Medulloblastoma in childhood: progressive intellectual deterioration


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Abstract. A series of 120 medulloblastomas in children operated on between 1967 and 1987 at the Hôpital des Enfants-Malades has been reviewed in order to check whether the conclusions of our study published 10 years ago have remained valid and, in particular, to verify whether the quality of life of these patients, which had been found to be poor at the time, had improved or worsened over the years. The postoperative mortality for the whole series was 6.5%; there have been no deaths in the 35 patients operated on after 1980. The overall survival rate for the 120 children was 60% at 5 years and 53% at 10 years; for the patients who completed radiotherapy, the survival rate was 73% at 5 years and 64% at 10 years. Survival rates were surprisingly better in patients treated when under 6 years of age than in older children. They were also better in girls than in boys, and in desmoplastic compared with other medulloblastomas; however, the differences were not significant. When comparing the groups after total or subtotal resection of tumors, survival rates were not significantly different, but were lower in the small group of partial resections. Cell differentiation did not influence the prognosis. Psychological sequelae were significant and worsened over the years. Five years after treatment 58% of the children showed an IQ above 80; 5 years later this group included only 15% of the patients. These psychological sequelae were related to age at the time of radiotherapy: the younger the child, the lower the final IQ. Five years after treatment, 40% of the children had a normal academic level; 5 years later this group was reduced to 11%. Ten years after treatment, 36% of the patients were unemployed and 64% worked in a protected environment. No patient had normal employment. These disastrous results concerning the quality of life of these medulloblastoma patients justify new trials with reduced doses of irradiation over the hemispheres, at least in low-risk groups.

Ten years ago, in reviewing our series of 57 medulloblastomas in children, we reached three main conclusions [17, 18]. Two of these conclusions were rather optimistic: the postoperative mortality was lower than in most of the series previously published [6, 12, 24], and the 5-year survival rate was highly improved compared with the rate observed in the series of children operated on between 1950 and 1970 [4, 9, 21, 22, 29, 31]. One conclusion was pessimistic: the neuropsychological sequelae were far more frequent than seemed apparent from the studies based on global appreciation [1-5]. Moreover, comparing these sequelae with those of our series of cerebellar astrocytomas, we demonstrated that radiotherapy of the craniospinal axis was mainly responsible for these sequelae.

However, due to the limited number of patients and to an insufficient follow-up period, the uncertainty bars of the actuarial survival graph were large and the actuarial survival rate at 10 years could not be evaluated. For the same reasons, the scholastic integration and the ability to procure employment could not be precisely estimated.

At the Hôpital des Enfants-Malades in Paris, 120 medulloblastomas were operated on between 1967 and 1987. We have reviewed this series to answer three questions: What is the operative risk to date? How many patients survive at 10 years and what are the factors that influence the survival rate? What is the neuropsychological status of these patients and their quality of life?

Patients and methods

Patients

Age and sex. Between 1967 and 1987, 120 children, all under 15 years of age, were operated on for a medulloblastoma. This series is comparable to other pediatric series in the literature [9]. The age distribution shows a peak at 5 or 6 years, but it is clear that between 1 and 15 years, all age groups can contract this disease. There were 74 boys and 46 girls. The male prevalence is again in accordance with the literature [9].

Key words: Children – Medulloblastoma – Psychological sequelae – Radiotherapy

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Clinical presentation. Only one child was comatose upon admission. The level of consciousness was normal in 78% of the patients and slightly depressed in 21%. Cerebellar ataxia was observed in 77% of the children, paralysis of the VI nerve in 18%, and paralysis of other cranial nerves in 14%, with pyramidal syndrome in 9%. The supratentorial cerebral ventricles were enlarged in 92% of the cases, but the importance of the dilation varied from one patient to another. The ophthalmological examination performed in 114 children showed papilledema in 74% of those examined.

Method

Surgical treatment. Total macroscopical removal of the tumor was always attempted and accomplished in 62 patients. However, when it was felt that it would be hazardous to remove the whole tumor, the resection was subtotal or partial. It was subtotal in 50 patients (i.e., only a few cubic millimeters of the tumor were left in place); of these children 47 presented with a tumor invading the floor of the IV ventricle. In 8 patients resection of the tumor was partial.

