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Medulloblastoma in pediatric age: a single-institution review of prognostic factors

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Abstract We report a retrospective study of 35 cases of medulloblastoma in pediatric patients treated at our institution during an 18-year period. Ten of the patients were infants (age <2 years) and 25 were children (age >2 years). The main factors affecting prognosis were total removal of the tumor ($P<0.01$) and tumor stage ($P<0.01$). There were no differences between the survival rate of infants and children, infants had a worse prognosis in regard to quality of life than children.

Key words Medulloblastoma
Pediatric brain tumor
Radiotherapy

Introduction

Medulloblastoma accounts for 4%–8% of primary brain tumors of neuroectodermal origin; in the pediatric age group it makes up 20%–30% of brain tumors [10, 19]. At present, 50%–70% of patients survive for up to 5 years, and 35%–45% for up to 10 years [6, 11, 18, 20, 25, 26]. The literature shows the main factors influencing prognosis to be age, histological type, type of treatment, and tumor stage. We report a retrospective study of 35 cases of medulloblastoma in patients of pediatric age, in an attempt to identify the main factors affecting prognosis in infants and in children.

Patients and methods

In the Neurosurgery Department of "La Sapienza" University of Rome, 35 pediatric patients were operated on for medulloblastoma between 1970 and 1988; 10 were infants (age <2 years) and 25 were children (age range 2–16 years). Tumor staging was performed according to the classification reported by Friedman et al. [19], completely in 22 of the 35 cases, using computed tomography (CT), myelography, and laboratory testing of cerebrospinal fluid (CSF). For each case, the diagnosis of medulloblastoma was subsequently confirmed by re-examining the histological samples. The prognostic factors considered were: age, type of treatment, tumor stage, and histological type. The statistical significance of the findings obtained was calculated using Fischer's exact test and the χ^2 test.

Results

Clinical characteristics

Of the 35 patients, 20 were male and 15 female (male:female ratio 1.3:1). The mean age was 5.3 years (range 8 months to 15 years), with peak frequency between 5 and 7 years (46% of cases).

The average length of clinical history was 3.1 months (range 2 weeks to 18 months) and symptoms (Table 1) were those due to endocranial hypertension in the major-

ity of cases (80%). The most frequent neurological signs were ataxia (80%) and papilledema (71%) (Table 1).

In the cases of the nine patients operated on before 1975, the neuroradiological diagnosis was by means of pneumoencephalography and ventriculography, which always showed indirect signs of the tumor. In the remaining 26 cases, it was made by computed tomography (CT) and in 5 of them by magnetic resonance imaging (MRI) as well. The tumor appeared hyperdense on CT in 69% of cases, isodence in 19%, and had a heterogenous appearance in 12%. The lesion always showed marked contrast enhancement. In 23 of the 26 cases triventricular hydrocephalus was present. MRI always showed a tumor as hypointense on T1-weighted images and hyperintense on T2-weighted images, with enhancement on administration of contrast medium.

All patients underwent surgical treatment. Tumor removal was total in 25 cases (71%) and partial in 9 (28%). In 1 case (3%), only biopsy was performed because the patient's condition was frail and the tumor had infiltrated the brain stem. Postoperative mortality was 14% (5 patients).

All 30 patients who survived surgery received postoperative radiotherapy to a total dose varying according to their age. In children the total dose was 50–52 Gy to the posterior cranial fossa, 25 Gy to the spinal cord, and 25 Gy to the brain. Infants were given a total dose of 40 Gy to the posterior cranial fossa, 24–25 Gy to the spinal cord, and 25 Gy to the brain.

The site of the tumor was median in 25 cases (71%), lateral in 7 (29%), paramedian in 2 (6%), and median with extension to the brain stem in 1 (3%). Tumor staging was carried our completely in 22 cases, with the following results: T1M0 in 7 cases (32%), T2M0 in 6 (27%), T3M0 in 5 (23%), T2M1 in 3 (14%), and T3bM2 in 1 (4%).

Histologically, the tumor was classic in 25 cases (71%) and desmoplastic in 10 (29%). In infants only the classic type was found.

