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White matter disease in children treated for malignant brain tumors

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Abstract *Objects:* The objects of the study reported were to recognize different patterns of white matter disease (WMD) in the follow-up of children after surgery, radiation and/or chemotherapy for malignant primary brain tumors and to evaluate statistical data on the incidence of WMD and various risk factors. *Methods:* Magnetic resonance imaging (MRI) records were evaluated retrospectively in the routine follow-up (range 6 months to 15 years after surgery) of 44 children with malignant primary brain tumors treated with surgery and radiotherapy and/or chemotherapy. *Results:* WMD was diagnosed in 28 children and subclassified into circumscribed white matter lesions (WML) and diffuse atrophy. WML were the most common finding (n=13), followed by atrophy (n=7) and the combination of both (n=8). Statistical analysis revealed slightly more frequent atrophy in children younger than 5 years. WML could be linked with supratentorial location of the tumor, follow-up longer than 5 years, and the presence of a ventricular shunt. Intrathecal chemotherapy was also a factor, but because of the small sample size of the group this might not be valid. None of the children had neurological deficits attributed to these findings, but the impact on neuropsychological development was not determined.

Keywords Brain tumor · White matter injury · Radiation · Chemotherapy

Introduction

Late central nervous system effects are not uncommon in children who have been treated with cranial radiation and/or chemotherapy for malignant disease. Abnormal neuropsychological, neurophysiological, neuroendocrinological, and neuroradiological findings have been documented in various follow-up studies. The results, however, are often contradictory, and comparison is difficult because of the different therapeutic strategies adopted for different diseases. White matter disease (WMD) is well documented in children after therapy of acute lymphoblastic leukemia (ALL), the abnormal findings recorded on imaging studies in long-term survivors including atrophy, leukoencephalopathy, calcification, and necrosis. The most important predisposing factors in the development of WMD are higher radiation dose, young age of the children, intrathecal administration of methotrexate, and a long posttherapeutic interval.

Adverse effects of radiation or chemotherapy in children with primary brain tumors are also well known, but the clinical importance of these findings has still to be determined. Evaluation of residual or recurrent tumor is usually the primary concern in the follow-up of these patients. Owing to improvements in the treatment of malignant brain tumors during the past 25 years, however, the number of long-term survivors is increasing. At most institutions MRI is routinely performed in the follow-up of

these children, allowing staging of the malignancy and detection of early and late effects on the brain. The purpose of this paper is to describe different patterns of WMD in the follow-up of children after surgery, radiation and/or chemotherapy of malignant primary brain tumors and to evaluate statistical data relating to the incidence of WMD and risk factors.

Methods and materials

MRI findings in the routine follow-up of 44 infants and children treated for malignant primary brain tumors with radiation, chemotherapy, or both were evaluated retrospectively. The ages of the children at surgery ranged from 1 month up to 17 years, with a mean of 8.3 and a median of 8.0 years. Ten children were 5 years old or younger and 5 of these were only 2 years of age or younger. There were 25 boys and 19 girls. Thirty-one children had infratentorial tumors (Table 1), predominantly medulloblastoma (*n*=28), astrocytoma (*n*=2), ependymoma (*n*=1). Supratentorial tumors (Table 2) in 13 children were classified as supratentorial PNET (*n*=5), pinealoblastoma (*n*=2), astrocytoma (*n*=1), ependymoma (*n*=1), oligodendroglioma (*n*=1), glioma (*n*=1), ganglioglioma (*n*=1), and germinoma (*n*=1). Fifteen children had a shunt for ventricular drainage of hydrocephalus.

Combinations of cranial radiation and chemotherapy were given in 31 children. Four of them had additional intrathecal methotrexate and one, intrathecal mafosfamide because of leptomeningeal spread of the tumor. Ten children had radiation alone and 3 young children had chemotherapy only, to prevent radiation damage to the immature brain.

