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Patient factors influencing a delay in diagnosis in pediatric spinal cord tumors

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ABSTRACT

The diagnosis of pediatric spinal cord tumor is frequently delayed due to the presence of non-specific symptoms. We investigated the factors influencing the delay between the first symptom presentation and the diagnosis for pediatric spinal cord tumor. We retrospectively analyzed 31 patients of age <20 years (18 men, 13 women) who underwent surgery for spinal cord tumor at a single center during 1998–2018. We extracted the relevant data on patients' symptoms, affected spinal location (cervical: C1-7, thoracic: T1-T12, and lumbosacral: L1-S), and tumor anatomical location (extradural, intradural extramedullary, and intramedullary tumor) that could potentially affect the duration of symptom presentation prior to the diagnosis. The most common symptom presented in the patients was pain (n = 22, 71.0 %). Motor symptoms such as paralysis was associated with early diagnosis (P = 0.039). The duration of symptoms prior to diagnosis was found to be significantly longer in patients with spinal tumor in the lumbar-sacral region than in those with the involvement of the cervical and thoracic regions (2.1 ± 1.7 months vs 13.6 ± 12.1 months; P = 0.006 and 2.9 ± 2.2 months vs 13.6 ± 12.1 months; P = 0.012, respectively). Our study results demonstrated that pain was the most common symptom in the examined patients, although it did not affect the delay in diagnosis, whereas the presentation of motor symptoms was helpful in the diagnosis of pediatric spinal cord tumor and the diagnosis could be delayed in lumbar-sacral spinal tumors.

Keywords: pediatrics spinal cord tumor, tumor characteristics, diagnostic delay

Abbreviations:
MRI: magnetic resonance imaging
M: male
F: female
MPE: myxopapillary ependymoma
LGG: low-grade glioma
HGG: high-grade glioma

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INTRODUCTION

Pediatric spinal cord tumor is an extremely rare disease, accounting for 1%–10% of all pediatric central nervous system tumors.[1] An annual incidence of pediatric spinal cord tumor has been estimated at 1.9 per 1 million children in the United States,[2] and 35% of all pediatric spinal cord tumors are reportedly intramedullary in nature.[3] This diagnosis of spinal cord tumor is frequently delayed due to the lack of specific clinical symptoms in majority of pediatric cases[4]: various symptoms can occur depending on the diversity of the spinal cord tumor, including pain, motor weakness, neurological deficits, and bowel and bladder dysfunctions.[5-7]

If we can identify the symptoms associated with pediatric spinal cord tumors, we can reduce the diagnostic delay; however, this is challenging because of the limited reports investigating the relationship between symptoms and patient/tumor characteristics for pediatric spinal cord tumors.

Back pain has been associated with diagnostic delay, but urinary disfunction and motor weakness can be detected early.[2] Loh et al reported that the risk factors for delayed diagnosis among pediatric solid tumors include younger age and the site of presentation, the points of first detection of symptoms, first healthcare contact, and first suspicion of malignancy.[8] It is, however, unclear as to what factors influence the diagnosis delay in pediatric spinal cord tumor. Therefore, the present study aims to investigate the factors associated with diagnostic delay in pediatric spinal cord tumor from the perspective of patients and tumor characteristics.

MATERIAL AND METHODS

Of the 42 pediatric patients who underwent surgery for spinal cord tumors between 1998 and 2018 at a single-center institute, 31 patients (18 men, 13 women) were retrospectively analyzed. This present study protocol was approved by our Institutional Review Board. Informed consent was obtained from all patients who participated in this study. We reviewed patients aged <20 years with spinal cord tumor. The analysis of the distribution of the patients according to the 3 groups were as follows: pre-school age (range: 0–6 years, n = 5; 16.1%); school age and early adolescence (range: 7–14 years, n = 15; 48.4%); and late adolescence (range: 15–20 years, n = 11; 35.5%). We excluded the cases with no magnetic resonance imaging (MRI) for evaluation, intramedullary infiltration of extramedullary tumor based on our intraoperative findings, and local recurrence.

All patients underwent pre and postoperative MRI. We determined the anatomical location of the tumor (ie, extradural, intradural extramedullary, or intramedullary) based on the surgical findings. The following data was collected for our analysis: sex, age at surgery, pathological diagnosis, the follow-up period, the duration of the onset of symptoms prior to diagnosis, location of the tumor (cervical: C1-7, thoracic: T1-T12, and lumbar-sacral: L1-S), tumor anatomical location. We also assessed symptoms such as motor paralysis, sensory symptoms, and urinary retention. We defined motor symptoms as manual muscle test scores less than 4, sensory disturbances as numbness, and urinary retention as urinary abnormalities, including subjective symptoms. We defined the delayed diagnosis as being diagnosed more than 1 month later from the onset of symptoms.