Table 1 Clinical symptoms and signs of medulloblastoma in our patients

	%
Headache	80
Vomiting	80
Ataxia	80
Papilledema	71
Nystagmus	54
Cerebellar dysfunction	20
Dysarthria	14
VII cranial nerve palsies	11
Increased head circumference	11
Hemiparesis	3

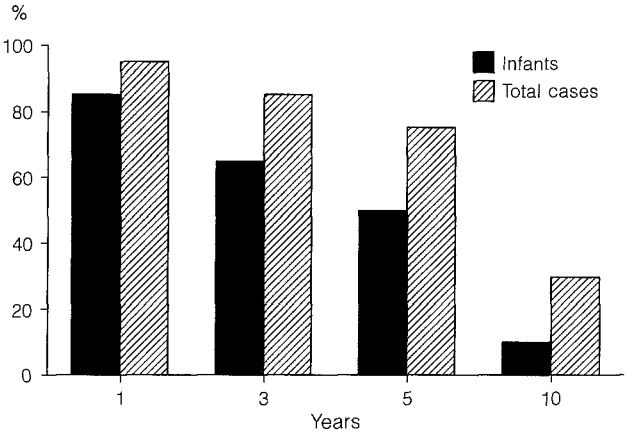

Fig. 1 Survival in our patients

Survival

At an average follow-up of 15 years (median 14 years; range 5–23 years), 6 patients were still alive and 23 had died as a result of recurrence and/or metastasis. Average survival was 5.1 years (range 6 months to 14 years); 90% of patients survived 1 year, 75% 3 years, 60% 5 years, and 20% 10 years (Fig. 1).

Recurrences and metastases

Recurrences occurred in 23 patients (77%) following disease-free intervals averaging 24 months (range 5 months to 9 years). Ten of these patients were infants and 13 were children. Twenty had classic-type tumors and 3 had desmoplastic ones.

Of the 23 patients with recurrences, 16 were preoperated on. Nine of the patients who were reoperated on also underwent radiotherapy. Seven did not have any type of treatment because of their frail clinical condition.

On admission, CSF analysis revealed neoplastic cells in three patients; in one other there were seedings in cerebellar subarachnoid spaces. Subsequently, two of these four patients developed central nervous system (CNS) metastasis; one died postoperatively and the other showed no signs of metastasis 5 years after treatment.

Ten patients (33%) presented metastasis of the CNS, but extracerebral metastasis did not occur in any case. Of the ten patients with metastasis, four were infants and six children. Eight of them had a spinal metastasis at the lumbar level that manifested itself clinically after an average interval of 17 months (range 8–24 months) after treatment of medulloblastoma. In four of these eight patients, the metastasis was accompanied by a recurrence of the primary tumor. The tumor was of the classic type in all cases. Four of the eight were reoperated on, while the other four did not undergo any type of treatment. One

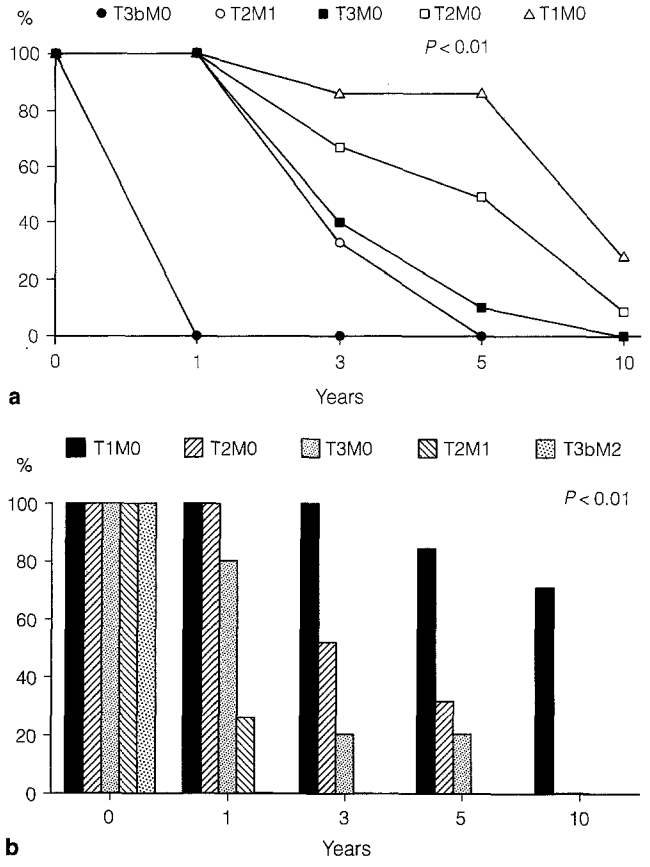

Fig. 2a, b Prognostic significance of tumor stage: relation to **a** survival and **b** disease-free interval in our patients

patient presented a frontal metastasis with clinical onset 12 months after treatment of the medulloblastoma, which had been of the classic type. This patients was reoperated on.

