Neurotoxicity of Radio/Chemotherapy In Children: Pathologic and MR Correlation

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The success or failure of medical care is judged by a comparison of benefits to be gained versus the risks involved. This is especially evident in the therapeutic use of irradiation and chemotherapy, both of which have proven to be of benefit in the treatment of systemic and central nervous system (CNS) neoplasms in children. Over the past several years, the trend has been to use higher doses of irradiation, including radiosurgical techniques, to combine radio- and chemotherapy, and to make use of multidrug chemotherapeutic regimens to improve survival from childhood malignancies (Table 1). Although this approach has met with some success in improving overall survival, toxicity to normal brain tissue from either form of therapy may also be increasing. Early recognition of toxic injury to normal brain tissue is important to evaluate the overall success and efficacy of therapy, to institute early treatment of neurotoxic complications, and to judge the effectiveness of newer drugs that may actually prevent or attenuate injury to normal brain tissue. Unfortunately, cross-sectional imaging, such as computed tomography (CT) and magnetic resonance (MR) imaging, are recognized to be of limited benefit in the detection of neurotoxic injury and in the separation of injury from recurrent tumor (1–3). In addition, without proper correlation between clinical signs and symptoms and the timing of administration of therapy, it is not always possible to understand or appreciate what is seen on cross-sectional imaging. Future directions using "functional" brain imaging such as positron emission tomography (4), MR spectroscopy (5), and single photon emitted computed tomography (SPECT) (6) offer new hope for the early diagnosis of neurotoxic injury secondary to irradiation and/or chemotherapy. However, to obtain the greatest measure from any form of imaging, neuroradiologists should first become familiar with the clinical presentation, natural history, and histopathology of neurotoxic injury to better understand its relationship to both anatomic and functional imaging.

Classification

Most classifications of neurotoxic brain injury from either irradiation or chemotherapy are based on a timing of the clinical presentation (1). The frequent identification of abnormalities on cross-sectional imaging, even when the patient remains asymptomatic, suggests a need to include neuroimaging results in classifying the CNS injury. Based on the timing of clinical signs and symptoms, previous reports have divided neurotoxic injury into three major groups: acute reactions, occurring within 1–6 weeks; early "delayed" reactions occurring within 3 weeks to several months; and late "delayed" reactions occurring within several months to years following therapy (1–3). Most of our attention has focused on late "delayed" reactions due to the frequent presence of neurologic signs and symptoms and the availability of histopathologic correlation by biopsy or autopsy. Acute or early "delayed" reactions can be identified on cross-sectional imaging; however,

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TABLE 1: Radio-chemotherapy in pediatric CNS neoplasia

	Radiotherapy (cGy)	Experimental Radiotherapy (cGy)	Chemotherapy
Brain-stem glioma	7000–7200 (hyperfractionation)	7800	No
Ependymoma	5400–6000	7200	No
Malignant glioma	6000		Yes
Low-grade glioma	5400–6000		No
PNET[a] (>3 yr)	5400		Yes
CNS prophylaxis	3600		
OPG[b]/hypothalamic glioma	4500–5400		No
Craniopharyngioma	4500		No
ALL[c]: therapeutic	2400		Yes
prophylaxis	1800		

[a] PNET, primitive neuroectodermal tumor of childhood.
[b] OPG, optic pathway glioma.
[c] ALL, acute lymphocytic lymphoma.

the patients often remain asymptomatic or have a benign, transient, self-limiting course, where histologic confirmation becomes unnecessary.

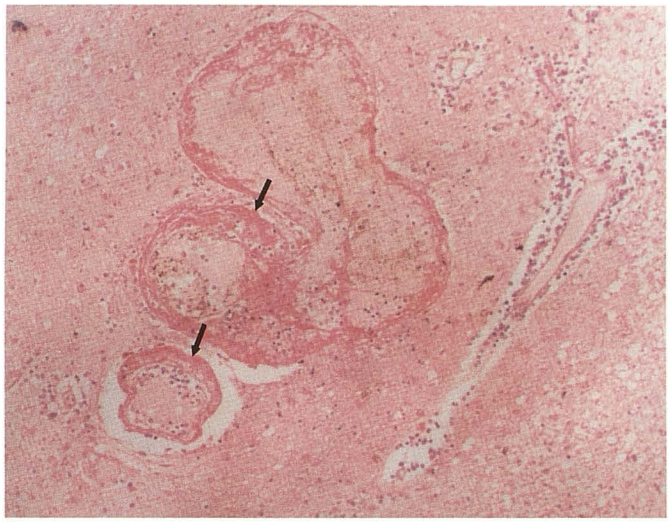
Pathophysiology

A number of factors may influence the occurrence of neurotoxicity due to irradiation and/or chemotherapy. These include the age of the patient at the time of therapy, the cumulative dose of irradiation and how it is administered (eg, hyperfractionation vs accelerated radiotherapy), combining radiotherapy with chemotherapy, and the sequence in which they are administered (7, 8). The age of the child at the time of therapy is especially important in understanding the effect of toxic injury upon normal growth and development.

The pathophysiology of neurotoxic injury to normal brain parenchyma from irradiation or chemotherapy is said to occur from one of three mechanisms. The most widely accepted explanation is that of vascular injury leading to obstruction of small and medium-sized blood vessels, spontaneous thrombosis, ischemia/infarction, and parenchymal necrosis (1, 9). A vascular mechanism readily explains the frequent occurrence of morphologic blood vessel injury, with infarction and necrosis of normal brain, found in association with irradiation or chemotherapy. Support for a vascular theory has been the subject of numerous reports including that of Reinhold and Hopewell (10), and Hopewell et al (11), who, working in concert, found histologic proof of a vascular mediated mechanism in the irradiated rat model. From their work, the authors popularized the term "tissue injury unit" (TIU) (12). The four parameters comprising the TIU are dilatation of the capillary vessel lumen, thickening of the endothelial lining of the blood vessel wall, enlargement of endothelial nuclei, and a secondary hypertrophy of adjacent astrocytes. Whether or not a TIU actually exists, their work focuses on small blood vessels as the primary target for injury from irradiation. Further animal investigations by Fike et al (13), and Russell et al (14), confirmed that radiation induced vascular injury often precedes, and is the reason for, brain parenchymal necrosis.

As a result of injury to the endothelial lining, focal alterations in the fibrinolytic enzyme system may also contribute to the vascular pathogenesis of radiation-induced injury to normal brain. Both endothelial proliferation, which may markedly reduce blood flow, and a decrease in fibrinolytic activity may lead to spontaneous thrombosis, ischemia, and infarction. The role of an altered fibrinolytic system in producing injury is controversial. Early reports by Ts'ao and Ward (15) indicate that plasminogen activator activity may actually be decreased in nonneuroendothelial cells following irradiation. This, however, is in distinct contrast to a report by Soreq and Miskin (16), who found an overall increase in plasminogen activator activity in neurons in both the cortex and cerebellum 2 weeks following irradiation. Further investigation into the effect of irradiation on plasminogen activator activity may be helpful in understanding what role an altered fibrinolytic system may have in producing spontaneous thrombosis in irradiated blood vessels.

The vascular mechanism has been challenged by other authors including Withers et al (17), who



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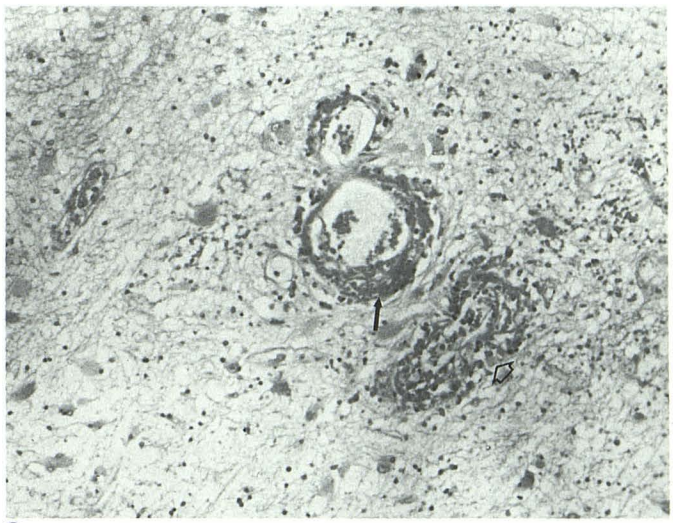

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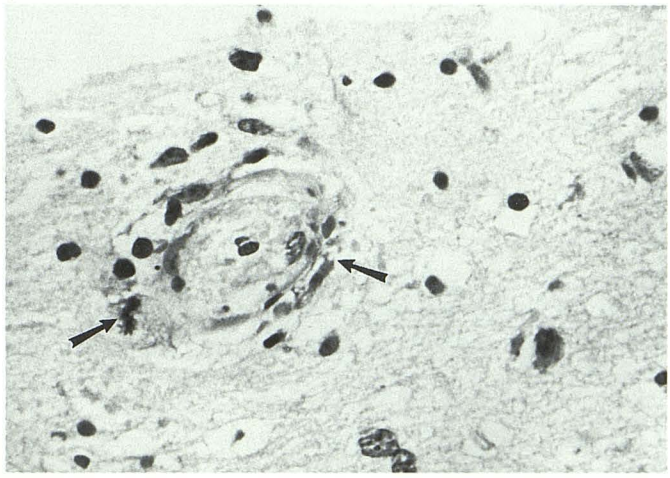

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Fig. 1. Vascular injury from irradiation. Dilatation and ectasia of the blood vessels are due to irradiation, and may mimic the neovascularity of recurrent tumor. Vessel wall thickening is partly a result of hyaloid deposition (*arrows*).

