Most central nervous system tumours in children are diagnosed with little delay after admission

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ABSTRACT

INTRODUCTION: Children with central nervous system (CNS) tumours often have a long symptom interval before diagnosis. We investigated delays in diagnosis and surgical management after the first admission with tumour-related symptoms.

MATERIAL AND METHODS: This study reviewed the medical records of 46 consecutive children with a CNS tumour admitted to a paediatric department. Clinical findings at the time of the first admission, duration of symptoms, time to radiological diagnosis and time to initial surgical procedures were recorded.

RESULTS: The series comprised 26 supratentorial, 19 fossa posterior and one spinal tumour with equal numbers of high-grade and low-grade tumours. Headache, vomiting and lethargy were the most frequent symptoms, and pre-admission delay depended on tumour grade as well as location. Six cases had been diagnosed prior to admission; of the 40 undiagnosed cases, 32 (80%) were scanned within four days, but in four cases (10%) diagnosis was delayed for more than a week. Resection was performed within four days of diagnosis in 68% of children with resectable tumours (21/31). Initial surgical management of tumours causing hydrocephalus was completed within four days of diagnosis in 83% (20/24).

CONCLUSION: Delay in diagnosis and surgical management after the primary admission with symptoms caused by a tumour may influence the outcome negatively. In this review from a small centre, the majority of the cases were diagnosed and managed surgically within four days of admission and diagnosis, respectively. Criteria for good performance, i.e. accepted standards for time to diagnosis and intervention, need to be specified.

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Despite therapeutic advances, children with central nervous system (CNS) tumours still have a rather poor prognosis, the five-year survival being 65-70% [1], and the incidence of significant disabilities among survivors is high [2, 3]. The median interval from onset of symptoms to diagnosis is two months or more [4-8], and diagnostic delay may play a role in the development of disabilities [9]. Consequently, guidelines to assist healthcare professionals in early referral of these children have been introduced [10]. Delays occurring after hospital admission have attracted less attention. Benchmark standards for management after referral have been specified [11], but studies describing current practice are sparse [12]. Post-admission delays may contribute to a poor outcome.

We have reviewed an eleven-year consecutive series of children treated at a single paediatric oncology centre. The primary purpose was to describe the process of diagnosis and management after first admission with tumour-associated symptoms and to analyse the process in relation to clinical presentation and radiological findings. The aim was to evaluate our clinical efficiency.

MATERIAL AND METHODS

Medical records were reviewed for all children aged 0-17 years treated for a primary CNS tumour at the Paediatric Neuro-oncology Service, Aalborg University Hospital, Denmark, from January 2000 to December 2010 (n = 51). Children with pituitary adenomas causing exclusively endocrine manifestations (n = 4) and one child with congenital medulloblastoma who died shortly after birth were excluded, leaving 46 cases for study. The children were referred, with or without tumour suspicion, from primary care physicians or, occasionally, from secondary care departments, to one of three paediatric departments in the region. The Neurosurgical Department was involved after the diagnosis was made.

We obtained data on the date of first admission to a paediatric department with tumour-related symptoms, sex and age of the child, and duration from onset of symptoms to admission. The main symptoms were recorded and categorised (headache, vomiting, lethargy, seizures, visual impairment, gait disturbance). Physical findings present on admission were noted (level of consciousness, neurological deficits, blood pressure, and papilloedema).