Polychemotherapy was administered in 34 cases, with 5 children having two courses and 1, three courses of chemotherapy. Cranial ra-

Table 1 Infratentorial tumors (*n*=31) in infants and young children and in older children. *M* male, *F* female, *Med* medulloblastoma, *Astro* astrocytoma, *Epen* ependymoma, *PNET* primitive neuroectodermal tumor, *Olig* oligodendroglioma, *Gangl* ganglioglioma, *Pin* pineoblastoma, *Gliom* malignant glioma, *Germ* germinoma, *Chemo* chemotherapy, *Poly* polychemotherapy (no. of repeated courses in brackets), *ITC* intrathecal chemotherapy, *WMD* white matter disease, *WML* white matter lesions

Patient no.[a]	Age[b]	Sex	Histology	Shunt	Radiation[c]	Chemotherapy	Follow-up (years)	Diffuse WMD	Focal WMD (WML), grade[d]
Infants and young children (*n*=6)									
1	3.5	M	Med		35 (55)	Poly	1	Atrophy	1
2	5	F	Astro		?		4	Atrophy	
3	4	M	Epen	Yes	35 (35)	Poly	5		
4	2	F	Med	Yes	–	Poly, ITC	6	Atrophy	1
5	5	M	Med		35 (55)	Poly	7	Atrophy	
6	1.5	F	Med		(54)	Poly	8		
Older children (*n*=25)									
1	10	F	Med	Yes	35 (55)	Poly	0.5		
2	11	F	Med		35 (55)	Poly	0.5		3
3	12	M	Med		45 (55)	Poly (2)	0.5	Atrophy	
4	7	M	Med		35 (55)	Poly	1		
5	7.5	F	Med	Yes	35 (55)	Poly	1	Atrophy	
6	8	M	Med		35 (55)	Poly	1		
7	13.5	M	Med		(55)	Poly	1		
8	9	F	Med		35 (55)	Poly	1.5		
9	12.5	M	Med		37 (57)		1.5		
10	7	M	Med		35 (55)	Poly	2	Atrophy	1
11	9	M	Med		35 (35)	Poly	2		
12	9.5	F	Med		35 (55)	Poly	3	Atrophy	
13	12.5	M	Med		35 (55)	Poly (2)	3		1
14	17	F	Med		35 (55)	Poly	3.5		
15	13.5	F	Med		35 (55)	Poly	4		
16	13	M	Med		(55)	Poly	4.5		
17	6	F	Med		35 (55)	Poly	5		
18	10	M	Med	Yes	35	Poly (3) ITC	5.5		1
19	6	M	Med	Yes	35 (35)	Poly, ITC	7		2, 3
20	12	M	Astro	Yes	(50)		10.5	Atrophy	1
21	7	M	Med		36		12.5		
22	10.5	F	Med	Yes	(55)		12.5		3
23	9.5	M	Med	Yes	(56)	Poly	14.5		1, 3, 4
24	9	F	Med		(50)	Poly (2)	15		4
25	13	F	Med	Yes	?	Poly (2)	15	Atrophy	

[a] Patients numbered according to increasing length of follow-up in each group
[b] Age at surgery (years)
[c] No radiation,? radiation dose not available; first dose shown is whole-brain dose (Gy), dose in round brackets is local dose (Gy)
[d] Grade 1: small patchy lesions, grade 2: large confluent lesions, grade 3: cystic lesions, grade 4: hemorrhagic lesions

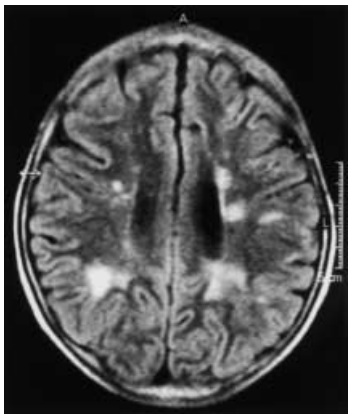

Fig. 1 Diffuse lesions. Predominantly patchy and ill-defined lesions of the supratentorial periventricular white matter on fluid-attenuated inversion recovery (FLAIR) images in a 9-year-old boy and a follow-up of 1.5 years after surgery and combined chemo-/radiotherapy of a medulloblastoma

