Initial symptoms and diagnostic delay in children with brain tumors at a single institution in Japan

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Abstract

Background. A prolonged interval between onset of symptoms and diagnosis of childhood brain tumor is associated with worse neurological outcomes. The objectives of this study are to determine factors contributing to diagnostic delay and to find an interventional focus for further reduction in the interval between symptom onset and diagnosis in Japan.

Methods. We retrospectively analyzed 154 patients younger than 18 years with newly diagnosed brain tumors who visited our institution from January 2002 to March 2013.

Results. The median age at diagnosis was 6.2 years and the median total diagnostic interval (TDI) was 30 days. Patients with low-grade tumors and cerebral midline tumor location had significantly long TDI. Durations between the first medical consultation and diagnosis (diagnostic interval, DI) were exceedingly longer for patients with visual, hearing, or smelling abnormalities as the first symptom (median, 303 days). TDI and DI of patients who visited ophthalmologists or otolaryngologist for the first medical consultation were significantly longer. Among these patients, longer DI was associated with worse visual outcome.

Conclusion. Raising awareness of brain tumor diagnosis among ophthalmologists and otolaryngologists may reduce diagnostic delay and may improve the neurological impairment of children with brain tumors in Japan.

Keywords

brain tumor | children | initial symptom | diagnostic delay | visual, hearing, and smelling abnormalities

Brain tumors are the most common solid tumor during childhood, with a reported annual incidence of 18 cases per million in Japan.^{1,2} They account for a large portion of cancer deaths in children,³ and the majority of survivors of childhood brain tumors suffer from neurological sequelae.^{4,5} A prolonged interval between the onset of symptoms and diagnosis of brain tumor does not affect the survival of brain tumor patients⁶; however, it is associated with worse neurological outcomes.^{7,8} Several risk factors contributing to

delay in diagnosis of childhood brain tumors were previously reported,^{6,9–12} namely, age at diagnosis, low-grade tumor, and tumor location.

On the other hand, in the “HeadSmart: Be Brain Tumour Aware” campaign, information about childhood brain tumors was distributed to health care professionals and to the public in the United Kingdom; it succeeded in raising awareness of childhood brain tumors and in reducing the interval from symptom onset to diagnosis.¹³ There is a difference between

Japanese and the UK medical systems: Whereas patients can see medical specialists according to their initial symptoms on the first visit in Japan, patients usually see their general practitioners regardless of initial symptoms in the United Kingdom. We hypothesized that this difference might cause the different reasons of diagnostic delay and require a different strategy to reduce the interval from symptom onset to diagnosis. The objectives of this study are to determine the factors contributing to diagnostic delay and to find an interventional focus for further reduction in the interval between symptom onset and diagnosis in Japan.

Methods

We retrospectively analyzed patients younger than 18 years with newly diagnosed brain tumors who visited the National Center for Child Health and Development, Tokyo, Japan, from January 2002 to March 2013. The following information was obtained from the hospital medical record: age at diagnosis, sex, underlying tumor predisposition syndrome (TPS), the first symptom, subsequent symptoms, pathological diagnoses, location of tumors, the onset date of the first symptom and subsequent symptoms, the time and the department of first medical consultation, the time of diagnosis by MRI or CT, and residual sequelae at last follow-up. Total diagnostic interval (TDI) was defined as the duration between the onset of the first symptom and the time of imaging diagnosis. TDI was divided into "patient interval (PI)," a duration between the onset of the first symptom and the initial presentation to health care, and "diagnostic interval (DI)," the duration between the initial presentation to health care and the time of imaging diagnosis, in accordance with the Aarhus statement.¹⁴ Patients with asymptomatic tumors found incidentally or by surveillance for TPS, and patients with insufficient data including being diagnosed without a pathological record, were excluded. Exceptionally, patients with diffuse intrinsic pontine glioma, tectal glioma, and optic glioma, who were usually diagnosed without biopsy, were included.