Statistical analysis

All statistical analyses were performed by using the BellCurve add-ons for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). The Mann–Whitney *U*-test and the Kruskal-Wallis with post-hoc Bonferroni test were used to compare the mean values of continuous

variables. The Chi-square test and residual analysis was applied for examination through cross tabulation. Stepwise binary logistic regression analysis was used to validate symptoms that may affect diagnosis within 1 month. The threshold value for significance was set at $P < 0.05$.

RESULTS

The summary of background data and characteristics of all patients is shown in Tables 1 and 2, respectively. The mean age of the patients at the time of surgery was 12.5 ± 4.8 years (age range: 2–19 years). The follow-up period was 73.2 ± 58.6 months. The mean duration of presentation of the symptoms prior to diagnosis was 6.2 ± 8.6 months.

The most common spinal tumor location was the lumbar-sacral region in 10 patients (35.7%), followed by the cervical and thoracic regions in 9 patients each (32.1%). The anatomical tumor locations determined were as follows: extradural, intradural extramedullary, and intramedullary in 11 (35.5%), 11 (35.5 %), and 9 (29.0%) patients, respectively.

Table 1 Demographic data for children (N=31)

Feature/Characteristic	Value
Male/Female	18/13
Age at Surgery (yrs)	12.5±4.8
Follow-up periods (months)	73.2±58.6
Symptom-diagnosis interval months (months)	6.2 ± 8.6
Tumor location	
Cervical	9 (29.0%)
Thoracic	9 (29.0%)
Lumbar-Sacral	10 (32.3%)
Tumor anatomical location	
Extradural	11 (35.5%)
Intradural extramedullary	11 (35.5%)
Intramedullary	9 (29.0%)
Symptom (each symptom was overlapped)	
Back pain	14 (45.2%)
Neck pain	2 (6.5%)
Extremity pain	10 (32.3%)
Motor symptom	17 (54.8%)
Sensory symptom	13 (41.9%)
Urinary retention	11 (35.5%)

Table 2 Summary characteristic of all patients (N=31)

Age at surgery (years)	Sex	Tumor location	Pathology	Pain	Back pain	Neck pain	Extremity pain	Motor symptom	Sensory symptom	Urinary retention
2	F	T2T5	LGG	+	-	-	+	+	+	-
2	M	L2L5	Neuroblastoma	+	-	-	+	-	-	-
4	F	L3S1	Epithelioid tumor	+	-	-	+	-	-	-
4	F	C3C4	Arachnoid cyst	-	-	-	-	+	-	+
6	F	T8S1	MPE	+	-	-	+	+	-	+
8	M	L3S1	MPE	+	-	-	+	+	-	+
10	F	T11L2	Lymphoma	-	-	-	-	+	-	+
10	F	C7T1	Cavernous angioma	+	+	-	-	+	+	+
11	M	C7	Osteoid osteoma	-	-	-	-	+	-	-
12	F	L5	Osteoblastoma	-	-	-	-	-	-	-
12	M	C2T4	Ependymoma	-	-	-	-	+	+	+
13	M	T5T7	LGG	+	+	-	-	+	+	+
13	M	C2	Osteoid osteoma	+	+	+	-	-	-	-
13	M	T11T12	Neurofibroma	+	+	-	-	+	+	-
13	M	C5C6	Neurofibroma	-	-	-	-	+	+	-
13	M	L4	Schwannoma	+	+	-	-	-	-	+
13	M	L4L5	Schwannoma	+	-	-	+	-	-	-
14	M	T3T7	Liposarcoma	-	-	-	-	+	+	+
14	M	C2C3	HGG	+	+	+	-	-	-	-
14	M	C2C4	HGG	-	-	-	-	+	+	-
15	M	C6	Cavernous angioma	+	-	-	+	-	-	-
15	M	T1T2	Metastatic tumor	+	+	-	-	+	+	+
16	M	L1	Schwannoma	+	+	-	+	+	-	-
16	F	T1T2	Myxolipoma	-	-	-	-	-	-	-
16	F	T9T10	Neuroblastoma	+	+	-	-	-	-	-
17	F	L1L2	Arachnoid cyst	+	+	-	-	-	+	-
18	F	S3	Osteoblastoma	+	+	-	-	-	-	-
18	M	L1L2	MPE	+	+	-	+	-	+	-
18	M	C1C2, C7	Neurofibroma	+	+	-	-	+	-	-
19	F	C6C7	Medulloblastoma	+	-	-	+	-	+	-
19	F	T9T11	LGG	+	+	-	-	+	+	+