Fig. 2. Vascular injury from irradiation. Deposition of hyaloid (*arrow*), and endothelial wall proliferation (*open arrows*) contribute to vessel wall thickening and vascular occlusion.

Fig. 3. Vascular injury from irradiation. Endothelial proliferation (*arrows*) is a result of injury to the capillary wall from radiotherapy.

postulate that radiation necrosis is a result of direct injury to the cerebral parenchyma, including the microglia, oligodendrocytes, and axons. A reduction in glial parenchymal elements following irradiation and/or chemotherapy within an animal model have supported this theory (18). Specific injury to the oligodendrocyte and axonal fiber may explain the frequent occurrence of demyelination often found in association with irradiation or chemotherapy.

Finally, an immunologic mechanism secondary to an allergic hypersensitivity response and an autoimmune vasculitis was proposed by Crampton and Layton (19). Of the three potential mechanisms of injury, however, histologic confirmation supports either a vascular or glial theory, whereas evidence is lacking to support immunologic compromise as a mechanism of injury.

Histopathology

The pathologic features of injury to normal brain parenchyma as the result of either irradiation or chemotherapy reflect both a vascular and glial mechanism of injury. Acute radiation reactions occurring within weeks following therapy most likely are the result of transient vasodilatation and increased capillary permeability leading to vasogenic edema (1). Due to the transient nature of the clinical course and the hazards of biopsy so soon following therapy, histologic correlation is usually lacking. The same is true of early "delayed" radiation injury where transient vasogenic edema and demyelination along with a benign clinical course are found in association with minimal radiographic changes (20).

Most of what we know and understand pathologically about therapeutically induced neurotox-

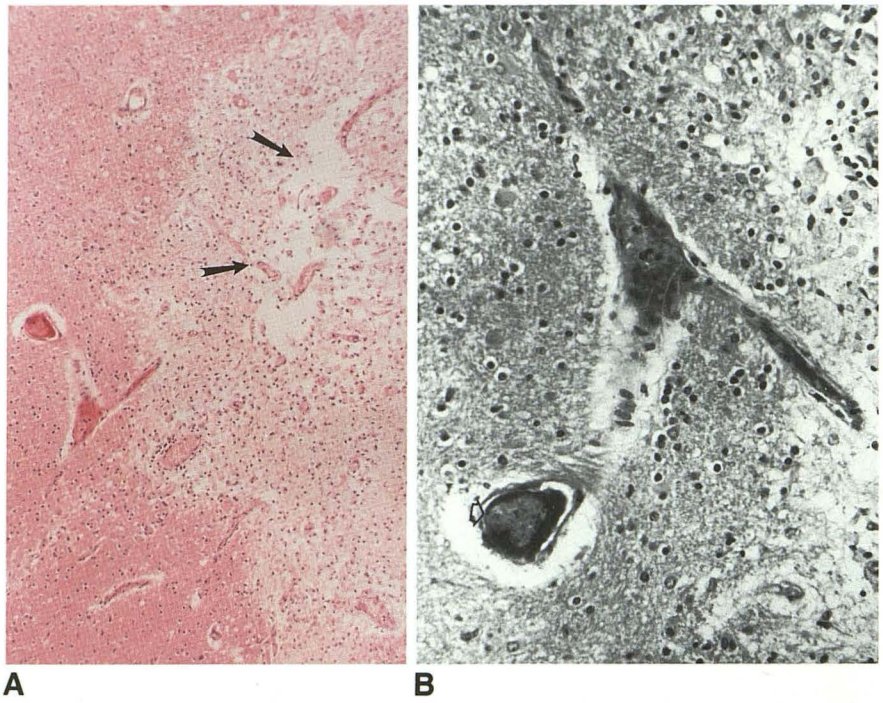


Fig. 4. Vascular injury from irradiation.

A, Extensive areas of white matter necrosis and infarction (*arrows*) in an area of demyelination are a result of spontaneous thrombosis of peripheral blood vessels.

B, Thrombosis of cortical arterioles is a result of endothelial injury and alterations in the fibrinolytic pathway.

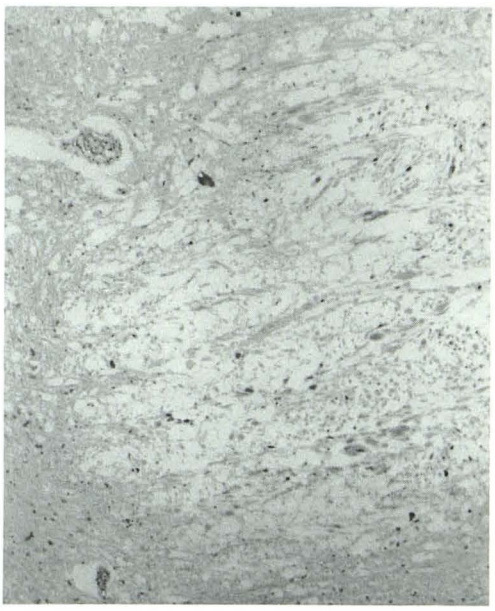


Fig. 5. White matter necrosis from irradiation. An extensive area of infarction leads to white matter necrosis, fragmentation of myelin, cellular injury, and a loss of neuropil.

icity falls under the category of late "delayed" injury (1, 2, 21–23). The pathologic features are variable and include vascular endothelial injury, infarction, white matter necrosis, focal or diffuse demyelination, and an atypical cellular response. Morphologic evidence of vascular injury plays a prominent role in both pathologic and radiographic descriptions. A breakdown in the capillary endothelial lining may lead to exudation of fibrin from the blood vessel lumen. With loss of capillary wall integrity, there is also functional loss in the blood-brain barrier. Vasodilatation, vascular ectasia, and proliferation of small blood vessels may mimick the neovascularity of recurrent tumor (23) (Fig. 1). With time, the capillary walls became hyalinized (Figs. 1 and 2). Proliferation of the endothelial lining may further contribute to compromise of the vessel lumen and a decrease in blood flow (Fig. 2 and 3). Initially, a perivascular mononuclear inflammatory response may be present; however, in later stages of injury, a significant inflammatory response is usually lacking (9). Ischemia and/or infarction are the direct result of alterations in local blood flow due to endothelial wall proliferation and spontaneous thrombosis (Figs. 4A and 4B). Infarction of white matter consists of areas of necrosis, with rarefaction and fragmentation of myelin, cellular disruption, and a loss of neuropil (23) (Fig. 5).

Intravascular and perivascular microcalcifications form a characteristic pathologic pattern known as mineralizing angiopathy, and is found most often in children receiving both irradiation and chemotherapy for acute childhood leukemia (24, 25) (Fig. 6). Involvement of the basal ganglia, the junction of cortical gray/white matter, and

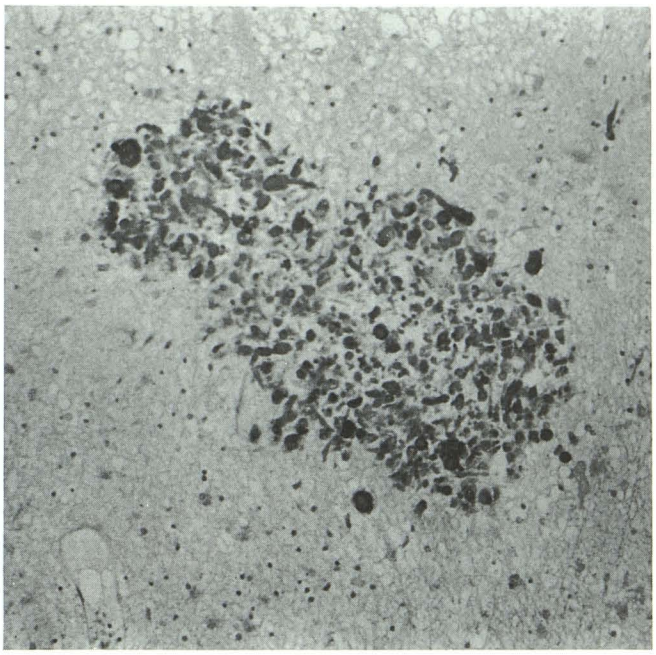


Fig. 6. Parenchymal calcification from irradiation. Dystrophic calcification results from radiation-induced injury to the parenchyma, and is commonly found within the basal ganglia and at the junction of white and gray matter.

