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Brain Tumor in the First Year of Life
A Single Institute Study

Brain tumors in infants present special diagnostic and therapeutic challenges. To figure out the clinical features, pathological classification of the tumors and the treatment outcome of infantile brain tumors, 458 children (age<16) with brain tumors were reviewed retrospectively. Among them 21 cases (4.6%) were diagnosed during the first 12 months of life. Two tumors were definitely of congenital origin. The majority of infants with brain tumors presented with increased intracranial pressure. Fourteen tumors were located at the supratentorial area. Sixteen cases had neuroepithelial tumors; astrocytoma (optic pathway), supratentorial primitive neuroectodermal tumor (PNET) and medulloblastoma were found in three cases each. There were two treatment-related mortalities. Compared with the outcomes in older children, the treatment outcome was poorer in medulloblastoma and the optic pathway glioma which showed a higher growth potential. Because of the limited application of postoperative adjuvant therapy, radical surgical removal played a more important role in this age group. The prognosis of patients in whom the tumors could not be totally removed, largely depended on the pathological malignancy of the tumors. Though the treatment outcome was not always dismal, immaturity of the brain, higher growth potential, perioperative risks, limitations in adjuvant therapy, and pessimistic attitude on the part of parents made management more challenging

Key Words : *Brain tumors, Infant, Astrocytoma, Primitive neuroectodermal tumor, Medulloblastoma, Outcome*

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INTRODUCTION

Brain tumors diagnosed within the first year of a patient's life are frequently reported in the literature and have some outstanding features compared to those in older children (2, 4-7, 7-13, 15, 20). Recently, a worldwide survey of the brain tumors of this specific age group has been carried out (2, 11, 12).

For practicing clinicians, the intracranial neoplasms in neonates and infants present special diagnostic and therapeutic problems, although remarkable advancements in neuroimaging, perioperative intensive care, and postoperative adjuvant therapy have been achieved. The lack of specificity in the symptoms and the ability of the immature brain and skull to adapt to increased intracranial pressure may cause diagnostic delay. Although surgical resection of the tumor appears to be the most effective therapeutic modality due to the limited roles of radiation and chemotherapy (6, 16, 21, 22), a high operative mortality rate has been usual in these extremely small patients (5, 6, 8, 9, 12-14).

Because of the improvements in diagnostic technique, a larger number of brain tumors are being discovered in early childhood. The management of these tumors has become a more practical issue than it was before. To enhance our clinical insight and awareness of this specific group of brain tumors, we reviewed 21 infants with brain tumors diagnosed during a period of 20 years in our institute, and investigated the clinical presentation, location, pathological diagnosis, and treatment outcome of the tumors. To our knowledge, this is the first clinical report that deals with this issue in Korea.

CLINICAL MATERIAL AND METHODS

During a period of 20 years (1977-1996), 458 children (under the age of sixteen) with brain tumors were operated on at the Department of Neurosurgery, Seoul National University Hospital. Among them, 21 children (4.6%) underwent surgery during the first 12 months of life. The medical records of these children were reviewed

to analyse the clinical features (age, sex, presenting symptoms and signs, location, pathological diagnosis of the tumor, treatment and outcome) of this age group with brain tumors. Histological confirmation was available in all but one case. Computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the brain were performed on all patients preoperatively. The mean follow-up duration was 28.2 months (1-102 months).

RESULTS

The clinical features of each patient are summarized in Table 1.

Clinical presentation

The male to female ratio was 1.1 to 1 (11:10), and the mean age at diagnosis was 5.8 months. Two patients (9%) presented within the first month of life. Both of them were diagnosed during prenatal life with ultrasonography. In 11 patients, the symptoms and signs of increased intracranial pressure such as large head, vomiting and irritability were evident. Seizures, limb weakness, diencephalic syndrome, abnormal eyeball movement, and lower cranial nerve dysfunction were the minority of the presenting symptoms (Table 2). Signs of raised intracranial pressure were almost always evident in this group of patients. Only in four infants were the head

