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ORIGINAL PAPER

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Delay in the diagnosis of paediatric brain tumours

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Abstract The pre-diagnostic period of 252 children (median age 6.3 years, range 0–16.9 years) with primary brain tumours was assessed to analyse their clinical presentation and reasons for any delay in diagnosis. The median pre-diagnostic symptomatic interval (PSI) was 60 days (range 0–3010 days) with a parental delay of 14 days (range 0–2310 days) and a doctor's delay of 30 days (range 0–3010 days). Only 33% of brain tumours were diagnosed within the 1st month after the onset of signs/symptoms. PSI correlated significantly with patients' age and tumour histology, but not with gender, year of diagnosis or tumour location (supratentorial hemispheric, supratentorial midline, infratentorial). In children older than 2 years, most common initial signs/symptoms were headache, nausea/vomiting, seizures, squint/diplopia, ataxia and behavioural changes. In children younger than 2 years, most common initial signs/symptoms were seizures, vomiting, head tilt and behavioural changes. These signs/symptoms are by no means pathognomonic features of brain tumours, making the diagnosis in the early course often difficult. *Conclusion:* given the fact that the vast majority of patients (88% in the present study) develop further signs/symptoms, a high level of awareness, a detailed medical history and repeated correctly interpreted neurological examinations should lead to an earlier diagnosis and to a higher probability of total tumour resection.

Keywords Brain tumour · Diagnosis · Presentation · Headache

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Abbreviations *ICP* intracranial pressure · *PSI* pre-diagnostic symptomatic interval

Introduction

As a group, brain tumours are the most common solid tumours in children [5]. They differ from primary central nervous system tumours occurring in adults not only in histology, localization, management and prognosis, but also in clinical presentation [6]. At the onset of illness, the nature of neurological and systemic dysfunction is variable and relates not only to the site of tumour origin, but also to the child's age and developmental level [11].

Previous studies have indicated delays in the diagnosis of childhood brain tumours [3, 4, 9]. Gjerris et al. [4] found a pre-diagnostic symptomatic interval (PSI) of more than 6 months in 50% of 316 children in whom intracranial tumours were diagnosed during the years 1935–1959. Given the increasingly widespread availability of neuroimaging in the 1990s, diagnosis was expected at an earlier stage; however, studying 74 children diagnosed during the years 1990–1994, Edgeworth et al. [3] found an almost similar PSI of 5 months (mean value).

To identify factors related to PSI, we analysed a large group of paediatric brain tumour patients and compared PSI with age, gender, tumour location, histology, year of diagnosis and clinical presentation. We then identified patients' characteristics most strongly associated with long doctor's delays in an attempt to concentrate on efforts of early detection.

Patients and methods

A retrospective study was undertaken of 252 children with primary brain tumours admitted consecutively to the University Children's Hospital of Zurich, Switzerland from January 1980 to December 1999. The PSI was defined as the interval between the onset of signs/symptoms and the time of diagnosis by MRI, CT or other imaging techniques.

In 167 (66%) of the patients, medical charts allowed a separation of the PSI into an interval between sign/symptom onset and first medical consultation (parental delay) and that between first medical consultation and diagnosis by CT, MRI or other imaging techniques (doctor's delay).

Pearson's correlation was used to examine the relationship between the logarithm of PSI, parental delay and doctor's delay with age and year of diagnosis. In Fig. 1 and Fig. 2, this relationship was estimated by a locally weighted scatter plot smoother (LOWESS) [1] as implemented in the statistical environment S-Plus [10]. The equality of the delays within subgroups (gender, tumour location, tumour histology, increased intracranial pressure (ICP)) and the equality of parental and doctor's delays was tested nonparametrically by the Wilcoxon, Mann-Whitney and Kruskal-Wallis tests.

Results

Patient and tumour characteristics

The median age at diagnosis for all patients was 6.3 years (range 0.0–16.9 years). A total of 150 (60%) patients were male and 102 (40%) were female. Tumour location was infratentorial in 117 (46%), supratentorial hemispheric in 78 (31%) and supratentorial midline in 57 (23%) patients. Low-grade gliomas (21%), medulloblastomas (19%), high-grade gliomas (14%) and craniopharyngiomas (8%) were the most common brain tumours, followed by ependymomas (6%), germ cell tumours (6%), choroid plexus tumours (4%), oligodendrogliomas (2%), mixed gliomas (2%), neuronal and mixed neuronal-glial tumours (2%) and meningiomas (1%).

