by Flores et al[5] reveals no change to the time interval from symptom onset to definitive diagnosis over the past 30 years. Additionally, Pollock et al[6] published data in 1991 on the lag time of children treated on North American Pediatric Oncology Group therapeutic protocols and found among 380 children with brain tumors a mean time interval from symptom onset to diagnosis of 66 days.

More recent studies have been conducted internationally reviewing delays in diagnosis from time of symptom onset. In Canada, Mehta et al[8] demonstrated a mean time interval of 7.3 months among 104 cases of pediatric brain tumors. Wilne et al[7] published a review of 200 patients diagnosed in the United Kingdom. The authors found the median duration of symptoms to be 2.5 months. Haimi et al[9] reviewed 315 cases of pediatric cancer in Israel, and found the greatest mean and median delays in diagnosis in brain and bone tumors. Among 72 brain tumor patients, the mean and median lag time was 21.4 weeks and 7.5 weeks, respectively. A more recent study in Israel by Shay et al[10] found a mean time to diagnosis of 7.7 months among 330 pediatric brain tumor patients. Table 4 summarizes

Table 4 Summary of previously published work on delays in diagnosis for children with brain cancer

Author	Publication Year	Tumor Type	Cohort Size	Median Interval (weeks)	Mean Interval (weeks)
United States					
Flores et al	1986	All	79	6	26
Pollock et al	1991	Treated on Pediatric Oncology Group Protocols	380	4.5	9.4
Halperin et al	2000	Medulloblastoma	122	Not Reported	14.3
Arnautovic et al	2015	Low-grade Gliomas	260	8	Not Reported
Coven et al	2017	All	146	6	19.4
International					
Mehta et al (Canada)	2002	All	104	Not Reported	29.2
Haimi et al (Israel)	2004	All	72	7.5	21.4
Wilne et al (United Kingdom)	2006	All	200	10	Not Reported
Shay et al (Israel)	2012	All	330	Not Reported	34.5

published work for children with brain tumors experiencing delays in diagnosis.

In this present study, we were able to document health care-related visits pertaining to common symptoms of pediatric brain tumors. All patients included in the final analysis had at least 1 documented symptom at the time of definitive diagnosis. Moreover, 70% of our cohort had some documentation of health care visits prior to definitive diagnosis of a brain tumor (Table 5) and for the remaining 30% it was unclear whether care was sought for their symptoms. Not surprisingly, most visits were to their primary care physician or local emergency department. Additionally, most patients had only 1 to 3 reported visits prior to their definitive diagnosis. Furthermore, children were referred for their symptoms to nearly every pediatric subspecialty prior to definitive diagnosis. The most commonly visited pediatric subspecialties were neurology, ophthalmology, and gastroenterology. Interestingly, children less than 4 years of age at diagnosis were most often evaluated by their primary care provider or local emergency department, whereas children greater than 4 years of age experienced more subspecialty visits prior to diagnosis. By examining and documenting health care visits prior to diagnosis, it is evident that a broad-based approach, not just targeting primary care or emergency department providers, is necessary to improve the awareness of the signs and symptoms of pediatric brain cancer.

Table 5 Health care visits by provider (n = 237)

Health care provider	n
Primary care physician	61
Emergency medicine/urgent care	56
Unknown	31
Neurology	26
Ophthalmology	14
Radiology	11
Gastroenterology	10
Hospital admissions	9
Endocrinology	4
Neurosurgery	3
Physical therapy	3
Ear, nose, and throat	1
Dietician	1
Hematology	1
General surgery	1
Cardiology	1
Rheumatology	1
Infectious disease	1
Behavioral	1
Orthopedics	1

Limitations of this Study

Due to this study's retrospective nature, nearly 45% of our data were missing or were not accurately recorded at the time of diagnosis. The study period included a transition from paper-based charts to electronic medical records. Although missing data could impact the interpretation of results, this study reviewing all tumor types among children with brain cancer for delays in diagnosis represents one of the largest and most comprehensive conducted in the United States over the past 25 years. Lastly, plans for a future prospective study to obtain the symptom interval for children with newly diagnosed CNS tumors would allow for more complete data collection.

Our data were dependent upon the original documentation; therefore, symptoms may have been present that were not reported in the consultation or history and physical notes. A prospective research design would overcome this disadvantage and provide a more accurate description of all presenting symptoms, including the primary symptom experienced by the patient. Although most patients had a very clear time interval documented, it is likely recall bias may have contributed to over-reported duration of symptoms prior to the diagnosis.[19,20]

Our study represents one of the first to describe health care visits prior to definitive diagnosis among children with brain cancer. However, 30% of patients had no documented contact with the health care system prior to diagnosis of their brain cancer. Although this might be accurate, it may be more likely that primary care providers or emergency department services outside of our catchment area evaluated these children prior to diagnosis. Even among children with only 1 to 3 reported health care visits, the range of symptoms occurred over a significant time period, suggesting that more visits possibly may have occurred than were reported. Further research into the consequences of prior health care visits with practitioners both within and beyond the formal health care system and delays in diagnosis warrants further investigations.

Conclusions

Delay in the diagnosis of children with brain cancer continues to be a significant problem. Only 1 prior report within the past decade, in addition to the present study, has evaluated this in the United States (Qaddoumi et al at St. Jude,[21] confined to children diagnosed with low-grade gliomas). Both reports disappointingly show no substantial reduction in interval from first symptom to diagnosis in comparison with such reports published back in the 1980s and early 1990s.[5,6] Additionally, delays in diagnosis in children with brain cancer have clearly been associated with poorer outcomes; in particular, children with low-grade gliomas and other low-grade brain tumors—who represent approximately two-thirds of all children with brain cancer—have the longest delays in diagnosis, resulting in substantial adverse impacts upon quality of life (eg, blindness, paralysis, cognitive deficits, and shunt malfunctions) although

not perhaps overall survival, as well as greater sequelae from treatment.[23–30] Thus, we hypothesize that successful efforts to shorten the time interval from first symptoms to definitive diagnosis will result in marked improvements in patient quality of life and in socio-economic impacts of brain cancer. Lastly, we believe this work will bring attention for the need to document results of efforts to reduce the time interval by functional outcome instead of survival.

Our results provide the foundation for the adaptation and transformation of the United Kingdom web-based HeadSmart program[22,31,32] into a version more applicable to the primary care pediatrician practices within Ohio specifically and the United States in general. While the HeadSmart program is already well-established in the United Kingdom, such an approach has not previously been attempted in the United States. We believe that this program can significantly reduce the time interval from symptom onset to definitive CNS tumor diagnosis through increased primary health care provider and community awareness and education. Finally, the Aarhus statement can provide significant guidance on the proper design and implementation for such an intervention.[11]

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