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Rhabdoid tumors of the central nervous system

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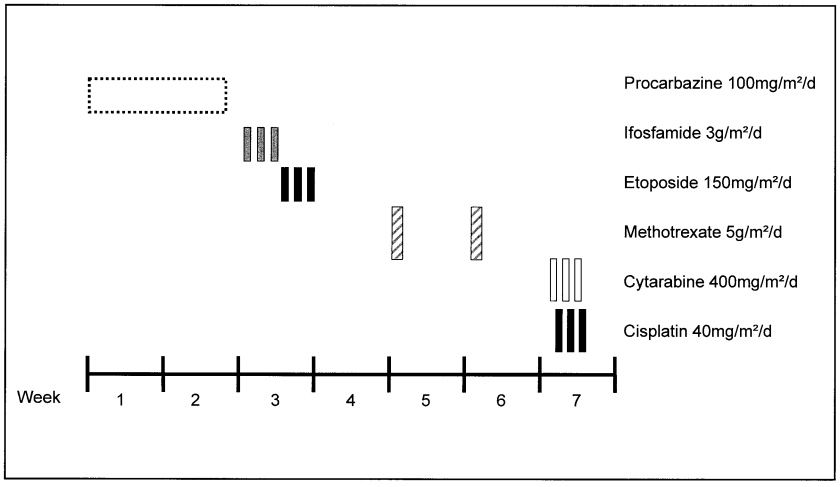
Abstract Rhabdoid tumors of the central nervous system are rare malignancies with a still almost uniformly fatal outcome. There is still no proven curative therapy available. We report our experience with nine patients with central nervous system rhabdoid tumors. Gross complete surgical removal of the tumor was achieved in six patients. Seven patients received intensive chemotherapy. Four of these were treated in addition with both neuroaxis radiotherapy and a local boost directed to the tumor region, while two patients received local radiotherapy only. The therapy was reasonably well tolerated in most cases. Despite the aggressive therapy, eight of the nine patients died from progressive tumor disease, and one patient died from hemorrhagic brain stem lesions of unknown etiology. The mean survival time was 10 months after diagnosis. Conventional treatment, although aggressive, cannot change the fatal prognosis of central nervous system rhabdoid tumors. As these neoplasms are so rare, a coordinated register would probably be a good idea, offering a means of learning more about the tumor's biology and possible strategies of treatment.

Key words Brain tumor · Rhabdoid tumor · Chemotherapy · Radiotherapy

Introduction

Rhabdoid tumors are among the pediatric malignant tumors with the worst prognosis. Originally described as a variant renal tumor by Beckwith et al. [2], rhabdoid tumors are now histologically defined as a separate entity [14, 15]. They resemble rhabdomyosarcomas, but immunohistochemical and ultrastructural features allow a clear distinction between the two types of tumors [2, 15]. Rhabdoid tumors are characterized by round tumor cells with an eccentric nucleus, prominent nucleolus, vacuolated cytoplasm and positive immunoreactivity for vimentin. Often morphologic and immunohistochemical features resembling primitive neuroectodermal tumors (PNET), mesenchymal neoplasms and epithelial differentiation can be found simultaneously. Karyotyping has revealed a high incidence of monosomy, deletion or other anomalies of the long arm of chromosome 22 [5, 16], which might lead to the loss of a tumor suppressor gene [17, 18]. Rhabdoid tumors can arise from many different organs; soft tissue seems to be the predominating origin [2, 20]. So far about 90 patients with rhabdoid tumors of the central nervous system (CNS) have been described [7, 15, 20]. The mean age at diagnosis is 2–3 years, but some adult patients have been described as well [1, 8, 11]. The sex ratio is 3:2, with boys more often affected than girls [15]. The tumors can be localized both supra- and infratentorially [7, 15]. The prognosis is still very

Fig. 1 Chemotherapy protocol



grave. Only a few children have survived for some years [4, 10], and no patient has been described with a disease-free interval longer than 5.5 years [13]. As yet no established protocol is available for the treatment of rhabdoid tumor patients.

We report our experience with nine patients affected by rhabdoid tumors of the central nervous system. Seven of them were treated with a combined approach including surgery, chemotherapy and radiation therapy (similar to protocol HIT 91 of the German Society for Pediatric Oncology/Hematology [GPOH; Fig. 1] with some modifications [12]).