Signs and symptoms

The initial signs/symptoms, i.e. signs/symptoms that appeared within the 1st day of the PSI, are shown in Table 1. At the time of diagnosis, only 30 (12%) patients were monosymptomatic. All other patients had two ($n=28$), three ($n=31$), four ($n=33$), five ($n=29$), six ($n=33$), and seven ($n=27$) or more ($n=41$) signs/symptoms. These are shown in Table 2.

Signs and symptoms of increased ICP (headache, nausea/vomiting, papilloedema, sixth-nerve palsy, enlargement of the head, gaze depression, bulging fontanelle, separation of cranial sutures) were noticed in 124 (49%) patients at sign/symptom onset and in 186 (74%) patients at diagnosis. Of these, 74% had hydrocephalus.

Prediagnostic symptomatic interval

The median PSI of all patients was 60 days (range 0–3010 days) with a median parental delay of 14 days (range 0–2310 days) and a median doctor's delay of 30 days (range 0–3010 days). Only 81 (32%) of the 252 brain tumours were diagnosed within 30 days after onset of signs/symptoms. PSI was 31–60 days in 49 (19%) patients, 61–180 days in 56 (22%) patients, 181–365 days in 33 (13%) patients and >1 year in 33 (13%) patients.

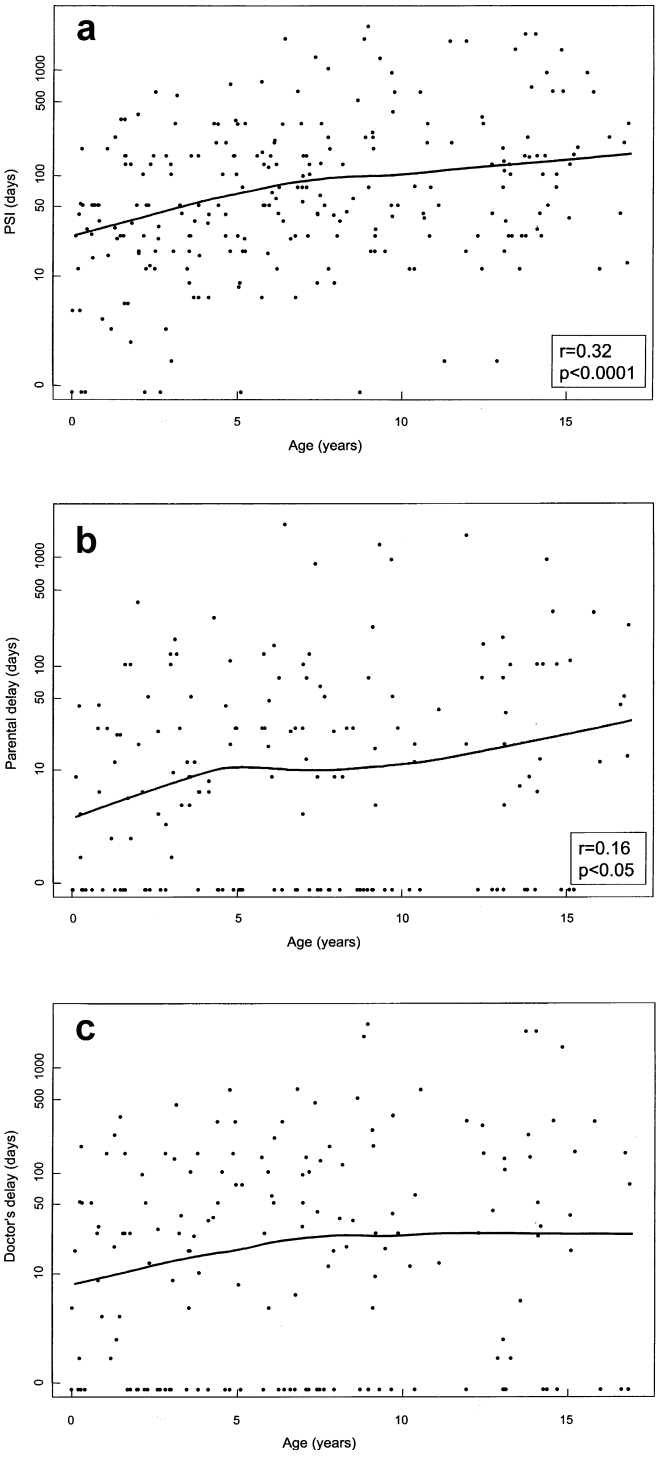

Fig. 1 Age at diagnosis compared with PSI (**a**), parental delay (**b**) and doctor's delay (**c**). Younger children had shorter PSIs and shorter parental delays, but not shorter doctor's delays

Age had a statistically significant correlation with PSI (Pearson's correlation $r=0.32$, $P<0.0001$) with shorter PSI for younger children (Fig. 1a). The parental delay was significantly shorter for younger children when compared with older children (Pearson's correlation $r=0.16$, $P<0.05$) (Fig. 1b). However, the

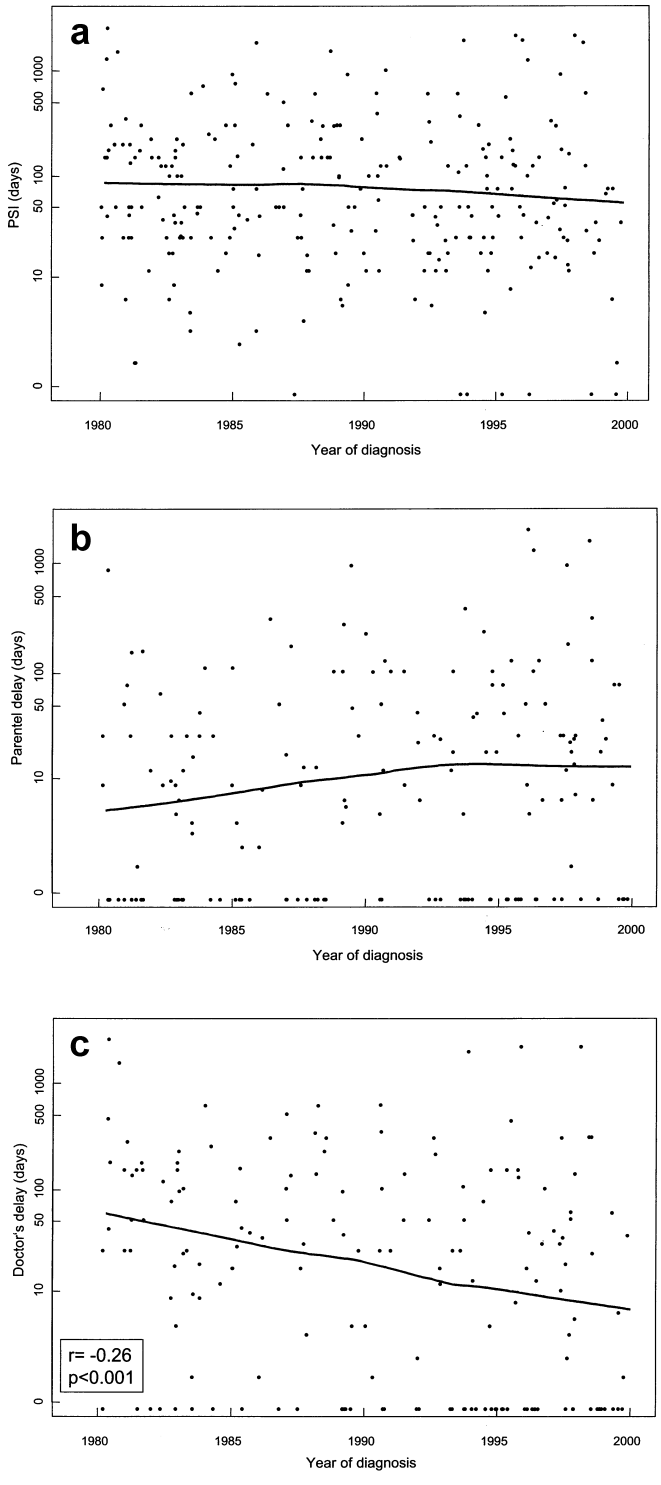

Fig. 2 Year of diagnosis compared with PSI (**a**), parental delay (**b**) and doctor's delay (**c**). Doctor's delay was shorter in the 1990s compared to the 1980s

doctor's delay did not correlate significantly with age (Fig. 1c).

