Turkish Neurosurgery 2006, Vol: 16, No: 2, 77-80

Original Article

Atypical Teratoid/Rhabdoid Tumors

Burçak BİLGİNER[1]
Gökhan BOZKURT[2]
Nejat AKALAN[3]
Figen SÖYLEMEZOĞLU[4]
Faruk ZORLU[5]
Münevver BÜYÜKPAMUKÇU[6]

[1,2,3] Department of Neurosurgery,
[4] Department of Pathology,
[5] Department of Radiation Oncology,
[6] Department of Pediatric Oncology,
School of Medicine, Hacettepe University Ankara, Turkey

ABSTRACT

Central nervous system atypical teratoid/rhabdoid tumor (AT/RT) of infancy and childhood is a unique histological entity with an extremely aggressive natural history. In spite of multiple treatment regimens consisting of maximal surgical resection, radiation therapy, and multiagent aggressive chemotherapy, the prognosis is very poor. Here in this study we analyze the charts, presenting symptoms, imaging studies, surgical procedures and adjuvant therapy modalities of 10 AT/RT patients between 1995 and 2004.

KEY WORDS: Atypical teratoid/rhabdoid tumor, Brain tumor, Primitive neuroectodermal tumor

INTRODUCTION

The most common biologically malignant central nervous system (CNS) tumor occurring during the first decade of life is a primitive neuroectodermal tumor (PNET). Historically, atypical teratoid/rhabdoid tumors were frequently misdiagnosed as PNETs because of their similar histologic features. This unique, biologically aggressive CNS neoplasm is formed totally or partly by rhabdoid cells, areas resembling typical PNET, and malignant mesenchymal and/or epithelial tissue (3). Atypical teratoid/rhabdoid tumor (AT/RT) of the CNS is a highly malignant and clinically aggressive tumor of infancy and childhood. The majority of the patients are under two years of age at diagnosis. The tumor occurs both in the posterior fossa and in the supratentorial compartment. The tendency to arise in the cerebello-pontine angle with invasion of surrounding structures is a distinct feature of AT/RT. Despite multinodal therapy, including extensive surgery, conventional radiotherapy and systemic chemotherapy, the survival remains very poor (5).

The aim of this study was to determine the prognosis of AT/RT.

PATIENTS AND METHODS

Neurosurgery, oncology and pathology databases from 1995 to 2004 were evaluated retrospectively to identify children with presumed AT/RT at the Hacettepe University Hospital, Ankara, Turkey and 10 patients were identified. All patients underwent magnetic resonance imaging (MRI) of the brain and six also underwent spinal MRI and intravenous administration of contrast material at 0.1 mmol/kg. All patients underwent surgery for removal of their intracranial masses. Their charts, presenting symptoms, imaging studies, surgical procedures and adjuvant therapy modalities were analyzed to determine the prognosis of the AT/RT.

Nine male and one female patients were included in the study. At the time of diagnosis the mean age was 16 months (from 2 months to 78 months). Presenting symptoms depended on tumor location and included vomiting, ataxia, cervical tilt, cranial nerve deficits, extremity

Received : 08.10.2005
Accepted : 01.11.2005

This clinical study was presented at the 18th Scientific Congress of the Turkish Neurosurgical Society (Antalya, Turkey, 2004

Correspondence address:
Burçak BİLGİNER
Hacettepe Üniversitesi Tıp Fakültesi,
Nöroşirürji Bölümü, Ankara, TURKEY
Phone : +90 0312 3051715
Fax: : +90 0312 3111131
E-mail : burcak@tr.net

weakness, headache, tremor and convulsion. Brain MRI was performed on all patients and spinal MRI on six patients. The primary tumor was infratentorial in six patients (Figure 1), two patients had supratentorial intraventricular lesions (Figure 2) while one patient had a hemispheric lesion and one patient had a spinal tumor. On MRI, the solid component of the masses were heterogeneous and showed increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted images. All patients underwent surgical excision of the tumor. Five of the patients had gross total resection and five had subtotal resection. All patients were treated with chemotherapy. The chemotherapy protocols were 'cisplatin + etoposide' for 7 patients and 'carboplatine + etoposide' for 3 patients. Four patients were also treated with radiotherapy besides surgery and chemotherapy. All tumors stained with vimentin, glial fibrillary acidic protein and epithelial membrane antigen. Eight patients died within 15 months following diagnosis. Two of them are still alive with a survival rate of 8 months and 25 months from diagnosis. The five patients that underwent gross total tumor resection had an average of 14.9 months survival and the other 5 patients that underwent subtotal tumor resection had 4.62 months survival. The mean survival rate was 14.8 % for two years. (Table I) shows the comparison of age range, site of origin of the tumor and median survival of some series.