Quality of life

Of the 30 surviving patients, 22 were assessed for functional outcome. Fourteen patients (64%) had an IQ of more than 80 and eight (36%) an IQ below 90; six of the latter were infants. Of the eight with an IQ of less than 80, three were in special-education classes and five did not go to school.

There was severe dysarthria in 9 of the 22 patients and marked ataxia in 5. Five of the 30 surviving patients were found to have a growth hormone deficiency; all of them were infants.

Prognostic factors

The main factors significantly influencing prognosis were tumor extension (stage T1M0) ($P<0.01$) and total tumor removal ($P<0.01$). Furthermore, tumor stage T1M0 also influenced the disease-free interval ($P<0.05$) (Figs. 2, 3).

It was not possible to assess the significance of radiotherapy because it was given to all the patients in this series.

Another factor that influenced prognosis, though not in a statistically significant manner, was the histological type of the tumor ($P=0.1$) (Fig. 4).

Prognosis was not affected by the patients' age, or sex or the length of their clinical history.

Discussion

The findings in our series of 35 consecutive cases of medulloblastoma differed from those of many other authors [1, 10, 14, 18, 19] in that the prognosis in regard to survival was found to be no worse in infants than in children. Other authors explain their findings by the fact that infants are given a lower total dose of radiotherapy and frequently present with a tumor of higher stage [15, 19]. In our series, infants received a smaller total dose of radiotherapy than children but there was no difference in tumor stages. On the other hand, infants did have a higher incidence of recurrence (100% vs 65%) and metastasis (44% vs 28%). Another factor differentiating between the two age groups is that none of the infants presented with the desmoplastic type of tumor, compared with 40% of the children. Some authors [8, 16] noticed a correlation between desmoplastic tumors and longer survival in pediatric patients. In our series, the desmoplastic type did not significantly influence survival ($P=0.1$); however, in the ten patients with desmoplastic medulloblastoma, the following characteristics differentiating against the classic type were observed: (1) a lower incidence of recurrence (30% vs 100%); (2) a lower incidence of metastasis (0% vs 50%); (3) longer average survival time (6 years vs 4.2 years). Our observations are probably

