Symptoms and time to diagnosis in children with brain tumours

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ABSTRACT
INTRODUCTION: Clinical symptoms in brain tumours in children are variable at onset and diagnosis is often delayed. Symptoms were investigated with regard to brain tumour localisation, pre-diagnostic symptomatic intervals and malignancy.

MATERIAL AND METHODS: Clinical data from children aged 0-17 years from Southern Denmark were analysed retrospectively and the results were correlated with data on prehospital symptoms obtained from interviews with parents and general practitioners.

RESULTS: A total of 55 children diagnosed during a period of five years were indentified and 31 interviews were obtained. A total of 19 (41%) of the tumours were supratentorial hemispheric and midline and 27 (59%) were infratentorial. At supratentorial localisations, 42% experienced vomiting as their first symptom followed by seizures in 37% and headache in 31%. At infratentorial localisations, headache occurred in 62%, vomiting in 55% and ataxia in 48% of the cases. The pre-diagnostic symptomatic interval had a median duration of 30 days with vomiting (range 3-330 days), a median of 75 days with headache (5-730 days) and a median 75 days with ataxia (1-730 days).

CONCLUSION: Diagnosis is often late in relation to the presenting symptoms. An earlier diagnosis may be achieved if a brain tumour is considered as soon as any child presents with the relevant symptoms.

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Brain tumours (BTs) of the central nervous system account for approximately 25% of all cancers in children aged 1-19 years. Nearly 70% of children with BTs are cured owing to multimodal treatment approaches, but many suffer significant long-term deficits involving physical, sensory, cognitive, neurologic and endocrine complications [1]. It is not known whether early diagnosis contributes significantly to a better prognosis and reduced long-term deficits, but the diagnosis is often delayed due to the insidious onset of symptoms which depends on the localisation of the BTs [2].

The aim of this retrospective case note review and interview study was to evaluate early clinical symptoms, localisation and type of BTs in children aged 0-17 years living in the Southern Denmark Region who were diagnosed between 1 January 2004 and 31 December 2009, as well as to evaluate their pre-diagnostic symptomatic interval (PSI).

MATERIAL AND METHODS
Children aged 0-17 years with BTs diagnosed during the aforementioned period were identified from the Danish Cancer Registry and the regional patient registry (FPAS). The International Classification of Diseases 10 codes C71.0-71.9, D33.0-33.2, D33.9 and DD35.3 were applied, and data from medical charts were analysed together with data from telephone interviews with parents and general practitioners.

The details collected included age at diagnosis, gender, death prior to 1 June 2010, clinical symptoms, neurological deficits obtained from clinical examination, BT localisation, type and staging. Pituitary tumours and tumours localised to the eye and optic nerves were excluded in cases with endocrine symptoms only or neurological or other local symptoms at diagnosis.

A histology classification was performed according to the International Classification of Childhood Cancer, third edition [3].

PSI was staged as the time from the parents’ first account of symptoms to their first contact to the general practitioner (PSI-1), from the time of the first consultation with a general practitioner to referral (PSI-2) and from the time the letter of referral was received at hospital until the diagnosis was made by computed tomography and/or magnetic resonance imaging, prompting further referral to a centre for child oncology (PSI-3). Sudden symptom onset followed by acute admission within 24 hours was not considered a delay.

Trial registration: ISRCTN88306789.

RESULTS
Patient contacts
A total of 55 patients were identified. Among those, seven were excluded because of pituitary tumours. Another two patients who had optic glioma were also excluded. Thus, 46 children were included and their data...
TABLE 1

Reported symptoms of brain tumours, duration and relation to localisation and malignancy.

