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# Brain Tumors in Children: Initial Symptoms and Their Influence on the Time Span Between Symptom Onset and Diagnosis

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Brain tumors are the most common solid tumor entity in childhood. Symptoms are often unspecific, depending not only on the localization of the tumor, but also on the age of the child. The aim of this study was to detect factors influencing the time span between the occurrence of symptoms and the diagnosis to alert health professionals to the early symptoms of pediatric brain tumors. The records of 245 consecutive patients treated for brain tumors between 1980 and 2004 at the neuropediatric department of the University of Muenster were analyzed regarding their primary symptoms, tumor location, entity, and, in 151 cases, the primary electroencephalogram findings. The median time span between symptom onset and diagnosis in our study was 24 days. Multivariate analysis showed a significant influence of 6 parameters on the interval between symptom onset and diagnosis. An additional symptom had a significant influence on the time span between symptom onset and diagnosis in the univariate analysis. The findings that several symptoms influence the interval between symptom onset and diagnosis emphasize the necessity to systematically inquire about the key symptoms of brain tumors. The challenge for every consultant is to decide in which cases cerebral imaging is appropriate. As the most frequent symptoms are unspecific and often underestimated, a detailed anamnesis is crucial to detect possible brain tumor patients. In doubtful cases, a systematic interrogation regarding the catalogue of symptoms can be helpful.

**Keywords:** brain tumors; neuro-oncology; central nervous system tumors

Brain tumors are the most common solid tumor entity in children and constitute 15–20% of all childhood malignancies. Their incidence is approximately 3/100 000 per year between 0 and 15 years of age.[1] In contrast to most other pediatric neoplasms, the dilemma of brain tumors lies in their proximity to vitally important structures and in the low specificity of the primary symptoms, which decreases the chances of diagnosis at an early stage. Early studies have shown a diagnostic delay of up to 6 months in more than 50% of the patients,[2] whereas newer studies revealed a distinctly shorter diagnostic interval, indicating the value of neuroimaging techniques that are now more widely available.[3–6]

It is well-known that any delay in diagnosis leads to further tumor progress and thus worsens the outcome and the risk of additional brain damage due to the prolonged increased intracranial pressure, making an early diagnosis crucial. Symptoms depend on the location of the tumor but also on the age of the patients. Whereas increased intracranial pressure leads to an increase of head circumference in the first year of life, which might prevent a rapid development of symptoms, increased intracranial pressure, headaches, and diplopia are common symptoms of the older child. Early morning vomiting and increased fatigue are frequent symptoms of both younger and older children.[4,7–9]

Depending on the location of the tumor, other possible symptoms are ataxia, gait abnormalities, or cerebral nerve deficits for infratentorial tumors; or seizures, motor dysfunction up to hemiplegia, endocrinological deficits, and visual dysfunctioning for supratentorial tumors. Due to their proximity to the fourth ventricle, infratentorial tumor progress results in a faster development of increased intracranial pressure than in supratentorial tumors.[7,10,11]

The aim of this retrospective study was to identify constellations of primary symptoms, age and gender of the patient, location, type and grade of the tumor, and primary EEG findings that point toward the existence of a brain tumor and might, therefore, contribute to an earlier diagnosis. These parameters, together with the year and place of

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diagnosis, and the specialization of the treating physician were analyzed with regard to the interval between the date of the symptom onset and the date of diagnosis in a large number of brain tumor patients. The findings should contribute to a better education of medical professionals concerning the symptoms of this common childhood tumor.

## Patients and Methods

The records of all patients with brain tumors seeking medical advice at the neuropediatric department of the University Hospital of Muenster between January 1980 and October 2004 were inspected. Of those 326 records, 52 were excluded for incomplete data, mostly because of preliminary treatment in other hospitals. Additionally, 23 patients with neurofibromatosis or tuberous sclerosis were excluded. In most of those cases, no clinical symptoms but regular control imaging or ophthalmologic examinations led to diagnosis. Also, the patients and their parents had already been educated concerning their disease and its possible symptoms. Another 6 patients were excluded as they presented no clinical symptoms but attracted attention in routine screening examinations. The records of the remaining 245 patients were analyzed regarding the dates of symptom onset and diagnosis, age, and gender of the patient, the kind of primary symptoms and the location. The tumor entity, diagnosed per biopsy or by neuroimaging, and if available the electroencephalogram (EEG) findings at the time of diagnosis were also recorded. From the dates of symptom onset and diagnosis, the time span between symptom onset and diagnosis was calculated.

