Received: 17 January 2022 | Revised: 10 May 2022 | Accepted: 31 May 2022

DOI: 10.1002/pbc.29850

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

Prospective registration of symptoms and times to diagnosis in children and adolescents with central nervous system tumors: A study of the Swedish Childhood Cancer Registry

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Abstract

Background: The elapsed time taken to diagnose tumors of the central nervous system in children and adolescents varies widely. The aim of the present study was to investigate such diagnostic time intervals at a national level in Sweden as they correlate with clinical features.

Methods: Data prospectively accumulated over a 4-year period in the Swedish Childhood Cancer Registry from patients aged 0–18 years were pooled, and diagnostic time intervals were analyzed considering tumor location, tumor type, patient age and sex, initial symptoms, and clinical timelines. All six pediatric oncology centers in Sweden contributed to collection of data. Time points for calculating the total diagnostic interval (TDI) defined as the time from symptom onset to diagnosis were reported in 257 of 319 patients (81%).

Abbreviations: CI, confidence interval; CNS, central nervous system; DI, diagnostic interval; PI, patient interval; TDI, total diagnostic interval; WHO, World Health Organization.

Results: The time from symptom onset to the first healthcare consultation, median 2.6 weeks, did not vary significantly between patients categorized according to tumor type or location. The median TDI was 8.3 weeks for the 4-year study period. Patients with optic pathway glioma (TDI 26.6 weeks), those with tumors of the spinal cord (TDI 25.9 weeks), and those with midline tumors (TDI 24.6 weeks) had the longest lead times. Additionally, older age, too few initial symptoms, and seeking initial redress outside an emergency ward were factors associated with a longer time to diagnosis.
Conclusion: This study identified several factors associated with delayed diagnosis of central nervous system tumors among Swedish children and adolescents. These novel data ought to help direct future efforts toward clinical improvement.

KEYWORDS
adolescent; central nervous system, child, diagnosis, tumors

1 | INTRODUCTION

Tumors of the central nervous system (CNS) are the second most common malignancies in childhood, surpassed only by leukemia.[1] Although long-term survival has improved to 75%–80% in high-income countries, a high proportion of survivors will still require long-term support from healthcare facilities and society at large.[2,3]

The time between symptomatic onset of the disease and its diagnosis has been found to vary widely in previous studies, and appears to be dependent on a variety of factors such as patient age as well as tumor type and location.[3,4] Moreover, the level of vigilance of healthcare professionals may also play a role. Notably, there have been efforts made to shorten the time to diagnosis; an example is the "HeadSmart" campaign in the United Kingdom,[5] which aims to increase awareness of symptoms associated with pediatric brain tumors among healthcare professionals as well as the public. The benefits of reducing the time to diagnosis include minimizing the time with debilitating symptoms, limiting secondary brain injury caused by the tumor, reducing late effects, and possibly increasing survival.

Population-based registries in the Nordic countries, which rely on universal and tax-funded healthcare systems and where all residents have personal identity numbers, constitute a unique resource for research aimed at improving public health.[6] In Sweden, children diagnosed with CNS tumors are listed in the National Swedish Childhood Cancer Registry, which has been used by previous investigators for their studies of demographic data and long-term effects in survivors.[7,8] To address a gap in knowledge regarding prediagnostic events, additional parameters have been added to the registry in recent years; these include initial tumor symptoms as well as time points during the patients' course of disease encompassing symptom onset, diagnosis, and the start of treatment. A better understanding of the potential reasons for delayed diagnoses is essential for devising interventions targeting different levels of the Swedish healthcare system.

The aims of the present study were to investigate the time intervals involved in the diagnostic and clinical course of events between onset of the disease and the time of the diagnosis, and how they are related with the presenting symptoms and clinical features such as type and location of the tumor, of children and adolescents with CNS tumors in Sweden.

2 | METHODS

2.1 | Data source and study subjects

Children and adolescents aged 0–18 years who were diagnosed with tumors of the CNS and treated at one of the six pediatric centers for oncology and neurosurgery in Sweden are documented in the Swedish Childhood Cancer Registry for CNS tumors, which is a component of the Swedish Childhood Cancer Registry. The database includes information on clinical characteristics, treatment, and (to a certain extent) outcomes. Following an initiative by the Swedish Childhood CNS Tumor Working Group, the registry began to incorporate data on the patients' symptoms at presentation as well as diagnostic time intervals in 2013. Time points indicating the intervals between clinical events were included in the registry, in line with the recommendations of the Aarhus statement.[9]

For the purpose of this study, anonymized data collected between January 1, 2013 and December 31, 2016 were retrieved from the registry. The information included tumor location, tumor type, presenting symptoms, facility of first consultation, and the patient's sex and age at diagnosis. The data also included information on the following time points: symptom onset, first presentation at a healthcare facility, referral for radiological investigation, referral to a neuro-oncology center, radiological diagnosis, histological or cytological confirmation, and start of treatment. Tumors were classified according to the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System[10] over the study period, using a combination of pathology reports and clinical information.