Symptoms were divided into the following 9 categories: 1, headache; 2, nausea or vomiting; 3, seizures or disturbance of consciousness; 4, focal weakness; 5, unsteadiness; 6, endocrine disorders; 7, behavior or learning difficulties; 8, visual, hearing, or smelling abnormalities; and 9, increase in head circumference.

Tumor grade was categorized as high or low grade. High grade includes high-grade glioma, pontine glioma, embryonal tumor, ependymoma, and germ cell tumor. Low grade includes low-grade glioma, craniopharyngioma, and other benign tumors.

The department of the first medical consultation was categorized as pediatrician, ophthalmologist, otolaryngologist, internist, neurosurgeon, and others.

The Mann-Whitney *U* test was used for 2-subgroup analysis, the Kruskal-Wallis test with Bonferroni correction for more than 2 subgroups analysis, and the log-rank test for overall survival and time to event analysis. All statistical analyses were conducted by EZR software,¹⁵ and *P* less than .05 was considered statistically significant for all

analyses. This study was approved by the institutional review board.

Results

Patients and Tumor Characteristics

A total of 201 patients with a brain tumor were identified from the institutional oncology registry, and 47 patients were excluded. A total of 154 patients were included for the analysis (Figure 1). There were 4 patients diagnosed with TPS preceding the diagnosis of brain tumor: 2 with neurofibromatosis type 1 and 2 with tuberous sclerosis. The median age at diagnosis was 6.7 years (range, 0 months to 16.1 years). The male-to-female ratio was 1:0.73. Tumor locations were cerebral hemisphere in 47 (30%), cerebral midline in 45 (29%), posterior fossa in 41 (27%), and brainstem in 21 (14%). Pathological diagnoses were available for 142 patients (92%). Nine diffuse intrinsic pontine glioma, 2 tectal glioma, and 1 optic glioma were diagnosed from typical symptoms and imaging findings of each disease without tumor biopsy. More than 70% of patients presented to a pediatrician. The characteristics of patients are summarized in Table 1. The vast majority of patients lived in Tokyo (53%) and neighboring prefectures (41%).

Symptoms

The most frequent first symptom category was headache (21%), followed by seizures (18%), nausea or vomiting (18%), focal weakness (12%), unsteadiness (8%), visual, hearing, or smelling abnormalities (8%), and endocrine disorders (6%). Behavior or learning difficulties and increase in head circumference occurred as the primary symptoms in approximately 5%. Sixty patients (39%) had only one symptom, whereas 94 patients (61%) developed additional symptoms. Nausea or vomiting was the most common additional symptom and the most common symptom at diagnosis. A total of 62 patients (40%) had nausea or vomiting at diagnosis, followed by headache (30%) and unsteadiness (23%) (Figure 2). The primary tumor sites for each symptom are described in Figure 3.

Figure 1. Flowchart of All Patients. TPS, tumor disposition syndrome.

Table 1. Patient Characteristics

		n	%
All patients		154	
Sex	Male	89	57.8
	Female	65	42.2
Tumor predisposition syndrome	Neurofibromatosis type 1	2	
	Tuberous sclerosis	2	
Median age at diagnosis, y (range)	6.7 (0-16.1)		
Tumor location	Cerebral hemisphere	47	30.5
	Right/left side	19/21	
	Bilateral	7	
	Cerebral midline	45	29.2
	Posterior fossa	41	26.6
	Brainstem	21	13.6
Histological or clinical diagnosis	High-grade glioma	12	7.8
	Low-grade glioma	44	28.6
	Diffuse intrinsic pontine glioma	16	10.4
	Embryonal tumor	28	18.2
	Ependymoma	10	6.5
	Germ cell tumor	20	13.0
	Craniopharyngioma	11	7.1
	Others	13	8.4
No. of symptoms at diagnosis	1	60	39.0
	2 or more	94	60.0
Department of first consultation	Pediatrician	110	71.4
	Ophthalmologist	14	9.1
	Otolaryngologist	7	4.5
	Internist	13	8.4
	Neurosurgeon	5	3.3
	Others	5	3.3