The data were collected and statistically analyzed using SPSS 12. Statistical test procedures include $\chi^2$ and log rank tests as univariate procedures and Cox regression as a multivariate analysis. Values for $P < .05$ were considered significant.

## Results

### Patient Characteristics

The records of 245 patients were included in the analysis: 135 (55.1%) were male and 110 (44.9%) were female. The male:female ratio was 1:0.81. Median age at symptom onset was 6.83 years, with a minimum at 0 and a maximum at 19.2 years. For age distribution, see Figure 1.

Practitioners from a range of specialties initiated treatment. A total of 132 (53.9%) patients were sent for additional diagnostical procedures by the treating pediatrician, 61 (24.9%) by general practitioners, 48 (19.6%) by other specialists, and 4 (1.6%) through other means.

There were 170 (69.4%) patients who received their diagnosis at the university hospital, and 75 (30.6 %) who were transferred to the university clinic for treatment after diagnosis at another hospital.

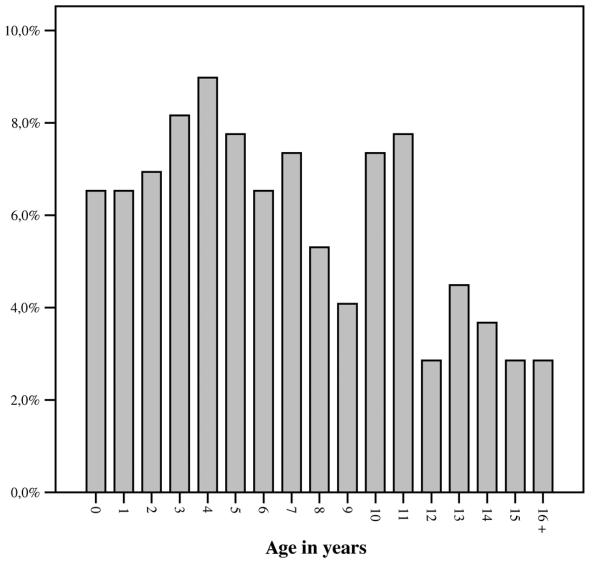


**Figure 1.** Age distribution of the patient cohort. The 2 peaks, 1 around the age of 4 and 1 at the age of 11, are consistent with typical age distribution of childhood brain tumors.

### Symptoms

The kind and incidence of the primary symptoms as reported by the patients or their parents were recorded. Table 1 shows symptoms in order of their frequency of occurrence. Headaches and early morning vomiting are by far the most common symptoms with a frequency of more than 50% each. Forty-two percent of the children suffered from both symptoms.

The $\chi^2$ test was performed to analyze if the occurrence of individual symptoms correlates with the tumor grade or the classified tumor location (see below). A positive correlation was detected between the symptoms of early morning vomiting ($P < .005$) and ataxia/gait abnormality ($P < .05$) and the tumor grade, showing that those symptoms occur significantly more often in patients with high-grade tumors. A positive correlation was shown for the occurrence of disturbed vision ($P < .005$) and tumor grade, indicating a significantly higher occurrence in patients with low-grade tumors.

With regard to the tumor location, the symptoms of early morning vomiting ($P < .005$), disturbed eye motility ($P < .05$), and ataxia ($P < .005$) showed a positive correlation to the tumor location, occurring significantly more often in patients with infratentorial tumors. The symptoms of seizures ($P < .005$), disturbed vision ($P < .05$), and other