M: male
F: female
MPE: myxopapillary ependymoma
LGG: low-grade glioma
HGG: high-grade glioma

No significant difference was noted among the 3 age groups with respect to the tumor location, and the intradural extramedullary tumors tended to be more common in the lumber-sacral regions (P = 0.023) (Table 3).

Table 3 Relationship between tumor location and other parameters

	Anatomical location			Clinical presentation				Age		
Tumor location	Extra-dural	Intradural extra-medullary	Intra-medullary	Pain	Motor symptom	Sensory symptom	Urinary retention	0–6 years	7–14 years	15–20 years
Cervical	3	2	4	5	5	3	1	1	1	2
(P value)	(0.428)	(0.153)	(0.100)	(0.413)	(0.154)	(0.484)	(0.181)	(0.371)	(0.371)	(0.260)
Thoracic	3	2	4	7	7	7	5	5	4	4
(P value)	(0.428)	(0.153)	(0.100)	(0.052)	(0.406)	(0.193)	(0.175)	(0.253)	(0.442)	(0.306)
Lumbar-Sacral	4	6	0	9	2	2	2	3	4	4
(P value)	(0.362)	(0.023)	(0.006)	(0.021)	(0.103)	(0.175)	(0.438)	(0.329)	(0.350)	(0.477)

$P < 0.05$ by Residual analysis.

The most common symptom (n = 22, 71.0%) was pain, including back pain (n = 14, 45.2%), neck pain (n = 2, 6.5%) and extremity pain (n = 10, 32.3%). Motor symptoms, sensory symptoms, and urinary retention were recorded in 17 (54.8%), 13 (41.9%), and 11 patients (35.5%), respectively (Table 1). The patients with tumor in the lumbar-sacral region tended to experience relatively more pain based on their complaints (Table 3; $P = 0.021$). Further, 31 patients (29%) had pain in the lumbar-sacral region (Table 3), 5 patients (16%) had back pain, and 6 patients (19%) had extremity pain (Table 2). The patients of school age and in their early adolescence (age: 7–14 years) also tended to experience relatively more pain (Table 4; $P = 0.046$).

Table 4 Relationship between age and other parameters

	Anatomical location			Clinical presentation			
Age	Extradural	Intradural extra-medullary	Intra-medullary	Pain	Motor symptom	Sensory symptom	Urinary retention
0–6 years	1	3	1	1	2	4	3
(P value)	(0.215)	(0.106)	(0.314)	(0.593)	(0.869)	(0.249)	(0.866)
7–14 years	5	5	5	7	5	8	8
(P value)	(0.404)	(0.404)	(0.305)	(0.046)	(0.269)	(0.713)	(0.256)
15–20 years	5	3	3	1	6	5	8
(P value)	(0.195)	(0.239)	(0.436)	(0.091)	(0.193)	(0.602)	(0.180)

$P < 0.05$ by Residual analysis.

The duration of symptoms prior to diagnosis was significantly longer in the first half periods as 1998–2007 than that in the latter half of the periods as 2008–2018 ($P = 0.002$).

The duration of symptoms prior to diagnosis was significantly longer in patients with spinal tumor in the lumbar-sacral region than in those with the tumor in the cervical and thoracic regions (2.1 ± 1.7 months vs 13.6 ± 12.1 months; $P = 0.006$ and 2.9 ± 2.2 months vs 13.6 ± 12.1 months; $P = 0.012$), respectively (Fig. 1). No significant difference was noted among the 3 age groups with respect to the duration of symptoms prior to the diagnosis (Fig. 2). The presence of motor symptoms was associated with early diagnosis ($P = 0.039$, Fig. 3, 4). However, there was no significant difference noted with respect to the duration of symptoms prior to the diagnosis among the tumors in the 3 different anatomical locations (Fig. 5). In binary logistic regression analysis, symptoms-diagnosis interval was associated with motor symptoms (AUC: 0.78, 95%CI: 0.61–0.95, $P < 0.01$).