The first symptoms or signs noticed by the patients or caregivers were categorized according to Wilne et al.[11] Endocrine symptoms were defined as disturbances of puberty or growth, diabetes insipidus, or other endocrine symptoms. The date of first symptom was registered according to a standardized instruction defining how any approximate time-estimates should be reported. For example "a couple of days" equals 2 days, and "during spring" equals April 15. Clinical events were recorded with respect to the mode of first presentation at a healthcare facility (i.e., a primary care center, specialized outpatient clinic, regional hospital emergency room, or university hospital emergency room). Specific time intervals from symptom onset to treatment were calculated for all patients for whom data regarding two or more time points were available. The total diagnostic interval (TDI), defined as the time from symptom onset to radiological or pathological diagnosis; patient interval (PI), defined as the time from symptom onset to presentation to a healthcare facility; and diagnostic interval (DI), indicating the time from presentation to pathological or radiological diagnosis, were further analyzed for the following parameters: tumor location, tumor type, patient age, patient sex, initial symptoms, and clinical timelines. The study was approved by the Swedish Ethical Review Authority (No. 2020-06185) in accordance with the Declaration of Helsinki.

2.2 | Statistics

Descriptive analyses were performed to characterize the study population. The average annual age-specific incidence rate (source: Statistics Sweden) and 95% confidence interval (CI) were estimated and standardized to the 2012 European standard population. For time interval data, non-normal distribution was assumed and both mean and median are presented. For exploratory analyses, the chi-square or Fisher's exact test was applied for categorical data, while the Mann–Whitney *U*-test or Kruskal–Wallis test was used for ordinal or continuous data, as appropriate. All statistical tests were two-tailed, and the level of significance was set at a p-value $<.05$. Cumulative rate charts were constructed to demonstrate diagnostic time intervals. All statistical analyses were performed using the R software, version 3.6.1.

3 | RESULTS

3.1 | Patient characteristics

According to the registry, 319 individuals younger than 18 years with a diagnosis of a CNS tumor were treated at one of six pediatric neuro-oncology centers during the study period. The annual age-standardized incidence was 4.0 (CI: 3.6–4.5) per 100,000 individuals, and 59% ($n = 189$) were male. The mean age at diagnosis was 8.0 years (median 7.2 years). At the time of diagnosis, 8% ($n = 24$) were under 1 year of age, 51% ($n = 163$) were 1–9 years old, and 41% ($n = 132$) were 9–18 years old (Figure S1).

3.2 | Tumor classification and location

The distributions of the diagnosed tumors are shown in Table 1; low-grade astrocytic tumors comprised the largest group (25.4%, $n = 81$). The tumors had a supratentorial location in 50.8%, infratentorial in 42.6%, and spinal in 4.4% (Table 1). Multifocality was reported in 2.2% of the patients, and approximately one-third (36%) of the supratentorial tumors were located in the midline regions, including the visual pathways. Three quarters (74%) of the infratentorial tumors were located in the cerebellum or fourth ventricle and one-quarter in the brainstem. The tumor location was associated with age ($p = .044$) and type of tumor ($p < .001$); cerebral hemispheric tumors (57%) were most frequent in the 9–18-year age group, whereas midline (62%), cerebellar (64%), and brainstem (69%) tumors were most frequent in the age 0–9-year age group. Supratentorial location was most common in patients with high-grade astrocytoma (56.0%), whereas infratentorial locations were most common in those with embryonal tumors (72.5%), low-grade astrocytomas (56.7%), and ependymal tumors (55.0%).