**Table 1.** Distribution of Symptoms in Order of Their Frequency of Appearance

| Symptoms | Number | Percentage |
|---|---|---|
| Headache | 146 | 59.6 |
| Early morning vomiting | 144 | 58.8 |
| Ataxia/gait abnormality | 64 | 26.1 |
| Disturbed eye motility | 56 | 22.9 |
| Disturbed vigilance | 49 | 20.0 |
| Fatigue | 35 | 14.3 |
| Drowsiness | 14 | 5.7 |
| Disturbed vision | 42 | 17.1 |
| Disturbed motor function | 30 | 12.3 |
| Simple | 20 | 8.2 |
| Hemiplegic | 10 | 4.1 |
| Change in growth/weight | 29 | 11.9 |
| Weight loss | 19 | 7.8 |
| Disturbed growth | 10 | 4.1 |
| Other focal dysfunction[a] | 26 | 10.6 |
| Dizziness | 24 | 9.8 |
| Seizures | 22 | 8.6 |
| Disturbed speech | 19 | 7.8 |
| Head tilt | 18 | 7.3 |
| Neck stiffness | 12 | 4.9 |
| Facial nerve paresis | 7 | 2.9 |
| Disturbed cognitive activity | 6 | 2.4 |
| Change of character | 5 | 2.0 |
| Other symptoms of increased intracranial pressure | 2 | 0.8 |

a. Other focal dysfunction is a heterogenous group containing several symptoms of low-frequency, localized sensorial dysfunctioning, hearing abnormalities, aura-like visual phenomena, or altered sense of taste.

**Table 2.** Location of the Tumors and Classification of the Location Into Infra- or Supratentorial[a]

| Localization | Number | Percentage | Class |
|---|---|---|---|
| Posterior fossa | 127 | 51.8 | Infratentorial |
| Cerebral hemispheres | 46 | 18.8 | Supratentorial |
| Suprasellar | 28 | 11.4 | Supratentorial |
| Middle brain/middle line | 16 | 6.5 | Supratentorial |
| Lower brainstem/pons | 14 | 5.7 | Infratentorial |
| Thalamus/basal ganglia/ lateral ventricle | 12 | 4.9 | Supratentorial |
| Multifocal growth | 2 | 0.8 | Supratentorial |
| Total | 245 | 100 | |

a. In accordance to general experience, more than half of the brain tumors are located in the posterior fossa or the lower brainstem/pons, thus, infratentorially.

**Table 3.** Tumor Entity and Grade[a]

| Entity | Number | Percentage | Grade |
|---|---|---|---|
| Low-grade glioma | 71 | 29.0 | Low |
| Medulloblastoma | 69 | 28.2 | High |
| High-grade glioma | 33 | 13.5 | High |
| Craniopharyngioma | 20 | 8.2 | Low |
| High-grade ependymoma | 13 | 5.3 | High |
| Glioma of the pons region | 10 | 4.1 | High |
| Low-grade ependymoma | 7 | 2.9 | Low |
| Other | 7 | 2.9 | Unknown/low/high |
| Tumors of the meninges | 6 | 2.4 | Low |
| Germ cell tumors | 5 | 2.0 | Unknown |
| Tumors of the pineal tissue | 4 | 1.6 | High |
| Total | 245 | 100.0 | |

a. The grading is in accordance to the World Health Organization classification of central nervous system tumors.[12] The distribution of the tumor entities is in accordance to the general knowledge of childhood brain tumors, with low-grade gliomas and medulloblastomas as the most frequent tumor entities.

focal pathology ($P < .005$) correlated positively with the tumor location showing a higher occurrence in patients with supratentorial tumors.

### Tumor Characteristics

Magnetic resonance tomography was the first diagnostic imaging step in 143 (58.4%) cases and cranial computer tomography in 102 (41.6%) cases. Primary EEG findings were recorded in 151 cases of which 58 (38.4%) were normal, 29 (19.2%) showed unspecific abnormalities, and 64 (42.4%) showed a focal pathology (deceleration and/or ictal patterns). See Table 2 for the distribution of tumor location.

The location of the tumor was classified into infratentorial in 141 (57.6%) cases and supratentorial in 104 (42.4%) cases. In 2 cases, tumor growth occurred in multiple places, mainly in the hemispheres and was, therefore, counted as supratentorial.

To find an answer to the question if EEG findings point toward tumor location, the $\chi^2$ test was performed showing a statistically significant correlation ($P < .05$) between the EEG findings and the classified tumor location (see above). Supratentorially growing tumors presented more often a focal pathology than did infratentorially growing tumors.