Table 1. Summary of 21 operated infantile brain tumor cases

No. of case	Year of surgery	Age (mos)	Sex	Symptoms & signs	Location of tumor	Pathologic diagnosis	Treatment*	Outcome**
1	1980	3	M	ICP	4V	anapl ependymoma	PR	operative mortality
2	1981	6	M	ICP	cbll, 4V	medulloblastoma	PR, RT	22, dead
3	1984	3	F	ICP	PO	PNET	PR, RT	2, lost, PD
4	1985	9	M	ICP	Pf	not explored	shunt only	–
5	1986	6	M	ICP	SS	astrocytoma	PR	31, lost, PD
6	1987	2	M	ICP	thal, LV	teratoma	STR	102, lost, SD, MR, KPS=50
7	1987	3	M	ICP	TP	MNTI	STR, ChT	74, KPS=100, static residual mass
8	1989	4	M	ND, DS	SS	astrocytoma	STR, RT	28, lost, SD, KPS=40
9	1990	12	M	Sz, ND	T	PNET	GTR, ChT	82, NED, KPS=90
10	1990	4	M	ICP	LV	CPP	GTR	39, NED, KPS=100
11	1991	3	M	ICP	cbll	medulloblastoma	GTR, ChT	4, lost during ChT
12	1993	1	F	ICP	cbll	rhabdomyosarcoma	PR	2 wk, PD, dead
13	1993	9	F	ND	SS	rhabdomyosarcoma	GTR, ChT	37, NED, KPS=90 (hypopituitarism)
14	1994	8	M	Sz	T	oligodendroglioma	GTR	32, no Sz, NED, KPS=100
15	1994	9	F	ICP, ND	FT	PNET	GTR, ChT, RT	26, NED, KPS=90
16	1994	9	F	ICP	LV	ependymoblastoma	GTR, ChT, RT	25, NED, KPS=100
17	1995	2	F	ICP	LV	CPC	NTR	11, PD, KPS=40 (MR)
18	1995	8	F	ICP, DS	SS	astrocytoma	STR	24, PD, KPS=90 (hypopituitarism, hemiparesis)
19	1995	4	F	ICP, Sz	PO	glioblastoma	GTR, ChT	13, NED
20	1996	10	F	ND	cbll	medulloblastoma	STR, ChT	1, dead during ChT (sepsis)
21	1996	1	M	ICP	stem	ganglioglioma	PR	9, SD, KPS=90

abbreviations (in alphabetical order): 4V=fourth ventricle; anapl=anaplastic; cbll=cerebellum; ChT=chemotherapy; CPC=choroid plexus carcinoma; CPP=choroid plexus papilloma; DS=diencephalic syndrome; F(sex)=female; F(location)=frontal; GTR=gross total removal; ICP=increased intracranial pressure; KPS=Karnofsky performance scale; LV=lateral ventricle; M=male; MNTI=melanotic neuroectodermal tumor of infancy (melanotic progonoma); mos=months; MR=mental retardation; ND=neurological deficit; NED=no evidence of disease; NTR=near total removal; O=occipital; P=parietal; PD=progressive disease; Pf=posterior fossa; PNET=(supratentorial) primitive neuroectodermal tumor; PR=partial removal; RT=radiation therapy; SD=stable disease; SS=suprasellar; stem=brain stem; STR=subtotal removal; Sz=seizure; T=temporal; thal=thalamus

* Extent of surgical removal is classified as follows: GTR, no residual on operative and postoperative radiological findings; NTR, >95% removed; STR, >75%, <95% removed; PR, <75% removed.

** Number is the duration of follow-up in months.

Table 2. Main presenting symptoms of the patients (N=21)

Presenting symptoms	No. of patients
Large head	6
Vomiting	3
Irritability	2
Seizure	2
Abnormal eyeball movement	2
Apnea	1
Cranial asymmetry	1
Hemiparesis	1
Poor weight gain	1
Lethargy	1
Hoarseness	1

circumferences less than 90 percentile. Interestingly, in two patients who presented with diencephalic syndrome, the head circumferences were exceptionally small (less than 3 percentile and 10 percentile), in spite of the substantial tumor size (4 cm and 5 cm in maximum dimension, respectively). Both of them were diagnosed as having chiasmatic-hypothalamic astrocytomas.

Two cases had 'definitely congenital' tumors. Case 12 (rhabdomyosarcoma) was diagnosed as brain tumor and hydrocephalus with fetal ultrasonography, and had symptoms of hydrocephalus and a mass on her cheek at birth and the MRI showed a large cerebellar mass. In case 21 (ganglioglioma), hydrocephalus and a cystic tumor at the brain stem were shown on the fetal sonography. There were additional six cases in whom the tumor was diagnosed during the first three months of life and regarded as a 'possibly congenital' tumor.