Case reports

Case 1

This girl aged 2 years and 3 months presented after a short period of vomiting and headache. She developed increased intracranial pressure as the result of a large left-sided fronto-temporal brain tumor attached to the tentorium; there was no evidence of any metastases. After surgical removal of the tumor the patient received a first course of chemotherapy according to the HIT protocol including procarbazine (Fig. 1). A recurrent tumor was removed 3 months after the first operation. After a second course of chemotherapy and craniospinal and local boost radiotherapy the patient's condition was good and she had no clinical symptoms. No major side effects delayed therapy. However, 2 months later the child died of a second recurrence of the large tumor at the original site, 11 months after the initial diagnosis had been made.

Case 2

This 5-year-old girl developed headache, vomiting and palsy of the left IVth cranial nerve. One month after the onset of symptoms a large intraparenchymatous tumor of the right cerebellar hemisphere was diagnosed by magnetic resonance tomography (MRT). There was no evidence of metastases. After surgical removal of the tumor, cytostatic therapy according to the HIT protocol was given, followed by craniospinal radiation at a dose of 35 Gy and a local tumor boost of 20 Gy. Radiotherapy was interrupted for 2 weeks owing to bone marrow suppression. Radiological examination revealed minimal residual/relapsed tumor without progression. After a period of 8 months without symptoms the patient developed meningeosis carcinomatosa and died about 16 months after the diagnosis.

Case 3

This 6-month-old boy developed vomiting, muscle hypotonia and loss of consciousness. A large brain tumor located in the left temporo-parietal hemisphere without metastases was detected by cranial computed tomography (CCT). After surgical removal there was no evidence of residual tumor. Cerebrospinal fluid examination did not reveal the presence of any tumor cells. Only 2 months later local relapse occurred, leading to a second surgical resection of the tumor, which was now firmly attached to the dura mater. The original diagnosis of fibrosarcoma was revised to one of malignant rhabdoid tumor. The patient received three cycles of chemotherapy (HIT) without procarbacin. No residual tumor was seen after the surgical and cytostatic therapy. Radiotherapy was not applied in view of the young age of the patient. A second tumor relapse occurred at the original site 3 months later, leading to death 10 months after the initial diagnosis.

Case 4

This 4-month-old girl developed vomiting, gaze deviation to the left and a slight hyperreflexia of the left side 2 days before diagnosis of a large intraparenchymatous tumor of the left hemisphere. After subtotal surgical removal the patient developed opisthotonus, hyperexcitability and hyperreflexia. Shortly thereafter the tumor recurred at the original site with rapid progression. The child died at the age of 13 months, 9 months after diagnosis.

Case 5

This boy aged 5 years and 6 months had suffered from vomiting and headache for 6 weeks, and double vision was noted 2 weeks before admission. Nuclear magnetic resonance tomography revealed a 2-cm tumor in the area of the septum pellucidum, without evidence of metastases (Fig. 2a, b). The neurological symptoms disappeared after surgical removal of the tumor. The patient received chemotherapy according to the HIT protocol. In

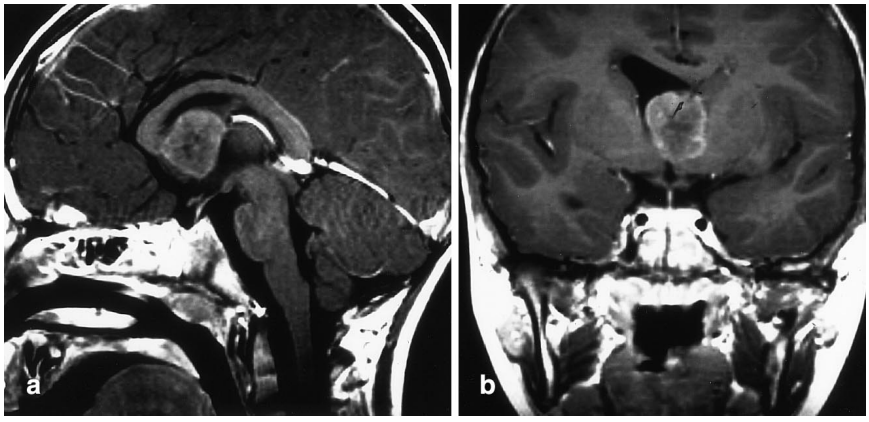


Fig. 2 a, b Nuclear magnetic resonance imaging of the rhabdoid tumor (patient 5) after gadolinium application