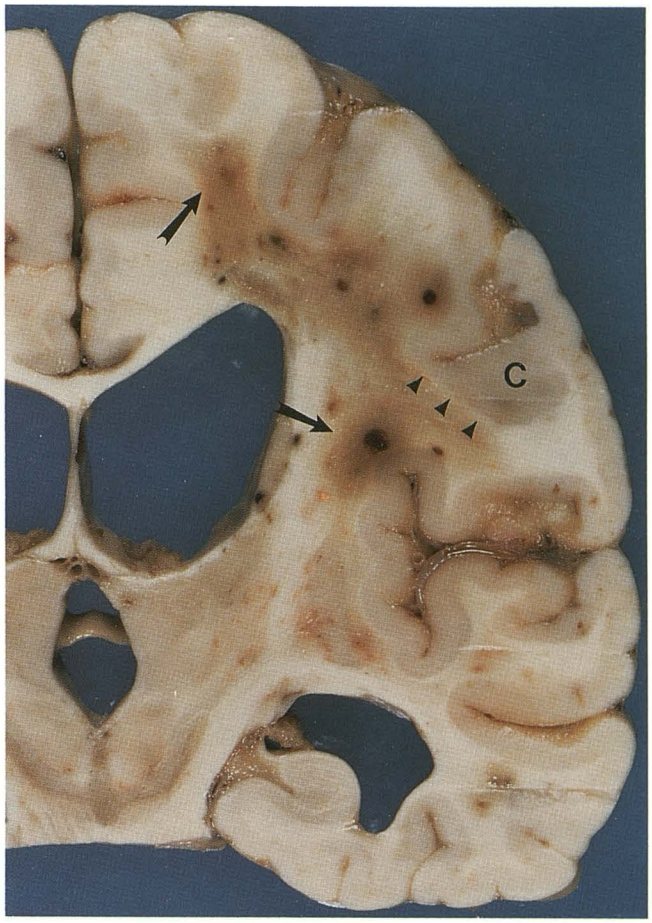


Fig. 7. White matter injury from irradiation. Multifocal areas of hemorrhagic infarction and necrosis (*arrows*) are identified within the deep white matter with relative sparing of subcortical tracts (*arrowheads*) and the overlying cortex (*C*).

less commonly, the pons, is typical of a microvascular angiopathy, and should not be confused with larger deposits of calcium within areas of extensive white matter necrosis. As one would expect with small vessel disease, CNS neurotoxicity, either from irradiation or chemotherapy, predominately involves the deep white matter with early sparing of subcortical white matter and the overlying cortex (Fig. 7). Zones of demyelination (Fig. 8) may be interspersed with areas of white matter necrosis depending upon the severity of injury. Cortical involvement is less common, and may result from large vessel injury or diffuse atrophy; however, patterns of focal neuronal gigantism and cortical thickening rarely have been reported (25).

Radiation-induced injury to large vessels may lead pathologically to early changes of atherosclerosis, endothelial proliferation with narrowing of the vessel lumen, subintimal dissection, or fibrosis of the blood vessel wall (26).

Cross-Sectional Imaging

When clinical signs and symptoms are present, we rely on cross-sectional imaging to provide

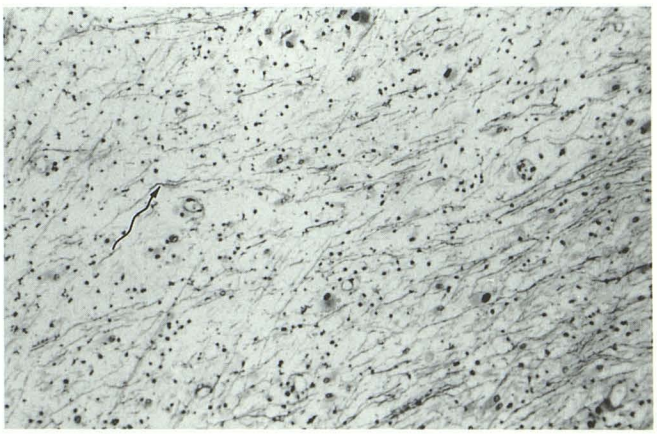


Fig. 8. Demyelination from chemotherapy. Extensive loss of neuropil and myelin with relative preservation of axonal fibers (*arrow*) are consistent with zones of demyelination (Bodian stain for axons).

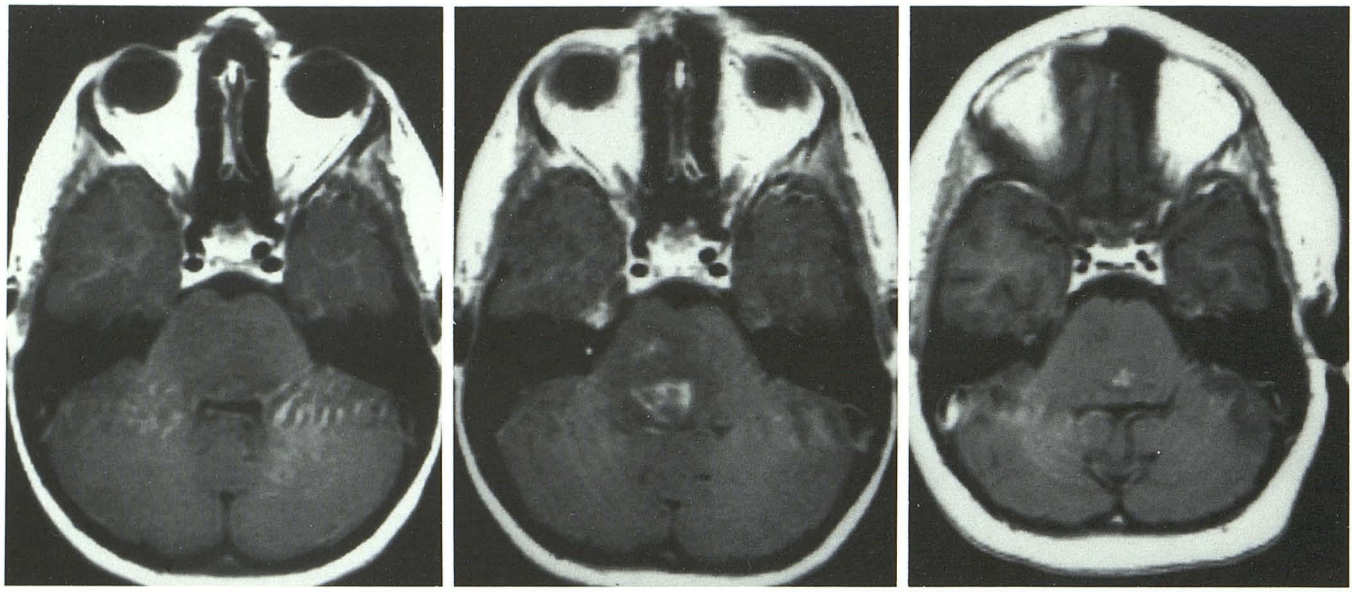


Fig. 9. Acute radiation reaction.

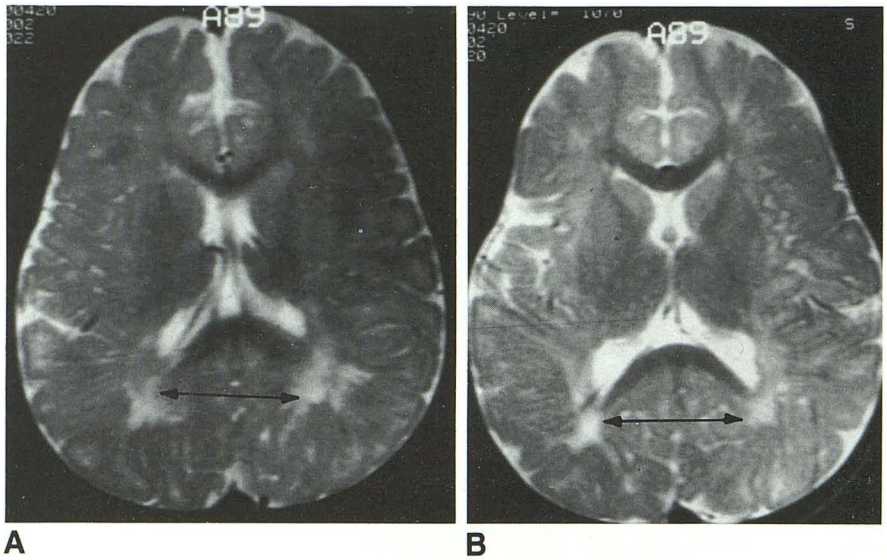
A, A pontine glioma presented with enlargement of the pons, compression of the fourth ventricle, and low signal due to a prolonged T1-relaxation.