Tumour histology also correlated with PSI. Aggressive fast-growing tumours (glioblastoma multiforme, medulloblastoma, germ cell tumours, anaplastic astrocytoma) had a shorter PSI when compared with slowly growing tumours (pilocytic astrocytoma, craniopharyngioma) (data not shown).

Table 1 Frequency of initial signs and symptoms depending on age

Signs and symptoms	All ($n=252$)	Age <2 years ($n=50$)	Age ≥ 2 years ($n=202$)
Headache	35%	2%	43%
Nausea/vomiting	26%	18%	28%
Seizures	14%	20%	12%
Behavioural changes (irritability, mood, character, school)	10%	12%	9%
Ataxia	8%	8%	8%
Squint/diplopia	8%	6%	8%
Lethargy	5%	4%	5%
Hemiparesis/quadriparesis	5%	8%	4%
Head tilt	5%	12%	3%
Anorexia	3%	6%	2%
Growth failure	3%	–	3%
Sleep disturbance	2%	2%	2%
Polyuria/polydipsia	2%	–	3%
Visual loss	2%	2%	2%
Weight loss	2%	4%	1%
Facial nerve palsy	2%	4%	1%
Enlargement of the head	2%	8%	–
Cranial neuropathies other than III, IV, VI, VII	1%	–	1%
Gaze depression/separation of cranial sutures/bulging fontanelle	1%	4%	–
Dizziness	1%	–	1%
Nystagmus	1%	4%	–
Papilloedema	1%	–	1%
Amenorrhoea	0.5%	–	0.5%
Proptosis	0.5%	–	0.5%

Patients with signs/symptoms of increased ICP had a statistically shorter PSI (median 60 versus 152 days; $P=0.007$, Mann-Whitney test) and shorter doctor's delays (median 20 versus 60 days; $P=0.02$, Mann-Whitney test) when compared with the children without increased ICP. However, the parental delays for these two groups of patients were similar.

Tumour location (supratentorial hemispheric, supratentorial midline, infratentorial) and gender did not correlate with PSI, parental delay or doctor's delay (data not shown).

During the studied period of 20 years, there were no statistically significant changes in the PSI (Fig. 2a) and in the parental delay (Fig. 2b). However, the doctor's delay decreased significantly (Pearson's correlation $r=-0.26$, $P<0.001$; Fig. 2c). This might be explained by a better availability of non-invasive imaging techniques. At the Children's Hospital of Zurich, CT was introduced in 1982 and MRI in 1986.

In 75 (45%) patients, the doctor's delay was more than 30 days indicating misinterpretation of signs and/or symptoms. Common diagnostic difficulties included the correct interpretation of headache, nausea/vomiting, seizures, behavioural changes and squint/diplopia (Table 3).

Table 2 Frequency of signs and symptoms at diagnosis depending on age

Signs and symptoms	All ($n=252$)	Age <2 years ($n=41$)	Age ≥ 2 years ($n=211$)
Nausea/vomiting	60%	54%	61%
Headache	54%	5%	64%
Ataxia	46%	17%	52%
Hemiparesis/quadriparesis	35%	37%	35%
Squint/diplopia	35%	17%	38%
Papilloedema	35%	10%	39%
Seizures	21%	27%	19%
Behavioural changes (irritability, mood, character, school)	22%	29%	20%
Gaze depression/separation of cranial sutures/bulging fontanelle	15%	41%	10%
Cranial neuropathies other than III, IV,VI,VII	15%	15%	16%
Facial nerve palsy	14%	10%	15%
Head tilt	14%	20%	13%
Lethargy	13%	15%	13%
Visual loss	13%	15%	13%
Weight loss	12%	15%	12%
Nystagmus	11%	5%	12%
Decreased level of consciousness/drowsiness	9%	10%	9%
Enlargement of the head	9%	32%	5%
Visual field defects	6%	–	8%
Sleep disturbance	6%	10%	5%
Hemisensory loss	4%	–	5%
Anorexia	4%	10%	2%
Growth failure	4%	–	4%
Polyuria/polydipsia	3%	–	4%
Dizziness	2%	–	3%
Temperature regulation disturbance	2%	5%	2%
Parinaud syndrome	1%	–	1%
Amenorrhoea	1%	–	1%
Dysarthria	1%	–	1%
Proptosis	1%	2%	0.5%
Bulimia	1%	–	1%
Sexual precocity	1%	–	1%
Tinnitus	0.5%	–	0.5%