<table>
<thead>
<tr>
<th>Symptoms at any time before diagnosis, n (%)</th>
<th>Duration of symptom, days, median (range)</th>
<th>Supra-/infratentorial localisation, n (%)</th>
<th>Benign/malignant tumour, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting 23 (50)</td>
<td>30 (3-330)</td>
<td>8/15 (42/55)</td>
<td>9/14 (36/66)</td>
</tr>
<tr>
<td>Headache 23 (50)</td>
<td>75 (5-730)</td>
<td>6/17 (32/63)</td>
<td>12/11 (48/52)</td>
</tr>
<tr>
<td>Ataxia 16 (35)</td>
<td>75 (1-730)</td>
<td>3/13 (16/48)</td>
<td>7/9 (28/43)</td>
</tr>
<tr>
<td>Drowsiness 12 (26)</td>
<td>25 (1-730)</td>
<td>5/7 (26/30)</td>
<td>6/6 (24/28)</td>
</tr>
<tr>
<td>Nausea 13 (28)</td>
<td>30 (3-300)</td>
<td>5/8 (25/30)</td>
<td>6/7 (24/33)</td>
</tr>
<tr>
<td>Anorexia 10 (22)</td>
<td>30 (4-330)</td>
<td>1/9 (5/33)</td>
<td>2/8 (8/38)</td>
</tr>
<tr>
<td>Reduced psychomotor development 7 (15)</td>
<td>75 (7-730)</td>
<td>3/4 16/15</td>
<td>6/1 (24/5)</td>
</tr>
<tr>
<td>Seizures 9 (20)</td>
<td>90 (1-365)</td>
<td>7/2 (17/7)</td>
<td>9/0 (16/0)</td>
</tr>
<tr>
<td>Fine motor difficulties 7 (15)</td>
<td>240 (18-730)</td>
<td>3/4 (16/15)</td>
<td>6/1 (24/5)</td>
</tr>
<tr>
<td>Double vision 6 (13)</td>
<td>7 (1-210)</td>
<td>1/5 (5/18)</td>
<td>3/3 (12/14)</td>
</tr>
<tr>
<td>Vertigo 5 (11)</td>
<td>60 (1-270)</td>
<td>2/3 (10/11)</td>
<td>1/4 (4/19)</td>
</tr>
<tr>
<td>Clumsiness 4 (9)</td>
<td>45 (1-730)</td>
<td>2/2 (10/7)</td>
<td>3/1 (12/5)</td>
</tr>
<tr>
<td>Apathy 6 (13)</td>
<td>25 (1-225)</td>
<td>3/3 (16/11)</td>
<td>2/4 (8/19)</td>
</tr>
<tr>
<td>Irritability 3 (7)</td>
<td>2 (1-730)</td>
<td>0/3 (0/11)</td>
<td>2/1 (8/5)</td>
</tr>
<tr>
<td>Squinting 3 (7)</td>
<td>3 (1-120)</td>
<td>1/2 (5/7)</td>
<td>1/2 (4/9)</td>
</tr>
</tbody>
</table>

Analysed. Nine died prior to 1 June 2010 and for ethical reasons their parents were not contacted. The parents of six children could not be contacted. A total of 31 interviews were thus conducted.

The median age at diagnosis was 8.4 years (2 months-17.4 years) and the male-to-female ratio was 1:1.2 (21 males and 25 females).

Tumour classification
The pathological diagnosis was ependymomas in seven cases, choroid plexus tumours in two (IIia) cases, astrocytomas in 15 (IIib) cases, medulloblastomas in 11 cases, spinal PNET tumours in three cases and atypical teratoid/rhabdoid tumours in two (IIIc) cases. Mixed and unspecified gliomas were seen in four (IIId) and neuronal and mixed neuronal-glial tumours in one together with meningeoma in one (IIle) case. A total of 25 tumours were benign and 21 malignant. The tumour localisation was classified as supratentorial (hemispheric and midline) in 19 (41%) and infratentorial in 27 (59%) cases.

Symptoms before diagnosis
The most frequent clinical symptom at diagnosis was vomiting, which occurred in 23 (50%). In 20 children (87%), vomiting was present in the morning or occurred at other times during the day, while 13% had no vomiting in the morning. In eight (35%) cases, the vomiting was characterised as explosive. Headache was present in 23 cases, was focal in character in 16 (69%), awoke the child from sleep in nine (39%), had no effect of analgesics in six (26%) and was worsened by use of the Val-salva manoeuvre in nine (39%) cases. Ataxia occurred in 16 (35%) cases.