3.3 | Initial symptoms

Data on initial symptoms were available for 262 patients (82%). Individuals for whom these data were not available did not differ significantly with respect to age at diagnosis, sex, tumor classification, or topography. A combination of two or more initial symptoms was reported in 161 of 262 patients (61%), whereas 101 patients reported one initial symptom. The most common initial symptoms reported were headache (36%, $n = 95$), which often occurred with other symptoms ($n = 78$), and nausea (36%, $n = 95$), followed by motor symptoms (26%, $n = 69$), and visual symptoms or signs (24%, $n = 62$). The natures of the initial symptoms varied according to tumor location (Figure 1); seizures were most common in patients with supratentorial hemispheric tumors, nausea and headache in those with infratentorial tumors, and visual and endocrine symptoms in those with midline tumors. Initial symptoms were reported for 12 of the 14 patients with spinal tumors; among them, back pain was the most common (58%, $n = 7$), followed by bladder and/or bowel dysfunction (42%, $n = 5$), and abnormal gait (42%, $n = 5$). Other reported initial symptoms in this subgroup were sensory disturbance (16%, $n = 2$), spinal deformity (8%, $n = 1$), coordination difficulties (8%, $n = 1$), weight loss (8%, $n = 1$), and headache (8%, $n = 1$).

3.4 | Clinical course of events

Data regarding the time and place of the first medical consultation were available for 260 patients (82%). The first assessment was made by a primary care physician in 32.3% of the subjects; furthermore, 17.7% were assessed by a specialized physician working in an outpatient practice (e.g., a pediatrician or ophthalmologist), 28.1% were assessed at the emergency ward of the local hospital, and 21.9% were assessed in the emergency ward of a university hospital.

TABLE 1 Distribution of childhood CNS tumors diagnosed in Sweden between 2013 and 2016

Tumor classification (WHO 2007) ($n = 319$)	Frequency (n)	Proportion (%)	CI[a]
Astrocytic tumors: low grade	81	25.4	20.7–30.5
Astrocytic tumors: high grade	25	7.8	5.2–11.4
Embryonal tumors	51	16.0	12.1–20.5
Ependymal tumors	20	6.3	3.9–9.5
Optic pathway gliomas	17	5.3	3.1–8.4
Other gliomas	37	11.6	8.3–15.6
Neuronal/mixed neuronal-glial tumors	13	4.1	2.2–6.9
Germ cell tumors	12	3.8	2.0–6.5
Craniopharyngiomas	12	3.8	2.0–6.5
Other, intracranial, and intraspinal[b]	51	16.0	12.1–20.5
Topography	**Frequency (n)**	**Proportion (%)**	**CI[a]**
Cerebral hemisphere	76	23.8	19.3–28.9
Midline	86	27.0	22.2–32.2
Cerebellum	100	31.3	26.3–36.8
Brainstem	36	11.3	8.0–15.3
Spinal cord	14	4.4	2.4–7.3
Multifocal	7	2.2	0.9–4.5

Abbreviations: CI, confidence interval; CNS, central nervous system; WHO, World Health Organization.
[a]95% CI calculated using Clopper–Pearson exact method.
[b]Includes choroid plexus tumors ($n = 3$), pituitary adenomas and carcinomas ($n = 4$), pineal parenchymal tumors ($n = 5$), meningiomas ($n = 9$), and other specified or unspecified intracranial and intraspinal neoplasms ($n = 30$).