Table 3 Frequency of signs and symptoms noticed by medical doctors >30 days prior to diagnosis

Signs and symptoms	Patients (n)	Patients with this sign/symptom (%)
Headache	31	23
Nausea/vomiting	28	19
Seizures	18	35
Behavioural changes (irritability, mood, character, school)	15	29
Ataxia	11	9
Squint/diplopia	10	11
Head tilt	7	19
Weight loss	7	23
Hemiparesis/quadriparesis	6	7
Polyuria/polydipsia	6	75
Lethargy	5	15
Growth failure	4	44
Facial nerve palsy	3	8
Visual loss	6	3
Papilloedema	2	8
Enlargement of the head	2	9
Cranial neuropathies other than III, IV, VI, VII	2	5
Sleep disturbance	2	13
Anorexia	2	22
Dizziness	2	33
Gaze depression/separation of cranial sutures/bulging fontanelle	1	3
Visual field defects	1	6
Temperature regulation disturbance	1	17
Tinnitus	1	100

Discussion

In the present study, we found a high variability of presentation and considerable delays in the diagnosis of paediatric brain tumours. PSI correlated with patient's age and tumour histology, but not with gender or tumour location.

Infants had a shorter PSI than older children. Different reasons may account for this observation. Infants are under a closer physicians' care than older children and much more consideration is given to non-specific signs/symptoms by parents as well as by physicians. In addition, the biology of brain tumours for infants is often aggressive with an increasing number of signs/symptoms within a relatively short period of time.

In the present study, 74% of the patients had signs/symptoms of increased ICP at diagnosis. These patients had a shorter PSI when compared to patients without increased ICP. Although signs/symptoms of increased ICP may be difficult to interpret in the beginning, brain tumour patients with increased ICP have the potential to deteriorate very rapidly. Without a high level of awareness, initial signs of increased ICP may be overlooked very easily. Increased ICP in brain tumours may be caused directly by infiltration or compression of normal CNS structures or indirectly by non-communicating hydrocephalus. Initial features of elevated ICP often are insidious, nonspecific and non-localising. Among school-aged children, fatigue, personality changes and vague intermittent headaches are common. Over time, morning headache and vomiting ensue. Sixth-nerve palsy and papilloedema may develop if the pressure is long-standing. Brain tumours in infants causing increased ICP are notorious for their protean clinical manifestations, which may include irritability, listlessness, vomiting, failure to thrive and excessive, for parents difficult to spot, head growth [6]. Hydrocephalus is compensated by open fontanelles and split sutures and less likely to produce classical signs of elevated ICP.

The presenting signs/symptoms of supratentorial midline tumours reflect their compression or infiltration of adjacent structures. Lesions around the optic chiasm and hypothalamus, such as chiasmatic-hypothalamic gliomas, produce a combination of visual loss, neuroendocrine dysfunction, and behavioural and appetite disturbances. Pineal region tumours typically manifest

with eye movement abnormalities, such as Parinaud syndrome (i.e. upward gaze palsy, lack of convergence, failure of accommodation). Both groups of tumours often produce signs/symptoms of increased ICP from obstruction of the CSF pathways.

Infratentorial tumours manifest in a variety of ways, depending on the tumour type. Diffuse intrinsic brainstem gliomas typically produce rapidly progressive cranial neuropathies (typically VI and VII) and long-tract signs, such as hemiparesis/quadriparesis and ataxia but no signs of increased ICP. In contrast, cerebellar astrocytomas often exhibit a long history of ataxia and signs/symptoms of elevated ICP resulting from gradual obstruction of the fourth ventricle. With progressive tumour enlargement, neck pain may develop as a result of tonsillar herniation. Medulloblastomas produce signs/symptoms that are similar to those of a cerebellar astrocytoma, although there is generally a swifter progression. Because ependymomas typically arise from the floor of the fourth ventricle, nausea and vomiting as a result of compression or invasion of the ''vomiting centre'' near the obex is often an initial symptom. With progressive enlargement, these tumours occlude the fourth ventricle, producing obstructive hydrocephalus.