Tumor entities were listed and classified as low-grade and high-grade tumors using the World Health Organization classification.[12] A total of 106 (43.3%) tumors were low-grade and 131 (53.5%) high-grade. In 8 cases (3.3%), classification was not possible. Table 3 shows a list of the tumor entities and grades.

We addressed the question of whether the tumor location correlated with the grade of the tumor. A significant correlation ($P < .005$; $\chi^2$ test) between tumor location, classified tumor location, tumor entity, and tumor grade could be shown, with more high-grade tumors presenting at an infratentorial location and more low-grade tumors with a supratentorial location. The 8 cases where the tumor grade could not be established were excluded from this analysis.

### Interval Between Symptom Onset and Diagnosis

Special emphasis was given to the interval between the onset of initial symptoms of the tumor and the definitive diagnosis. The median interval between symptom onset

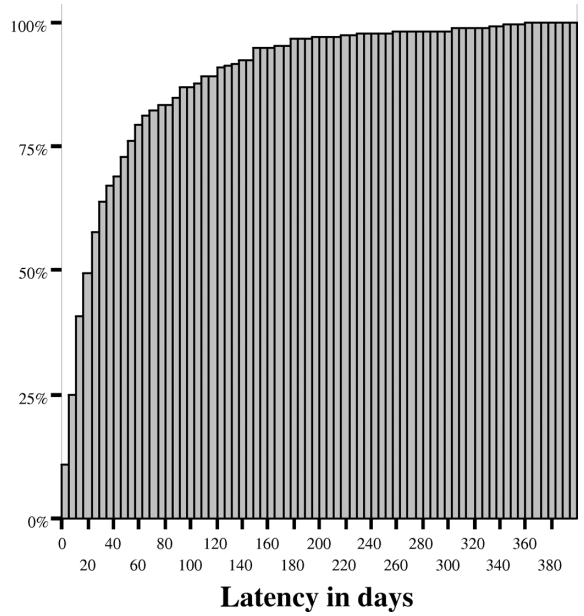


**Figure 2.** Cumulative distribution of the interval between symptom onset and diagnosis in days. Twenty-five percent of the patients had received their diagnosis after 12 days, 50% after 24 days, and 75% after 58 days. To facilitate the display, the range of this histogram has been shortened to 400 days.

and diagnosis was 24 days (mean, 59.3 days), with a minimum of 0 and a maximum of 795 days. In 74.3%, diagnosis was achieved during the first 8 weeks, in 86.1% during the first 4 months, and in 92.7% during the first 6 months. Seven patients received diagnosis on the same day following an acute symptom onset. Twenty-five percent of the patients were diagnosed after 12 days, 50% after 24 days, and 75% after 58 days. See Figure 2 for a cumulative distribution.

For the following statistics the Kaplan–Meier plot, log rank test, and Cox regression have been used. The influence of single symptoms, tumor location, tumor grade, age of the patient, specialty of the treating doctor, and the year of diagnosis on the interval between symptom onset and diagnosis were also analyzed using the log rank test.

Of those parameters, tumor grade ($P < .005$), the appearance of the symptoms of disturbed motor function ($P < .001$), disturbed vigilance ($P < .05$), and change in growth ($P < .05$) positively correlated with a shorter interval between symptom onset and diagnosis.

A multivariate analysis, the Cox regression model with stepwise inclusion, was then performed with the catalogue of primary symptoms, the tumor location, and the tumor grade to investigate the existence of parameters that have an independent influence on the interval between symptom onset and diagnosis. Of all parameters, 6 were included in the analysis indicating an independent, significant influence on the interval between symptom onset and diagnosis. Those parameters were tumor grade ($P < .005$), disturbed motor function ($P < .005$), other focal dysfunction ($P < .05$), early morning vomiting ($P < .05$), disturbed eye motility ($P < .05$), and disturbed vigilance ($P < .05$).