Location and pathological diagnosis of tumors

The locations of the tumors are shown in Table 3. Fourteen children had supratentorial (eight axial and six hemispheric), and seven had infratentorial tumors. One patient born with cerebellar rhabdomyosarcoma had a mass on the right cheek, of which the pathologic diagnosis was the same as the cerebellar mass.

Histological diagnoses were available in 20 cases (Table 4). One patient with a posterior fossa mass which showed strong enhancement and severe hydrocephalus on CT scan was managed with ventriculoperitoneal shunt

Table 3. Location of the tumors

Location		No. of cases
Supratentorial	Axial and ventricular	8
	Hemispheric	6
Infratentorial		7
Total		21

Table 4. Pathologic diagnoses of 21 patients (classified according to WHO Classification)

Diagnosis	No. of patients
Astrocytoma	3
Glioblastoma	1
Oligodendroglioma	1
Anaplastic ependymoma	1
Choroid plexus papilloma	1
Choroid plexus carcinoma	1
Ganglioglioma	1
Primitive neuroectodermal tumor (supratentorial)	3
Medulloblastoma	3
Ependymoblastoma	1
Mature teratoma	1
Rhabdomyosarcoma	2
Melanotic neuroectodermal tumor of infancy	1
Unknown	1
Total	21

without surgery on the tumor. Among 13 different pathological diagnoses, 16 were neuroepithelial tumors. Of those, astrocytoma, supratentorial primitive neuroectodermal tumor (ST-PNET), and medulloblastoma were found in three cases each. Rhabdomyosarcoma was diagnosed in two cases. All astrocytomas were located at the optic chiasm and hypothalamus. Twelve tumors (60%) were malignant.

Treatment

Surgical resection of the tumor mass was achieved in all cases except one which underwent a ventriculoperitoneal shunt for an enhancing posterior fossa mass. More than 75% of the mass was removed (gross total, near total, or subtotal resection) in 14 cases (70%). Gross total removal was possible in eight cases. Partial removal was performed in six (30%) of the 20 cases.

Adjuvant therapy was indicated when the pathologic findings were considered to be malignant. Five patients were able to complete postoperative chemotherapy. In one patient, chemotherapy was stopped at the parents' request (case 11, medulloblastoma) and another died of sepsis during the treatment (case 20, medulloblastoma). Radiation therapy was performed in five cases. In two cases which were managed in the early period of this series, radiation therapy was given during infancy because of the rapid growth of the tumors (case 2, medulloblastoma, and case 3, ST-PNET) and in the other three, radiation therapy was started after 18 months of age. In two cases, whole neuroaxis radiation was performed (case 2, medulloblastoma, and case 15, ST-PNET). Chemotherapy and radiation therapy were combined in two

cases (case 15, ST-PNET, and case 16, ependymoblastoma).

Outcome

Among 21 patients, follow-up information was not available in one case. The mean follow-up duration was 28.2 months (1-102 months). Four cases were followed up until death. There were two treatment-related mortalities. One died of intraoperative bleeding (case 1, anaplastic ependymoma) and the other of sepsis during chemotherapy (case 20, medulloblastoma). The other two mortalities were due to rapid growth of the tumor (case 2, medulloblastoma, and case 12, rhabdomyosarcoma). In the latter case, poor clinical condition did not allow chemotherapy. Though we did not confirm the actual death, the tumors were growing rapidly at the last follow-up of three cases (case 3, ST-PNET, case 5, astrocytoma, and case 17, choroid plexus carcinoma) and death was expected in the near future. In one case (case 11, medulloblastoma), in spite of gross total removal, the prognosis seemed poor because postoperative adjuvant therapy was rejected. Among 12 malignant tumors, seven showed discouraging results while among eight benign tumors, one revealed a poor outcome.

Of the three chiasmatic-hypothalamic astrocytomas, one showed rapid growth after partial removal (case 5). Radiation therapy was deferred as long as possible. No further information was available after postoperative 31 months. Another (case 8) demonstrated regrowth and received radiation therapy which stabilized the tumor growth, and in the other (case 18) regrowth was noted during 2 years' follow-up. In the last case, further treatment was deferred because of the slow growth of the tumor and the patient's young age.

