Predictors of Delayed Diagnosis of Pediatric CNS Tumors in the Emergency Department

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Objective: Central nervous system (CNS) tumor diagnoses are frequently delayed in children, which may lead to adverse outcomes and undue burdens on families. Examination of factors associated with delayed emergency department (ED) diagnosis could identify approaches to reduce delays.

Study Design: We performed a case-control study using data from 2014 to 2017 for 6 states. We included children aged 6 months to 17 years with a first diagnosis of CNS tumor in the ED. Cases had a delayed diagnosis, defined as 1 or more ED visits in the 140 days preceding tumor diagnosis (the mean prediagnostic symptomatic interval for pediatric CNS tumors in the United States). Controls had no such preceding visit.

Results: We included 2828 children (2139 controls, 76%; 689 cases, 24%). Among cases, 68% had 1 preceding ED visit, 21% had 2, and 11% had 3 or more. Significant predictors of delayed diagnosis included presence of a complex chronic condition (adjusted odds ratio [aOR], 9.73; 95% confidence interval [CI], 6.67–14.20), rural hospital location (aOR, 6.37; 95% CI, 1.80–22.54), nonteaching hospital status (aOR, 3.05, compared with teaching hospitals; 95% CI, 1.94–4.80), age younger than 5 years (aOR, 1.57; 95% CI, 1.16–2.12), public insurance (aOR, 1.49, compared with private; 95% CI, 1.16–1.92), and Black race (aOR, 1.42, compared with White; 95% CI, 1.01–1.98).

Conclusions: Delayed ED diagnosis of pediatric CNS tumors is common and frequently requires multiple ED encounters. Prevention of delays should focus on careful evaluation of young or chronically ill children, mitigating disparities for Black and publicly insured children, and improving pediatric readiness in rural and nonteaching EDs.

Key Words: delayed diagnosis, central nervous system tumors, brain tumors

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BACKGROUND

Failure to diagnose a child with a central nervous system (CNS) tumor in the emergency department (ED) is a missed opportunity for earlier intervention.[1] Early treatment may decrease morbidity for pediatric CNS tumors, which account for the highest burden of disease-related deaths among children in the United States.[1–4] Recurrent ED visits before diagnosis create additional financial and emotional burdens for families.[5] Despite this, delayed diagnosis frequently occurs.[4,6–11]

Importance

Little is known about the nature of US health care visits preceding a diagnosis of a pediatric CNS tumor.[6,8,9] Many patients have more than three health care encounters before diagnosis.[6–8,11] The prediagnostic symptomatic interval (PSI), or the period from onset of tumor-related symptoms until diagnosis, is the most commonly studied aspect of delayed diagnosis in pediatric CNS tumors.[6–9,11,12] Previous work has focused on patient- and tumor-related factors associated with prolonged PSI, but the ED setting itself and, in particular, factors that contribute to a delayed ED diagnosis are unclear. By examining ED factors associated with delayed diagnosis and characterizing ED visits preceding delayed diagnoses, we may be able to minimize future diagnostic delays for children with CNS tumors.

Goals of This Investigation

Our primary objective was to perform a population-based case-control study to identify both patient- and ED-level predictors of a delayed diagnosis of pediatric CNS tumor in the ED. Our secondary objectives included examining the prevalence of delayed ED diagnosis over time and characterizing ED visits preceding delayed diagnoses.

METHODS

Study Design and Data Sources

We performed a case-control study using the Healthcare Cost and Utilization Project (HCUP) State ED and Inpatient Databases from July 2014 to December 2017 for 6 states (IA, FL, MD, NE, NY, and WI).[13] These databases capture all statewide ED and inpatient visits and were ideal for this study because most pediatric patients with a new CNS tumor in the United States are either seen in the ED and/or admitted to the hospital. In addition, HCUP databases include general EDs, where most pediatric emergency visits occur in the United States.[14,15] These specific states were chosen because they include longitudinal identifiers that allow patients to be tracked across hospitals.

