Radiation-induced Brain Damage in Children
—Histological Analysis of Sequential Tissue Changes in 34 Autopsy Cases—

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Abstract

The nature and sequence of the radiation-induced changes in the brain were studied postmortem in 34 children with glioma, 22 of whom underwent central nervous system radiation therapy. Twenty received whole-brain or whole-neuroaxis radiation at a total mean dosage of 4063 cGy. Brain tissue alterations were analyzed histologically by means of various staining methods, including immunohistochemical techniques. The histological features of irradiated brains were compared with those of non-irradiated brains. Microscopic findings included demyelination (seven cases), focal necrosis (six cases), cortical atrophy (four cases), endothelial proliferation (four cases), and telangiectatic vascular proliferation with vascular thickening and oozing of a thick fluid (one case). Such findings were rare in non-irradiated patients. Demyelination was observed earliest in a patient who died 5 months after radiation therapy and was more common after 9 months. Focal necrosis was first observed 9 months post-irradiation but was more advanced and extensive after 1 year. Calcified foci were found only after 60 months. Various vascular changes such as vascular thickening and thrombosis suggested ischemic insult to the brain as a late effect of radiation injury. The results of this study suggest that the immature brain may be more sensitive to radiation than is the adult brain, and that the manifestations of radiation-induced injury depend on the time elapsed after irradiation.

Key words: glioma, radiation therapy, demyelination, radiation necrosis

Introduction

It is well known that, although radiation therapy is effective in prolonging remission in patients with certain types of brain tumors, it can have adverse effects, especially on immature brains. When radiotherapy injures the hypothalamic pituitary axis of a child, hypopituitarism may result in growth retardation, short stature, and lack of sexual development. Whole brain irradiation in children can also cause delayed mental development. Growth retardation and spinal deformity after megavoltage irradiation of the spine have been also reported.

Although the clinical evidence of the disadvantages of radiation therapy in children are well documented, description of the specific pathological and morphological features of radiation injury in children is scant. The purpose of this investigation was to chronologically delineate the pathological changes in the brains of children treated by irradiation. To this end, we studied 34 autopsy cases of children with glioma; to our knowledge, this is one of the very large postmortem studies of the pathological effects of radiation therapy in children.

Materials and Methods

The results of 34 autopsies of children with glioma were analyzed. The histological diagnoses included 17 medulloblastomas, seven astrocytomas, five epen-
dymomas, four glioblastomas, and one primitive neuroectodermal tumor (Table 1). The patients were treated from 1963 to 1979 at Children’s Memorial Hospital (Chicago, Illinois, U.S.A.), 1980 to 1987 at Kobe University Hospital (Kobe, Japan), and 1982 to 1987 at National Kagawa Children’s Hospital (Kagawa, Japan). The clinical data from diagnosis to autopsy were analyzed. In the five most recent cases, immunohistochemical studies, including myelin basic protein (MBP), neuron specific enolase, and factor VIII (F-VIII) were reviewed as well.

<table>
<thead>
<tr>
<th>Table 1 Types of brain tumors</th>
<th>Table 2 Radiation therapy regimens</th>
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</thead>
<tbody>
<tr>
<td>Type of tumor</td>
<td>Range (mean, cGy)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Whole neuroaxis (n = 13)</td>
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<tr>
<td>Astrocytoma</td>
<td>local</td>
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<tr>
<td>Ependymoma</td>
<td>whole brain</td>
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<tr>
<td>Glioblastoma</td>
<td>whole spine</td>
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<tr>
<td>Primitive neuroectodermal</td>
<td>Whole brain (n = 7)</td>
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<tr>
<td>tumor</td>
<td>local</td>
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<tr>
<td></td>
<td>whole brain</td>
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<tr>
<td>Total</td>
<td>1 (0)</td>
</tr>
<tr>
<td></td>
<td>500–6000 (3173)</td>
</tr>
<tr>
<td></td>
<td>3000–5000 (4063)</td>
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<tr>
<td></td>
<td>2760–4000 (3289)</td>
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<td>3200 (3200)</td>
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<tr>
<td></td>
<td>5000–5400 (5150)</td>
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<tr>
<td></td>
<td>500–5940 (5470)</td>
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<td>RT: radiation therapy.</td>
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</table>

The patients’ ages ranged from 7 weeks to 13 years (mean, 6.5 years). The tumors were located in the posterior fossa in 28 cases and in the supratentorial space in six. Twenty-two of the 34 patients underwent radiation therapy (Table 1). Cobalt irradiation was given before 1980 and a 10 MV linear accelerator was used thereafter, at the rate of 800–900 cGy/week in five fractions. Whole-neuroaxis or whole-brain radiation was given in 20 cases and local irradiation in two. The radiation dosages for whole-neuroaxis irradiation were: 3000–5000 cGy (mean, 4063 cGy) to the whole brain; 2760–4000 cGy (mean, 3289 cGy) to the whole spine; and 500–6000 cGy (mean, 3173 cGy) for local irradiation. In cases of whole-brain irradiation alone, 5000–5400 cGy (mean, 5150 cGy) was delivered, and patients treated with local irradiation alone received 5000–5940 cGy (mean, 5470 cGy). The treatment regimens are given in Table 2.