addition, methotrexate was given four times intrathecally, a single dose being 12 mg. Chemotherapy was very well tolerated. After chemotherapy routine radiological study revealed anomalies suggestive of relapse at the original tumor site. Radiotherapy of the neuroaxis with 30 Gy plus 20 Gy as an additional tumor boost led to a transient halt of tumor progression. The patient was subsequently treated with oral trofosfamide and etoposide. The tumor recurred at the original site about 6 months after radiotherapy and led to the patient's death about 15 months after diagnosis.

Case 6

When the patient was 6 months old a large tumor localized parieto-occipital on the right side was completely removed. About 5 weeks later a second operation was done to remove a locally relapsed tumor. Intensive chemotherapy was given, including cyclophosphamide, vincristine and intraventricular (8 times) methotrexate. The patient died 8 months after the onset of chemotherapy because of a second local relapse.

Case 7

In this 4-year-old girl a rhabdoid tumor in the area of the sulcus centralis on the right side was completely removed, and intensive chemotherapy (HIT 91) followed during the next 5 months. Four months later a second operation was done to remove a local relapse. After local radiotherapy with 54 Gy a second chemotherapy course was started with vincristine, lomustine and carboplatin. Five months later a second relapse occurred at a site that was also intracerebral but was distant from the primary location. The patient died 18 months after diagnosis.

Case 8

This 14-year-old patient developed right-sided ptosis, focal seizures and left-sided hemiparesis 3 months before diagnosis of a 2.5-cm tumor within the brain stem. The tumor was partly removed. Local radiotherapy with 45 Gy led to a marked reduction in residual tumor size and in neurological impairment. Two months later routine radiological analysis revealed both local tumor relapse and three metastases along the spinal axis. Two courses of chemotherapy in addition to spinal radiation with 30 Gy led to only a transient minimal tumor regression. The patient developed rapid tumor progression and died 2 months later.

Case 9

This 12-year-old girl developed headache and vomiting only a few days before diagnosis of a large 5-cm tumor in the left hemisphere without evidence of metastases. After partial resection local radiotherapy was done with a dose of 54 Gy accompanied by weekly injections of vincristine; residual tumor size was not changed by this treatment. Two months after diagnosis the patient died from central cardiac and respiratory arrest. Cranial computed tomography showed hemorrhagic brain stem lesions.

Results

Clinical features

Nine patients with primary rhabdoid tumor of the central nervous system are described; the clinical data are summarized in Table 1. The diagnoses were made by local pathologists and confirmed in all cases by independent reference pathologists. The tumor was localized supratentorially in seven patients and infratentorially in two. At diagnosis none of the patients had evidence of any metastases as judged by nuclear magnetic resonance tomography of the cerebrospinal axis and/or cerebrospinal fluid examination. The median age at diagnosis was 4 years, with a range from 4 months to 14 years.

Treatment

The treatment in our patients was heterogeneous. In all nine children a neurosurgical operation was done. However, gross total resection could be achieved in only six of the nine patients; routine postoperative radiological examinations revealed substantial parts of the tumor left in three patients. Adjuvant chemo- and/or radiotherapy was administered in eight patients. Six patients received intensive chemotherapy, in four cases followed or accompanied by radiotherapy; two patients received radiotherapy with subsequent intensive chemotherapy or with concomitant vincristine injections (see Table 1).

