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Original Article

From Symptom to Diagnosis—The Prediagnostic Symptomatic Interval of Pediatric Central Nervous System Tumors in Austria

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ABSTRACT

BACKGROUND: Children with central nervous system (CNS) tumours may present with a multitude of symptoms, ranging from elevated intracranial pressure to focal neurological deficit. In everyday practice, some signs may be misleading, thereby causing prolonged prediagnostic symptomatic intervals. Prediagnostic symptomatic intervals are longer for pediatric brain tumors than for other childhood malignancies. This study evaluated prediagnostic symptomatic intervals and parental and diagnostic intervals for pediatric patients with CNS tumours in Austria. It also considered socioeconomic factors. **METHODS:** Patients ≤ 19 years of age treated at the Medical University of Vienna and diagnosed during the years 2008 to 2013 were included. Patients diagnosed incidentally or by screening were excluded. **RESULTS:** Two hundred twelve consecutive patients were included in the study. They reflected the expected spectrum of CNS tumors. Patients presented with a median of five symptoms at diagnosis, most frequently with signs of elevated intracranial pressure. The median prediagnostic symptomatic interval was 60 days (0 days to seven years), the median parental interval was 30 days (0 days to 6.7 years), and the median diagnostic interval was three days (0 days to 6.5 years). In spinal tumors alone (n = 7), the median prediagnostic symptomatic interval was 70 days (ten days to seven years), and three of seven patients had a prediagnostic symptomatic interval longer than 320 days. Young age, higher tumor grade, and ataxia were associated with a shorter prediagnostic symptomatic interval. Localization in the supratentorial midline, histology of craniopharyngioma, and endocrine symptoms prolonged the prediagnostic symptomatic interval. There was a clear trend for longer prediagnostic symptomatic interval in non-native speakers. **CONCLUSIONS:** Results are comparable to other industrialized countries. However, long delays in diagnosis of central nervous system tumors still occur, urging increased awareness.

Keywords: brain tumor, spinal tumor, central nervous system tumor, latency, presymptomatic interval, children

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Introduction

Central nervous system (CNS) tumors constitute the largest group of solid neoplasms in childhood and are therefore the leading cause of morbidity and cancer-related death in children.[1] On average, 5.57 of every 100,000 children and adolescents are affected by a CNS malignancy during the first 20 years of life.[2]

In children, tumor location and age at diagnosis affect the clinical presentation. During the first year of life, tumors are predominantly located in the supratentorial midline, whereas in school-age children, infratentorial tumors occur more frequently.[3]

Symptoms fall into two categories: first, focal neurological deficits, and second, signs of elevated intracranial pressure (ICP).[3] Focal symptoms are due to infiltration or destruction of normal areas of the brain with consecutive functional impairment. In contrast, an elevated ICP is caused either by the tumor mass itself or, more often, by occlusion of the cerebral fluid circulation.[4]

The prediagnostic symptomatic interval (PSI) describes the period from the onset of tumor-related symptoms until diagnosis. The PSI is a combination of the patient's or

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parental interval (i.e., time from the onset of symptoms to medical consultation) and the diagnostic interval (referring to the Aarhus consensus statement).[5]

Previous studies of PSI in pediatric patients with a CNS tumor in different Western countries (e.g., Canada, Denmark, France, Germany, Italy, Japan, Switzerland, the United Kingdom, and the United States[3,6-20]) have shown that, in comparison with all other pediatric malignancies, there is a delay in the diagnosis of a CNS tumor[14,21] with a median PSI around two to three months.[6,10,11,13,15] Only one third of patients is diagnosed in the first month after symptom onset with some children experiencing symptoms for up to eight years.[6,15] These studies found that, first, the symptomatology often changes over time—with the number of signs and symptoms increasing from onset to diagnosis.[3,6] Second, the time to diagnosis varies according to growth velocity (and thus tumor grade)[6,11] and type of symptoms.[15] Third, parents of younger children tend to seek medical advice earlier, leading to a significantly shorter prediagnostic interval.[6,21] Fourth, in a German study, around half the patients initially presented with signs and symptoms attributed to a divergent diagnosis (e.g., gastrointestinal infection, psychological problems, and squint) and were treated accordingly.[11] Fifth, patients are often seen by a series of physicians of the same or other subspecialties before being referred for neuroimaging studies.[11]