B, Within 3 weeks following hyperfractionation therapy, there is an increase in the size of the pontine mass and variable enhancement due to an acute radiation reaction.

C, By 3 months following radiation therapy, there is a decrease in the size and enhancement of the pontine glioma following resolution of the acute reaction.

Fig. 10. Early "delayed" injury.

A and *B*, Transient, diffuse, increased T2 signal within the white matter appeared 6–8 weeks following treatment of acute lymphoblastic leukemia with whole brain irradiation and methotrexate. Despite the MR appearance, the patient remained asymptomatic. The increased signal within the white matter (*arrows*) disappeared by a 9-month follow-up examination.



morphologic evidence of CNS injury. Unfortunately, CT and MR often lack the sensitivity and specificity necessary to detect early injury and to separate it from recurrent tumor. Despite these limitations, anatomic evidence of CNS injury can often be appreciated using cross-sectional imaging. Improved anatomic resolution, multiprojectional imaging, tissue characterization based on T1- and T2-relaxation parameters, and contrast enhancement with gadolinium have made MR the imaging modality of choice for investigating CNS toxicity and recurrent tumor.

Acute Radiation Injury Reactions

Acute reactions are a result of transient vasogenic edema that may lead to mass effect, prolongation of both T1- and T2-relaxation param-

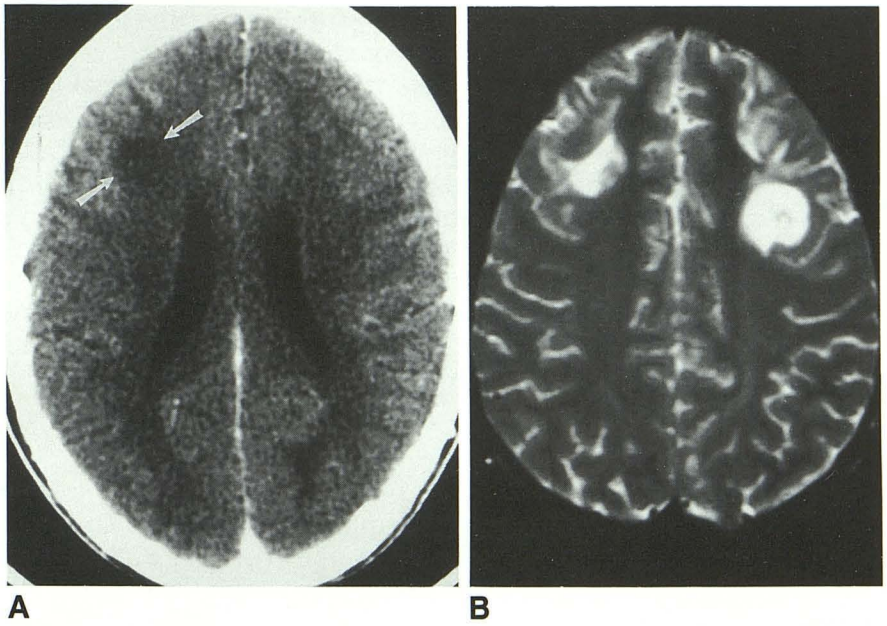


Fig. 11. White matter necrosis from chemotherapy.

A, CT shows a focal area of low attenuation without enhancement (*arrows*) within the white matter of the right frontal lobe.

B, This area corresponds to a focal area of increased signal on T2-weighted MR images. The left lesion was not seen on CT, even in retrospect. Biopsy confirmed white matter necrosis due to chemotherapy.

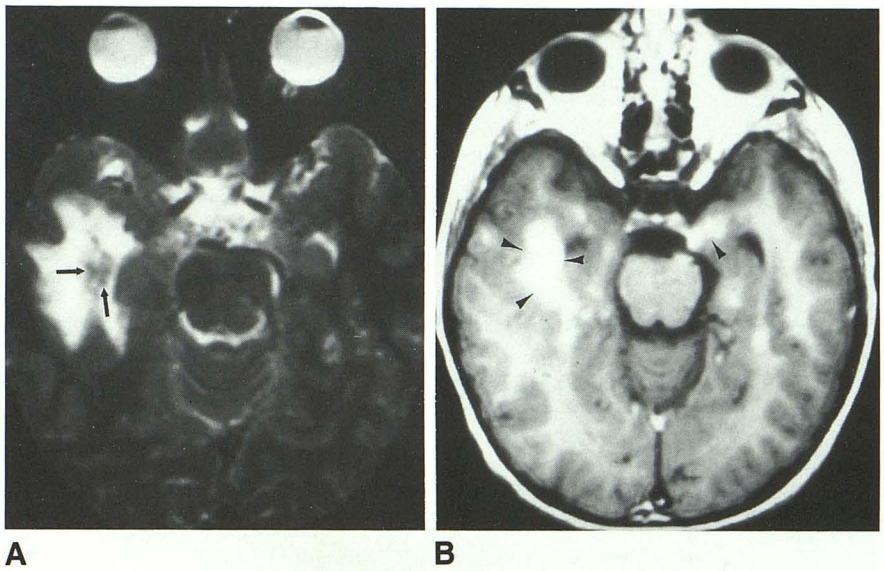


Fig. 12. Parenchymal injury from irradiation.

A, An extensive area of increased T2 signal is identified within the white matter of the right temporal lobe 9 months following irradiation for a midbrain glioma. Note the hypointense signal (*arrows*) likely representing petechial hemorrhage within the zone of injury.

B, Vascular injury with breakdown in the blood-brain barrier results in extensive enhancement following gadolinium administration (*arrowheads*).

eters, and rarely a change in enhancement patterns due to increased capillary permeability and a breakdown in the blood-brain barrier (Figs. 9A–9D). Acute radiation injury is most commonly found in children receiving hyperfractionation therapy for brain-stem glioma. We have found MR evidence of acute reactions in 20% of children treated with hyperfractionation radiotherapy for brain-stem glioma at our institution. Acute reactions often explain a transient decline in the neurologic function immediately following therapy. Typically, they disappear spontaneously over the ensuing weeks, or may require a short course of steroid administration to relieve symptoms. The decision to treat acute reactions depends upon the severity of clinical neurologic compromise rather than on the radiographic features.

Early "Delayed" Injury

Early "delayed" CNS injury is difficult to document, and is far less understood compared to late "delayed" reactions (2). Earlier studies in adults have described a transient and usually benign clinical course for this form of injury (27–29). Recent observations in children with acute childhood leukemia indicate that a transient form of demyelination following therapy may represent an early "delayed" reaction. Wilson et al (30) have

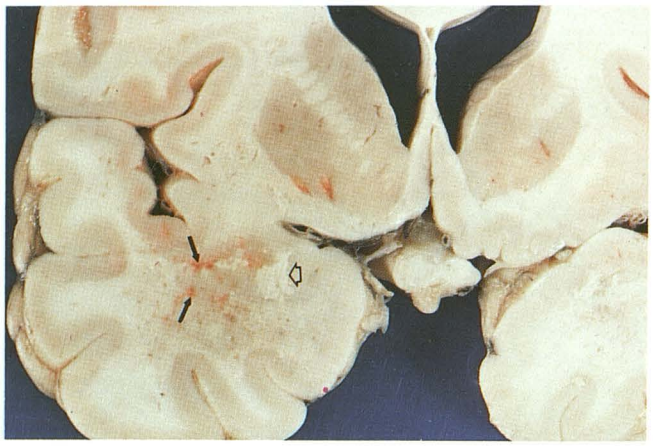


Fig. 13. Parenchymal injury from irradiation. As seen in Figure 12, the abnormalities found on MR correspond to zones of demyelination, edema, petechial hemorrhage (*arrows*), and white matter necrosis (*open arrow*).