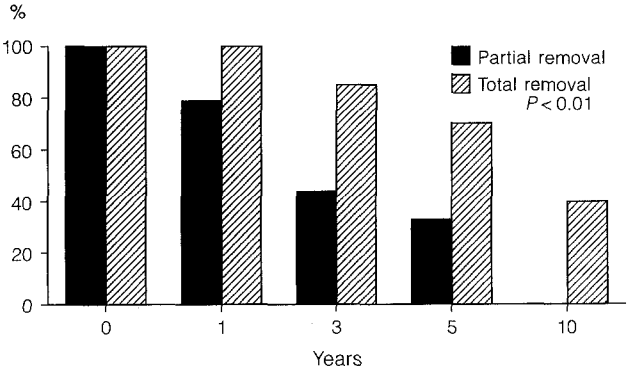

Fig. 3 Extent of tumor removal in relation to survival in our patients

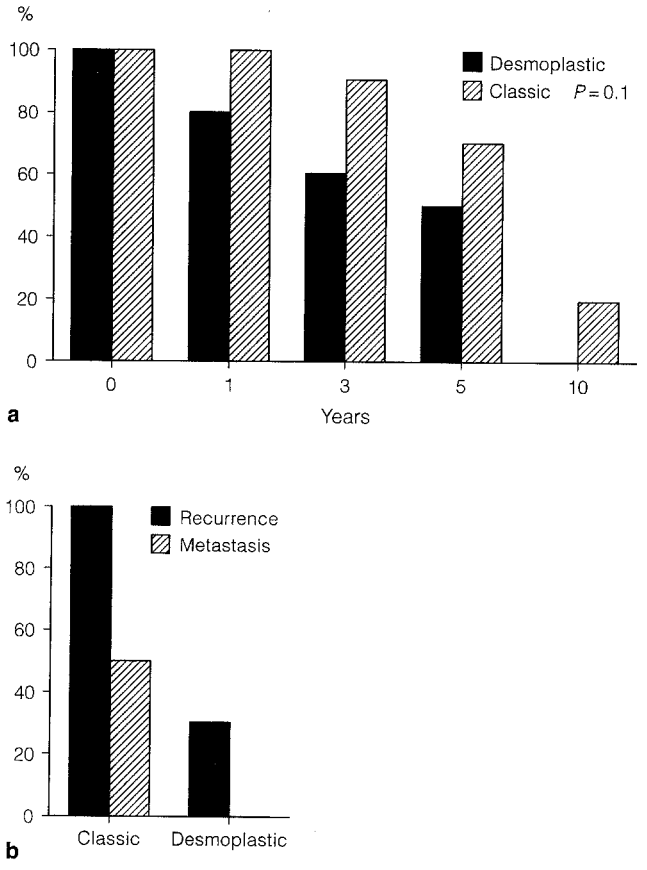

Fig. 4a, b Prognostic relevance of histological type of medulloblastoma: relation to **a** survival and **b** relapse in our patients

attributable to two factors: (1) the fact that desmoplastic tumors are frequently located in the cerebellar hemispheres (70% of cases), and (2) the fact that this histotype has a superficial nodular formation that makes total removal possible. In our series, in fact, total removal was achieved in 100% of the desmoplastic-type medulloblastomas, compared with 60% of the classic type.

Prognosis in ragard to quality of life was worse in infants because neuropsychologial and endocrinological sequelae affected this group almost exclusively (66% vs 33% and 100% vs 0% respectively). The high incidence of sequelae in infants has been attributed to radiotherapy [6, 9, 13, 27, 29], and recent studies [3, 25] have in fact suggested that radiotherapy should only begin after a course of chemotherapy in an attempt to avoid these sequelae.

Treatment of medulloblastoma is based on surgery, radiotherapy, and, more recently, chemotherapy. In our series, total removal increased survival time ($P<0.01$), although 14 of the 25 patients (56%) treated in this way suffered a recurrence. This seems to confirm Tomita's observation [31] that "... even after resection is achieved, in a great majority of cases, medulloblastoma cells seed spontaneously and microscopically in the subarachnoid space ..."

Radiotherapy is considered essential for survival, even though it does not rule out recurrence and metastasis [19]. In our series, the prognosis value of radiotherapy could not be assessed because it was performed in all patients. It did, however, help to avoid recurrence (77%) and metastasis (33%). These mainly affected infants, who were always given a lower total dose than children. However, survival in infants was no different to that in children. On the one hand, this finding seems to be corroborated by the observation of Caputy et al. [7] that outcome is not influenced by doses of 40 Gy or more to the posterior cranial fossa; on the other hand, some authors maintain that a dose of 50 Gy reduces the incidence of recurrence [4, 14, 23, 30]. The explanation for this probably lies in other factors, e.g., genetic ones. Bigner et al. [5], in a study of seven medulloblastomas, found that amplification of the *c-myc* gene brought on early death, regardless of the type of treatment performed.

Chemotherapy is thought to be particularly useful in high-risk patients (those with partial removal, recurrence, or metastasis, and infants) [2, 3, 18, 27]. We were unable to assess its prognostic value because it was not performed in our patients.

Most authors [1, 10, 21, 24, 28] consider tumor stage a fundamental prognostic factor. In our series, stage T1M0 influenced not only outcome ($P<0.01$), but also the disease-free interval ($P<0.05$). It appears logical that patients with a higher tumor stage should have a higher risk of early progression of the disease.

Twenty-four percent of our patients suffered local and/or long-term tumor regrowth, in accordance with Collins' rule [12]. However, exceptions to Collins' rule are reported in 0–43% of published cases [10, 17].

From the present study it emerges that: (1) total remove and tumor stage (T1M0) are extremely important prognostic factors and are correlated; (2) there are no differences between survival in children and in infants (it is likely that this last observation can be related to morphological and/or genetic factors observed by some authors [5], as the exceptions to Collins' rule seem indirectly to confirm); (3) infants have a worse prognosis in regard to quality of life than children. In our opinion, further therapeutic trials are necessary in order to avoid debilitating sequelae in younger children.

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