The main argument for curtailing complete removal of the tumor was the occurrence during surgery of cardiovascular abnormalities (bradycardia or increased blood pressure). Such abnormalities occurred 19 times.

Before 1977 a preoperative ventricular drain was inserted in 26 children. In that year, computed tomography (CT) became easily available, which changed the general preoperative strategy. With the diagnosis now being easily and rapidly obtainable, the child was operated on as soon as possible, usually the day after admission without any external preoperative drainage (only 3 cases after 1977). Six patients had been systematically shunted in other centers before surgery. Of the remaining 114 children, 18 (i.e., 16%) required a permanent shunt after surgery [14].

Radiotherapy. The entire central nervous system (CNS) was irradiated over a 6-week period after surgery (50 Gy on the posterior fossa and 35 Gy on the cerebral hemispheres and the spinal cord). In children below 3 years of age, the dose was reduced to 45 Gy on the posterior fossa and 30 Gy on the rest of the CNS. After 1984, a group of low-risk patients was isolated [26]; the dose delivered to the cerebral hemispheres in the 9 children of this group was reduced to 25 Gy. All in all, 98 patients completed radiotherapy.

Chemotherapy. Chemotherapy was given to 73 patients. The drugs, doses, and selection of patients varied throughout the years. Intrathecal methotrexate was given to 12 patients in the first years of this study. In accordance with the protocol of the first cooperative study of the International Society of Pediatric Oncology (SIOP) [5], 49 children received a combination of vincristine and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).

After 1984, our patients followed the second phase III trial of the SIOP, in which chemotherapy is started between surgery and radiotherapy [26].

Follow-up. All patients, except three, were followed up regularly for periods extending from 1 to 20 years (mean follow-up: 5 years; median: 3 years). However, if only the patients who completed radiotherapy are taken into account, the follow-up duration is slightly longer (mean: 6 years; median: 5 years).

Immediately after surgery, a myelography was performed in 105 patients; spinal cord metastases were found in only 3 of these patients. Most children were seen twice in the 1st year, then once each year, and more often if clinical symptoms resurred. Follow-up included CT scans, and neurological, psychological, and endocrinological assessment.

Results

Postoperative mortality

Postoperative mortality defined as mortality in the 1st month after surgery was 6.5% for the whole series. Five of the eight children who died after the operation were under the age of 3 years. The postoperative mortality was lower in the 62 children who underwent a total resection (4.8%) than in 50 patients who had a subtotal resection (10%). However, it should be noted that this group of 50 patients includes 47 cases in which the brain stem was involved. It is very likely that the increased postoperative mortality is due rather to the brain-stem involvement than to the subtotal resection per se. A more interesting fact is the following: the postoperative mortality was nil in the 35 children operated on after 1980. However, radiotherapy could not be started or completed in 14 patients who showed severe postoperative complications; these patients finally died several months after surgery either as a result of their complications or from tumor recurrence.

Survival rate

Overall survival rates. Actuarial survival rates were calculated according to Greenwood’s method [15]. When these rates are calculated for the 120 children, thus including the patients who died in the 1st month after surgery as well as those who died later on without having completed radiotherapy, the overall survival rate is 60% at 5 years and 53% at 10 years (Fig. 1). When they are calculated for the 98 patients who completed radiotherapy, the actuarial survival rate is 73% at 5 years and 64% at 10 years (Fig. 1).

Factors influencing survival rates. It has been claimed in other studies that several factors could influence the survival rate. We have therefore analyzed our series to see whether our results confirmed or invalidated the conclusions of these previous studies. For obvious reasons, that research applies only to the 98 children who completed radiotherapy.

Age appeared to be a significant factor that influenced the survival rate in an unexpected direction (Fig. 2). There were 48 patients below the age of 6 years: their 10-year survival rate was 77%, whereas it was 46% for the 50 children between 6 and 15 years of age. This difference is significant (P = 0.005).

Sex seemed also to be a prognostic factor. In accordance with most studies already published [4, 9, 30], girls seemed to fare a little better than boys: 73% versus 53% survival at 10 years. However, in this study, the difference is not significant (P = 0.2).

There was no difference between the 10-year survival of the patients who underwent a total resection of their tumor and those in whom a subtotal resection was performed: 67% versus 62%. However, the children who only underwent a partial resection or a simple biopsy did not do well; five out of eight died, two of them within 2