Total Diagnostic Interval, Patient Interval, and Diagnostic Interval

TDI ranged from 0 to 2280 days with a median value of 30.5 days (interquartile range [IQR], 8-88.5 days). The median PI was 16 days (range, 0-1413 days; IQR, 3-48 days) and the median DI was 4 days (range, 0-2083 days; IQR, 0-22 days). Low-grade tumors for long TDI and cerebral midline tumor location for long DI were significant risk factors. Other tumor characteristics were not associated with TDI, PI, or DI (Table 2).

Associations between the first symptom categories and TDI, PI, or DI are shown in Figure 4. Median TDI was particularly short for seizures (7 days) and nausea or vomiting (18 days). Median TDI was particularly long for endocrine disorders (114 days) and visual, hearing, or smelling abnormalities (347 days). These box plot charts show that PI seems to be long for endocrine disorders (median, 53 days)

and DI seems to be exceedingly long for visual, hearing, and smelling abnormalities (median, 303 days). Time-to-event analyses comparing intervals of patients with specific first symptoms and without them revealed that these difference were statistically significant: short TDI and PI for patients with seizure ($P = .018$, 0.041), short TDI and PI for patients with nausea or vomiting ($P = .025$, 0.01), long TDI and PI for patients with endocrine disorders ($P = .019$, 0.003), and long TDI and DI for patients with visual, hearing, and smelling abnormalities ($P < .001$, $< .001$). Associations between the department of the first medical consultation and TDI, PI, or DI are shown in Figure 5. PI was not associated with department, whereas patients who visited ophthalmologists had significantly longer TDI and DI and patients who visited otolaryngologists for the first consultation had significantly longer DI than patients visiting pediatricians.

Patients With Visual, Hearing, or Smelling Abnormalities

Twelve patients with visual, hearing, or smelling abnormalities as the first symptom were included in this study. These patients had a significantly longer DI, as described earlier. The primary symptoms were low vision in 5, nystagmus in 3, difficulties in hearing in 2, photophobia in 1, and olfactory illusion in 1. These patients consisted of 6 with low-grade glioma, 2 with craniopharyngioma, and 1 each with meningioma, immature teratoma, glioblastoma multiforme, and hamartoma. Seven out of 9 patients with visual abnormalities presented to the department of ophthalmology and 4 of them were followed up without imaging studies for more than half a year. All 4 patients suffered from persistent visual impairment. On the other hand, 4 out of 5 patients with a TDI of less than 6 months had no visual impairment. Similarly, the 2 patients with hearing abnormalities were followed up without imaging studies for more than half a year at otolaryngology clinics.

Follow-Up Duration and Overall Survival

The median follow-up duration was 95 months (range, 47 days to 210 months). Of 154 patients, 36 patients died. One patient with pilomyxoid astrocytoma died of influenza encephalopathy, one with a primitive neuroectodermal tumor died of sclerosing mesenteritis 12 years after the end of brain tumor treatment, and all the other patients died of the primary brain tumor. The 5-year overall survival rate was 77.6% (CI, 69.9%-83.5%). Patients with a more than 30-day TDI had better overall survival than those with a TDI of less than 30 days—86.4% and 69.2%, respectively ($P = .016$). Patients with a high-grade tumor or with a tumor located at the brainstem had a significantly worse 5-year overall survival ($P < .001$).

Discussion

We retrospectively analyzed factors contributing to diagnostic delay in pediatric patients with brain tumors,

Figure 2. Frequency of Symptoms in 154 Patients With Brain Tumors.

focusing on the relationship between the first symptom and diagnostic intervals. We evaluated the association between the first symptom and PI or DI. This study revealed that patients with visual, hearing, or smelling abnormalities as the first symptom had an exceedingly longer DI; most of them were followed by specialists other than pediatricians, indicating the possibility for intervention.