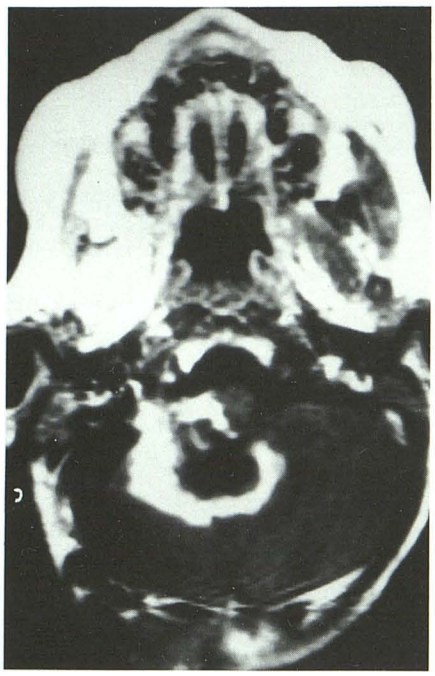


Fig. 14. Radiation injury following stereotactic radiosurgery. Intense enhancement surrounds the zone targeted for stereotactic radiosurgery 4 months earlier. Enhancement is a result of radiation-induced vascular injury with a breakdown in the blood-brain barrier.

described a transient leukomalacia on MR examination in children receiving both irradiation and chemotherapy for acute lymphoblastic leukemia. In its timing of appearance, this transient leukomalacia would be consistent with an early "delayed" reaction (30). In their study, 44% of children at 15 weeks following therapy exhibited transient, often diffuse, increased signal within the white matter on T2-weighted images (Figs. 10A and 10B). By 1 year follow-up, the increased signal had disappeared in all but one subject. Clinical assessment by neurodevelopmental testing found no correlation with the demyelination in most of their patient population. Only those children who received therapy under 5 years of age had evidence of neurodevelopmental delay. These findings likely represent a transient demyelination due to the synergism between low-dose whole brain irradiation and chemotherapy (eg, methotrexate) used in the treatment of acute childhood leukemia (31).

Late "Delayed" Injury

Most literature emphasizes the imaging and pathologic features of late "delayed" CNS injury from irradiation or chemotherapy. Late reactions have a variable appearance on cross-sectional imaging, reflecting a wide range of pathology. The pattern of injury may vary from a single focal mass to more diffuse white matter injury. Knowledge of field ports for radiotherapy will often help predict those areas at most risk for injury; whereas, following chemotherapy, white matter abnormalities may be focal, multifocal (Figs. 11A and 11B), or diffuse, and may arise anywhere within the brain.

Vascular involvement leads to ischemia, infarction, and necrosis. Areas of infarction or necrosis produce signal abnormalities with a variable prolongation of T1- and T2-relaxation (Figs. 12A and 12B). Focal areas of necrosis are more common in adults than children. They may appear as mass lesions that mimic neoplasm. Areas of petechial hemorrhage from capillary endothelial injury appear as multifocal areas, with short T2-relaxation superimposed on more extensive zones of hyperintense signal from demyelination or edema (Figs. 12A, 12B, and 13).

Injury to the endothelial lining of small blood vessels results in damage to the blood-brain barrier. Enhancement following gadolinium administration, therefore, is common, and often coincides with the clinical onset of symptoms. The pattern of enhancement may wax and wane and eventually disappear completely. However, the active phase of injury may persist for several months (Fig. 14). Multifocal enhancement may also be seen in diffuse white matter involvement, where small areas of petechial enhancement are found within the centrum semiovale (Figs. 15A and 15B).

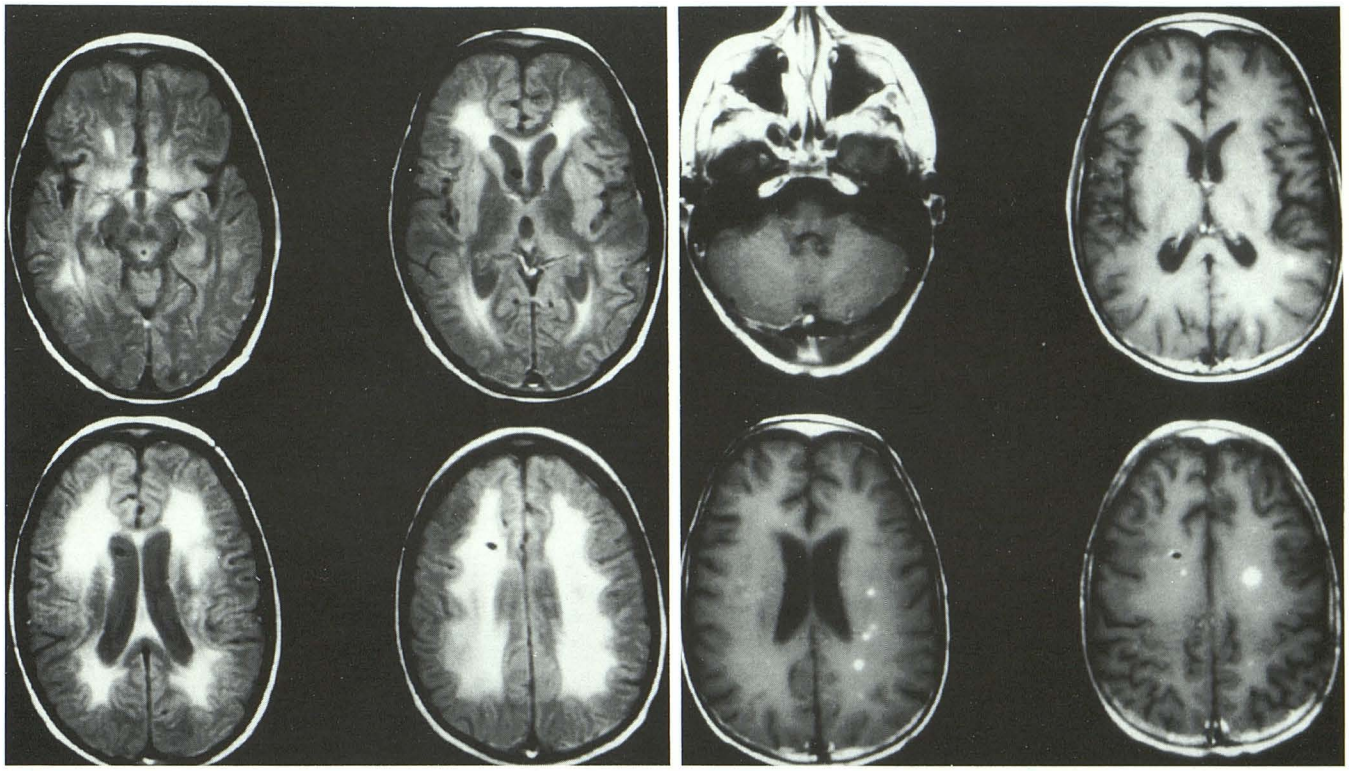


Fig. 15. White matter injury from irradiation.

A, Diffuse hyperintense signal appears on intermediate weighted images and represents demyelination and edema as a result of late "delayed" radiation injury.

B, Multifocal areas of enhancement within the deep white matter are a result of vascular injury and a breakdown in the blood-brain barrier.

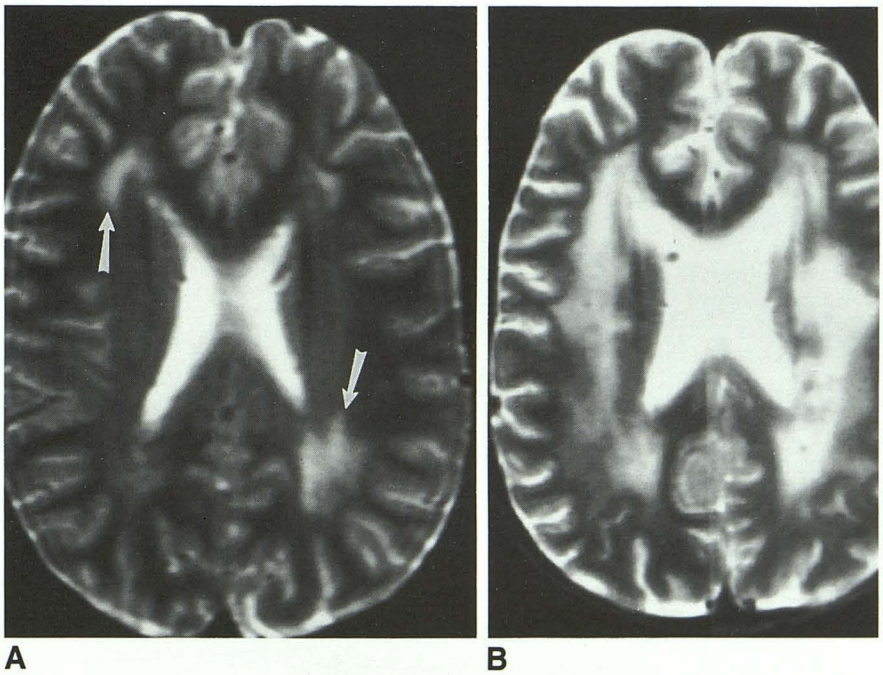


Fig. 16. Demyelination from combined irradiation and chemotherapy.

A, Small patchy areas of increased T2 signal (*arrows*) appeared within the white matter 8 to 10 months following combined therapy.