The dates of diagnostic imaging, computerised tomography (CT) and/or magnetic resonance imaging (MRI) were recorded and the time from admission determined. From the descriptions, the following tumour characteristics were noted: location, size (mm in largest diameter), peritumoral oedema, presence and degree of hydrocephalus. Depending on location, tumours were classified as supratentorial (ST: hemispheric, central,

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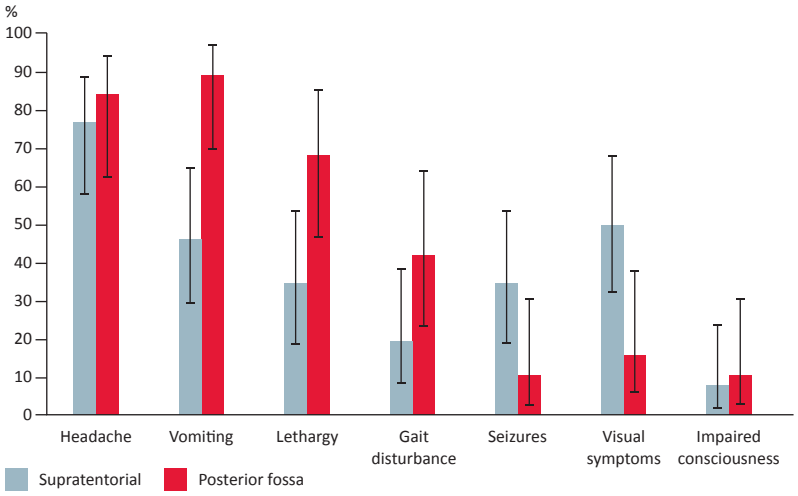
FIGURE 1

Frequency of symptoms in 26 children (21 aged > 5 years) with supratentorial and 19 children (11 aged 0-5 years) with posterior fossa tumours. A child with spinal ependymoma presenting with gait disturbance is not included.



pineal, mesencephalic), posterior fossa (PF: cerebellar, fourth ventricle, pons) or spinal. The dates of initial neurosurgical interventions (third ventriculostomy, placement of ventriculoperitoneal shunt, stereotactic biopsy, surgical resection) were noted and the time from admission and diagnosis determined. Pathology reports were reviewed and tumour histology specified using the International Classification of Childhood Cancer, third edition [13]. For tumours not resected or biopsied, a presumed histology was stated based on imaging characteristics. Tumours were classified as low-grade (LG: grade I-II) or high-grade (HG: grade III-IV) according to the World Health Organization's classification [14].

Data were entered into a study database approved by the data-regulating authorities. Registration was anonymous. The retrospective design obviated requirement for ethical approval and informed consent. Data were analysed using descriptive statistics. Some proportions were compared using Fisher's exact test. Associations were assessed by means of odds ratios (OR) with 95% confidence intervals (CI).

Trial registration: not relevant.

RESULTS

The series comprised 30 boys and 16 girls with a median age of eight years (range 1-17 years). The tumour was ST in 26 cases, located in PF in 19, and in the spinal cord in one case. ST and PF tumours were equally large (average 43 versus 45 mm), while HG tumours were larger than LG tumours (51 versus 39 mm). PF tumours caused hydrocephalus in 16/19 (84%) cases, ST tumours in 10/26 (38%). HG and LG tumours were equally represented: Among ST tumours, 13 were HG (primitive neuroectodermal tumour 4, glioblastoma 4, germinal cell tumour 2, atypical teratoid rhabdoid tumour 1, anaplastic meningeoma 1, anaplastic oligodendroglioma 1) and 13 LG (astrocytoma 6, craniopharyngeoma 3, unspecified 3, oligodendroglioma 1); among PF tumours, 9 were HG (medulloblastoma 7, ependymoma 1, plexus carcinoma 1) and 10 LG (astrocytoma 7, pontine glioma 2, ependymoma 1). The spinal tumour was LG (ependymoma). Tumour location and grade differed in young and older children. In 17 children aged 0-5 years, most tumours were located in the PF (65%) and most were HG (59%). In 29 children aged 6-17 years, the majority were ST (72%) and LG (59%).