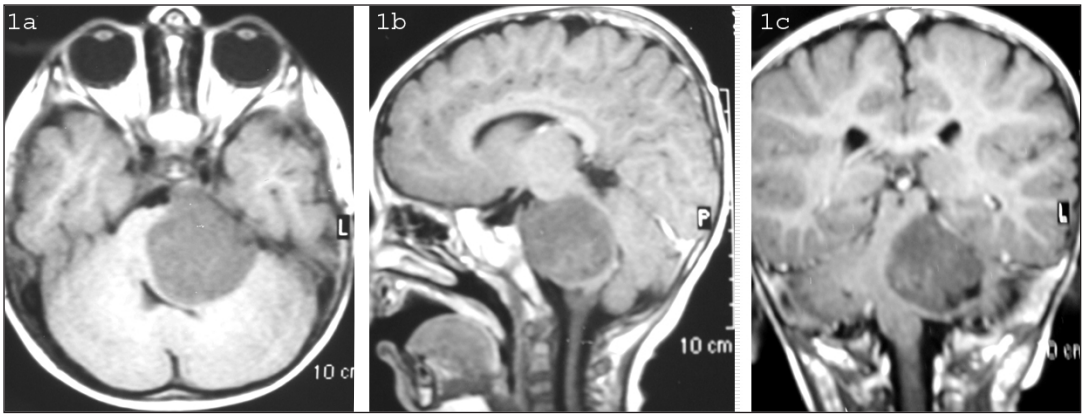

Figure 1: Axial (**A**), sagittal (**B**) and coronal (**C**) T1 MR images of the infratentorial tumor.

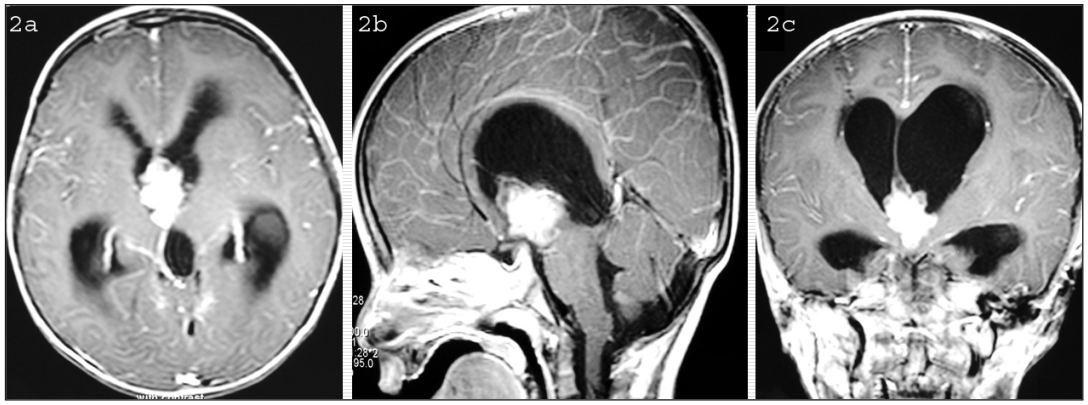

Figure 2: Axial (**A**), sagittal (**B**) and coronal (**C**) gadolinium-enhanced MR images of the supratentorial tumor.

Table 1 : Comparison of some previously reported series with our patients.

Series	# of Patients	Age Range	Site of Origin %	Median Survival
Bhattacharjee	56	22 days-15 yr	Infra 65, Supra 28	6 months
Hilden	4	10 mo-4 yr	Infra 50, Supra 50	19 months
Ho	11	7 mo-9 yr	Infra 91, Supra 9	15.3 months
Dang	3	1 mo-2 yr	Infra 66, Supra 33	10 months
Zimmerman	4	14 mo-11yr	Supra 100	35.5 months
Present Study	10	2 mo- 6 yr	Infra 60, supra 30	14.8 months

mo= month, yr = year, Infra = Infratentorial, Supra = Supratentorial

DISCUSSION

Brain tumors in infancy and childhood are often highly malignant and difficult to classify due to overlapping morphologic and immunohistochemical findings. Malignant rhabdoid tumors are biologically aggressive neoplasms that occur most frequently in the kidneys of infants and children. Similar tumors occur in other locations, including the central nervous system. In the brain, they may be composed purely of rhabdoid cells or have a mixture of rhabdoid cells, neuroepithelial, epithelial and mesenchymal elements. The tumor is histologically different from more familiar teratomas and is negative for routine germ-cell markers (3,5). AT/RT is a tumor of infancy and childhood and very rare in adults. The mean age of the patients is 2.9 years with a male predominance. In our study the mean age was 16 months and nine of the patients were male. AT/RT was included for the first time in the World Health Organization classification of tumors of the CNS in 2000, although it had been recognized during the early 1980s as a rhabdoid tumor of the CNS with an unfavorable prognosis. These tumors can arise at any location in the CNS, with approximately half of all tumors arising in the posterior fossa (1). Similarly, six of our patients had their primary tumor at the posterior fossa. Clinical presentation depends on the age of onset and the location of the tumor. Children younger than 3 years of age usually present with nonspecific symptoms and signs, such as vomiting, lethargy, irritability, loss of weight, macrocephaly, and failure to thrive. Older patients commonly present with increased intracranial pressure or localizing signs. Cranial nerve palsies, headache, and hemiplegia are common (2). The main complaints of our patients were vomiting, ataxia, cervical tilt, cranial nerve deficits, extremity weakness, headache, tremor and convulsion. The radiologic features of AT/RT are nonspecific, but may be similar to PNET-MB. There is increased density on nonenhanced CT and heterogeneous contrast enhancement. Cysts and hemorrhage are common. On MRI, there is decreased signal intensity on T1-weighted images, iso or decreased density on T2-weighted images (due to hypercellularity) and heterogeneous enhancement post-gadolinium. In our study we did not perform CT, but MRI showed decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. Therefore, the radiological differential diagnosis before histochemistry analysis includes PNET-MB, teratoma, astrocytoma, choroid plexus papilloma and ependymoma (3). Light microscopic examination of AT/RT reveals a diffuse growth pattern of predominantly polygonal cells arranged in a focally trabecular or alveolar fashion, cells with vesicular nuclei and prominent nucleoli, and scattered cells with globular hyaline cytoplasmic inclusions in the vicinity of the nuclei. Electron microscopy shows whorls of filaments in the cytoplasm, which can be classified as intermediate filaments and represent vimentin. Results of the immunohistochemical studies are positive for three antibodies whose epitopes are almost always expressed: Epithelial membrane antigen (EMA), vimentin and smooth-muscle actin (SMA) (2). All of our patients' tumors stained with vimentin, EMA and glial fibrillary acidic protein. More recently, cytogenetic abnormalities have been used for improved diagnostic classification. Monozomy 22 or deletions of chromosome band 22q11 with alterations of the hSNF5/INI1 gene are shown in patients with AT/RT (1), but we did not perform cytogenetic studies.