II. Autopsy data

The brains were examined grossly and with standard histological techniques. Gross inspection was particularly aimed at detection of recurrent tumor, metastatic foci, and radiation-induced tissue alterations within the brain and metastasis to other organs. In all cases, whole brain sections were prepared for routine histological evaluation with hematoxylin and eosin (HE). In some cases special stains, such as the Klüver-Barrera (K-B) and Luxol fast blue methods, were applied. In the five most recent cases, selected sections were also examined immunohistochemically.

As mentioned above, 12 of the 34 patients did not undergo radiation therapy but were examined by autopsy, which included study of the whole brain. In most non-irradiated patients, death was due to operative intervention or tumor progression. Irradiated and non-irradiated brain tissues were compared histologically. In all cases, tissue alterations considered to be radiation-induced were confirmed to be distant from tumor and therefore were not tumor effects.

Results

Among the irradiated brains, there were seven with definite demyelination, six with focal vacuolation or necrosis, four with cortical atrophy, four with endothelial proliferation, two with vascular thrombosis and telangiectatic vascular proliferation, vascular thickening, exudate of thick albuminous fluid in one individual case. These findings were rare in non-irradiated brains. Neuronal degeneration, cerebral edema, and gliosis were common in both irradiated and non-irradiated brains. There was no significant difference between the two groups in terms of the incidence of cerebral edema and gliosis.

Each finding was analyzed in terms of the time from radiation therapy to death (Table 3). Demyelination was observed earliest in a patient who died 5 months after radiation therapy and became more common as the survival time lengthened. Demyelination, if present, was more severe in patients who survived longer (Figs. 1–3). Focal necrosis was first observed at 9 months and was more advanced and extensive in patients who died after 1 year. Calcified foci were not found before 60 months. Microscopic vascular changes were notable after 9 months. Endo-
thelial proliferation occurred first and later became associated with vascular thickening, thrombosis, and angiectasis (Fig. 4).

Immunohistochemical studies disclosed further details concerning the sequence of these radiation-induced tissue alterations. Demyelination has been already recognized at 9 months after radiation therapy. However, a patient who died 60 months after whole neuroaxis irradiation was found to have more marked neuronal structural damage. The entire cerebral hemisphere became diffusely atrophic and necrotic in some cases (Fig. 3). Parenchymal changes were most severe in the white matter and included prominent foci of demyelination, reactive astrocytes, and vascular changes associated with coagulation necrosis and calcium deposition. Special staining with monoclonal antibodies related to myelin, such as MBP, revealed the degree of demyelination (Figs. 2 and 3). In one patient who died 9 months after irradiation, endothelial proliferation was already evident. At that time, F-VIII remained in the proliferating endothelium. In the brain of a longer survivor, however, F-VIII was not present in the thickened and hyalinized vascular wall but had exuded into the surrounding perivascular space (Fig. 4).

Discussion

Although the benefits of radiation therapy for brain tumors, which include retardation of tumor growth and remission of clinical symptoms, are evident, it is well known that the delayed effects may entail permanent neurological deficits. Central nervous system (CNS) reactions to irradiation can be divided into three types, according to the time of appearance: 1) acute reactions that occur during the course of irradiation; 2) early delayed reactions, which appear from a few weeks to 2 or 3 months after completion of radiation therapy; and 3) late delayed reactions, which typically manifest from several months to many years later. There appear to be no significant differences between adults and children in terms of acute and early delayed reactions, which are usually transient and disappear without therapy. Late delayed reactions, however, are often irreversible and progressive, and sometimes fatal. In adults, the symptoms of late effects include altered mental status and/or focal or diffuse neurological deficits. The features of this CNS damage in children tend to be more specific and include growth retardation, impaired sexual development and, in cases of progressive destruction of white matter, psychomotor retardation. Raimondi and Tomita emphasized the disadvantages of postoperative prophylactic whole-CNS radiation therapy in children. Others have pointed out that neuronal and glial sensitivity to radiation is probably greater in children than in adults.