The majority of children had symptoms of increased intracranial pressure: headaches 78%, vomiting 63% and lethargy 48%. Consciousness was impaired on arrival in 9%. Visual symptoms had been noted in 35%, gait disturbance in 33%, and seizures had occurred in 24%. Symptom frequencies differed depending on tumour site (**Figure 1**). PF tumours had significantly higher frequency of vomiting (89% versus 46%, OR 9.9, CI 1.9-51.9) and lethargy (68% versus 35%, OR 4.1, CI 1.2-14.4), ST tumours of visual problems (50% versus 16%, OR 5.2, CI 1.2-22.8). Vomiting was more frequent in children with hydrocephalus (81% versus 42%, OR 5.8, CI 1.5-21.9). The duration of symptoms ranged from a few days to more than one year (five cases) with a median of two months. Determined from onset of symptoms, 15% were admitted to hospital within one week, 39% within one month, 61% within three months, and 76% within six months. Time to admission was considerably shorter for PF tumours than for ST tumours, the majority being referred in less than two months, and in both groups time to admission was shorter for HG than for LG tumours (**Figure 2**A). Preschool children, in whom PF tumours predominated, had a shorter time to admission than school-age children (Figure 2B).

Six children were diagnosed before admission, four by a scan on the preceding day. In the 40 undiagnosed cases, a scan was performed on the day of admission in 58%, the following day in 15%, and later in the first week in 18% (weekends and holidays included). After four days, 32/40 (80%) had been diagnosed. In two cases, diagnosis was delayed for more than three weeks: a plexus carcinoma in the fourth ventricle in a one-year-old girl with failure to thrive, vomiting and obstipation in whom Hirschsprung's disease was suspected; and a diffuse hemispheral oligodendroglioma in a girl with acute hemiparesis misinterpreted initially as encephalitis. Until 2005, the initial diagnostic imaging modality was CT in 19/23 (83%) cases, followed by an MRI usually on the same or following day (12/19). In 2006, the MRI capacity

FIGURE 2

Pre-admission diagnostic delay: Cumulative percentage of children who have been admitted to hospital after onset of symptoms. **A.** Comparison of children with high-grade (n = 9) or low-grade (n = 10) posterior fossa tumours and with high-grade (HG) (n = 13) or low-grade (LG) (n = 13) supratentorial tumours. **B.** Comparison of preschool children aged 0-5 years (n = 17) and school-age children aged 6-17 years (n = 29).