Selection of Participants

We included children aged 6 months through 17 years if their first diagnosis of CNS tumor was made in the ED, inclusive of transferring EDs. The CNS tumor diagnoses were identified using International Classification of Diseases (ICD)-9 and ICD-10 codes (Supplemental Table 1, http://links.lww.com/PEC/B90).

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We excluded patients who had a preceding CNS tumor diagnosis in a lookback period from January to June 2014. We also excluded children with any previous diagnosis of a malignancy or tumor predisposition syndrome (neurofibromatosis type 1 and 2, tuberous sclerosis, or Von-Hippel-Lindau; Supplemental Table 2, http://links.lww.com/PEC/B91).[6,8] Finally, we excluded those with a missing longitudinal identifier, which would preclude determining case-control status.

Outcomes

The main outcome was delayed diagnosis of a CNS tumor, defined as the presence of at least 1 ED visit in the 140 days before an ED diagnosis visit for CNS tumor. The period of 140 days was chosen based on the mean PSI for pediatric CNS tumors in the United States.[6] Varied estimates of PSI exist in international literature; we chose this time frame recognizing that PSI is influenced by the unique nature of health care in the United States. Case patients had 1 or more ED visits in the 140 days before their diagnosis. In these patients, the index ED visit was defined as the most recent ED visit preceding diagnosis. For control patients, the index ED visit was the diagnosis visit. Among case patients, we also determined the total number of preceding ED visits required before reaching a diagnosis as well as most common diagnoses at the index visit.

Predictors

Potential predictors of delayed diagnosis were selected based on previous evidence of their association with delay.[6–12,16–18] Patient-level predictors included age (<5 years, 5 to <10 years, 11+ years), sex (male, female), race (White, Black Hispanic, Asian/Pacific Islander, Native American, other), area deprivation index (ADI), insurance type (private, public, other), urban-rural patient home location (large metro, small metro, rural), presence of a complex chronic condition (CCC), tumor behavior, and tumor location. The ADI is a surrogate for socioeconomic status ascertained at the ZIP code level.[19] It assigns a percentile of disadvantage of a neighborhood based on income, education, employment, and housing quality. We assigned urban-rural status to patient home location using HCUP definitions of urban-rural counties, which is a simplified adaptation of the US Economic Research Service's Urban Influence Codes.[20] The CCC status was determined using diagnostic codes that identify pediatric patients with chronic illnesses that either involve several organ systems or 1 system severely enough to likely require hospitalization in a tertiary care center.[21] The updated classification system includes 12 categories (neurologic and neuromuscular, cardiovascular, respiratory, renal and urologic, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defect, malignancy, premature and neonatal, technology dependence, and transplantation) and encompasses 14,639 ICD-10 codes. Examples of common CCC subcategories include cerebral palsy, chronic renal failure, muscular dystrophy, heart and great vessel malformations, inflammatory bowel disease, cystic fibrosis, and patients with gastrostomy tubes or tracheostomies. Insurance type was determined by HCUP definitions and included private (commercial carriers including BlueCross, HMOs, PPOs), public (Medicare, Medicaid), and other (Worker's Compensation, CHAMPUS, CHAMPVA, Title V, other government programs).[22] Tumor behavior (benign, malignant, or unknown) and location (supratentorial, infratentorial, spinal, multiple locations, or unknown) were characterized using billing codes, and classifications were assigned a priori to the determination of case-control status (Supplemental Table 1, http://links.lww.com/PEC/B90). The final behavior was assigned as follows: both benign and malignant codes; unknown, malignant, and unspecified codes only; malignant, benign, and unspecified codes only; benign, only unspecified codes; or unknown.