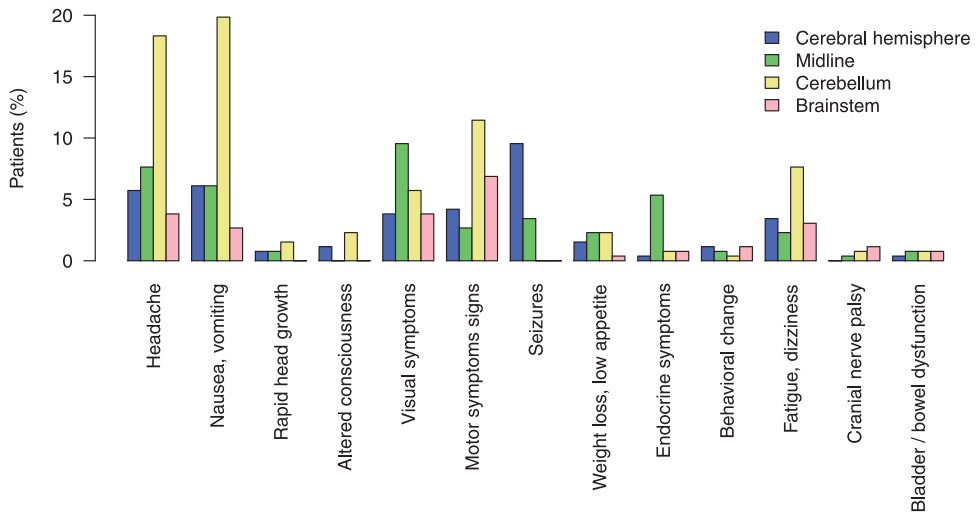

FIGURE 1 Symptoms at presentation categorized by tumor location

3.5 | Diagnostic intervals

Specific time intervals between symptom onset and the start of treatment are presented in Table 2. Sufficient time points for calculating the TDI were available for 257 patients (81%); those for whom these data were unavailable did not differ significantly with respect to age at diagnosis, sex, tumor classification, or topography. The median total interval from symptom onset to start of treatment was 9.9 weeks (mean 29.3 weeks), with a median TDI of 8.3 weeks (mean 26.5 weeks) and a median PI of 2.6 weeks (mean 10.0 weeks). The mean-over-median ratios, which were calculated as indicators of skewed distribution, were highest in the doctor and primary care intervals. The TDI did not differ significantly over the 4-year period comparing 4-month episodes ($p > .3$) (Figure S2).

TABLE 2 Time intervals (weeks)

Time intervals	Median	IQR	Mean	SD	Mean/median	*n*
Total time (symptom to start of treatment)	9.9	3.7–30.2	29.3	55.4	3.0	231
Total diagnostic interval (symptom to diagnosis[a])	8.3	2.7–25.3	26.5	57.0	3.2	257
Patient interval (symptom to presentation at a healthcare facility)	2.6	0.3–8.4	10.0	22.7	3.8	228
Diagnostic interval (presentation at a healthcare facility to diagnosis[a])	2.0	0.1–12.0	16.9	55.1	8.4	231
Treatment interval (diagnosis to start of treatment)	0.6	0.1–2.9	5.2	20.3	8.7	253
Doctor interval (presentation at a healthcare facility to referral[b])	0.9	0–7.7	14.6	55.0	16.2	224
System interval (referral[b] to treatment)	1.3	0.4–4.6	7.3	22.4	5.6	227
Primary care interval (presentation at a healthcare facility to referral to an oncology center)	1.7	0.1–12.0	18.3	57.4	10.8	227
Secondary care interval (referral to an oncology center to start of treatment)	0.9	0.3–2.9	3.9	16.6	4.3	231

Abbreviations: IQR, interquartile range; SD standard deviation.
[a]Pathology or radiology diagnosis.
[b]Referral for radiological investigation or to the pediatric oncology center.

The healthcare facility of first clinical consultation showed significant differences in TDI (15.9, 20.3, 5.2, and 3.0 weeks for primary care-level facilities, specialized outpatient practices, local hospitals, and university hospitals, respectively; $p < .001$) and in DI (7.1, 4.4, 1.0, and 0.1 weeks, respectively; $p < .001$), but not in PI (3.0, 3.3, 2.0, and 1.8 weeks, respectively; $p = .17$). The manner in which patients sought the first consultation was not independent of tumor location ($p = .0039$) and tumor type ($p = .00089$). A majority of patients with supratentorial (63%) and multifocal (57%) tumors had their first clinical consultation in an emergency ward, whereas patients with midline (including visual) (34%) and spinal (25%) tumors comprised a minority while those with infratentorial tumors (48%) were more evenly distributed. Moreover, 63% of children with embryonal tumors had their first clinical consultation at an emergency ward compared to 44% of those with low-grade astrocytic tumors.

There were significant differences in the intervals from symptom onset to the start of treatment between tumors of different locations (Figure 2A) and classifications (Figure 2B). The tumor location had a significant impact on TDI ($p = .0012$) and DI ($p = .012$) but not PI ($p > .3$) (Table 3). Tumors of the spinal cord had the longest TDI with a median of 25.9 weeks (DI: 13.9 weeks; PI: 2.1 weeks), followed by midline tumors at 24.6 weeks (DI: 6.3 weeks; PI: 2.7 weeks) and brainstem tumors at 6.7 weeks (DI: 1.4 weeks; PI: 3.9 weeks). Similarly, patients with different tumor subtypes showed varying TDIs ($p = .0045$) and DIs ($p = .047$), but not PIs ($p > .3$) (Table 3). Patients with optic pathway gliomas had the longest median TDI at 26.6 weeks (DI: 4.6 weeks; PI: 2.3 weeks), followed by patients with miscellaneous tumors at 17.4 weeks (DI: 6.1 weeks; PI: 4.2 weeks), and low-grade astrocytic tumors at 12.7 weeks (DI: 1.2 weeks; PI: 1.9 weeks).