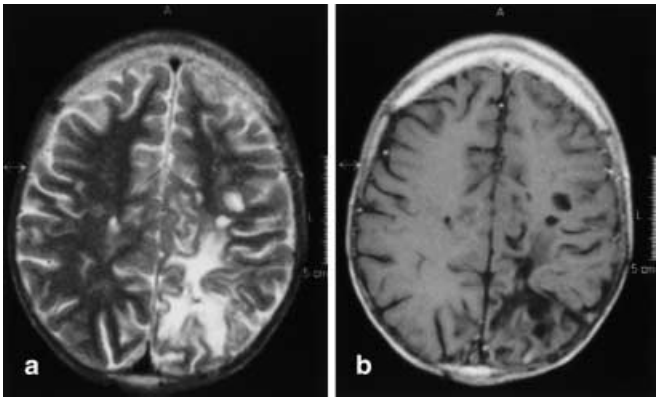

Fig. 2a, b Cystic lesions. Cystic lesions adjacent to the parenchymal defect of the left parietal lobe on T2-weighted images (**a**) in a 14-year-old boy and a follow-up of 6 years after surgery, and combined chemo-/radiotherapy of a supratentorial PNET. The lesions are well defined on T1-weighted images (**b**)

Table 2 Follow-up of children with supratentorial tumors (*n*=13)

Patient	Age	Sex	Histology	Shunt	Radiation	Chemotherapy	Follow-up (years)	Diffuse WMD	Focal WMD (WML), grade
Infants and young children (*n*=4)									
1	1	M	Astro		–	Poly	1	Atrophy	1
2	0	M	PNET	Yes	–	Poly	2		1
3	1.5	F	PNET	Yes	24 (54)	Poly (2) ITC	2.5	Atrophy	1
4	4	M	Olig		(49)		9		1, 3, 4
Older children (*n*=9)									
1	6	M	PNET		(55)	Poly	1		1
2	13	F	Gangl	Yes	(60)		3		3
3	15.5	F	Pin	Yes	35 (35)	Poly	3	Atrophy	3
4	12.5	M	Gliom		(53)		3.5		
5	7	F	Epen		(60)	Poly	4	Atrophy	
6	7	M	PNET	Yes	35 (55)	Poly, ITC	5.5		2, 3
7	8	M	PNET		35 (55)	Poly	6	Atrophy	1, 2
8	5.5	M	Pin		(60)		11.5		2
9	6.5	F	Germ		36 (50)		11.5		

diation was performed in 41 children with local doses of 35–57 Gy in the posterior fossa and 49–60 Gy in supratentorial tumors. The whole-brain dose ranged from 24 to 45 Gy in both groups. In 2 children the exact dose could not be determined (Tables 1, 2).

The length of the MRI follow-up varied from 6 months to 15 years, with a mean interval of 5.1 years, but the median was only 3.8 years, indicating that the majority were followed up for about 4 years. Eighteen children were long-time survivors with a follow-up of 5 years or longer, and 10 of these had been followed up for 8 years or longer.

The last available MRI in the follow-up of each patient was evaluated retrospectively by U.D., M.M., I.W., and M.F. Circumscribed parenchymal defects with perifocal gliosis or sequelae of ventricular shunting were interpreted as normal postoperative findings. White matter changes were subclassified into diffuse cerebral atrophy and circumscribed white matter lesions (WML) not related to surgery. Atrophy was diagnosed when ventricular dilatation and/or sulcal enlargement were found. WML was diagnosed if there were areas with an abnormal signal intensity on T1-weighted, T2-weighted, or fluid-attenuated inversion recovery images (T1WI, T2WI, FLAIR). WML were subclassified into four grades: grade 1 embraces small ill-defined areas with high signal on T2WI and FLAIR indicating subtle leukencephalopathy (Fig. 1) and grade 2, larger confluent areas; grade 3 and 4 WML are cystic or hemorrhagic lesions with high signal on T2WI and low on FLAIR and T1WI indicating cystic vasculopathy (Fig. 2) or lesions with either high signal on T1WI and/or low signal on T2WI or proton density images suggesting hemorrhage (Fig. 3).

The patients were divided into two groups: children with infratentorial tumors, predominantly medulloblastoma, and those with supratentorial tumors of diverse histology (Tables 1, 2). They were also subdivided by age, with 5 years as the cut-off point. In each table the patients are arranged according to the length of follow-up, the child with the shortest period at the top and the one with