Of the three medulloblastoma cases, one died of tumor progression 22 months after surgery (case 2) and another died of sepsis during chemotherapy 37 days after surgery (case 20). The other patient (case 11) was lost during follow-up at 4 months after surgery. Because of the clinical deterioration during the 4 months' period of treatment, the parents gave up further treatment. None of the three tumors could be removed totally and all of them had an evidence of seeding of the tumor cells along the cerebrospinal fluid pathways.

Among the three ST-PNET cases, two were alive without tumor recurrence at 82 and 26 months after surgery (cases 9 and 15, respectively). Case 9 received chemotherapy and was able to avoid radiation therapy. One patient with partially resected cerebral PNET in the early phase of our experience (case 3) demonstrated an aggressive growth in spite of radiation therapy which is not generally indicated in infancy. Radiation therapy was stopped and further treatment was rejected.

Two rhabdomyosarcoma patients showed different courses. Case 12 had a posterior fossa rhabdomyosarcoma extending to the supratentorial area, of which the long diameter was about 9 cm, and another small rhabdomyosarcoma in her right cheek. In spite of shunt surgery and partial removal, the tumor grew rapidly. The mass on the cheek also grew fast. Case 13 was free of recurrence after gross total removal and chemotherapy at 37 months after surgery, though she had hypopituitarism.

Seven of eight patients who underwent total resection (two benign and six malignant tumors) showed no recurrence of tumor keeping KPS $\geq$ 90. One of the eight (case 11, medulloblastoma) was lost during chemotherapy. In others in whom the tumor could not be totally resected and the follow-up information was available (five benign and six malignant tumors), only five patients with benign tumors showed clinical or radiological improvements or stabilization of disease.

In summary, the prognosis largely depends on pathological diagnosis, extent of surgical removal, general condition which allows chemotherapy, and parents' permission to treat these very young patients.

DISCUSSION

Many extensive series of brain tumors presented during the first year of life have been reported (8, 9, 11, 12, 14, 19). The proportion of brain tumor in this age group among childhood brain tumors ranged from 1.3% to 11% in previous reports (6, 8, 10, 14). In our series during the past 20 years, there have been 21 cases of brain tumors presented within the first year of life. They accounted for 4.6% of children with brain tumors in the same period. In spite of the limited size of patient population and incomplete follow-up information of the present study, it revealed a certain aspect of Korean statistics and the attitude of Korean people to this one of the 'serious diseases' of very young patients.

According to the International Society for Pediatric Neurosurgery (ISPN) world-wide survey reported by Di Rocco et al. (2), the 10 common intracranial tumors in the first year of life were astrocytoma, ependymoma, medulloblastoma, choroid plexus papilloma, ST-PNET, teratoma, sarcoma, meningioma, ganglioglioma, and neuroblastoma in order of frequency. In the present series, numbers of cases were more than one for astrocytoma, ST-PNET, medulloblatoma, and rhabdomyosarcoma. Astrocytomas were the most common tumors in many series of this age group (2, 9, 13, 15, 20). All three of the astrocytomas in this series were located at the optic chiasm and hypothalamus.

Oi et al. (13) stressed the ethnic or racial differences in the incidence and types of brain tumor in the reports of 307 cases of the five Far-Eastern countries. Medulloblastomas were significantly higher in incidence compared with the report of Di Rocco and colleagues. Medulloblatomas made up 14% of our series. ST-PNET and intracranial sarcoma were included in many previous reports although not as frequently as astrocytoma or medulloblatoma (1, 2, 3, 10-13, 15, 18, 23). Although the small size of the patient population of our study hinders statistical comparison of these data, it can be accepted that the proportions of each tumors in our series were not exceptional to the previous reports.

As described in previous reports (8, 9, 11, 12, 14, 19), supratentorial location was more frequent than infratentorial (14:7) in this age group and no significant sex predilection was found. The symptoms and signs of increased intracranial pressure were the main feature of presentation. Probably, this is mainly due to immaturity of the brain and the incapability of the patients to complain of specific symptoms, resulting in a large size of the tumor.

CT scan or MRI of the brain is mandatory in diagnosis and treatment of the tumor. Ultrasonography of the brain is an invaluable diagnostic tool in the prenatal period, and provides definite evidence of the congenitality of the tumor. In the present series, intrauterine diagnoses were made in two cases, one with a posterior fossa rhabdomyosarcoma and the other with brain stem ganglioglioma. Although Solitare and Krigman (17) defined "definitely congenital" tumors as tumors which present or produce symptoms at birth, babies with truely congenital brain tumors may go undetected because of the nonspecificity of symptoms. Wide use of ultrasonography during the prenatal period will contribute to the detection of congenital brain tumors.