The ED-level predictors included annual ED volume of children, urban-rural hospital location (metro, micro, rural), and teaching status. Annual pediatric ED volume categories of low (<1800), medium (1800–4999), medium-high (4999–9999), and high (>10,000) were defined using National Pediatric Readiness Project cutoffs.[23] Urban-rural hospital location was assigned using HCUP's urban-rural hospital designation, in which a hospital is determined to be urban or rural based on their residing county's Core Based Statistical Area (CBSA) classification.[24] Hospitals were considered a teaching hospital if they either (1) were a member of the Council of Teaching Hospitals or (2) were both affiliated with a medical school and had a ratio of residents to beds of 0.25 or higher.[22]

Analysis

We first evaluated whether delayed diagnosis rates have changed over time. We used a logistic regression model with case-control status as the outcome and time (categorized quarterly over the study period) as the independent variable, which yielded an odds ratio corresponding to the change in odds for a missed diagnosis for every 3-month period of the study. We used descriptive statistics to characterize cases and their index ED visit diagnoses.

We constructed logistic regression models to examine the association of patient-level and ED-level predictors with delayed diagnosis, defined by case-control status. First, we created a patient-level model to explore which patient characteristics were associated with a delay in diagnosis. This model included all potential patient-level predictors. We then created a full model incorporating both patient-level and ED-level predictors to evaluate the role of ED characteristics after adjusting for patient-level differences between hospitals.

We conducted a preplanned sensitivity analysis defining cases more strictly, using a 30-day instead of a 140-day lookback period. The goal of this sensitivity analysis was to evaluate how a patient's overall ED usage might impact being a case versus a control because high users would be more likely to have an unrelated ED encounter before their diagnosis, given a long enough window.

All models accounted for intrahospital correlation using clustered sandwich standard errors. Analyses were performed using StataSE 16 (StataCorp, College Station, Tex.) and R 4.1.0 (R Foundation, Vienna, Austria). Statistical significance was predefined at alpha = 0.05. The institutional review board deemed this study exempt from review.

RESULTS

Characteristics of Study Subjects and Case Analysis

A total of 2828 children (2139 controls, 76%; 689 cases, 24%) were included. Six hundred twenty-eight children were excluded for having either previous malignancy or a tumor predisposition syndrome, and 2061 children were excluded for lacking a longitudinal identifier. Case and control characteristics are shown in Table 1. The case rate did not significantly change over time (quarterly odds ratio, 1.01; 95% confidence interval [CI], 0.98–1.03). Among cases, 68% had 1 preceding ED visit, 21% had 2 visits, and 11% had 3 or more visits (Table 2). In descending order, the most frequent primary diagnoses rendered during index ED visits preceding a delayed diagnosis were: "epilepsy; convulsions", "headache; including migraine", "other nervous system disorders", "nausea and vomiting", and "other gastrointestinal

TABLE 1. Case and Control Characteristics (n = 2828)

	Controls (n = 2139)	Cases (n = 689)	*P*
Age (y)*			
0 to <5	537 (25.1%)	217 (31.5%)	0.003
5 to <10	751 (35.1%)	212 (30.8%)	
11+	851 (39.8%)	260 (37.7%)	
Sex*			
Female	996 (46.6%)	325 (47.7%)	0.78
Male	1143 (53.4%)	364 (52.8%)	
Race*			
White	1157 (56.8%)	347 (53.5%)	<0.001
Black	234 (11.5%)	124 (19.2%)	
Hispanic	276 (13.5%)	107 (16.6%)	
Asian/Pacific Islander	87 (4.3%)	19 (2.9%)	
Native American	9 (0.4%)	1 (0.2%)	
Other	275 (13.5%)	48 (7.4%)	
Missing	101	43	
Insurance*			
Private	1244 (58.2%)	298 (43.3%)	<0.001
Public	775 (36.2%)	349 (50.6%)	
Other	120 (5.6%)	42 (6.1%)	
ADI†			
Median [IQR]	36.6 [16.8–62.6]	50.6 [23.3–66.5]	<0.001
Missing	130	44	
CCC*	84 (4.0%)	180 (26.2%)	<0.001
Tumor behavior*			
Benign	387 (18.1%)	150 (21.8%)	0.003
Malignant	1338 (62.6%)	380 (55.2%)	
Unknown	414 (19.4%)	159 (23.1%)	
Tumor location*			
Supratentorial	674 (31.5%)	229 (33.2%)	0.11
Infratentorial	537 (25.1%)	145 (21.0%)	
Spinal	96 (4.5%)	38 (5.5%)	
Multiple locations	41 (1.9%)	20 (2.9%)	
Unknown Location	791 (37.0%)	257 (37.3%)	
Urban-rural status*			
Large metro	1360 (64.5%)	398 (57.8%)	0.004
Small metro	520 (24.6%)	211 (30.6%)	
Rural	230 (10.9%)	80 (11.6%)	
Missing	29	0	

*P value was derived from an χ^2 test comparing cases and controls.