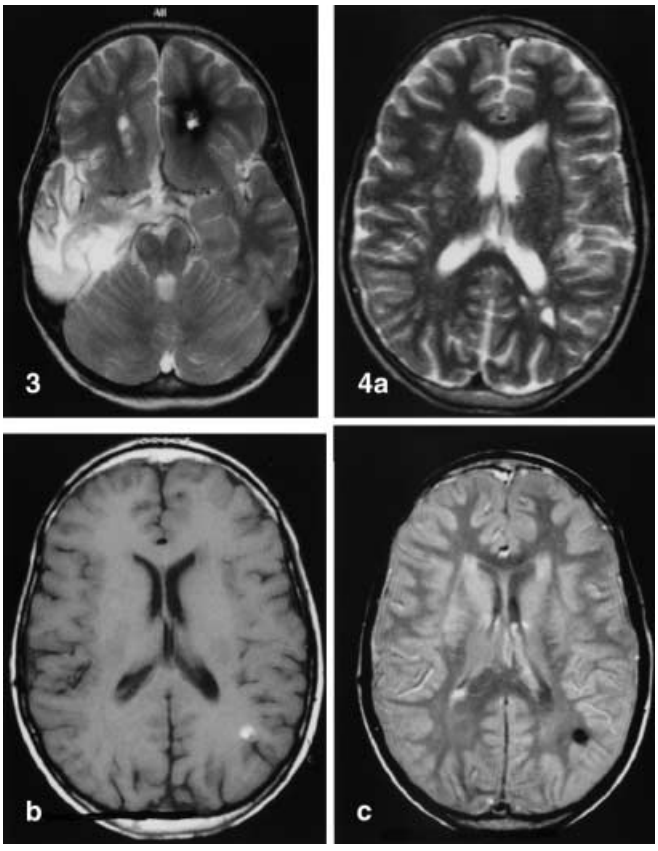

Fig. 3 Hemorrhagic lesion. T2-weighted image reveals a large deposition of hemosiderin similar to cavernoma of the left frontal lobe and a cystic nonhemorrhagic lesion of the right frontal lobe in a 13-year-old boy 9 years after therapy of a malignant oligodendroglioma. Postoperative defects and gliosis of the right temporal lobe are normal postoperative findings

Fig. 4a–c Development of hemorrhagic lesions. A 21-year-old patient with cystic and diffuse lesions of the white matter and the right basal ganglia developed new cystic lesions adjacent to the left posterior horn seen on T2-weighted imaging (**a**) 12 years after therapy of a medulloblastoma. The largest of them showed subacute hemorrhage on the T1-weighted image (**b**), which was confirmed by hemosiderin deposition on proton density imaging 2 years later (**c**)

the longest at the bottom of the table, to allow visual correlation of white matter changes with the length of follow-up.

The Chi-square test was used to compare discontinuous variables: gender, age, presence of a shunt, kind of therapy, radiation dose, courses of chemotherapy, intrathecal chemotherapy, site of the tumor, and length of follow-up. Continuous variables (age, length of follow-up) were cut off to become discontinuous (e.g., age ≤2 years, follow-up >5 years). A stepwise discriminant analysis was performed to identify the discriminatory power of the variables in relation to the variable of interest. All statistical evaluations were performed with the SAS PC Statistical Analysis System (SAS Institute, N.C., USA).

Results

MRI results for 16 of the children showed either local parenchymal defect, perifocal gliosis, or sequelae of shunt procedures, which were classified as normal postoperative findings. Fourteen of them belonged to the posterior fossa group and only 2 to the group with supratentorial tumors. MRI in 28 children showed evidence of diffuse and/or circumscribed white matter injury. Atrophy was diagnosed in 15 children, with a similar distribution in the infratentorial (10/31) and supratentorial (5/13) tumor groups (P=0.692). It was the only pathologic finding in 7 cases, and in 8 it was combined with WML. MRI scans of 21 children revealed circumscribed WML, which were significantly more frequent (P=0.012) in children with supratentorial tumors (10/13) than in children with infratentorial tumors (11/31). Different patterns of WML in the same patient were not uncommon, including diffuse grade 1 lesions in 13, grade 2 lesions in 2, cystic lesions in 10, and hemorrhagic lesions in 3 children.

The gender of the children had no influence on the presence of either atrophy (P=0.328) or WML (P=0.208). There was no correlation between atrophy and the presence of a ventricular shunt for hydrocephalus, but there was a significant correlation between shunt and the presence of WML on follow-up MRI (P=0.014).

Concerning age at the beginning of the therapy there was a weakly significant correlation between elevated incidence of atrophy and age 5 years or younger (P=0.049). Although 4 of 5 children aged 2 years or under and 8 of 10 children aged 5 years or under had WML, this was statistically not significant (P=0.125, P=0.377).