A median PSI of 60 days seems unacceptably long. However, when compared with the results reported by Gjerris et al. [4] and Edgeworth et al. [3], the PSI found in the present study was significantly shorter. Better availability of CT and MRI since the 1990s resulted in shorter doctor's delay; however, this correlation did not result in a shorter PSI. This underlines the importance of a detailed medical history and an immediate neurological examination, as is true in the management of children with headache. Headache frequently heralds the development of a brain tumour in a child. Headache, however, is suffered by 5%–30% of elementary school children, whereas the annual incidence of brain tumours in this age group approximates only 3/100,000 (0.003%) [12]. Uncritical imaging would result in a large number of normal neuroimaging studies. In our study, most children with headache as initial symptom showed additional signs/symptoms within a relatively short period. This is consistent with a large study of the Childhood Brain Tumor Consortium [12]. Analysing 3276 patients, less than 3% of children with headache and a brain tumour had no abnormality on neurological examination.

Although not yet proven, a shortened PSI may lead to the detection of smaller brain tumours that are easier to resect. The value of extensive tumour resection, which is controversial for malignant brain tumours in adults, has been confirmed for a variety of childhood brain tumours including medulloblastoma, supratentorial primitive neuroectodermal tumours, ependymoma and astrocytoma [2, 7, 8, 13,14].

In conclusion, early diagnosis of paediatric brain tumours has not become easier since the introduction of CT and MRI. Only a high degree of awareness, a targeted medical history and repeated correctly interpreted neurological examinations lead to an immediate diagnosis.

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References

1. Cleveland WS (1979) Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74: 829–836
2. Cohen BH, Zeltzer PM, Boyett JM (1995) Prognostic factors and treatment results for supratentorial primitive neuroectodermal tumors in children using radiation and chemotherapy: a Children's Cancer Group randomized trial. J Clin Oncol 13: 1687–1696
3. Edgeworth J, Bullock P, Bailey A, Gallagher A, Crouchman M (1996) Why are brain tumours still being missed? Arch Dis Child 74: 148–151
4. Gjerris F (1976) Clinical aspects and long-term prognosis of intracranial tumors in infancy and childhood. Dev Med Child Neurol 2: 145–159
5. Gurney JG, Smith MA, Bunin GR (2000) CNS and miscellaneous intracranial and intraspinal neoplasms. In: SEER Pediatric Monograph, National Cancer Institute, pp 51–63 http://seer.cancer.gov/Publications/
6. Pollack IF (1994) Brain tumors in children. N Engl J Med 331: 1500–1507
7. Pollack IF (1999) Pediatric brain tumors. Semin Surg Oncol 16: 73–90
8. Pollack IF, Gerszten PC, Martinez AJ, Lo KH, Shultz B, Albright AL, Janosky J, Deutsch M (1995) Intracranial ependymomas of childhood: long-term outcome and prognostic factors. Neurosurgery 37: 655–666
9. Pollock BH, Krischer JP, Vietti TJ (1991) Interval between symptom onset and diagnosis of pediatric solid tumors. J Pediatr 119: 725–732
10. S-PLUS 2000 Guide to Statistics, MathSoft Volume 1, Seattle
11. Strother DR, Pollack IF, Fisher PG, Hunter JV, Woo SY, Pomeroy SL, Rorke LB (2001) Tumors of the central nervous system. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott-Raven, Philadelphia, pp 751–824
12. The Childhood Brain Tumor Consortium (1991) The epidemiology of headache among children with brain tumor. J Neurooncol 10: 31–46
13. Wisoff JH, Boyett JM, Berger MS, Brant C, Li H, Yates AJ, McGuire-Cullen P, Turski PA, Sutton LN, Allen JC, Packer RJ, Finlay JL (1998) Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group Trial No. CCG-945. J Neurosurg 89: 52–59
14. Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, Allen JC, Stevens KR, Stanley P, Li H, Wisoff JH, Geyer JR, McGuire-Cullen P, Stehbens JA, Shurin SB, Packer RJ (1999) Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol 17: 832–845