Patients reporting headache with additional symptoms ($n = 78$) had a median TDI of 5.1 weeks, which was significantly shorter than those with only headache ($n = 17$), who had a median TDI of 17.6 weeks ($p = .028$), and was also shorter than those presenting with other symptoms ($n = 167$), who had a median TDI of 10.3 weeks ($p = .077$) (Figure 3A). The median DI and PI were 0.7 and 3.3 weeks, respectively, for patients with headache and additional symptoms; 0.9 and 2.9 weeks, respectively, for patients with only headache; and 4.0 and 2.1 weeks, respectively, for patients with other symptoms. The DI ($p < .001$) but not the PI ($p = .19$) showed significant differences according to symptoms.

The cumulative percentages of children diagnosed after symptom onset according to age and sex are presented in Figure 3B,C. The median TDIs were 2.4 weeks in the 0–1-year age group, 8.3 weeks in the 1–9-year age group, and 11.0 weeks in the 9–18-year age group ($p = .0057$). There were no significant differences between the sexes in terms of TDI, DI, or PI; the median TDIs for boys and girls were 8.9 and 6.3 weeks, respectively; the median DIs were 2.3 and 1.8 weeks, respectively; and the median PIs were 2.6 and 2.6 weeks, respectively (all $p > .3$).

4 | DISCUSSION

This study produced novel data on lead times involved in the process of diagnosing pediatric patients with CNS tumors in Sweden. The implementation of new parameters regarding diagnostic time intervals in the national quality registry made it possible to analyze and continuously follow these timelines at national or regional levels, thereby allowing for clinical improvement efforts.

The initial symptoms reported by patients and caregivers in this study varied based on tumor location, with headache and nausea being the most common. The variability of the presenting symptoms and of

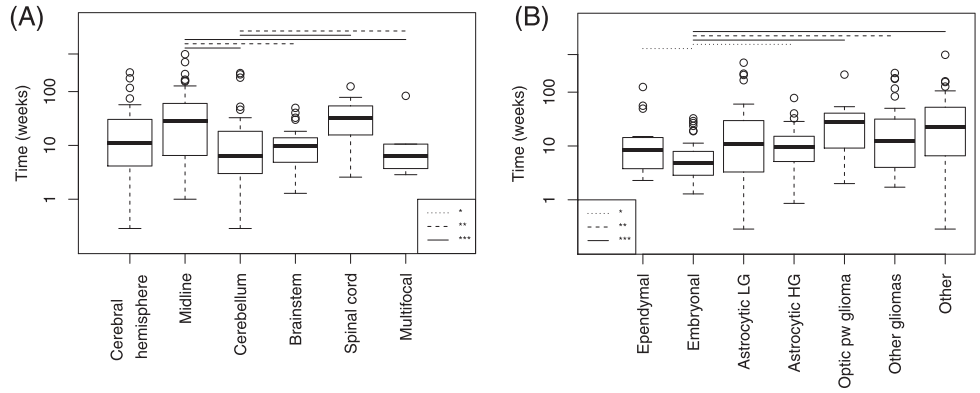

FIGURE 2 Boxplots showing the total times from symptom onset to the initiation of cancer treatment according to tumor locations and types. Lines between groups indicate significant differences according to post hoc exact Kruskal–Wallis tests using the Nemenyi–Wolfe–Damico–Dunn procedure with joint ranks. HG, high grade; LG, low grade; pw, pathway

TABLE 3 Time intervals (weeks) in various patient subgroups ($n > 10$)