Most children received a combination of chemo- and radiotherapy (n=31). When radiotherapy alone (n=10) was compared with combined radio- and chemotherapy there was no significant difference in the incidence of atrophy (P=0.360) or WML (P=0.655). There was also no significant difference according as whether the children had two courses of chemotherapy or more. Three young children had chemotherapy alone to prevent radiation damage to the developing brain, but all were found to have WML on follow-up MRI. This small group was not evaluated statistically. Four children received intrathecal methotrexate and 1, intrathecal mafosmamide, and all developed WMD. This was statistically significant with P=0.028, but because of the small sample size this may not be a valid result. All patients who received intrathecal chemotherapy had a ventricular shunt. Stepwise discriminant analysis showed that both were independent predictors of WML and neither could be removed without significant loss of the single variables (Wilks' lambda=0.815, Prob>F=0.0153). Radiation doses were similar in most children, with a large overlap for whole-brain doses and for local doses, so that statistical analysis was not recommended.

With reference to tumor location there was a higher incidence of WML in children with supratentorial tumors (P=0.012), but no significant difference in the incidence of atrophy (P=0.692) compared with children who had infratentorial tumors. Discriminant analysis showed a discriminant power for this variable, with Wilks' lambda=0.697 and Prob>F=0.022. Children with supratentorial tumors developed WML even if they had a short follow-up. In the group with infratentorial tumors, however, a higher frequency of WML was only observed in children with a long follow-up (P=0.015).

In both groups the number of children with normal findings decreased if the follow-up was longer than 5 years: the increasing incidence of WML was statistically significant (P=0.035) if the follow-up was longer than 5 years, but there was no significant difference for atrophy (P=0.764). Regarding the different pattern of WML, the incidence of grade 3 and 4 lesions was then higher (cystic lesions: P=0.012, hemorrhagic lesions: P=0.018), whereas the frequency of diffuse grade 1 and 2 lesions was not significantly different (P=0.092). In our series hemorrhagic lesions occurred in children with a follow-up of 9, 14.5, and 15 years, respectively (Fig. 4).

Discussion

Progress in the treatment of children with primary brain tumors has meant better imaging, surgery and postoperative treatment, which has resulted in dramatically improved survival rates in many cases. One consequence is an increasing number of patients with secondary problems caused by different types of aggressive antineoplastic therapy. There is increasing concern about late damage to the developing brain leading to intellectual impairment and poor quality of life, but radiotherapy combined with neoadjuvant chemotherapy is necessary in most children with malignant brain tumors. Total-dose and fractionated-dose irradiation and different types and schedules of chemotherapy have been developed to minimize late adverse effects.

MRI performed in the follow-up of children with ALL revealed that WMD was present in 26% of all cases showing vascular infarction, diffuse periventricular white matter changes, and cystic areas representing infarction or hemorrhage [8]. In children treated for systemic cancer, findings on late cranial MRI were classified into atrophy and circumscribed WML with high-signal changes, low-signal changes, or heterogeneous foci suggesting calcification or old hemorrhage [13]. Besides radiation dose, age less than 5 years is considered the most important risk factor for developing CT scan abnormalities after cranial radiation. A second risk factor is systemic or intrathecal administration of methotrexate leading to acute or chronic edema, atrophy, or multifocal white matter necrosis visible on MRI [1]. In our series there was no difference in the incidence of WMD regarding radio- or chemotherapy singly or in combination. The gender of the patients did not have any role. Almost all children under 2 years old developed WML, but this was not significant. We believe that in our patients other factors were dominant in elevated frequency of WML. With reference to atrophy, we found a statistical trend to a higher incidence in the age group 5 years or younger.

Classification of toxic brain injury from either irradiation or chemotherapy is based on division of the children into three groups by timing of their clinical presentation relative to therapy: acute (<3 weeks after), early delayed (3 weeks to 3 months), and late delayed injury (>3 months after therapy) [20]. Late delayed injury means an irreversible and dose-limiting complication of radiation, which might be progressive and even fatal. It is subdivided into focal injury, including necrosis, infarction, or hemorrhage, and multifocal or diffuse injury with cerebral atrophy, necrotizing leukencephalopathy, mineralizing microangiopathy, and radiation injury of large arteries. There is no clear differentiation of these types of lesions, while areas of increased signal intensity on T2WI begin as small foci in the deep white matter adjacent to the lateral ventricles. They spread into peripheral regions, increase in size and intensity, and coalesce until they involve large areas of the white matter. Finally, cystic areas may result from focal necrosis or hemorrhage, with replacement of brain tissue by astrogliosis. This development takes several years, and the incidence of WML therefore increases if the posttherapeutic interval is long enough. In our series we found cystic and hemorrhagic WML more frequently in children who had a follow-up longer than 5 years, and the difference was statistically significant.