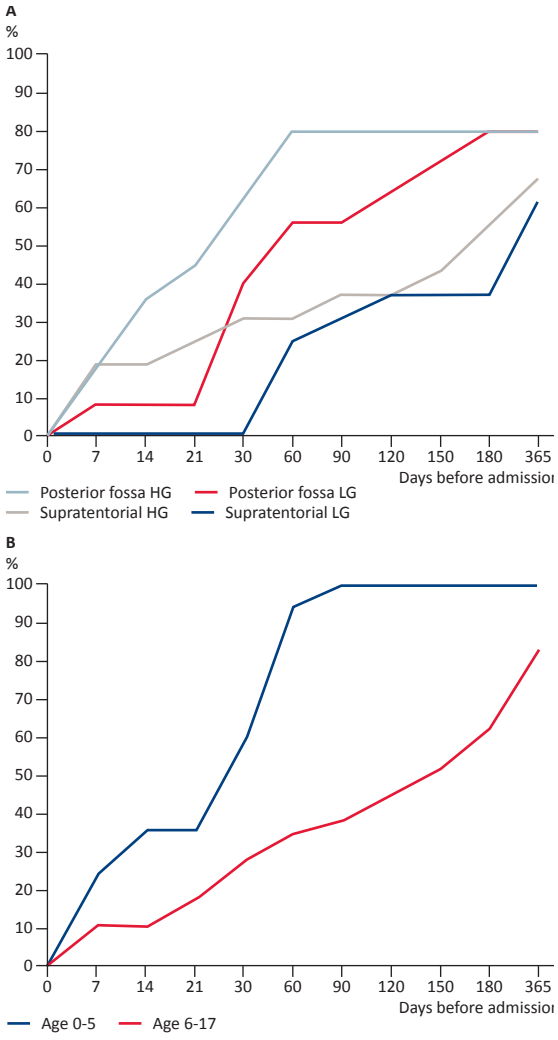
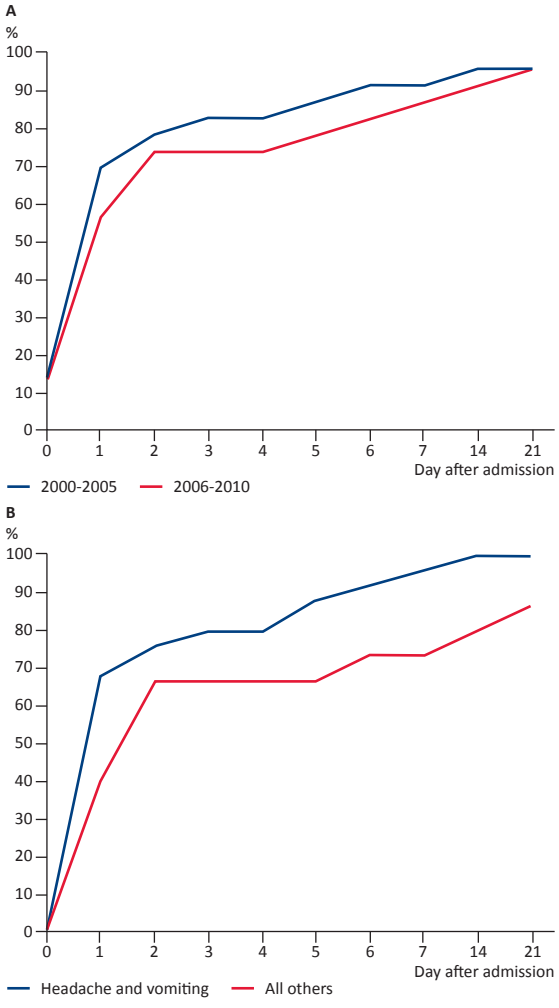


FIGURE 3

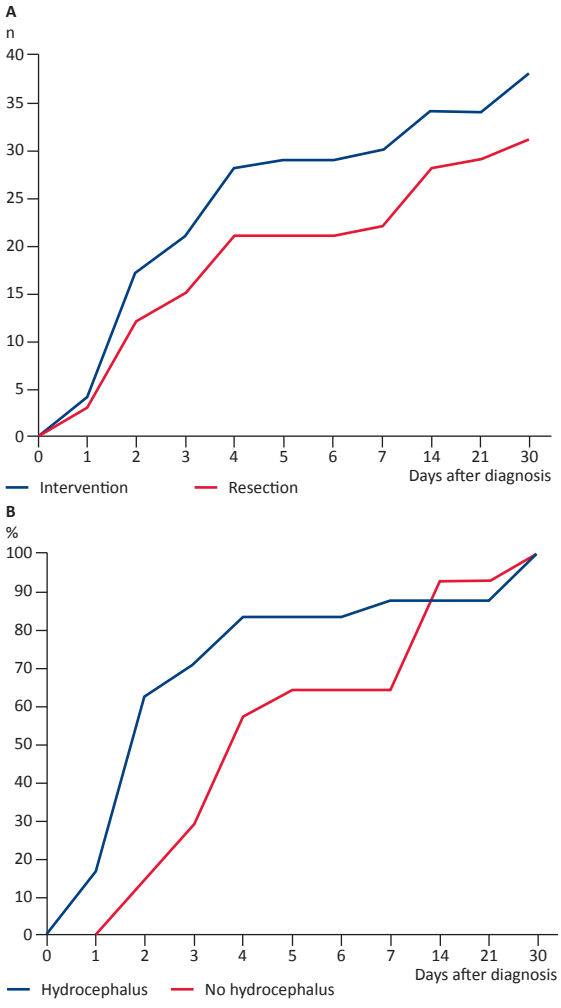
Time from first hospitalisation with tumour symptoms to diagnosis: cumulative percentage of children diagnosed by imaging in the days following admission. Note the changing units in time axis. **A.** Comparison of diagnosis before (n = 23) and after (n = 23) the magnetic resonance imaging capacity was increased in 2006. In both periods, three children had been diagnosed at the time of admission. **B.** Comparison of diagnosis in children with the combination of headache and vomiting (n = 25) versus those with only one or none of the two symptoms (n = 15).