Finally, there is no correlation between a longer PSI and a decrease in overall survival following diagnosis. This finding is because fast-growing malignant tumors tend to be diagnosed sooner than lower-grade tumors. (Note, however, that death may still occur before the correct diagnosis is made.)[4,7,9,11,18] On the other hand, a longer PSI may increase the persistent neurological sequelae (e.g., visual impairment and neurocognitive deficits).[22,23]

The present study analyzed the PSI in pediatric patients in Austria with a CNS tumor, and evaluated the clinical and social factors affecting the prediagnostic interval.

Materials and Methods

This retrospective, unicentric study was approved by the ethics committee of the Medical University of Vienna (MUV). Data were collected as part of a master thesis (KH).

Patients

The study included patients age zero to 20 years who were receiving primary care for a CNS tumor at the Department of Pediatrics and Adolescent Medicine, MUV, Austria, from 2008 to 2013. Patients referred by other oncology centers for a second opinion or further treatment were excluded.

Methods

Data were collected by chart review or parent questionnaires completed during an interview at a follow-up visit. Data included age, sex, histologic diagnosis, tumor location, date of diagnosis (first imaging), onset of symptoms, signs and symptoms at diagnosis, outcome (alive or dead), parental education, migration background, native language, and place of residence (to evaluate the number of inhabitants and distance to the nearest pediatric department).

Statistics

IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation, Armonk, NY) was used for statistical analyses. Descriptive statistic methods were applied to characterize the study population. The influence of the different variables on the PSI was evaluated using either a Kruskal-Wallis test (with a Bonferroni correction for multiple comparisons) or a Mann-Whitney test when appropriate. A P value of <0.050 was seen as significant.

Results

Patient characteristics

Three hundred seventy-seven patients had their first contact at the neuro-oncology unit of the Department of Pediatrics and Adolescent Medicine, MUV. Two hundred twelve of these patients were eligible for the study (Fig 1); 50.0% were male. Data were retrieved by a chart review of all patients. The questionnaire was answered during an interview in 13 instances (conducted one to six years following diagnosis). The mean age at diagnosis was 8.49 years (range 0.2 to 19.9 years, S.D. 5.0). Patient characteristics are summarised in Table 1.

Two hundred five patients suffered from an intracranial neoplasia. The remaining seven had a spinal tumor. The characteristics of intracranial tumors are listed in Table 2. The ratio of high-grade to low-grade tumors was 77:128 (38% versus 62%). Low-grade glioma comprised the largest group (48%). Tumors were most frequently located in the posterior fossa (36.1%) followed by the supratentorial midline (32.2%) and the cerebral hemispheres (28.7%).

Twenty-seven patients (13.2%) suffered from a cancer predisposition syndrome: 21 (10.2%) from neurofibromatosis type 1 (NF-1) (in 1 patient, tumor diagnosis coincided with diagnosis of NF-1), four (2.0%) from tuberous sclerosis; and two from other syndromes.

In 25 patients (12.2%), the CNS tumor was diagnosed during a routine magnetic resonance imaging (MRI) screening of patients with a known tumor predisposition syndrome. Two patients with NF-1 had an MRI scan because they had tumor-related symptoms. Sixteen patients (7.5%) had undergone MRI for reasons that were neither related nor attributable to their respective CNS tumors (e.g., head trauma; see Supplementary Table S1). The 41 patients diagnosed incidentally or during screening were excluded from the analysis of diagnostic intervals (Table 2).

Approximately a quarter of the patients' families (27.2%) had a migration background. Fifty patients (26.6%) came from families for whom German was not the native language. Of these patients, 21 (42%) needed an interpreter to communicate with doctors and a quarter were bilingual (see Supplementary Table S2). Table 1 sets out the highest educational level of the parents, information on the size of the residential municipality, and the distance from the patient's home to the nearest pediatric department or hospital.

Symptoms

Tumor-related symptoms found in our study population are detailed in Tables 3 and 4. At symptom onset, the patients had a median of two symptoms (range one to eight).