Tumor classification (WHO 2007)	Md TDI (IQR, *n*)	Md DI (IQR, *n*)	Md PI (IQR, *n*)
Optic pathway glioma	26.6 (1.6–51.6, 13)	4.6 (0.1–28.3, 13)	2.3 (0–8.7, 13)
Other intracranial and intraspinal	17.4 (4.1–47.4, 67)	6.1 (0.1–18.7, 63)	4.2 (0.1–17.7, 62)
Astrocytic tumors: low grade	12.7 (2.9–25.8, 66)	1.2 (0.1–13.9, 56)	1.9 (0.3–7.0, 54)
Ependymal tumors	8.7 (2.8–11.5, 16)	0.9 (0.1–6.4, 15)	3.0 (0.9–11.1, 15)
Astrocytic tumors: high grade	5.5 (2.6–12.0, 18)	1.4 (0.2–10.9, 18)	2.0 (0.7–3.1, 18)
Other gliomas	5.4 (2.6–13.5, 34)	2.1 (0.9–7.5, 28)	2.6 (0.8–4.3, 28)
Embryonal tumors	3.6 (2.2–8.0, 43)	0.7 (0.1–2.6, 38)	2.1 (0.7–5.3, 38)
Topography	**Md TDI (IQR, *n*)**	**Md DI (IQR, *n*)**	**Md PI (IQR, *n*)**
Spinal cord	25.9 (2.9–53.1, 12)	13.9 (2.5–24.7, 11)	2.1 (1.3–27.8, 11)
Midline	24.6 (4.4–53.4, 65)	6.3 (0.6–25.3, 65)	2.7 (0–10.6, 63)
Cerebral hemisphere	5.4 (1.9–20.5, 60)	1.0 (0.1–9.6, 53)	2.0 (0.1–5.9, 53)
Cerebellum	6.1 (2.8–17.9, 84)	0.9 (0.1–4.4, 71)	2.8 (0.8–8.3, 70)
Brainstem	6.7 (2.1–17.3, 30)	1.4 (0.1–6.1, 27)	3.9 (1.1–7.9, 27)
Multifocal	5.1 (3.6–7.1, 6)	3.9 (3.4–4.9, 4)	1.3 (0–3.1, 4)
Age	**Md TDI (IQR, *n*)**	**Md DI (IQR, *n*)**	**Md PI (IQR, *n*)**
0–1 year	2.4 (0.6–4.9, 15)	0.9 (0.1–3.5, 15)	0.0 (0.0–1.9, 15)
1–9 years	8.3 (2.7–21.1, 135)	1.9 (0.1–12.0, 123)	2.6 (0.4–7.9, 121)
9–18 years	11.0 (3.0–34.1, 107)	2.7 (0.1–15.6, 93)	2.4 (1.0–11.5, 92)

Abbreviations: IQR, interquartile range; Md DI, median diagnostic interval (presentation at a healthcare facility to diagnosis); Md PI, median patient interval (symptom onset to presentation at a healthcare facility); Md TDI, median total diagnostic interval (symptom to diagnosis); WHO, World Health Organization.

the often-nonspecific signs and symptoms that precede diagnosis rendered early detection challenging, although having a combination of different symptoms was associated with shorter diagnostic time intervals. Consistent with our study, a Danish study of 55 children and adolescents found that headache and vomiting were the two most common symptoms at diagnosis, occurring in 50% of the patients. A shorter pre-DI (4.3 weeks) was associated with vomiting, whereas headache and ataxia were both associated with pre-DIs of 10.7 weeks.[12] Our study indicates that physicians are more likely to associate headache combined with nausea or other symptoms with a mass effect and increased intracranial pressure. For earlier diagnosis, attention should also be paid to other signs and symptoms such as visual and endocrine irregularities, which are common in patients with midline tumors, motor symptoms, seizures, and lethargy. In children with back pain, it is important to consider an uncommon etiology such as a spinal tumor. Spinal tumors account for a disproportionate degree of morbidity and disability in children with cancer, and neurological deficits are often only at best partially reversible.[13,14]

We also found significant differences in TDI and DI, but not PI, according to the healthcare facility of initial clinical consultation. Half