was increased as part of a national cancer management plan, making MRI the preferred initial modality (16/23, 70%). After 2006, fewer children were diagnosed on the day of admission (57% versus 70%), but after two days the diagnostic rate was identical (74% versus 78%) (**Figure 3**A). Diagnostic scanning was somewhat delayed in children who did not have both headache and vomiting (Figure 3B). Tumour resection was undertaken in 31 cases, in two preceded by a shunting procedure. The rate of partial or complete resection was 13/26 for ST tumours, 17/19 for PF tumours, and 1/1 for spinal tumour. Biopsy was performed in five of the remaining cases, in one combined with shunting. Ten tumours were considered unresectable or were selected for non-surgical observation or management, but with shunt insertion in two cases. These tumours were hemispheral (n = 2), central (n = 3), mesencepalic (n = 2), pontine (n = 2) and pineal (n = 1). Thus, neurosurgical intervention was performed in 40 cases. In 17 (43%), primary intervention was performed on the day of diagnosis or the following day. Four days after diagnosis 28/38 (74%) procedures and 21/31 (68%) resections had been performed (**Figure 4**A). Hydrocephalus was the main determinant of rapid intervention, with 15/24 (63%) initial procedures being completed within two days of diagnosis (Figure 4B).

FIGURE 4

Time from diagnosis to neurosurgical intervention in 38 children with central nervous system tumour: absolute numbers (**A**) and cumulative percentages (**B**) for children in whom a neurosurgical procedure was performed in the days after diagnosis. A. Absolute numbers for initial procedure (shunting procedure, biopsy, resection, n = 38) and complete or partial resection (n = 31). B. Comparison of intervention rates for children with (n = 24) and without (n = 14) hydrocephalus.



DISCUSSION

This retrospective single-centre study of an unselected cohort of 46 children with primary CNS tumours describes initial management after admission with tumour-related symptoms. We found that 80% of undiagnosed tumours were detected within four days and 65% of tumours amenable for surgery had been partially or completely resected within four days of diagnosis. Hydrocephalus was the most important determinant of time from diagnosis to intervention. The review of the clinical presentation of the children yielded results according to expectations, i.e. symptoms depend on tumour location and presence of hydrocephalus, and duration of symptoms depends on tumour grade.

The patient series is complete and unselected, including all cases under 18 years of age from our centre, but the validity of our findings may be limited for two reasons. First, the cohort is small so some of the multiple different CNS tumour subgroups are likely to be over- or underrepresented. Thus, there were fewer astrocytomas/other gliomas (36%) and more embryonal tumours (28%) than expected, population figures being approximately 50% astrocytomas/other gliomas, 15-20% embryonal tumours and 10% ependymomas [15]. Similarly, the equal representation of LG and HG tumours and the excess of boys must also be attributed to the small sample size. The variability in composition of small series is evident compared with another Danish series of 46 children in which LG tumours and girls predominated [8]. Second, retrieval of data by review of records may be subject to biases and inaccuracies, especially regarding symptoms and their duration. The dates of admission, scanning and surgical procedures, however, are not subject to error, and the description of the patient management is therefore accurate.