Twenty-eight out of 201 patients were excluded from our analysis for asymptomatic tumors. That was consistent with the Brain Tumor Registry of Japan, in which brain tumors with no clinical symptoms account for 11% of all brain tumors. We expected that more tumors associated with TPS would be diagnosed by surveillance as previous reports of single-institution surveys^{16,17}; however, only 4 tumors were diagnosed by surveillance in this study. It may reflect the lower surveillance rate in our population.

The median age at diagnosis in our study was similar to those in Brain Tumor Registry of Japan¹⁸ and similar studies in Japan¹² and other Western countries.^{6,11,17,19,20} The proportion of tumor types and locations were similar to the Brain Tumor Registry of Japan, including the higher frequency of germ cell tumor.

Headache was the most frequent primary symptom, as previously reported.^{11,12,17,20} The second most frequent symptom was seizures, which was less frequent in the previous reports. It is hypothesized that more patients with seizures might be referred to our institution because of our active emergency and neurology departments. Regarding symptoms at diagnosis, nausea or vomiting and headache were the first and the second most frequent symptoms, respectively, similar to previous reports. In this report, the

number of patients with visual difficulties was smaller than in previous reports. The reason might be that patients with eye movement disorders resulting from oculomotor nerve disorders, such as diplopia or strabismus (5 as the first symptom, 6 as an additional symptom), were classified into the focal weakness category in this study.

In previous studies, the following parameters were associated with longer TDI: older age at diagnosis,^{6,10,11} supratentorial tumor location,⁵ and low-grade tumor.^{10–12} In our study, low-grade tumors and cerebral midline tumors also correlated with longer TDI, but age was not statistically different. This discrepancy could simply be due to the smaller number of patients included in the present study.

We analyzed the association between multiple time intervals and first symptom categories. Patients with seizure and nausea or vomiting as the first symptom had short TDI and PI. Short PI might lead short TDI in these symptom categories. On the other hand, patients with endocrine disorders and visual, hearing, or smelling abnormalities as the first symptom had significantly long TDI along with long PI or long DI. These results might explain the longer TDI of cerebral midline tumor, which often presents with such symptoms.

The relationship between TDI and the first symptom has been discussed in only one report; furthermore, the relationship between PI or DI and the first symptom has apparently not been reported. Wilne et al reported that median TDI was shorter for headache than for growth or endocrine problems and seizures, whereas visual difficulties were not a risk factor for diagnostic delay.¹¹ In their report, patients with hearing or smelling abnormalities were not included. They included patients with eye movement disorders, such as diplopia or strabismus, as

Figure 3. Distribution of Tumor Sites for Each Primary Symptom.

Table 2. Comparisons of Total Diagnostic Interval, Patient Interval, and Diagnostic Interval According to Tumor Group

		n	Median TDI, d	P	Median PI, d	P	Median DI, d	P
Age at diagnosis, y	≤ 6	72	25.5		11.5		2	
	> 6	82	41.5	.067	17	.287	4.5	.093
Location	Cerebral hemisphere	45	30		14		3	
	Cerebral midline	45	38		25		9	
	Posterior fossa	41	30		14		5	
	Brainstem	21	20	.13	7	.63	0	.023
Tumor grade	High	84	23		12		3	
	Low	70	53	.016	28	.088	5	.37
Hydrocephalus	Present	62	23.5		11.5		3	
	Absent	92	40.5	.068	18.5	.35	5	.15
No. of symptoms	Single	60	35		16		3	
	Multiple	94	30	.604	16	.93	4	.58
Laterality of hemisphere	Right side	19	45		14		1	
	Left side	21	15	.49	10	.45	5	.36
Residual sequelae	Absent	30	44		26		1	
	Present	81	36	.698	14	.477	8	.084

Abbreviations: DI, diagnostic interval; PI, patient interval; TDI, total diagnostic interval.
Bold indicates significant value ($P < 0.05$).

in the category of visual difficulties. By contrast, we included these patients in the category of the focal weakness. Because eye movement disorders tend to raise the index of suspicion more readily than visual difficulties, their analysis might fail to detect the longer TDI in patients with pure visual difficulties.