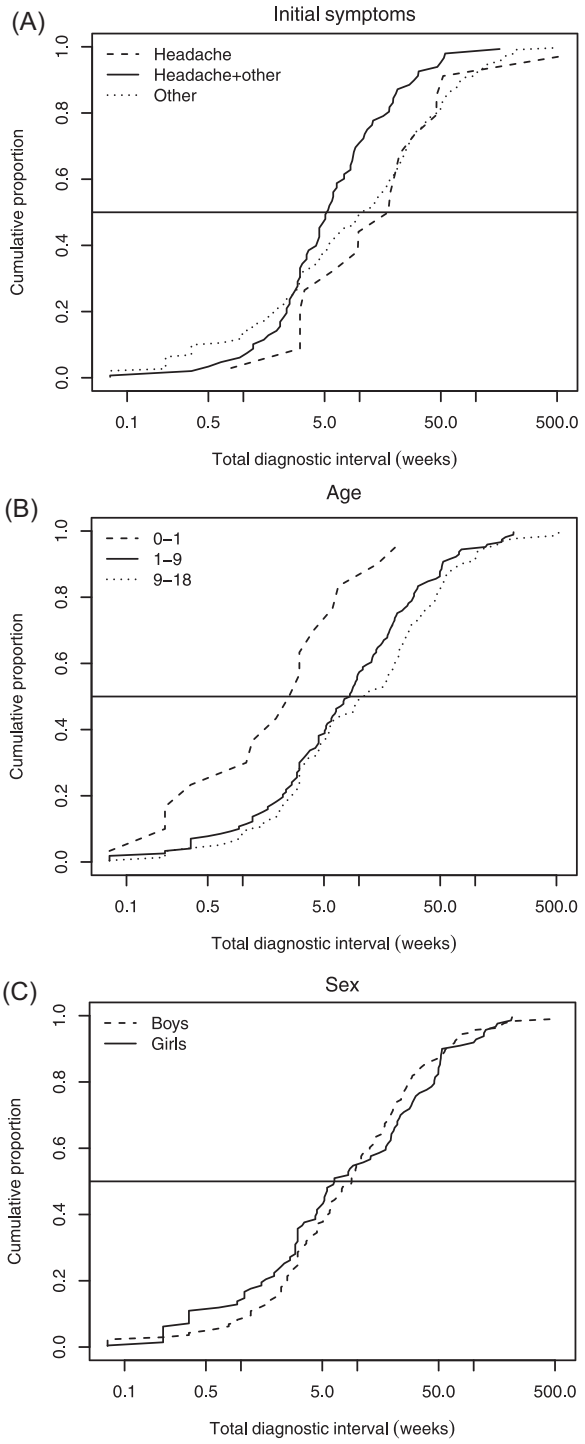

FIGURE 3 Cumulative total diagnostic interval (TDI) proportions in children and adolescents. (A) Initial symptoms were headache ($n = 17$) with a median TDI of 17.6 weeks, headache and associated symptoms ($n = 78$) with a median TDI of 5.1 weeks, and other ($n = 167$) with a median TDI of 10.3 weeks ($p = .028$). (B) The median TDIs were 2.5 weeks for patients aged <1 year ($n = 15$), 8.4 weeks for those aged 1–9 years ($n = 135$), and 11.1 weeks for those aged 9–18 years ($n = 107$) ($p = .0057$). (C) The median TDIs for boys ($n = 152$) and girls ($n = 105$) were 8.9 and 6.3 weeks, respectively ($p > .3$)

of the patients reported having the first assessment at an emergency ward, resulting in a shorter time to diagnosis. Although the manner in which patients sought the first consultation was dependent on tumor location and classification (likely indicating different symptom burdens), it is nevertheless reasonable to postulate that differences in preparedness and experience in interpreting symptoms, along with rapid access to neurological imaging, could also influence the diagnostic time intervals. The availability of equipment such as MRI scanners is a factor that varies between different regions in Sweden. There may thus be clinically unacceptable, long waiting times, especially for MRI of children in general anesthesia.[15]

The median and mean TDIs for the cohort were 8.3 and 26.5 weeks, respectively, and did not differ significantly over the 4-year period. This could be compared to a TDI of 9.1 weeks (mean 25.2 weeks) in the United Kingdom prior to the launch of an awareness campaign versus 6.7 weeks (mean 21.3 weeks) afterwards.[5] Reports from other countries in recent decades have found TDIs to be in the range of 2.9–32.9 weeks, with the shortest reported in Japan and the longest in the eastern provinces of Canada.[5,12,16–22] Regarding the situation in less developed countries, there are few and limited reports describing challenges in access to diagnostic facilities and neuro-oncological expertise.[23,24] In our current study, we found that younger age was associated with shorter TDIs, whereas sex was not. The same tendency has been found in other studies,[19–22,25] and is probably in part owing to distinct tumor characteristics in individuals of different ages. However, it may also point to a greater parental surveillance of small children than of teenagers, especially as the latter may be more reluctant to communicate diffuse symptoms themselves.