At supratentorial localisations, 42% had vomiting as a symptom at any time before diagnosis, followed by seizures in 37% and headache in 31% of cases. At infratentorial localisations, headache occurred in 62%, vomiting in 55% and ataxia in 48% of the cases. Duration of the symptoms and their relation to localisation and malignancy are illustrated in Table 1 with the duration of symptoms spanning from one day in cases with squinting to 730 days in cases with fine motor difficulties.

Objective findings
The objective findings at diagnosis were: Motor signs with paresis in eight (17%) cases, abnormal finger-nose test in eight (17%), hyperreflexia in five (11%), positive Romberg’s sign in four (9%), increased muscle tone in three (7%), hypoflexia in two (4%), clonus in two (4%), decreased muscle tone in one (2%) and abnormal knee-heel test in one (2%). In relation to cranial nerves, double vision was observed in eight (17%), nystagmus in seven (15%), head tilt in six (13%), palatal palsy in four (9%), abnormal eye movement in three (7%), downward deviation of eyes in one (2%), difficulties swallowing in one (2%) and deviation of tongue in one (2%) case.

Papilloedema was diagnosed in four (9%) and reduced vision in one (2%) case.

Reduced hearing was observed in two (4%) cases.

Mortality
Within four years of diagnosis, nine of the 46 children died, including three out of 11 with medulloblastomas, two out of seven with grade two ependymoma, two out of two with rhabdoid tumours and one out of two with a choroid plexus tumour. One child had pons glioma, representing the only benign tumour with a fatal outcome.

As a result, death occurred in one out of the 25 children (4%) with benign tumours and in eight out of the 21 children (38%) with malignant tumours.

Pre-diagnostic symptomatic interval
The median duration of PSI-1, i.e. the time from the first symptom observed by parents to their first contact with a general practitioner, was seven days (range 0-365); PSI-2, i.e. time from first evaluation by a general practitioner to referral, was nine days (range 0-730), and PSI-3, i.e. time from received referral letter to a confirmed diagnosis, was six days (range 0-231). The total PSI was 66 days (range 0-730).

The total PSI according to the initial symptoms is shown in Table 1. PSI-1, PSI-2, PSI-3 and total PSI in relation to benign and malignant tumours and supratentorial and infratentorial localisation are shown in Table 2.
The data demonstrate a lower median total PSI in malignant than in benign tumours.

DISCUSSION

BTs are relatively common in children, affecting 3,983 children aged 1-14 years out of a population counting 4.4 million children in a Nordic study during the 1985-2006 period [4]. According to a Danish Cancer Registry report from 2009, the prevalence was 130 boys and 126 girls. As approximately 20% of children live in the Southern Danish region, the expected prevalence was 51. We identified 55 children with BTs, so the prevalence was slightly higher than expected.

The presenting symptoms and signs are dependent on localisation with ataxia, cerebral nerve deficits and gait abnormalities present in infratentorial tumours (Figure 1), along with motor dysfunctions, seizures, visual dysfunctions and endocrinological abnormalities as the most frequently seen supratentorial localisations [2]. Symptoms of increased intracranial pressure with headache and vomiting, together with papilloedema, develop more rapidly in infratentorial tumours than at other localisations due to their proximity to the fourth ventricle.

We found a roughly equal range of symptoms compared with those reported in other studies [5-7]. In our study headache, vomiting and ataxia were the most common symptoms. Vomiting was equally frequent in the morning and during the day, which is contrary to the conventional teaching of an early morning presentation.

Other symptoms were less frequent, but presented a broad spectrum of signs and symptoms as also documented in other studies [2, 5-7].