Poor prognosis and high operative mortality in this age group have been reported (1, 2-6, 10, 12-15, 19, 20). Not only the risks in the anethesia (temperature, bleeding, etc.) and difficulties in postoperative care (for example, lack of voluntary control of water and salt intake, etc.), but the different biological behaviour of the tumor itself and the less active and pessimistic attitude of the parents to treatments in this very young age group are factors in poor outcomes.

Though astrocytomas of the optic chiasm and hypothalamus are pathologically benign, the clinical courses are not always benign because of the location and variable biological behaviour of the tumor. The location of the tumor makes total removal dangerous and not feasible. In addition, the growth of the tumor is usually faster in young infants (24), while the tumor is frequently large at the time of diagnosis and radiation therapy has limitations in these young children. These findings were also shown in the present study. In our series, one patient showed a rather rapid growth of the tumor after partial removal, and the other two patients had slowly growing tumors.

The three patients with medulloblastoma in our study showed much poorer outcomes than older children did. In 1994, the authors reported the treatment outcome for medulloblastoma in our institute (19). The 3-year and 5-year survival rates of 78 patients treated during 1972-1992 were 57.4% and 47.3%. Of three medulloblastomas diagnosed during infancy, none could be removed totally and all had evidence of seeding of the tumor cells along the cerebrospinal fluid pathways. Along with the limitation of radiation therapy and the lack of eagerness of parents giving permission for treatment in this age group, these tumor-related factors may have contributed to the poor prognosis.

Two patients with cerebral PNET who underwent gross total removal and received adjuvant chemotherapy and irradiation had satisfactory results. In our series of 27 cases (up to age 15) of cerebral PNET, 2-year and 5-year survival rates were 74% and 53%, respectively, and the univariate analysis showed better survival with radical surgical removal (unpublilshed data). These data suggested that the prognosis of infants with cerebral PNET is not worse than that of older children if they undergo radical surgical removal and adjuvant chemoradiotherapy. One patient with partially resected cerebral PNET in the early phase of our experience demonstrated an aggressive growth in spite of radiation therapy. Radiation therapy was discontinued and further treatment was rejected. We think that radical removal and chemotherapy could have brought better results in this case.

Intracranial sarcomas have been listed in previous reports (2, 3, 13, 18, 23), but made up a minority of the brain tumors in this age group. Considering the small population of our patients, the occurrence of two cases of rhabdomyosarcoma is unusual. One patient with a posterior fossa rhabdomyosarcoma had a small rhabdomyosarcoma in her right cheek. Regarding the size of the mass, the cheek mass might have been a metastatic lesion of the intracranial mass. In the other patient, the mass was in the suprasellar area without any other site of tumor. It seemed to be a primary intracranial sarcoma.

The extent of tumor removal was possibly an important prognostic factor. Seven of eight patients who underwent total resection (two benign and six malignant tumor cases) showed no recurrence of tumor keeping KPS $\geq$90 while the prognosis of patients in whom the tumors could not be removed totally largely depended on the pathological malignancy of the tumors. Because

of the proven limitations of radiation therapy in younger children, the total removal of the tumor has more significance in this age group. Unfortunately, brain tumors in this age group are frequently diagnosed when they become large masses because of the unfused cranial sutures and difficulty in detection of subtle neurological deficits. Early detection of the tumor should be emphasized since it can allow radical surgical removal before the tumor extends deep into the brain parenchyma and improve the quality of survival by treatments before the large tumor damages the immature brain.

Recently, the authors prefer to use chemotherapy as the adjuvant postoperative treatment modality in the management of malignant tumors and save the radiation therapy as the last option till the patients become 18 months at least.

In summary, infantile brain tumors are unique in their presentation and location. Because of the limited application of postoperative adjuvant therapy, radical surgical removal plays a more important role in this age group. The prognosis of patients in whom the tumors could not be removed totally largely depends on the pathological malignancy of the tumors. Though the treatment outcome is not always dismal, immaturity of the brain, higher growth potential, risks in anesthesia and surgery, limitations in adjuvant therapy, and a less active, pessimistic attitude of parents make management more challenging.

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