The doctor and primary care intervals showed the highest mean-over-median ratios, indicating their skewed distributions and establishing the possibility of shortening the diagnostic time in such outliers. Embryonal tumors, all of which are considered to be high grade in terms of malignant potential (WHO grade IV), had the shortest median TDI; conversely, optic pathway gliomas (the miscellaneous group) and low-grade astrocytic tumors had the longest TDIs. This suggests that a more rapid progression of symptoms in high-grade tumors may contribute to an earlier diagnosis. It is an important learning point that as much as one-third of the pediatric CNS tumors in our study were low-grade tumors, for which symptoms may wax and wane and be less distinct, with seemingly a substantial risk for a prolonged time to diagnosis, progressive disease, and thus risk of increased morbidity.[26–28] Regarding topography, midline and spinal tumors stood out as having the longest TDIs as well as the most skewed distributions, with the PIs shorter than the DIs. Our findings are consistent with a recent retrospective HeadSmart analysis in the United Kingdom, where patients of advanced age and those with central tumors experienced the longest diagnostic time intervals.[25]

Given that patients in our study with different tumor subtypes and locations showed varying TDIs and DIs, but not PIs, awareness campaigns ought to focus on healthcare professionals rather than the public. This is also supported by the findings from others that families tend to seek medical attention relatively early after symptom onset and often several times before correct diagnosis is made[16,19,29,30]

However, previous studies have indicated that socioeconomic factors may be related to cancer survival in Sweden; despite healthcare being state-funded and free for children, those born to parents with lower education experienced poorer survival than did those born to counterparts with higher education.[31] Awareness of where, how, and when to seek healthcare, how to navigate through the healthcare system, and being better able to understand and follow treatment protocols may be important factors in this respect.

The patients' ages at diagnosis were evenly distributed in the registry, with a slight frequency dip in the pre-adolescent age group. The annual age-standardized incidence over the study period was 4.0 (CI: 3.6–4.5) per 100,000 persons, with the majority being boys (59%); these findings were similar to those of other national and international studies.[7,8,32] However, this incidence rate may be slightly underestimated in our study, given that the coverage rate of the registry during the study period was approximately 90% when compared to the National Swedish Cancer Registry maintained by the National Board of Health and Welfare. We found that low-grade gliomas comprised the largest proportion of CNS tumors, followed by embryonal tumors; this was also consistent with previous pediatric cancer studies.[8,28] The location of the tumors was associated with age ($p = .002$) and diagnosis ($p < .001$), reflecting the fact that pediatric brain tumors are a heterogeneous group of diseases in which the incidences of various subtypes typically vary with age. Overall, our demographic findings were consistent with those of previous studies.

Using prospectively collected population-based data from the Swedish Childhood Cancer Registry for CNS tumors, which has a high coverage rate, is a major strength of this study. However, reflecting the fact that patient timelines to cancer diagnosis are rarely linear, a limitation of the study was that time-related data were not available for all patients and at all measurement points. Another limitation was that the time of onset of symptoms reported by patients or guardians was a subjective measure.

In terms of implications for the future, the present study identified several factors associated with prolonged diagnostic times. This information can be used to direct interventions, promote awareness campaigns targeting healthcare professionals in different specialties and levels of the healthcare system, and devise clinical guidelines that are then made readily available. Furthermore, the newly incorporated parameters within the quality register will make it possible to monitor changes in diagnostic time intervals at the regional and national levels, thereby aiding clinical improvement efforts. Future studies focusing on socioeconomic factors and diagnostic delays are warranted.

In conclusion, our study produced novel data regarding the diagnostic timeline intervals of pediatric patients with CNS tumors in Sweden. Children and adolescents with CNS tumors presented with diverse symptoms at various healthcare system facilities. Moreover, patients with different tumor subtypes and locations showed varying TDIs and DIs, but not PIs, suggesting possible avenues for improving relevant health services. The doctor and primary care intervals showed the highest mean-over-median ratios, indicating a skewed distribution and underscoring the potential for shortening the diagnostic time in outliers with prolonged intervals. The present study identified several factors associated with prolonged diagnostic time, such as having optic pathway gliomas, having spinal cord or midline tumors, being of adolescent age, experiencing isolated headaches as the initial symptom, and seeking initial redress outside an emergency ward. Initiatives for increased awareness among primary healthcare providers as well as among select specialized outpatient clinics, combined with effective referral systems, should now be prioritized in Sweden.

ACKNOWLEDGMENTS

The authors are very thankful to the staff of the registry and all collaborators from the treatment centers for continuously processing the data and ensuring the quality of the registry. The work of the registry was supported by a grant from the Swedish Childhood Cancer Foundation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rask O, Nilsson F, Lähteenmäki P, et al. Prospective registration of symptoms and times to diagnosis in children and adolescents with central nervous system tumors: A study of the Swedish Childhood Cancer Registry. *Pediatr Blood Cancer*. 2022;e29850. https://doi.org/10.1002/pbc.29850