†P value was derived from a Mann-Whitney test comparing cases and controls.

CCC, complex chronic condition; IQR, interquartile range.

disorders". Median ED revisit intervals ranged from 6 days for "epilepsy; convulsions" to 34 days for "other gastrointestinal disorders" (Table 3).

Main Results

Significant patient-level predictors of delayed diagnosis included age younger than 5 years (adjusted odds ratio [aOR], 1.57, compared with age 11+ years; 95% CI, 1.16–2.12), Black race (aOR, 1.42, compared with White race; 95% CI, 1.01–1.98), public insurance (aOR, 1.49, compared with private; 95% CI, 1.16–1.92), presence of a CCC (aOR, 9.73; 95% CI, 6.67–14.20). Patient sex, ADI, urban-rural home location, tumor behavior, and tumor location were not associated with delayed diagnosis (Table 4).

Significant ED-level predictors of delayed diagnosis included nonteaching hospital status (aOR, 3.05, compared with teaching hospitals; 95% CI, 1.94–4.80) and rural hospital location (aOR, 6.37, compared with metro hospital location; 95% CI, 1.80–22.54). Although medium (1800–4999) and medium-high (5000–9999) annual pediatric volume EDs predicted case status (aOR, 4.05; 95% CI, 2.04–8.02 and aOR, 3.29; 95% CI, 1.96–5.53, respectively) compared with high-volume EDs, low annual pediatric ED volume was not a significant predictor of delayed diagnosis (Table 4).

TABLE 2. Frequency of Preceding ED Visits Among Cases (N = 689)

Number of Preceding Visits in the 140 d Preceding Diagnosis	N (%)
1	468 (67.9%)
2	146 (21.2%)
3	46 (6.7%)
4	17 (2.5%)
5+	12 (1.8%)

Sensitivity Analysis

A sensitivity analysis using a 30-day cutoff for preceding ED visits for case patients found that CCC and nonteaching hospital status continued to be significant predictors of delayed diagnosis (2525 controls, 89%; 303 cases, 11%). Despite effect sizes that were similar to the main analysis, age younger than 5 years, Black race, public insurance, and rural hospital location were no longer significant predictors.

DISCUSSION

Among a large cohort of children with new CNS tumor diagnoses, one quarter had a delayed ED diagnosis. One third of children experiencing delay required 3 or more visits before their diagnosis. Children with CCCs had the highest risk of a delayed diagnosis. Rural and nonteaching EDs had the highest

TABLE 3. Most Frequent Primary Diagnoses Rendered During Index ED Visits Among Cases (N = 689)

Grouped Diagnosis Code	N (%)	Median (q1, q3) Revisit Interval (d)*
Epilepsy; convulsions	83 (11.5%)	34 (7, 73)
Headache; including migraine	63 (8.8%)	6 (1, 29)
Other nervous system disorders	62 (8.6%)	10 (1, 43)
Nausea and vomiting	35 (4.9%)	11 (2, 41)
Other gastrointestinal disorders	26 (3.6%)	21 (6, 69)

*Revisit interval was defined as the time between the index ED visit and the diagnosis ED visit.