B, There is a rapid increase in the amount of signal abnormality with coalescence to form broad bands of demyelination 6 months following the initial examination (*A*).

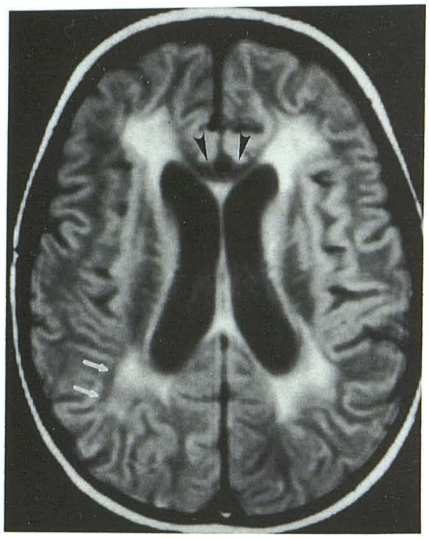


Fig. 17. Demyelination from chemotherapy. Broad zones of abnormal hyperintense signal appear on an intermediate weighted image, and represent diffuse demyelination with sparing of the subcortical tracts (*arrows*), and the corpus callosum (*arrowheads*).

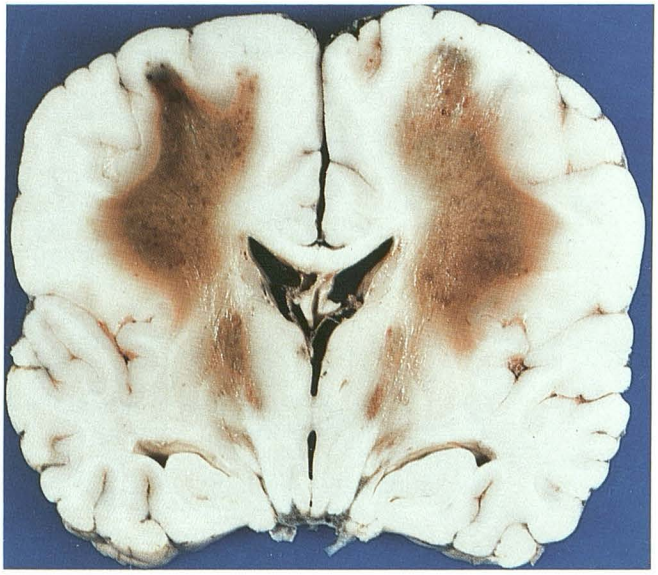


Fig. 18. Necrotizing leukoencephalopathy. Extensive broad zones of hemorrhagic white matter necrosis are a result of toxicity from chemotherapy (tumor necrosis factor).

Diffuse involvement with demyelination is more common in children than adults (32, 33). The increased signal on T2-weighted images may progress in size and intensity with time, but unlike early "delayed" reactions, is not usually reversible (Figs. 16A and 16B). Demyelination often begins as small foci of hypertense T2 signal in the deep white matter adjacent to the anterior and posterior horns of the lateral ventricles. These then spread into the more peripheral regions of the centrum semiovale, and eventually coalesce to involve the entire white matter zone, including the subcortical fibers (Fig. 17). The corpus callosum, anterior commissure, and hippocampal commissure are often spared despite extensive involvement of the deep white matter. The association of diffuse white matter demyelination on sequential examinations with a rapidly deteriorating clinical course is often referred to as "necrotizing leukoencephalopathy" (34, 35). Pathologically, necrotizing leukoencephalopathy represents an extensive form of demyelination, axonal injury, loss of neuropil, white matter necrosis, and eventual scarring with astrogliosis (Fig. 18). The pattern of involvement is similar to that found in less symptomatic patients, with, perhaps the exception of more extensive areas of white matter necrosis. Cystic areas of necrosis are replaced in time with scarring and focal astrogliosis. A decrease in white matter volume similar to that found in periventricular leukomalacia may occur as a result of diffuse injury from irradiation and chemotherapy (Figs. 19A, 19B, and 20). The appearance of white matter injury on imaging does not correlate well with the severity of clinical symptoms.

Microvascular angiopathy is best diagnosed on noncontrast CT, where punctate calcifications involve the basal ganglia (globus pallidus, putamen, caudate head) and/or subcortical white matter (Fig. 21). On MR examination, mineralizing angiopathy appears as increased signal on T1-weighted images, which declines in signal on the second echo of the T2-weighted sequence (Figs. 22A and 22B). Henkelman et al felt that this paradoxical appearance could be due to the effect that particulate calcium may have in reducing T1- and T2-relaxation time by a surface relaxation mechanism (36). The appearance of the calcification is consistent with a late pattern of injury and is irreversible. Symptoms of basal ganglia dysfunction are often lacking.

Neurodevelopmental Outcome

The previous discussion has focused on the morphologic changes of either focal or diffuse injury to normal brain tissue as a result of therapeutic irradiation or chemotherapy. In children, we must also be concerned with the effect of therapy on normal brain growth and development. In general, the younger the child at the time of therapy, the greater is the effect of neurotoxicity on normal development. Neurodevel-

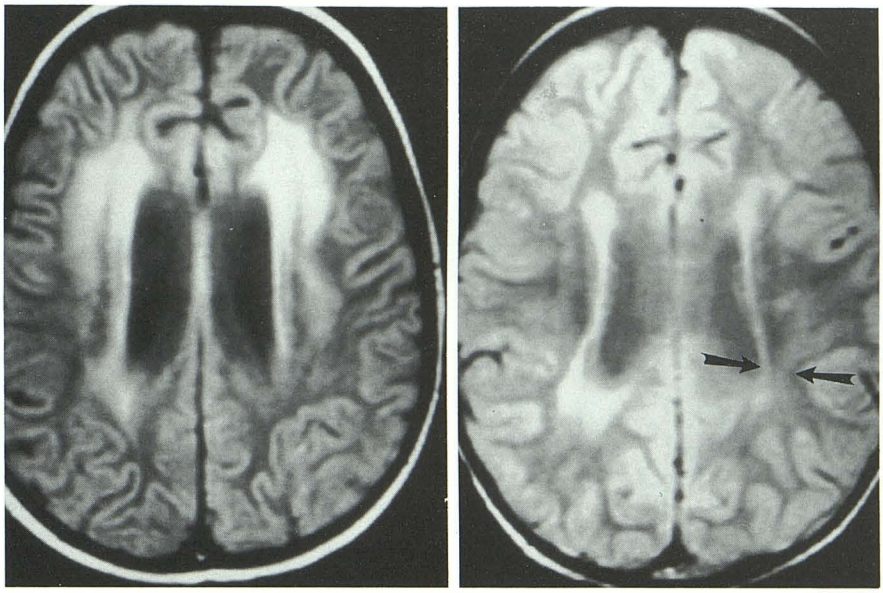


Fig. 19. Necrotizing leukoencephalopathy from chemotherapy.

A, Extensive zones of demyelination (increased T2 signal) are a result of chemotherapy.

B, On a 12-month follow-up examination, white matter volume appears to decrease as a result of the injury (*arrows*).

opmental delay may not be evident until years following therapy (37). In essence, these changes represent a variation of late "delayed" injury that may take years and extensive neurodevelopmental testing to detect. Unfortunately, the effect on normal brain development cannot be predicted morphologically from cross-sectional imaging. As reported by Kramer et al (38), neurodevelopmental abnormalities do not correlate well with the findings on MR imaging.

Evidence implicating irradiation and chemotherapy as a cause of neurodevelopmental delay is mounting. Fogarty et al (39), identified neurodevelopmental impairment consisting primarily of learning disabilities in 9 of 13 children surviving for an average of 6 years after treatment of acute leukemia with CNS irradiation. In a similar fashion, Meadows et al (40) found a 10 point or greater decline in IQ in 11 of 18 children followed 3–5 years after receiving therapy for acute leukemia. As previously reported by Wilson et al (30), Meadows also found the greatest IQ decline in children under 5 years of age. The severity of neurodevelopmental delay appears to be related to many factors, including the total dose of irra-

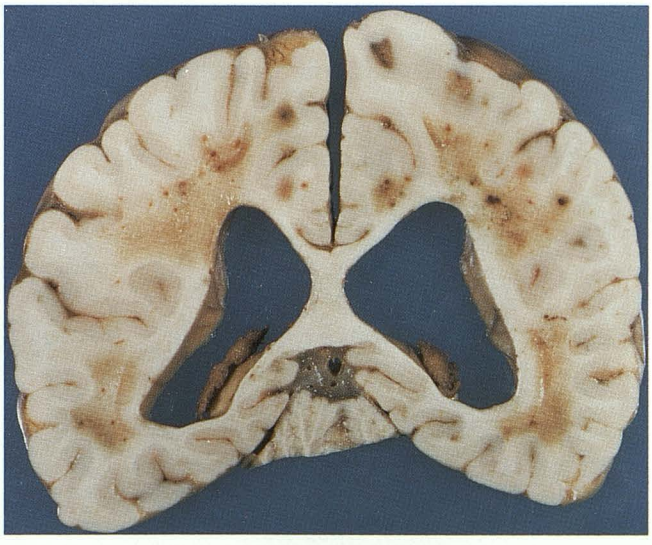


Fig. 20. White matter injury from irradiation. Scarring and astrogliosis have resulted in a diffuse loss of white matter volume with compensatory dilatation of the lateral ventricles.