Table 1 Clinical data on the patients (*CCT* cranial computed tomography, *MRT* magnetic resonance tomography of the craniospinal axis, *CSF* cerebrospinal fluid, *Gy* gray, *MTX* methotrexate, *HIT* treatment protocol devised for malignant brain tumors by the German Society of Pediatric Oncology and Hematology)

Case no.	Age (years)	Sex	Diagnostic procedures	Localization	Surgical removal	Chemotherapy	Radiotherapy	Relapse / progression	Localization of relapse	Treatment for relapse			Survival time from diagnosis (months)
										Surgery	Chemotherapy	Radiotherapy	
1	2.25	f	CCT, MRT	Left fronto-temporal	Gross total resection	HIT: 1 cycle		Relapse	Local	Gross total resection	HIT: 1 cycle	Craniospinal radiation 30 Gy; tumor boost 20 Gy	11
2	5	f	CCT, MRT, CSF	Right cerebellar	Resection >95%	HIT: 2 cycles	Craniospinal radiation 35 Gy; tumor boost 20 Gy	Relapse	Meningeosis carcinomatosa				16
3	0.5	m	CCT, CSF	Left temporo-parietal	Gross total resection			Relapse	Local	Gross total resection	HIT: 3 cycles (modified)		10
4	0.3	f	CCT, MRT	Left temporo-parieto-occipital	Resection 70–90%			Progression	Local				9
5	5.4	m	CCT, MRT	Septum pellucidum	Gross total resection	HIT: 2 cycles; 4× intrathecal MTX		Relapse	Local	None	Oral trofosfamide and etoposide	Craniospinal radiation 30 Gy; tumor boost 20 Gy	15
6	0.5	m	CCT, MRT, CSF	Right parieto-occipital	Gross total resection			Relapse	Local	Gross total resection	HIT: 1cycle (modified)		8
7	4	f	CCT, MRT, CSF	Right sulcus centralis	Gross total resection	HIT: 2 cycles		Relapse	Local	Gross complete resection	Vincristine, lomustine, carboplatin	Tumor boost 54 Gy	18
8	14	f	CCT, MRT, CSF	Brain stem	Resection, 60–70%		Tumor boost, 45 Gy	Progression	Local and spinal cord	None	HIT: 2 cycles	Spinal radiation 30 Gy	4
9	12	f	CCT, MRT, CSF	Left hemisphere	Resection, 70–90%	Vincristine weekly	Tumor boost 54 Gy						2
	Median: 4												Median 10

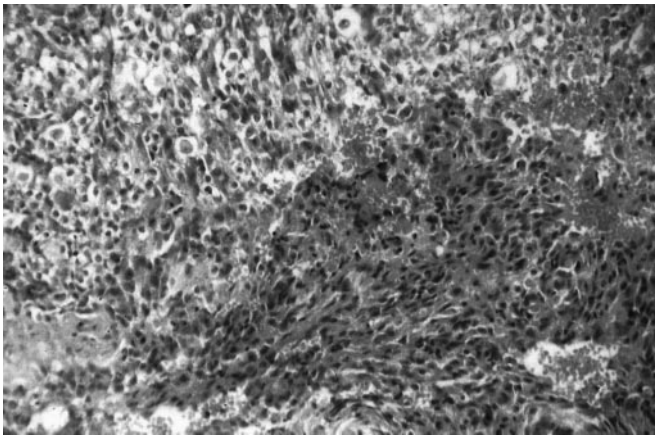


Fig. 3 Histological picture of rhabdoid tumor (patient 5). (Hematoxylin-eosin)

The therapy was reasonably well tolerated in most cases. Side effects of chemo- and/or radiotherapy were mild general infections, bone marrow hypoplasia and vomiting. Supportive treatment was sufficient to control these problems. None of the patients developed significant worsening of neurological symptoms as a result of chemotherapy or radiotherapy.

Outcome

The mean survival time after diagnosis was 10 months. A transient state of complete remission had been achieved by neurosurgery in six of the nine patients. In two children tumor progression occurred even during the adjuvant chemo-radiotherapy. Eight of the nine patients died from progressive tumor disease. In one girl etiologically unclarified hemorrhagic brain stem lesions led to death.

Sites of relapse or progression were local in six cases and disseminated in two cases as judged by craniospinal magnetic resonance tomography in seven cases and cerebrospinal fluid examination in one (case 3). There was no evidence of further tumor manifestations outside of the central nervous system.