The estimated mean time for the diagnosis of a brain tumour in children is 20-28 weeks. Moreover, an earlier diagnosis of tumours in the posterior fossa is expected [8], whereas other studies have shown time intervals ranging from three to 14 weeks [5-7, 9-11].

Correspondingly, we found the total PSI median time for supratentorial localisations to be 113 days (range 0-412) and for infratentorial tumours 36 days (range 3-730). This demonstrates that early diagnosis does take place in many cases, but that delays are considerable in others. Highly variable data on median PSI values reflect observed inconsistencies in time intervals within a relatively small group of children and with parents and doctors responding differently to presenting symptoms (Table 2). Further, this occurs in a natural history setting where overall time intervals are limited and late symptoms more marked.

Whether a tumour is malignant cannot be decided on the basis of pre-diagnostic symptoms alone. Our data have shown that total and PSI-3 median times and ranges are lowest in children with malignant tumours. This suggests that a more rapid progression of symptoms in malignant cases may contribute to an earlier diagnosis.

Symptoms such as headache, unstable gait and seizures are notoriously associated with long PSIs (Figure 2). Attention should be paid to these symptoms for earlier diagnosis of BTs.

Little is known about the importance of early diagnosis in children with BTs. The presence of hydrocephalus prior to an operation could worsen subsequent cognitive performance [12] and this may particularly apply to children with medulloblastomas [13]. Designing a treatment related to age at diagnosis does and will certainly play a more important role in the future, not only for survival, but also for the long-term outcome. This applies particularly to a more differentiated use of radiotherapy in the years to come [12-14].

An earlier diagnosis may be achieved if a brain tumour is considered as soon as any child presents with

| TABLE 2 |

Pre-diagnostic symptomatic intervals (PSI) in days related to localisation and malignancy, median (range).

<table>
<thead>
<tr>
<th></th>
<th>PSI-1</th>
<th>PSI-2</th>
<th>PSI-3</th>
<th>PSI-total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>3 (0-330)</td>
<td>3 (0-412)</td>
<td>14 (0-231)</td>
<td>113 (0-412)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>14 (0-365)</td>
<td>6 (0-730)</td>
<td>5 (0-85)</td>
<td>36 (3-730)</td>
</tr>
<tr>
<td>Benign</td>
<td>8 (0-365)</td>
<td>8 (0-730)</td>
<td>14 (0-231)</td>
<td>165 (3-730)</td>
</tr>
<tr>
<td>Malignant</td>
<td>6 (0-365)</td>
<td>3 (0-412)</td>
<td>6 (0-96)</td>
<td>51 (0-365)</td>
</tr>
<tr>
<td>Total</td>
<td>7 (0-365)</td>
<td>9 (0-730)</td>
<td>6 (0-231)</td>
<td>66 (0-730)</td>
</tr>
</tbody>
</table>

![FIGURE 1](image)

Magnetic resonance image showing an infratentorial tumour.
headache, nausea and/or vomiting, visual symptoms and signs, motor symptoms and signs, growth and development abnormalities, behavioural changes, diabetes insipidus, seizures and altered consciousness [15].

To assist paediatricians and other physicians in the early identification of children with brain tumours, diagnostic guidelines have been developed [15] and initiatives have been taken by the National Board of Health, Denmark to stress the importance of referring children who are suspected of having a brain tumour to the regional paediatric emergency ward for imaging studies and further referral to a childhood oncology centre [16]. Moreover, to increase knowledge of the complex symptomatology of brain tumours in children, regional referral guidelines have been made readily accessible on the web [16, 17].

Future studies are needed to prospectively evaluate the effects and to address possible further improvements of these initiatives which were implemented in 2009 [16].

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CONFLICTS OF INTEREST: none

LITERATURE


17. Childhood cancer at VisiInfoSyd. www.visinfosyd.dk/kraeftpakker/boerncancer-NI_VisiinfoSyd//Børncancer (B72, B73, B74, B75, N74, N75, N76, N18, D74, D75, D76, D77, D78, U73, U76, U77, U78, R84, R85, R86, L71 (1 May 2011).