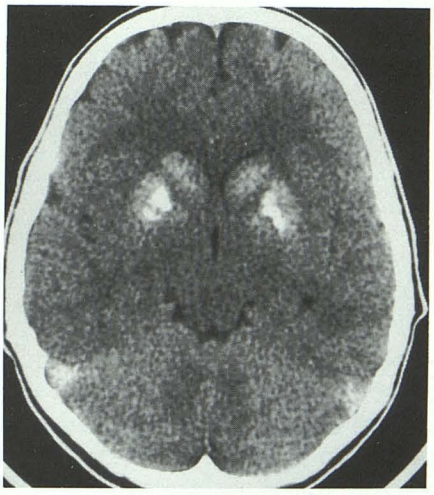


Fig. 21. Microvascular "mineralizing" angiopathy. Punctate calcifications within the basal ganglia (globus pallidus, putamen, caudate head) are a result of mineral deposition in and around blood vessels in this child receiving whole brain irradiation and chemotherapy for acute childhood leukemia.

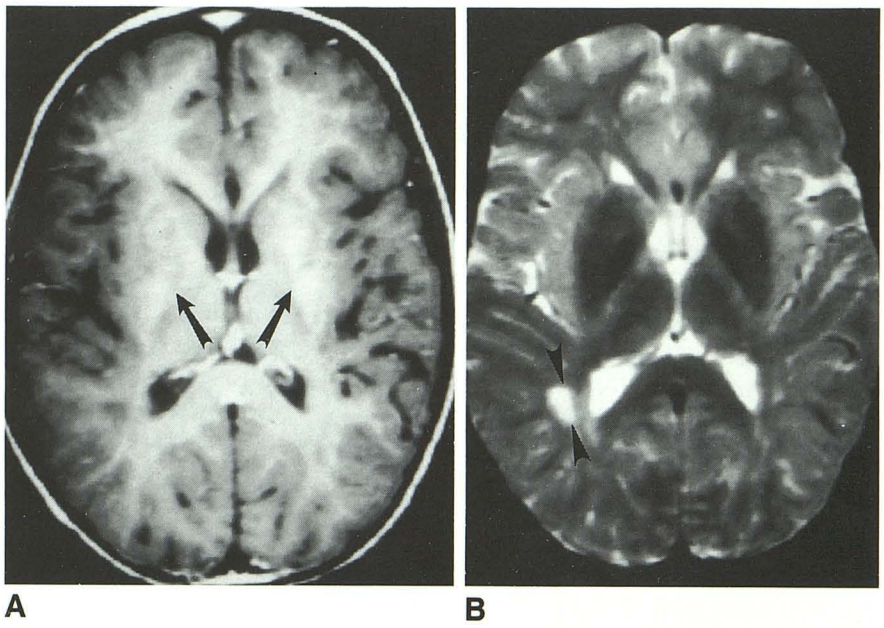


Fig. 22. Microvascular "mineralizing" angiopathy.

A, Calcification within the basal ganglia may appear as hyperintense signal on T1-weighted images (*arrows*).

B, These same areas appear hypointense on T2-weighted images. Note patchy areas of demyelination (*arrowheads*) as a result of injury to the deep white matter.

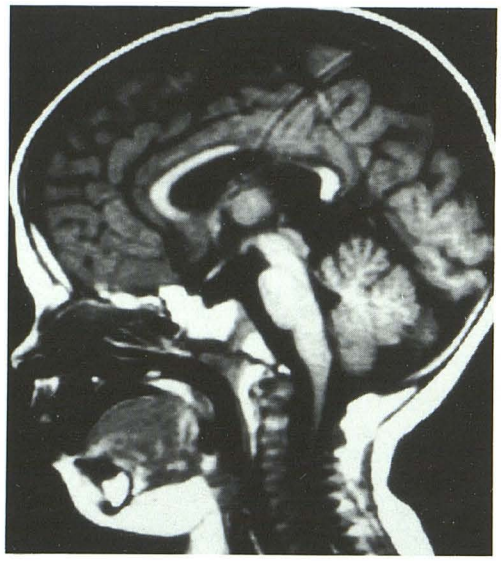


Fig. 23. Growth hormone deficiency from irradiation. Absence of both the pituitary stalk and the adenohypophysis were found 7–8 months following irradiation, and coincided with laboratory identification of a growth hormone deficiency.

diation, the combination of irradiation and chemotherapy, the route of administration of chemotherapy (eg, intrathecal vs intravenous methotrexate), the order in which the radiation and chemotherapy are administered, and the age of the patient at the time of treatment.

The incidence of neurodevelopmental delay following focal radiation such as in hyperfractionation therapy for brain-stem glioma may be less than for whole-brain irradiation used in the treatment of primitive neuroectodermal tumors, acute leukemia, or prior to bone marrow transplantation. Limited survival in children with tumors receiving focal irradiation often prevents accurate conclusions regarding the effect of such therapy on neurodevelopmental outcome. Neuropsychologic sequelae may be increased when whole-brain and spinal irradiation are used together to prevent the spread of metastatic disease. In analyzing the quality of life in 24 long-term survivors of posterior fossa medulloblastoma, Packer et al (41), found 79% of children functioned well in everyday activities. However, on neuropsychologic evaluation, specific learning disabilities, including memory and fine motor dysfunction, were found in over 50% of children. The routine use of neurodevelopmental testing gives us a more accurate assessment of the true incidence of neurocognitive delay as a result of therapy.

Neuroendocrine Disorders

Children receiving radiotherapy where field ports include the sella turcica and suprasellar region, are susceptible to developing neuroendocrine dysfunction as a result of injury to the hypothalamic/pituitary axis (42, 43). Neuroendocrine dysfunction is most commonly found in children treated for optic pathway/hypothalamic glioma, germinoma or craniopharyngioma, and in those given prophylactic whole brain irradiation. Rappaport and Brauner (4) concluded that the minimal harmful dose leading to neuroendocrine dysfunction was likely close to 1800 to 2000 cGy, well within the dose range used to treat suprasellar neoplasms in children. Dose ap-

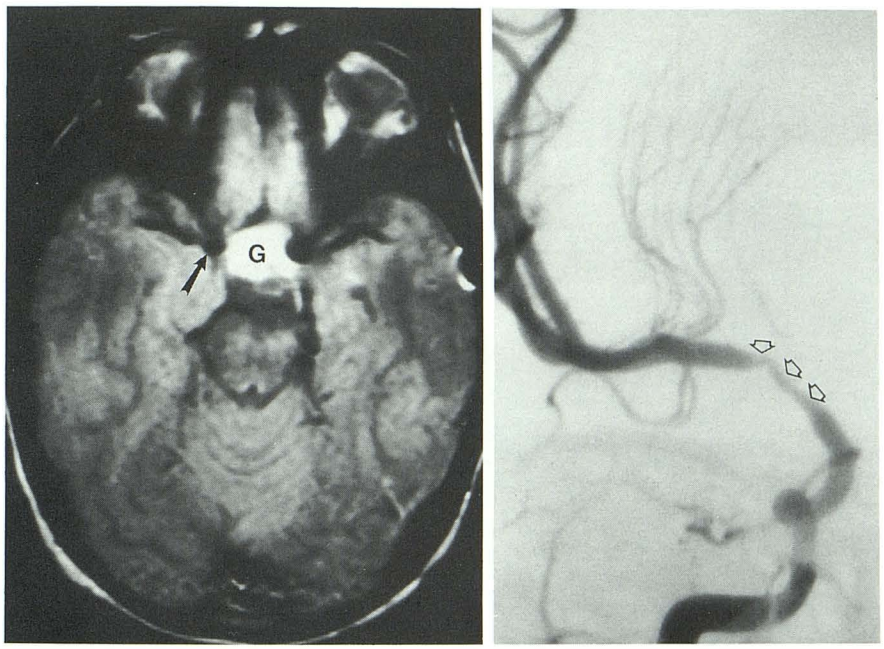


Fig. 24. Large vessel injury from irradiation.

A, A small carotid terminus is identified on the right (*arrow*) 1 year following irradiation for a midline hypothalamic glioma (*G*).