Histology

Histological examinations showed diffuse cellular sheets of undifferentiated cells with polymorphic nuclei in all cases. Typical rhabdoid tumor cells dominated, but nevertheless unclassified or PNET-like features were noted. Numerous mitotic figures and multinucleated cells were seen. The cytoplasm was abundant and eosinophilic and contained hyaline PAS-positive inclusions. Vimentin immunoreactivity in most of the tumor cells was seen in all patients. In five cases specific neuronal markers (NF 68/NF 160/ NF 200) were examined and indicated structures with a neuronal derivation. Immunoreactivities for myoglobin and desmin were negative, whereas actin was positive in all cases. Electron microscopic studies were done in five cases; the most prominent finding was the presence of intracellular filaments resembling tubular structures.

Discussion

Rhabdoid tumors of the central nervous system are rare and aggressive malignancies with manifestation in early childhood [15, 20]. They can be localized both supra- and infratentorially [3, 7, 15]. Primarily disseminated malignancy has been observed in 10–30% of the patients [15, 20]. The histological origin of the tumor is still somewhat uncertain, but most probably it develops from soft tissue structures. The resemblance to rhabdoid structures is striking, but there are often fields reminiscent of teratoid, mesenchymal, epithelial or primitive neuroectodermal tumors [3, 7, 15]. The definition of the rhabdoid tumors as a biological entity [15] is supported by a cytogenetic analysis that revealed numerical or structural anomalies of chromosome 22 in the brain tumor cells [5, 16–18]. Besides the central nervous system, rhabdoid tumors with similar cytogenetic anomalies can be found in many different organs as primary sites [5]. The prognosis of the tumor if located in the central nervous system is still very poor, since such tumors are almost uniformly fatal; it is slightly better in the case of extracerebral tumor manifestations [19]. Up to now there is no proven curative therapy known for cerebral rhabdoid tumors. No randomized study has been undertaken to compare different treatment options.

With few exceptions the prognosis of malignant brain tumors depends heavily on complete surgical removal [6]. Unfortunately this is often not possible in patients with rhabdoid tumors, as seen in our patients. In addition to the importance of complete surgery, it has been shown for several other malignant brain tumors that adjuvant antineoplastic therapy offers the only chance of a long-term cure [6, 9]. The most striking effect of adjuvant therapy has been shown in medulloblastoma patients who did not survive after exclusive surgical treatment. The prognosis was drastically changed by the introduction of adjuvant radiotherapy [6]. Further improvement, at least for some subgroups of patients, was achieved with additional chemotherapy [9, 12]. According to this experience a combined chemo-radiotherapy treatment schedule similar to a protocol of the German Society for Pediatric Oncology/Hematology [12], though with some modifications, has been used for most of the rhabdoid tumor patients in this study. This protocol was originally planned for medulloblastoma patients and has turned out

to be quite efficient [12]. In view of the known long-term neuropsychological side effects of radiotherapy at a young age, some patients with rhabdoid tumors were treated in first line with several courses of chemotherapy including etoposide (VP-16), high-dose methotrexate, cisplatin and vincristine. In two cases intrathecal/intraventricular administrations of methotrexate as suggested by Olson et al. [13] were added. Subsequently, radiotherapy of the neuroaxis with an additional local tumor boost was done.

Despite the aggressive antineoplastic therapy our results are no better than those described by other authors, who used a variety of different chemo- and radiotherapy modalities. The mean survival time in our patients was 10 months. This might represent some advantage over that in patients described in the literature who were treated by surgery only, with a mean survival time of 6 months [14]. A measurable regression of rhabdoid tumor when treated with chemo- or radiotherapy has been seen in only 10–20% of cases, as reported by Rorke et al. [14, 15]. Adjuvant antineoplastic therapy might lead to a somewhat longer survival, but in most cases does not result in long-term cure. Of the patients with rhabdoid tumor of the central nervous system described so far, less than 20% were still alive at the date of publication, with a maximal follow-up time of 5.5 years [7, 13, 15]. Only slightly better results are described for patients with rhabdoid tumors in extracerebral localizations [19].

Further investigation is necessary to learn more about the biology and origin of such tumors. As rhabdoid tumor of the central nervous system is so rare, centralized registration should be initiated. A decision for adjuvant antineoplastic therapy needs very critical judgement, with benefit and unwanted side effects carefully balanced. Experimental approaches should be considered to improve the poor prognosis of the disease.

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