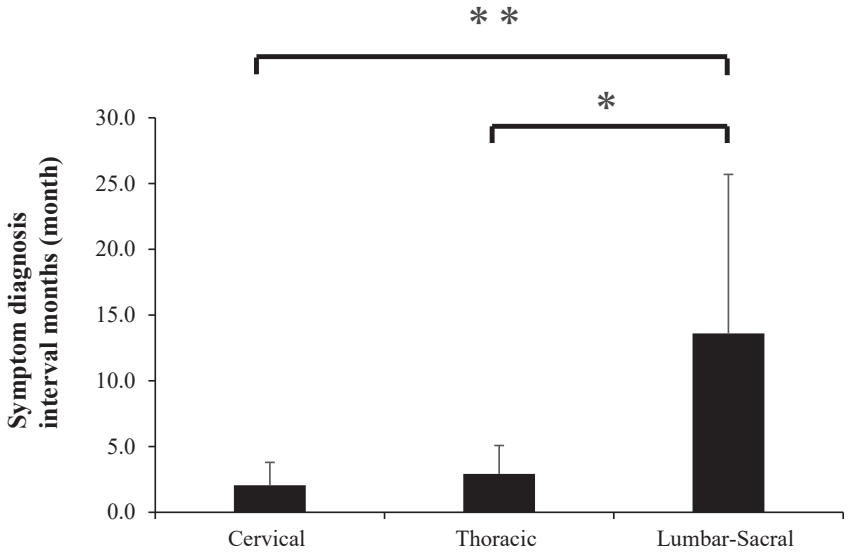

Fig. 1 Interval between the first symptom and diagnosis for each affected spinal location *P < 0.05 and **P < 0.01 by the Kruskal-Wallis with post-hoc Bonferroni test.

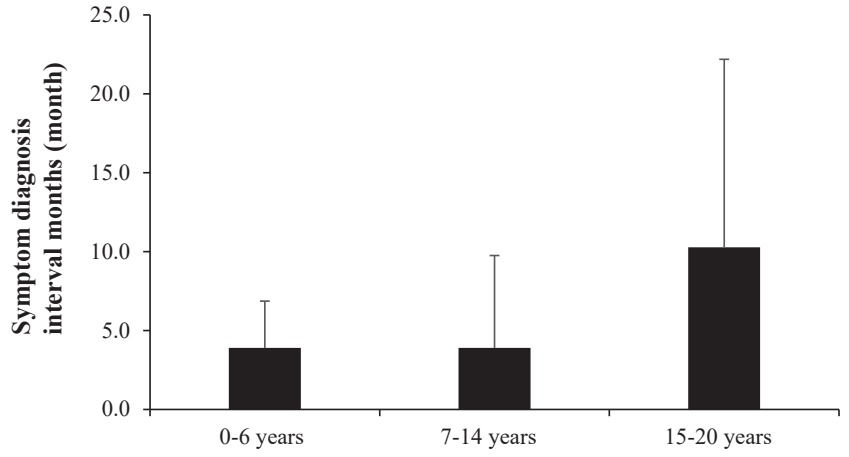

Fig. 2 Interval between the first symptom and diagnosis for each age

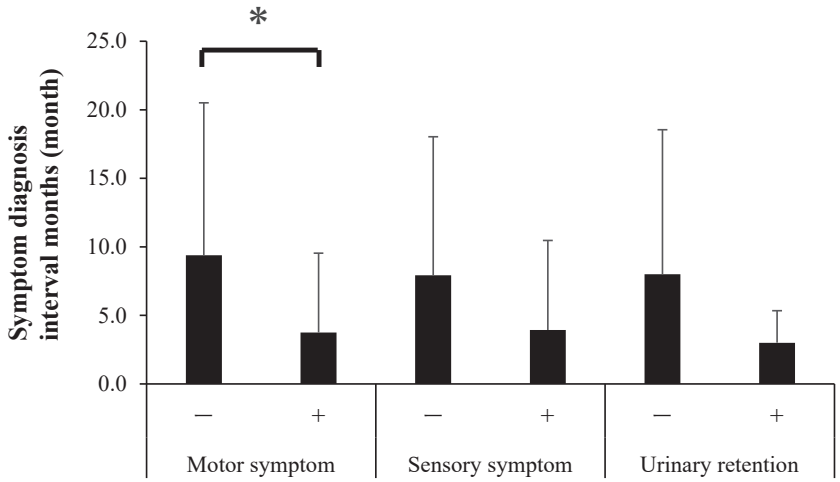

Fig. 3 Interval between the first symptom and diagnosis for each symptom other than pain
*P < 0.05 by the Mann-Whitney *U*-test.