Ogawa et al. performed a positron emission tomographic (PET) study of 13 patients who underwent whole brain irradiation with 50–60 Gy by a 10-MV linear accelerator followed by nitrosourea and 5-fluorouracil administration. They found that blood flow, blood volume, and oxygen consumption did not change significantly, whereas the oxygen extraction fraction, glucose consumption, and glucose extraction fraction decreased significantly in the normal gray matter within 1 month after radiation therapy. Hylton et al. measured regional cerebral blood flow (rCBF) by the 133Xe inhalation method in seven adult patients with early post-irradiation effects and monitored the transient CNS post-irradiation.
effects. They found a global decline in rCBF at about 10 weeks after irradiation and speculated that this phenomenon reflects a generalized, radiation-induced metabolic derangement rather than primary vascular changes.

There have been few reports on early post-irradiation morphological changes in the brain parenchyma. Burger et al. conducted a postmortem study of 17 patients irradiated with dosages of 50–60 Gy. Four developed “late delayed” radiation necrosis and one exhibited focal demyelination suggestive of “early delayed” radiation necrosis. Thus, mor-

Fig. 1 Photomicrographs of tissues obtained from irradiated cerebellar hemispheres of three patients. K-B stain, × 20. A: Cerebellar hemisphere of a non-irradiated brain. B: Nine months post-irradiation. Note the irregular and deranged neural tracts and cell depletion. C: Sixty months post-irradiation. Severe demyelination, cell depletion, parenchymal atrophy and volume loss, and vascular alterations are evident.

Fig. 2 Photomicrographs of MBP-stained tissue specimens from irradiated and non-irradiated cerebellar hemispheres. × 20. A: Cerebellar hemisphere of a non-irradiation brain. B: Nine months post-irradiation. This tissue is in the early phase of demyelination. C: Sixty months post-irradiation. There are multiple vacuoles, demyelination, and irregular neural pathways. Cell depletion in Purkinje cell layers is not prominent in this section.

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phological changes in the cerebral parenchyma seem to be rather rare despite the marked physiological changes documented in CBF and PET studies. One significant clinical symptom of early effects of brain irradiation in children may be somnolence. Freeman et al.\textsuperscript{7} reported that eleven of 28 children (39\%) who received cranial irradiation as CNS prophylaxis against lymphoblastic leukemia while in remission...
developed pronounced somnolence, anorexia, and lethargy some 6 weeks after the completion of treatment. In all cases the symptoms were transient, no focal neurological abnormalities were detected, and recovery was spontaneous and complete. The investigators concluded that this syndrome represents a transient radiation myelopathy caused by temporary disturbance of myelin synthesis.

In contrast, late delayed effects are rather complicated in terms of the mechanisms of neural destruction. In the present study, demyelination without vascular involvement was seen relatively early after irradiation, whereas various vascular structural changes appeared later. Although either transient or permanent demyelination was observed at all post-irradiation time points studied, focal vacuolation and necrosis were late parenchymal changes. At the same time, vascular thickening or thrombosis resulting in impairment of total or regional cerebral flow ischemic insult to the immature neural tracts. Immunological factors may also play a role in the occurrence of radiation necrosis, as suggested by the finding of perivascular exudate with plasma and fibrin. The strong tendency for this tissue response in the white matter adjacent to the neoplasm suggests a local sensitivity that may be engendered or enhanced by cerebral edema. Cerebral edema, neuronal degeneration, neural cell depletion and gliosis may be a direct consequence of brain irradiation or a secondary effect of brain tumor extension and increased intracranial pressure (Table 3).

Some microscopic tissue alterations may be detectable with diagnostic imaging. Before the computed tomography (CT) era, a dense region of abnormal uptake in radioisotope brain scans and a vascular mass with or without irregular or narrowed arteries in cerebral angiograms were considered characteristic of delayed radiation necrosis. CT may show an area of low attenuation with nodular or diffuse heterogeneous contrast enhancement. However, these lesions were often associated with mass effect mimicking tumor recurrence or metastasis. Davis et al. reported follow-up CT studies of 49 children who received conventional cranial radiation therapy for primary CNS tumors. They found that 51% developed generalized volume loss or atrophy and 28% had calcification in nontumorous parenchyma, with or without chemotherapy. In children still undergoing neural development, the incidence of such gross morphological changes may be much higher than that in adults. Since the introduction of magnetic resonance (MR) imaging, such tissue alterations as radiation effects have become more obvious. Curnes et al. found that nine patients who received radiation of 24-60 Gy to the brain all developed abnormalities in the periventricular white matter. A characteristic scalloped configuration at the junction of the grey and white matter was demonstrated by MR images of seven of nine patients and represented extensive white matter damage to the more peripheral arcuate fiber systems. They noted that CT generally failed to show the extent of white matter injury demonstrated by MR images.

The nature of radiation-induced brain injury may depend on both the radiation dosage and the time elapsed after irradiation. Age may be a factor as well, and the adverse effects of radiation therapy in children should be investigated further.

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References


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