## Discussion

Pediatric brain tumors differ in several ways from the adult tumor collective because of different tumor entities, location, and age-dependent circumstances, for example, an open fontanelle, open cranial sutures, and the age-dependent capability to reflect and articulate symptoms of tumor progression.[4] Due to the closeness to vitally important structures of the central nervous system, the prognosis of brain tumors especially depends on their expansion as even a small increase in size can have a dramatic effect on the patient's condition. Any delay before diagnosis may lead to further progress and decrease the chances of successful treatment. Considering the unspecificity of symptoms, other studies have found considerable doctors' delays after the first consultation, despite the parents' concern.[3,13] In 1 study, several parents reported not only that professionals often failed to put the presented symptoms at each consultation into context, but also that communication between parents and medical professionals in general was difficult and the parents' complaints not taken seriously enough.[13]

To evaluate the interval between the diagnosis and the onset of symptoms that were retrospectively reported as first symptoms of the tumor, we analyzed the data of our brain tumor collective treated in the Department of Neuropediatrics at the University of Muenster between 1980 and 2004. Additionally, we analyzed the kind of first symptoms to evaluate symptoms that should alert general practitioners and pediatricians. Our patient cohort is in accordance with what was expected from the literature regarding age, gender, tumor entity, grade, or location.[1,2,14]

More cranial computer tomographies than magnetic resonance tomographies were performed to confirm diagnosis in our study, because of the start of our period of examination. During the 1980s and beginning of the 1990s, computer tomography was the standard procedure in brain tumor diagnostics, until magnetic resonance tomography became more widely available.

In our study, neither patient gender nor age had a statistically significant influence on the interval between symptom onset and diagnosis. We observed a significantly shorter interval between symptom onset and diagnosis in high-grade tumors, but no correlation was found regarding the tumor location. By definition, high-grade tumors expand and affect healthy tissue more rapidly than low-grade tumors, thus provoking symptoms at an earlier stage. EEG findings correlated positively with the tumor location, indicating that infratentorial tumors tend to show either unspecific or more often no EEG abnormalities at all, whereas supratentorial tumors, especially when

located in the hemispheres often present focal EEG pathologies. As those foci often mirror the location of the tumor, the EEG can be regarded as an additional and functional method to underline an assumption in regard to the location of a tumor.[15,16]

We found that not only tumor location but also tumor grade had a statistically significant influence on the pattern of primary symptoms. While early morning vomiting and ataxia/gait abnormalities occur more frequently in high-grade tumors and infratentorial tumors, the symptom of disturbed vision was more frequent in patients with low-grade and supratentorial tumors. These findings are influenced by the high number of low-grade craniopharyngiomas as mostly supratentorial and high-grade medulloblastomas as mostly infratentorial tumors causing these specific symptoms. Seizures and the group of other focal pathologies occurred more often in supratentorial tumors, but were not influenced by the tumor grade. This finding is helpful information, especially before cerebral imaging is performed, as it narrows down the regions where tumor growth is probable.

The number of individual symptoms a child presented at the onset of symptoms had no statistical influence on the interval between symptom onset and diagnosis in our study. Some of the primary symptoms correlated positively with a shorter interval between symptom onset and diagnosis, for example, disturbed motor function, other focal disorders, early morning vomiting, disturbed vigilance, and disturbed eye motility in the multivariate analysis and additionally change in growth/weight in the univariate analysis. In our study, less frequent but more specific symptoms, such as motor dysfunction or other focal disorders, were perceived faster and led to an earlier diagnosis than more common but unspecific symptoms, such as headaches or ataxia/gait abnormality.

The only symptom that was frequent, not too unspecific, and that shortened significantly the interval between symptom onset and diagnosis was early morning vomiting. Although vomiting in general is a frequent symptom to many different medical conditions, the emphasis on early morning occurrence was often correctly interpreted as a possible symptom of increased intracranial pressure leading to further diagnostic steps and can, therefore, be used as a marker symptom of possible tumor growth.

The symptom of change in growth/weight, which also correlated significantly with a shorter interval between symptom onset and diagnosis in the univariate analysis, was reported most frequently by patients who suffered from frequent early morning vomiting (weight loss, 17/19 = 89.5%) or were diagnosed with a craniopharyngioma or another tumor in the suprasellar region (change in growth, 7/10 = 70%). Therefore, these symptoms might be helpful as they can be indicative regarding the probable tumor entity. Especially, failure to thrive is indicative of an affection of the pituitary pathways and a strong clue to the existence of a craniopharyngioma.