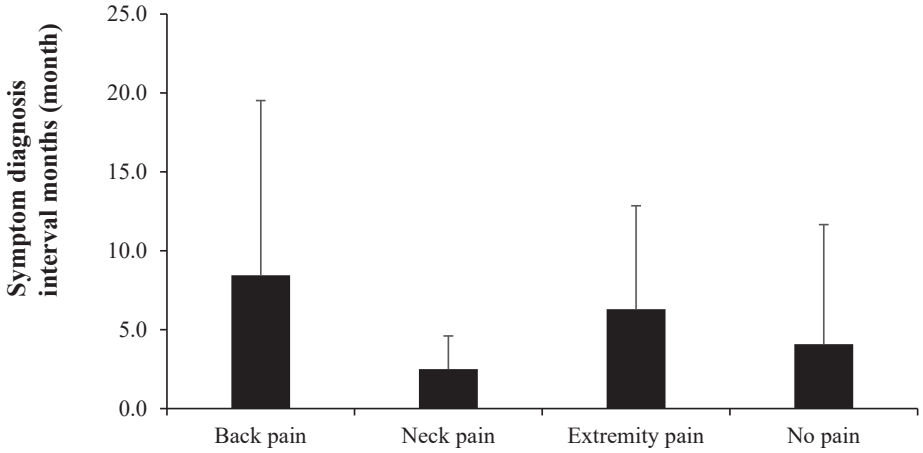

Fig. 4 Interval between the first symptom and diagnosis for patients with or without pain

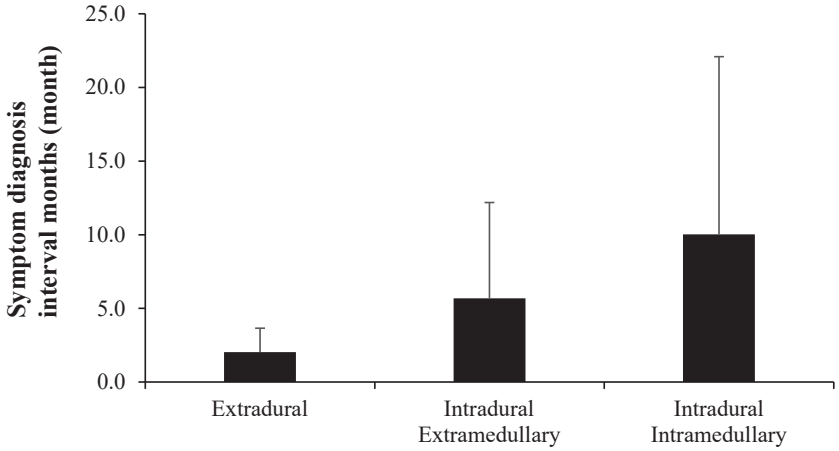

Fig. 5 Interval between the first symptom and diagnosis for each anatomical tumor location

DISCUSSION

Our observations in the present study indicated that pediatric spinal cord tumors occurred in equal frequencies at all spinal levels, with similar rates of occurrence at the extradural, intradural extramedullary, and intramedullary locations. The lumbar-sacral level tumors with several intradural extramedullary tumors showed a longer duration of symptoms prior to diagnosis, which differed from the spinal level. Furthermore, pain was the most common symptom (71.0%), and its complaint was significantly more frequent among patients of school age and adolescent patients. On the contrary, the chief complaint of motor and sensory paralysis was common among pre-school age children, which verified that the chief complaints significantly differed with the age groups.

Diagnostic delay is a common occurrence in pediatric spinal cord tumors. Crawford et al[2] reported that the mean duration of diagnosis was 7.8 months (range: 1 week to 5 years) and children with high-grade malignant tumors had a shorter duration of symptoms than those with a lower grade tumor. McGirt et al[9] also reported that the mean duration of symptoms was 8 months (range: 1–36 months) in intramedullary spinal cord tumor. As per some past studies, the duration of symptoms prior to diagnosis had a significant influence on the outcome in patients with astrocytoma,[10] brain stem gliomas,[11] ependymoma,[12] and medulloblastoma.[13] The early detection of spinal cord tumor provides a better clinical outcome. Bouffet et al[10] reported that the most important factors affecting the prognosis of pediatric spinal cord astrocytoma were the histology and the duration of the presenting symptoms. However, an average diagnosis delay ranged from 4.5 to 12 months, and poor clinical outcome possibly results from the delayed diagnosis in pediatric cases.[14] Thus, we considered that the most probable reason for the delay in diagnosis was the nonspecificity of symptoms due to multiple pediatric spinal tumors.