Owing to differences in histology, location, and therapy, the results of follow-up studies in children with brain tumors vary. In children who have undergone radiation therapy for brainstem glioma a high rate of WML is observed, including atrophy, leukoencephalopathy, diffuse microhemorrhages, dystrophic calcification, and infarction [4]. Other authors report a high incidence of WML in patients with tumors situated supratentorially, analogous to observations in our study [15]. The conditions underlying these findings are diverse. First, the local dose of cranial radiation is usually high in supratentorial tumors and the adjacent white matter will be more affected. Second, the therapeutic schedules for infratentorial tumors, especially medulloblastoma, are better tailored to prevention of damage to the white matter than are those for the heterogeneous group of supratentorial tumors. Third, it seems that the infratentorial white matter is less radiosensitive than the supratentorial white matter. Like other authors, we identified WML only in the frontal, parietal, and occipital white matter, which

seems to be more vulnerable owing to its sparse vascularity [14].

The vascular mechanism of WMD suggests damage to endothelial cells causing increasing vascular permeability and interstitial edema. Endothelial cells are metabolically active and therefore the most radiosensitive cells of the vessel wall. The result is endothelial proliferation with thrombosis, ischemia, and infarction. There is a general consensus that vascular injury is the most important factor in the pathogenesis of late radiation encephalopathy [12]. The distribution of WML corresponds to ischemic lesions of the deep perforating arteries in the deep white matter and brain stem. Damage to the endothelial cells appears earlier and precedes changes in glial cells. This results in cerebral atrophy and diffuse and/or circumscribed lesions with or without hemorrhage [2]. Injury to large vessels may lead to early atherosclerosis with narrowing of the vessel lumen and subsequent infarction.

A comparison of CT and MRI in the detection of brain radiation lesions reveals the evident superiority of MRI. From a radiological point of view it is justifiable to differentiate between diffuse WMD manifesting as atrophy and focal WMD with circumscribed WML. White matter changes are classified into different grades according to their size and extent, from minimal patchy foci up to global leukoencephalopathy or focal necrosis. In our study we defined grades as small patchy lesions (grade 1), large confluent lesions (grade 2) and cystic or hemorrhagic lesions suggesting focal necrosis (grade 3 and 4). WML usually occur late, with the earliest changes seen after 5 months to more than 10 years after radiotherapy. Owing to the difficulty in visualizing calcification on MRI, the reported number of patients recorded with mineralizing vasculopathy has decreased, whereas diffuse, cystic, and hemorrhagic lesions are seen more often. It seems reasonable to suppose that the same process as causes calcification also causes damage to the vessel walls, resulting in lesions depicted earlier on MRI. This explains the increasing numbers of delayed radiation-induced vasculopathies found in the follow-up of patients with cranial irradiation and/or chemotherapy [19].

Hemorrhagic lesions of the white matter ranging from small foci to large areas are reported in young patients after cranial radiation [6]. The average latency between radiation therapy and the appearance of hemorrhage on MRI was 32.5 months. A different study found no correlation of hemorrhage and outcome, original diagnosis, radiation dose, chemotherapeutic agent or dose, age at treatment, or interval between therapy and hemorrhage [15]. Only brain stem hemorrhage was associated with a poor outcome. The imaging appearance and pathologic findings of these lesions are often remarkably similar to those with cavernous angiomas. The development of a cavernous malformation after radiotherapy for medulloblastoma is well known [9]. Three children in our series showed hemorrhagic lesions similar to cavernous angioma, but histological examination was not performed.