A recent report from “Head Smart” shows that the tumor subtypes with the longest DI (“system interval” in their paper) were craniopharyngioma (median 3.3 weeks) and optic pathway glioma (median 3.3 weeks), which often present with visual difficulties.¹⁹ Though this trend corresponds to our results, the median DI of 8 patients

Figure 4. Relationships Between the First Symptom Categories and A, Total Diagnostic Interval; B, Patient Interval; and C, Diagnostic Interval in Children With Brain Tumors ($n = 154$).

Figure 5. Relationships Between Department Categories for the First Presentation and A, Total Diagnostic Interval (TDI); B, Patient Interval (PI); and C, Diagnostic Interval (DI) in Children With Brain Tumors ($n = 154$). Mann-Whitney U tests show the significant difference between patients who visited pediatricians and patients who visited ophthalmologists in TDI and DI, and between patients who visited pediatricians and patients who visited otolaryngologists in TDI. * $P = .016$. ** $P = .023$. *** $P = .03$.

with visual abnormalities in our study was 36.1 weeks. The difference in medical systems between the United Kingdom and Japan might cause this discrepancy. In the United Kingdom, patients with some symptoms present to a general practitioner and are referred to appropriate specialists. On the other hand, most patients with eye-related symptoms present to ophthalmology clinics in Japan. Similarly, most patients with hearing abnormalities present to otolaryngology clinics. The distribution

pattern of the first medical visit in our study might be the consequence of the Japanese medical system. Several patients with visual or hearing abnormalities were followed without imaging at specialist clinics for more than half a year, and they had exceedingly long DIs in this study. It may suggest a possible shortcoming in the medical system in Japan.

We could not show that early diagnosis makes for better overall survival—on the contrary, patients with

a more than 30-day TDI had better overall survival. The overall survival may strongly depend on the tumor biology as previously reported.⁵ In this study, more than half of surviving patients reported residual sequelae. TDI was not different according to the presence or absence of any residual sequelae. The sequelae are caused not only by the tumor itself but also its treatment; however, our study population underwent various treatments. Thus, the sample size was too small to analyze the association between TDI and sequelae independently. Nevertheless, the association between persistent visual impairment and longer TDI in patients with visual abnormality as the first symptom implies the importance of earlier diagnosis.

Our study has several limitations. First, the information was extracted retrospectively from medical records. Therefore, the determination of the onset of the first symptom was dependent on individual physician practice. Second, all patients were diagnosed based on World Health Organization classifications at that time and few molecular and genetic subtypes were available. Considering the intervention to shorter TDI, an additional campaign targeting ophthalmologists or otolaryngologists may further reduce DI and TDI in patients with visual or hearing abnormalities, particularly in Japan. We could not find specific symptoms or characteristics that distinguish patients with brain tumors from patients visiting ophthalmologists or otolaryngologists without brain tumors. Further study to identify specific visual and hearing symptoms that require prompt evaluation for brain tumors will be needed to find the balance between timely diagnosis and overdiagnosis of this relatively rare disease.

Conclusions

Our study showed that childhood brain tumor patients presenting with visual, hearing, or smelling abnormalities had longer DIs and TDIs than patients with another first symptom. Raising awareness of brain tumors among medical specialties other than pediatricians or general practitioners may reduce TDIs and DIs and may improve the neurological impairment of children with brain tumors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

We would like to thank Dr Clifford Andrew Kolba of the Division of Education for Clinical Research, National Center for Child Health and Development, for proofreading and editing this manuscript.

Conflict of interest statement. None declared.

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