The delay from onset of symptoms to admission is well known, and the median interval of two months in this study corresponds to previous reports [4-8]; in a recent Danish study, the median interval from first presentation to the general practitioner until diagnosis was one month [16]. A long symptom interval indicates a better prognosis [4, 7] since short intervals are associated with faster growing HG tumours [17]. In our series, the majority of children admitted within one month had a HG tumour. The diagnostic delay is influenced by the symptoms [8, 18] which depend on tumour location. It has been reported that classic pressure symptoms are present in under half of children with intracranial tumours [19], but in our series most children had headaches and/or vomiting, and half had become lethargic. Most children with PF tumours had symptoms of increased intracranial pressure and were admitted within one month, and none had a symptom duration longer than six months. ST tumours may be more difficult to recognise because pressure symptoms are less frequent. Visual deterioration or seizures were frequent manifestations of ST tumours, and headaches in children with these two symptoms should increase suspicion of a CNS tumour. The development of lethargy should be considered a "red flag" as pointed out in the guidelines for early referral [10].

Reduction of post-admission delays may also contribute to better outcomes [9]. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) has described treatment timelines and benchmark standards [11] that may be used to evaluate clinical practice. Thus, Goodden et al reviewed local practice for children with a tumour diagnosis, determining times

to post-operative imaging, histological results, disclosure of diagnosis to patient and family, and start of adjuvant therapy [12]. Our focus was different, viz. the time to diagnosis and neurosurgical treatment after admission to a paediatric department with tumour-related symptoms. In Denmark, an integrated pathway for children with suspected CNS tumours has been implemented, but the only waiting time requirement is for radiological imaging which must take place within three calendar days after referral [20].

Three quarters of children were radiologically diagnosed within two days of admission. A delay of two days may be ascribed to admission before a weekend, but about 10% were not diagnosed one week after admission, which suggests that a tumour was not immediately suspected. Doctor's delay from first consultation to diagnosis has been described [5], but to our knowledge no previous reports have described the post-admission "paediatrician delay". Benchmark standards in the NICE guidelines mainly concern management after the tumour has been found by diagnostic imaging [11]. Guidelines for imaging [10], however, apply equally before and after hospital admission and could help reduce post-admission delay. Worthy of note, the rate of diagnosis on the day of admission declined after the MRI capacity was increased in 2006, probably due to requirement for general anaesthesia in young children.

After diagnosis, the tumour should be resected by a paediatric neurosurgeon as soon as possible, promptly when needed. Benchmark standards for the time from diagnosis to surgery have not been established. In our analysis of practice, 65% of resections were performed within four days of diagnosis, but 10% were delayed for more than two weeks. The prognostic importance of the time to surgery is unknown, but in absence of pressure symptoms, postponement for a few days is probably unimportant. The presence of significant hydrocephalus, on the other hand, is an indication for rapid neurosurgical pressure relief. This should be established by resection alone or by ventriculostomy if possible; otherwise, temporary external drainage or insertion of a ventriculoperitoneal shunt is necessary. In this series, hydrocephalus was present in more than half, and drainage or resection was performed within two days of diagnosis in 63% of these cases. There are no published data with which we can compare these indicators of clinical performance. The frequency of urgent intervention, reflecting a poor clinical condition with threatened incarceration, underscores the need for earlier referral [10].

CONCLUSION

We have described the diagnostic and surgical performance of a single centre in the initial management of children with symptoms from a CNS tumour. We have found the cumulative rate charts useful in the analysis of practice. Overall, 90% of cases were diagnosed within one week of admission and 80% were managed surgically within one week of diagnosis. It should be noted that the analysis did not comprise the quality of interventions – degree of resection, complications, sequelae and outcome. Our centre is the smallest in Denmark, but short communication lines between paediatric, radiological and surgical team members probably facilitate rapid decision making. This study has established a basis for comparison against which future practice can be evaluated. The study also indicates the need to define accepted standards for timely diagnosis and intervention, against which performance can be measured in the continuing efforts to improve outcomes for children with CNS tumours.

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