Cerebral atrophy is a frequent finding after cranial irradiation and/or chemotherapy and is usually related to diffuse white matter injury. Ventricular enlargement indicates white matter atrophy, and enlargement of the cortical sulci suggests combined white/gray matter atrophy. Using serial volumetric MRI measurements a significant loss of white matter with a normal appearance was observed in children with medulloblastoma and craniospinal radiation, in contradistinction to the maturation normally expected [16]. It is believed that damage to the branches of the deep perforating arteries causes atrophy secondary to WMD. In infancy the white matter of the developing brain seems to be more susceptible to radiation injury owing to a high metabolic activity and low stability of the newly synthesized myelin. Although radiation alone may contribute to atrophy, other agents may be causative, such as chemotherapy, other drugs, repeatedly elevated intracranial pressure, subdural fluid collections, and nutritional disorders. In our series atrophy was diagnosed in 15 of 44 children, with a similar distribution in most subgroups but with a slightly higher incidence in children 5 years of age and under. Use of the T1-mapping technique on MRI makes it possible to define radiation injury to the gray and white substance, with the result that white matter T1 appeared unaffected by doses less than 20 Gy and gray matter T1 did not change with doses less than 60 Gy [18]. In the literature the limit for the development of white matter loss is given by a whole-brain dose of 24 Gy [5, 18], which is usually exceeded in the treatment protocols of malignant brain tumors.

The presence of a ventricular shunt was not correlated with atrophy in our series, but we found a significantly increased incidence of white matter lesions in children with a ventricular shunt. It is suggested that a continuously elevated level of intracranial pressure on the white matter fibers is the main factor in the development of WML, especially in the frontal lobes [17]. On the other hand, the presence of a shunt may reflect a more severe course of illness, including preoperative morbidity, postoperative complications, and tumor recurrence.

In patients with supratentorial brain tumors, the local radiation dose is usually high and may affect the adjacent white matter of the cerebral hemispheres. There is an continuous and significant increase in the frequency of white matter changes in patients with supratentorial malignant glioma if the radiation dose is increased to more than 55 Gy [3]. In our series children with medulloblastoma developed significantly fewer WML, and these only after a follow-up of more than 5 years. In contrast, almost all children with supratentorial tumors were found to have WML even after short periods of follow-up. This may be explained by the effect of local radiation doses on the white matter of the cerebral hemispheres. On the other hand, atrophy was more evenly distributed

in both groups and in different periods of follow-up. Perhaps we might suggest that smaller doses given in whole-brain irradiation, which were similar in both groups, can be linked to a more diffuse injury and the development of atrophy.

Atrophy and WML have gained increasing clinical importance in the literature. A multicenter study described a tendency to lower scores in psychological tests for the patient group with abnormal MRI or CT, but no correlation with neurological abnormalities [7]. There is, however, no increase in the severity of neuropsychological deficits if cranial radiation is combined with systemic chemotherapy [11]. Data collected from 36 publications indicated that whole-brain irradiation with doses more than 24 Gy comprise a substantial risk of worsening of the intellectual outcome even in older children with cranial irradiation [5]. Associated factors, such as hydrocephalus, extent of brain surgery, and degree of neurological deficit, may affect the intellectual performance of these patients. Diffuse loss or deficient development of white matter is obviously the anatomical substrate for neurocognitive deficits in children with medulloblastoma [10]. In children with supratentorial brain tumors a high rate of neurological deficits, intellectual impairment, and neuroendocrine dysfunction is reported [15]. In the study just cited there was no correlation between any two of diagnosis, age at treatment, presence of hydrocephalus, addition of chemotherapy, radiation dose or volume, and severity of intellectual disability. It is generally agreed, however, that the most severe sequelae of treatment in these children are neurocognitive disorders and neurobehavioral alterations leading to failure of academic and social development. The paucity of current data on the follow-up of patients with malignant brain tumors does not allow definite conclusions about any link between WMD and cognitive, emotional, or social deficits. The major drawback of our study is the retrospective analysis of data. There could be a bias in the sense that children with abnormal findings on MRI had more and longer follow-up studies than children with normal MRI. Well-designed prospective studies with enough patients bearing each entity of supratentorial brain tumors and examined by modern functional and imaging techniques have to be established before we can hope to determine reliable correlations between radiological findings and neuropsychological performance.

In conclusion, the follow-up of children treated for malignant brain tumors must not focus exclusively on residual or recurrent tumor. Different patterns of WML will occur in most long-time survivors, especially those whose tumors were located supratentorially. The presence of a shunt and intrathecal chemotherapy may facilitate these sequelae. Atrophy represents diffuse WMD, and younger children seem to be at the greater risk. Although the clinical significance of these findings is still unclear, detection and observations of different patterns of WMD is mandatory.

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