B, diffuse stenosis involves the carotid terminus and proximal middle cerebral artery (*open arrow*), with absence of the anterior cerebral artery by angiography.

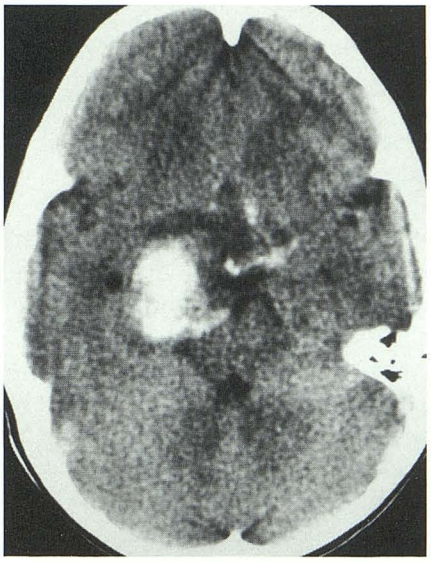


Fig. 25. Spontaneous hemorrhage from irradiation. Massive spontaneous hemorrhage occurred 21 months following irradiation for a hypothalamic glioma. Such hemorrhage may result from injury to the blood vessel wall or from aneurysm formation.

pears not only to correlate with the incidence of neuroendocrine dysfunction, but also with the type of hormonal involvement (43). Whereas a lower dose may lead to a selective deficiency in growth hormone alone, higher doses may produce panhypopituitarism. Growth hormone is the most commonly encountered deficiency resulting from radiotherapy. The function of the posterior pituitary gland (neurohypophysis) appears to be relatively spared. Growth hormone deficiency can be documented through routine laboratory analysis, but may not appear until 9–12 months following therapy. The clinical effect of a growth hormone deficiency may take years to manifest, and, therefore, laboratory surveillance is necessary to identify those children at risk, and to begin early replacement therapy.

In our experience, growth hormone deficiency found on laboratory evaluation does not always correlate with morphologic changes found on MR examination. Abnormalities that may be seen as a result of irradiation and/or chemotherapy include frequent absence of the posterior bright neurohypophysis, a small or absent adenohypophysis, or nonvisualization of the pituitary stalk (Fig. 23). The exact mechanism of injury to the hypothalamus/pituitary axis, and specifically the cause of growth hormone deficiency, remains a mystery. Some authors have suggested that a radiation-mediated injury to the microvasculature of the stalk may explain a disruption of neuroendocrine integrity between the hypothalamus and the anterior pituitary gland. Whether the injury is due to vascular compromise, or whether there is a direct effect upon the metabolically active parenchyma of the adenohypophysis remains unclear.

Large Vessel Injury

Small-vessel injury accounts for the majority of pathologic changes within the brain paren-

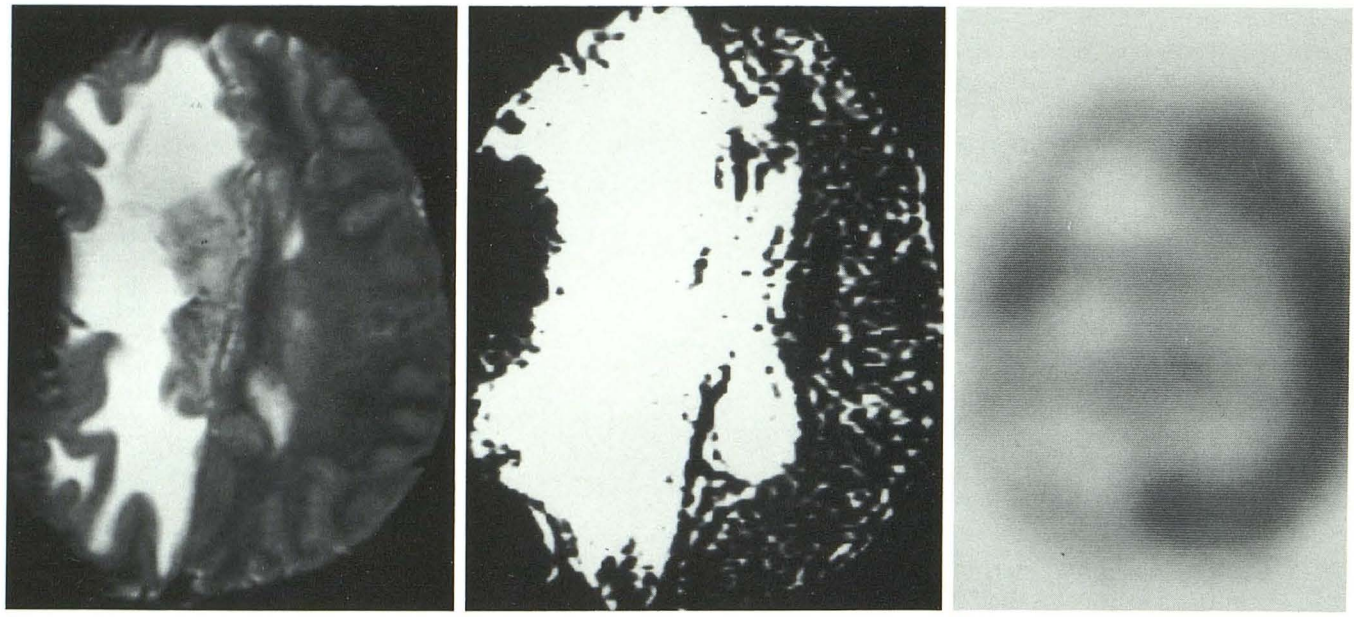


Fig. 26. Parenchymal injury from irradiation.

A, An extensive zone of hyperintense signal is found throughout the white matter of the right cerebral hemisphere on a T2-weighted MR image.

B, There is decreased perfusion throughout the right cerebral hemisphere, as demonstrated on a T2-weighted MR perfusion image.

C, Decreased perfusion on the right was confirmed on a Tc-99m HMPAO SPECT image.

chyma. However, injury to medium and large-sized vessels can also occur (44, 45). Large-vessel injury, at or near the circle of Willis and carotid siphon, may arise as a result of delayed radiation injury. Children at greatest risk are those receiving large doses directly to the sella/suprasellar region for optic pathway/hypothalamic glioma, malignant germinoma, or recurrent craniopharyngioma. Rarely, large-vessel occlusive disease may result from extracranial irradiation for facial hemangioma. Painter et al (46), described four children who developed intracranial vascular occlusive disease as a result of CNS irradiation. Angiographic evaluation demonstrated diffuse narrowing of the supraclinoid internal carotid artery and the proximal anterior (A1 segment) and middle (M1 segment) cerebral arteries (Figs. 24A and 24B). The walls of the vessel remain smooth and rarely exhibit the bead-like appearance found in fibromuscular disease. Occlusion of the carotid terminus produces a Moya-Moya pattern on MR or angiography, with collateral circulation in the region of the basal ganglia.

The pathophysiology of the large-vessel injury may result from premature atherosclerosis of the wall, injury to the vasa vasorum within the wall of the larger vessels, or from adventitial or periadventitial fibrosis (46). Endothelial proliferation may further compromise the vessel lumen and cause a spontaneous thrombosis with distal infarction.

Aneurysms may rarely develop within the anterior or middle cerebral arteries, and lead to massive spontaneous hemorrhage (47). Direct injury to carotid blood vessels, aneurysm formation, and neovascularity produced within the mass itself may explain sudden massive spontaneous hemorrhage found in children with hypothalamic gliomas months following radiotherapy (Fig. 25).

Conclusion

By understanding the pathophysiology and pathologic manifestations of injury to normal brain tissue from either irradiation and/or chemotherapy, we stand the greatest chance of diagnosing the injury on cross-sectional imaging. Early recognition is necessary in order to institute therapy and separate injury from recurrent tumor. Experience tells us, however, that even in the best of circumstances, MR imaging may inherently lack the sensitivity and specificity necessary to detect early injury and separate it from recurrent tumor in all cases. Through functional imaging, such as in the use of positron emission

tomography, we may be able to separate metabolically active tumor from metabolically inactive radiation necrosis (4). In the future, early neurotoxic injury to normal blood vessels producing a decrease in vascular flow, ischemia, and infarction may be identified by using MR spectroscopy, MR perfusion/diffusion imaging, or radionuclide (SPECT) imaging (Figs. 26A, 26B, and 26C). Identifying areas of compromised (decreased) blood flow within otherwise normal brain parenchyma due to either radiation or chemotherapy may allow us to separate neurotoxic injury from normal brain tissue or from tumor with normal or increased vascular flow. Whichever tools we use, our success in using neuroimaging to diagnose CNS injury from radio/chemotherapy depends upon our understanding of the pathology and pathophysiology of this disorder, its clinical presentation, and its natural history.

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