TABLE 4. Predictors of Delayed Diagnosis (N = 2513)

	Patient Factors	Patient and ED Factors
	aOR (95% CI)	aOR (95% CI)
Age (y)		
0 to <5	1.37 (1.02–1.83)	1.57 (1.16–2.12)
5 to <10	1.08 (0.83–1.40)	1.15 (0.87–1.52)
11+	Ref	Ref
Sex		
Female	Ref	Ref
Male	1.03 (0.85–1.26)	1.08 (0.88–1.32)
Race*		
White	Ref	Ref
Black	1.42 (1.02–1.96)	1.42 (1.01–1.98)
Hispanic	1.19 (0.84–1.67)	1.23 (0.87–1.74)
Asian/Pacific Islander	0.92 (0.52–1.65)	1.10 (0.59–2.03)
Native American	0.36 (0.06–2.32)	0.22 (0.03–1.51)
Other	0.67 (0.42–1.04)	0.79 (0.51–1.22)
Insurance		
Private	Ref	Ref
Public	1.57 (1.23–1.99)	1.49 (1.16–1.92)
Other	1.90 (1.16–3.12)	1.60 (0.97–2.66)
ADI by 10*		
Median [IQR]	1.09 (1.02–1.16)	1.03 (0.97–1.09)
Patient location*		
Large metro	Ref	Ref
Small metro	1.12 (0.77–1.63)	0.86 (0.64–1.15)
Rural	1.02 (0.65–1.60)	0.48 (0.30–0.78)
CCC		
No CCC	Ref	Ref
CCC	7.89 (5.45–11.41)	9.73 (6.67–14.20)
Tumor behavior		
Benign	Ref	Ref
Malignant	1.04 (0.73–1.48)	1.05 (0.74–1.49)
Unknown	0.94 (0.66–1.34)	1.06 (0.73–1.53)
Tumor location		
Supratentorial	Ref	Ref
Infratentorial	0.86 (0.67–1.12)	0.79 (0.60–1.04)
Spinal	0.76 (0.40–1.43)	0.70 (0.36–1.37)
Multiple locations	1.00 (0.51–1.97)	1.07 (0.53–2.15)
Unknown location	0.92 (0.71–1.18)	0.80 (0.62–1.03)
ED annual pediatric volume		
Low (<1800)	—	0.52 (0.20–1.36)
Medium (1800–4999)	—	4.05 (2.04–8.02)
Medium-high (5000–9999)	—	3.29 (1.96–5.53)
High (>10,000)	—	Ref
Hospital location		
Rural	—	6.37 (1.80–22.54)
Micro	—	1.30 (0.47–3.60)
Metro	—	Ref
Teaching hospital		
Teaching	—	Ref
Nonteaching	—	3.05 (1.94–4.80)

*Patients were excluded from this model due to missing ZIP code and race data. See Table 1 for details.

CCC, complex chronic condition; IQR, interquartile range.

prevalence of delayed diagnosis. Taken together, our findings indicate that delayed diagnosis of CNS tumors in children is common, particularly among young and medically complex patients and in rural and nonteaching EDs.

The case rate did not significantly change over the 3-year study period. This result affirms previous evidence showing that the PSI for children with CNS tumors in the United States has not changed significantly over time.[6] This diagnosis may be delayed due to its nonspecific presenting symptoms, the inability of young children to express tumor-related symptoms, and clinician lack of familiarity with this rare disease. The most frequent diagnoses given to cases during index ED visits overlapped with common pediatric CNS tumor symptoms. This suggests that patients may have been experiencing tumor-related symptoms at the time of their index ED visit, but ultimately required 1 or more additional ED visits to reach a definitive diagnosis, supporting past studies that examined presenting symptoms of CNS tumors in children with delayed diagnoses.[6,7,25,26]

Several patient features were associated with delayed diagnosis: age younger than 5 years, Black race, public insurance, and the presence of a CCC. Our study reinforces that younger children are at higher risk for delayed diagnosis, which may be because they are not developmentally able to express key symptoms such as headache or nausea.[6,27] Our findings agree with previous evidence showing that Black children and those with public insurance are at higher risk for mortality from CNS tumors.[2,16,17] This could be due in part to their initial delay in diagnosis because previous work has shown that Black children may be impeded by timely access to subspecialists and diagnostic evaluations, placing them at risk for advanced disease at diagnosis.[28–30] Lastly, children with CCCs pose a particular challenge to clinicians because characterizing brain tumor symptoms such as vomiting or seizures is difficult in chronically ill patients who may already experience these symptoms due to an underlying condition.[27,31]