Surprisingly, none of the many other symptoms had a statistically significant influence on the interval between symptom onset and diagnosis. Headaches, ataxia, or dizziness are also common symptoms of intracranial tumor growth but had no statistically relevant influence. Headaches alone are obviously too common and unspecific to be perceived as a warning sign. At the age of 16 years, more than 93% of all adolescents have already experienced at least 1 episode of fierce headaches, mostly due to benign causes.[17] Abu-Arafeh and Macleod have analyzed the data of children with chronic headaches, reporting that serious intracranial pathology is rarely the cause of chronic headaches.[18] The different kinds of brain tumor headaches in children have been analyzed by Honig and Charney,[19] underlining the value of a detailed interrogation and meticulous neurological and ophthalmological examination regarding possible cosymptoms of the tumor. Another study analyzed the cost-effectiveness of cerebral imaging in children with headaches,[20] indicating that children with a high risk of having a brain tumor profited most from magnetic resonance tomography. However, to establish the individual risk of a patient, detailed interrogation and neurological examination were crucial.

Ataxia and gait abnormalities, however, seem to be more specific signs but are still frequently underestimated. Ataxia and gait abnormalities can be difficult to observe especially in younger children who have not yet learned to walk steadily. Commonly, these symptoms might be misinterpreted by parents leading to no medical contact. Ataxia is probably a well-known brain tumor symptom for most medical professionals, thus making a targeted question concerning an increasing clumsiness or a regression in formerly well-commanded activities such as riding a bicycle helpful.

Typical brain tumor symptoms such as head tilt or neck stiffness are rarely observed in time or misinterpreted as orthopedic problems. Especially in older children, mood changes or cognitive problems might be attributed to puberty or character traits and are, therefore, only retrospectively estimated as tumor-related.

The median interval between symptom onset and diagnosis in our study of 24 days is distinctly shorter than the median intervals described in other studies (Gjerris et al: 6 months; Flores et al: 42 days; Pollock et al: 31 days; Mehta et al: 90 days; Dobrovoljac et al: 60 days).[2–6]

A general problem of this as well as other retrospective studies is the acquisition of data based on the admission forms of the patients. Results must, therefore, be interpreted with caution, as the plausibility of the data depends not only on the reliability of the patients' and their parents' statements, but also on the experience and interpretation of the admitting physician. However, because the former studies on this topic are also retrospective studies, differences in the time span are not likely to be caused by different study designs.

Gjerris,[2] Flores et al,[4] and Pollock et al[6] investigated patient data from the 1970s and 1980s. Computer tomography was not used as a standard diagnostical procedure until the mid-1980s, and magnetic resonance tomography was introduced even later. Mehta et al[5] and Dobrovoljac et al[3] collected patient data during the 1990s, when computer tomography and magnetic resonance tomography had been introduced, but were not yet available in every hospital, especially in rural areas. Both studies are located in countries with a considerable proportion of rural regions where the possibilities of neuroimaging are limited.

In contrast, in Germany, computer tomography and magnetic resonance tomography are widely available and performed regularly and without relevant time delay. We also assume that, because in Germany every patient has health insurance, and costs are covered by the insurance company, consultants and parents might be less reluctant to consider cerebral imaging even in cases of doubt, thus shortening the interval between symptom onset and diagnosis

The difficult task of dealing with parents' concerns appropriately, of evaluating unspecific primary symptoms correctly, and of carrying out cerebral imaging at an early stage, remain the most important steps toward an earlier diagnosis of pediatric brain tumors. In cases of doubt, primary care consultants should form a habit of taking a detailed history giving the most common symptoms and those statistically relevant, such as early morning vomiting, motor dysfunction, disturbed vigilance, disturbed eye motility, and change in growth/weight, a special emphasis. As the only measure to rule out a cerebral pathology is high-quality cerebral imaging using magnetic resonance tomography, it should always be initiated in children presenting 1 or a combination of symptoms.

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