Treatment was highly variable but most children received the multi-modality therapy of surgery, radiation and chemotherapy. The degree of surgical resection appears to be one of the most important factors in predicting prognosis. In our study, patients with complete resection had a median survival of approximately 14.9 months compared to 4.62 months for those with incomplete resection. Another important variable in the prognosis of the patients may be age and the inability to use full dose craniospinal irradiation, although rapid disease recurrence and progression typically occurs even in those patients who do receive full-dose craniospinal irradiation (8). Our two patients who received craniospinal irradiation had a good response with one surviving 8 months and the other free of disease 25 months from diagnosis.

The use of stereotactic radiosurgery (Gamma knife) in AT/RT has previously been described. This is a noninvasive therapeutic procedure, which delivers a single high dose of radiation therapy to a well defined target volume, while sparing normal brain tissue surrounding the tumor (4,5).

A great deal has been learned about the pathophysiology of AT/RT. Identification of the INI1 (also called SNF5) gene in many human tumors has provided a diagnostic test in patients whose

pathology lacks the classic appearance (8). The targeting of this gene has also given rise to a murine model of AT/RT although none have localized tumors to the CNS making pre-clinical evaluation of this or other therapies difficult (7).

In conclusion, CNS AT/RT is a distinct, highly malignant neoplasm that occurs in infants and young children, defined by the presence of rhabdoid cells and heterogeneity of cell type, and associated with deletion of chromosome 22. Children with AT/RT rarely respond to treatment despite the use of aggressive chemotherapy and/or radiotherapy. Survival is poor and unrelated to the age of the patient at the time of diagnosis, the extent of resection, or the type of adjuvant postoperative therapy.

REFERENCES

1. Arslanoğlu A, Aygun N, Tekhtani D, Aronson L, Cohen K, Burger PC, Yousem DM: Imaging findings of CNS atypical teratoid/rhabdoid tumors. Am J Neuroradiol 25; 476-480, 2004
2. Chung Y, Wang K, Shin S, Kim N, Chi J, Min K, Cho B: Primary intracranial atypical teratoid/rhabdoid tumor in a child: a case report. J Korean Med Sci 17; 723-726, 2002
3. Fenton LZ, Foreman NK: Atypical teratoid/rhabdoid tumor of the central nervous system in children: an atypical series and review. Pediatr Radiol 33; 554-558, 2003
4. Hilden JM, Watterson J, Longee DC: Central nervous system Atypical teratoid/rhabdoid tumor: response to intensive therapy and review of the literature. J Neurooncol 40; 265-275, 1998
5. Hirth A, Pedersen PH, Wester K, Mörk S, Helgestad J: Cerebral atypical teratoid/rhabdoid tumor of infancy: long-term survival after multimodal treatment, also including triple intrathecal chemotherapy and gamma knife radiosurgery - case report. J Pediatr Hematol Oncol 20; 327-332, 2003
6. Lopez-Gines C, Cerda-Nicolas M, Kepes J: Complex rearrangement of chromosomes 6 and 11 as the sole anomaly in atypical teratoid/rhabdoid tumors of the central nervous system. Cancer Genet Cytogenet 122; 149-152, 2000
7. Roberts CW, Galusha SA, McMenamin ME, Fletcher CD, Orkin SH: Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. Proc Natl Acad Sci USA 97(25); 13796-13800, 2000
8. Zimmerman MA, Goumnerova LC, Proctor M, Scott RM, Marcus K, Pomeroy SL, Turner CD, Chi SN, Chordas C, Kieran MW: Continuous remission of newly diagnosed and relapsed central nervous system atypical teratoid/rhabdoid tumor. J Neuro-oncol 72; 77-84, 2005