The ED features associated with delayed diagnosis included rural location and nonteaching hospital status. Rural and nonteaching hospitals may be associated with delay because they have lower pediatric readiness and face significant barriers to maintaining pediatric resources and implementing pediatric-specific policies.[23] Without appropriate infrastructure and clinician support, diagnosing rare pediatric diseases in these settings is difficult, particularly because these rare diseases occur extremely infrequently in a low-volume setting. It is not clear why EDs with medium and medium-high annual pediatric volumes were associated with delayed diagnosis, whereas EDs with low pediatric annual volumes were not. We may have lacked the power to detect a difference between low- and high-volume EDs. Another possibility is that these findings are in part due to community referral patterns. primary care physicians or caregivers may selectively refer to higher pediatric volume EDs, redirecting cases away from low-pediatric volume EDs. Lastly, low-pediatric volume EDs may lack the ability to provide definitive diagnosis via sedated imaging and pediatric specialty consultation; thus, they may be more likely to transfer patients to higher pediatric volume EDs before diagnosis.

Alongside previous work, our study suggests several ways to decrease ED delays in pediatric CNS tumor diagnoses. First, it reinforces that these patients experience recurrent ED visits before diagnosis in which they are diagnosed with benign pediatric illnesses. Previous evidence suggests that patients with CNS tumors have, on average, 3 health care encounters before their diagnosis.[6–8,11] This should prompt clinicians to consider the diagnosis of CNS tumor when evaluating seemingly benign, recurrent chief complaints, such as headache or vomiting. Evidence-based guidelines from HeadSmart, a campaign based in the United Kingdom that reduced the PSI of UK children with CNS tumors from

14.4 weeks to 6.7 weeks, offer specific recommendations regarding how to evaluate each potential CNS tumor-related symptom, including best practices for obtaining CNS imaging.[32] Second, it emphasizes the importance of thoroughly assessing preverbal children and those with CCCs because these are groups at highest risk for delayed diagnosis.[31] Guidelines from the American Academy of Pediatrics may help clinicians identify and evaluate new pain or irritability in pediatric patients with severe neurologic impairment, a population with significant overlap to patients with CCCs.[33] Third, it is important for ED clinicians to take active roles in addressing discriminatory systems that lead to disparate ED care for Black and publicly insured children. Guidelines for obtaining diagnostic CNS imaging in children and remote access to pediatric subspecialty consultation may help reduce these disparities.[29,30,34] Lastly, our findings challenge us to improve pediatric diagnosis in rural and nonteaching EDs. As the capability of most hospitals to provide definitive pediatric care wanes, diagnostic expertise may also decline, which may worsen delays in diagnosis for children with CNS tumors.[35,36]

Our study had several limitations. First, we used an administrative database, which uses diagnostic and procedural codes to identify diagnoses. We could not obtain tissue diagnoses, limiting our ability to provide tumor categorizations for behavior and location. We excluded a significant number of patients because they lacked the longitudinal identifier that allows tracking across EDs. Although this database does not include outpatient visits, the focus of our study was delayed diagnoses in the ED setting. Second, we were not able to definitively determine if preceding ED visits for cases were related to CNS tumor symptoms. Although it would be ideal to use the most common diagnoses rendered at preceding ED visits as predictors in our patient model, the provided diagnoses were not granular enough for this to be feasible. However, the overlap of diagnoses assigned at preceding ED visits with CNS tumor symptoms support our conclusion that case patients experienced delayed diagnosis.[25,26] Third, our 30-day sensitivity analysis resulted in a decreased number of cases; this reduced power likely led to the loss of significance of several predictors.

In summary, among 2828 children with new-onset CNS tumors, 24% experienced delayed ED diagnosis. One third of delays required 3 or more visits before diagnosis. Prevention of delays should focus on young or chronically ill children, as well as reducing ED care disparities for Black and publicly insured children. Improving pediatric readiness at rural and nonteaching EDs may decrease future delayed diagnoses of CNS tumors in children.

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