The extradural and intradural extramedullary tumor were the most common anatomical locations (35.5%) in the present analysis. Wetjen et al[15] summarized that the 10 large case series on pediatric spinal cord tumor published during 1953–1990 recorded extradural tumor in 233 patients (35.9%), intradural extramedullary tumor in 156 patients (24.0%), and intramedullary tumor in 189 patients (29.1%). Moreover, Spacca et al[4] reported the distribution of anatomical locations of pediatric spinal cord tumor as follows: extradural tumor (n = 53, 39.5%), intradural extramedullary tumor (n = 25, 18.7%), intramedullary tumor (n = 46, 34.3%), and paravertebral

(n = 10, 7.5%). Thus, these rates of extradural and intramedullary tumor were found to be similar to those in our study.

Considering the common spinal tumor location, the lumbar-sacral region was the most commonly affected location (35.7%) of all cases. Crawford et al[2] reported that the thoracic region was the most commonly affected one (68%), followed by cervical (36%), lumbar (28%), and sacral/cauda (28%) regions. Our results differed from this past report possibly because the patients in this past study were younger than our case patients (7.8 ± 5.6 years vs 12.5 ± 4.8 years, respectively), and the number of intramedullary spinal cord tumor patients in their study were more (60.0%). They also reported no significant difference in the age and the symptoms of pain and weakness; however, younger patients (average age: 2.5 years) tended to complain about neck pain. This result differed from ours in that, in the present study, patients of age 7–14 years tended to just complain about pain.

The presenting signs and symptoms of spinal cord tumor were varied and non-specific. Spinal tumor induces symptoms as a result of the compression of nerve root or cord and ischemia vascular compression. Hung et al[16] found that the most common symptom of primary cord tumors in the childhood was extremity pain/weakness, followed by back pain. Özkan et al[17] also reported the most common symptoms of patients with extramedullary spinal cord tumor to be pain/back pain (41%) and that of patients with intramedullary spinal cord tumor to be the common complaint of motor weakness of the extremities (52%). Spacca et al[4] reported that back pain in a healthy child with no history of injury is unusual, warranting serious consideration to spinal cord tumor. The present study indicated that motor symptoms such as motor paralysis were associated with the early diagnosis; however, other symptoms were difficult to diagnose due to the overlapping suspicions of abnormalities of the nervous system, including the spinal cord. Among the pediatric spinal cord tumors, the duration of symptoms prior to diagnosis was significantly longer in pediatric cases with lumber-sacral tumor than in those with cervical tumor in the present study. Thus, it was more difficult to recognize the signs of pediatric lumber-sacral spinal cord tumor. Because lumbar spinal cord tumors occur mainly at the level of the cauda equina, lower extremity pain and back pain can occur, albeit with less likely occurrence of lower motor paralysis. In the present study, there was a significant difference in the diagnostic delay between the first half and the latter half of the study period. This might be because of the fact that an MRI is easier to perform than before and that pediatric spinal cord tumors are more widely recognized by clinicians. As Spacca et al[4] suggested, spinal MRI should be performed in cases of chronic lower extremity or back pain with no history of injury, which may lead to early diagnosis of spinal cord tumors. The results of this study suggest that pediatricians, orthopedic surgeons, and family doctors should be informed that pain in children that lasts for >1 month may be caused by serious diseases such as spinal cord tumors in addition to non-specific causes.

The present study has some limitations. First, the present study was a retrospective study involving a relatively small number of cases. The symptom interview was based on the records that have been heard in detail by medical clerks and doctors, which offered a great advantage considering that detailed information could be recorded. However, as this was a retrospective study, it is possible that verification of this study and further detailed information can be obtained via a prospectively large case study in the future.

In conclusion, our study suggests that motor symptoms such as paralysis can help in the early diagnosis and that the presence of a tumor at the lumbar sacral region influences the delay in its diagnosis. Although pain was the most common symptom registered in all cases in this study, it had no effect on the delay in diagnosis.

CONFLICT OF INTEREST AND SOURCE OF FUNDING

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