ORIGINAL COMMUNICATIONS

CEREBRAL CALCIFICATION AND LEARNING DISABILITIES FOLLOWING CRANIAL IRRADIATION FOR MEDULLOBLASTOMA

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Six children who received craniospinal irradiation for medulloblastoma when they were under 10 years of age developed learning disabilities. Four exhibited associated temporal lobe calcification on computerized tomography of the brain. The pathogenetic mechanisms of postirradiation cerebral calcification and learning disabilities in these children are discussed. We present the hypothesis that irradiation-induced vasculopathy results in hypoxia, most pronounced in the hippocampus. Hippocampal damage can manifest radiologically as calcifications and clinically as memory and learning disabilities.

Key words • cranial irradiation • cerebral calcifications • learning disabilities

Cranial irradiation in childhood is often associated with the development of learning disabilities.[1,2] Children exposed to radiation treatment before age 10 have been found to be more susceptible.[3,4] Some of these children develop intracerebral calcifications which, when present, correlate with the severity of the learning disabilities.[5-7] Although there are several reports of postirradiation cerebral calcification and learning disabilities in children with acute lymphoblastic leukemia (ALL),[1,4,5] there are no reports of similar findings in children irradiated for medulloblastoma.

We reviewed the clinical and radiologic features in six children who received craniospinal irradiation when they were less than 10 years of age and who subsequently developed learning disabilities. Four of these patients developed associated intracerebral calcifications. Our hypothesis relates the pathogenesis of cerebral calcification to learning disabilities following cranial irradiation in children.

PATIENTS AND METHODS

Between 1969 and 1977, 21 patients with medulloblastoma were treated in the Department of Therapeutic Radiology at Tufts New England Medical Center, Boston. Eleven of the 21 patients survived 7 to 15 years after treatment. Six of these long-term survivors were under the age of 10 at the time of treatment and developed severe learning disabilities necessitating placement in special classes. These patients are the subject of this retrospective review.

The children underwent posterior craniectomy for resection of medulloblastoma. Postoperatively they received craniospinal irradiation on Cobalt 60 machine. The whole brain received 30 to 36 Gy in 4 weeks

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TABLE. CEREBRAL CALCIFICATIONS AND LEARNING DISABILITIES: CLINICAL DATA

Patient	Age at Diagnosis (yr)	Length of Follow-up (yr)	Follow-up CT Findings	Neuropsychologic Evaluation
1	2	12	No ventricular dilatation No recurrence; calcifications present in medial temporal lobes	WISC-R* scores: Full scale IQ = 84 Verbal IQ = 75 Performance IQ = 96 Severe reading, spelling, and language problems
2	2.8	10	No ventricular dilatation No recurrence; calcifications present in medial temporal lobes	Severe learning disability, requiring placement in special class. Detailed testing not done.
3	3.0	15	No ventricular dilatation No recurrence calcifications present in medial temporal lobes	WISC-R* scores: Full scale IQ = 79 Verbal IQ = 87 Performance IQ = 73 Summary: Patient functioning 2 years below grade level in academic skills.
4	3.5	11	No ventricular dilatation No recurrence; calcifications present in medial temporal lobes	No detailed testing performed. Patient required placement in a special school due to learning disability.
5	10	12	No ventricular dilatation No recurrence No calcification	WISC-R* scores Full scale IQ = 86 Verbal IQ = 75 Performance IQ = 82 Patient required placement in special class.
6	5	12	No ventricular dilatation No recurrence	Detailed testing not done. Patient required placement in a special class.

* Welcher Intelligence Scale for Children (Revised)

through lateral opposed ports; the posterior fossa received an additional dose of 20 Gy in 2 weeks through lateral opposed ports; and the spinal axis received 30 to 36 Gy in 4 weeks through a single posterior port.

The patients underwent regular follow-up neurologic examinations and computerized tomography (CT) of the brain. Detailed neuropsychologic assessments were available on three of the six patients who manifested learning difficulties in school.

RESULTS

A summary of clinical findings in each patient is presented in the Table. Four of the six patients with severe learning disabilities developed calcifications in the medial portion of the temporal lobe (Figure). The time interval between cranial irradiation and manifestation of intracerebral calcification was 1 to 6 years. None of the patients manifested ventricular enlargement or atrophy of the brain on CT.

Detailed test results were available in three patients. These patients had borderline or subnormal scores. The remaining three did not undergo detailed testing, but clearly manifested learning disabilities.

DISCUSSION

Intracerebral calcification following cranial irradiation has been reported in children with ALL.[2,7,8] The calcifications are typically seen in the anteromedial region of the temporal lobe.[2] Histologic findings consist of intimal fibrosis in the wall of small vessels, vascular occlusion, focal necrosis, and dystrophic calcification.[2] Children under 10 years of age at the time of irradiation have been found to be at greatest risk.[1,4,5,9]

Four of six patients in our series who received cranial

irradiation for medulloblastoma when they were younger than 10 developed cerebral calcification in the anteromedial region of the temporal lobe. Their clinical course and radiographic features were so similar to those reported in patients with ALL that we believe the pathogenetic mechanism of calcification seen in both groups is similar. We suggest that local tissue anoxia secondary to irradiation-induced vascular injury resulted in the cerebral calcification manifested by some of our patients.

All six patients in our series manifested poor performance in school following completion of treatment. The three who underwent detailed neuropsychologic assessment achieved subnormal scores (Table). Unfortunately, serial assessments were not carried out on these patients and none underwent pre- and posttreatment assessments. Nevertheless, they clearly demonstrated learning impairment and had significant difficulties in school. The cause of their learning disabilities is not clear. Possible etiologic factors include the effects of the tumor, operative procedures, chemotherapy, or cranial irradiation, and increased intracranial pressure.

Given the time over which the learning disabilities developed, it is unlikely that the tumor itself was a major causative factor. Increased intracranial pressure may have been a factor; however, this has not been shown to affect long-term intellectual capacity.[10] None of our patients received chemotherapy; therefore, chemotoxic effects played no role in their deficits. The surgical procedure used in our patients was limited to the posterior fossa. Consequently, any effect of surgery on higher functions should have been minimal. Indeed, children with cerebellar astrocytoma who underwent surgical procedures similar to those of the patients in our series, but who did not receive cranial irradiation, developed no significant learning disabilities.[11,12] Thus, cranial irradiation appears to be the major cause of intellectual impairment in these children. This finding has been confirmed by other studies.[13]

A strong association between postirradiation cerebral calcification and the development of learning disabilities has been demonstrated in children.[5,8] Cranial irradiation plays a major role in both processes.[3,5,6,11] Calcification in the region of the hippocampus is a known sequela of hypoxia.[14] Furthermore, the hippocampus is known to be selectively vulnerable to hypoxia.[15-17] Consequently, in posthypoxic states, cerebral damage is usually concentrated in the hippocampus.[18,19]

Studies have shown that in patients with disorders of memory and learning, the essential lesion involves the hippocampus.[20] Histologically, the brains of such patients demonstrate vascular changes similar to those found in children who have received cranial irradiation.[15,21,22] The extent of intellectual impairment parallels the extent of hippocampal damage.[23] The common features in these patients, as in patients who have received cranial irradiation, are the microvascular changes resulting in hypoxic damage, most prominent in the region of the hippocampus.[15,21,24]

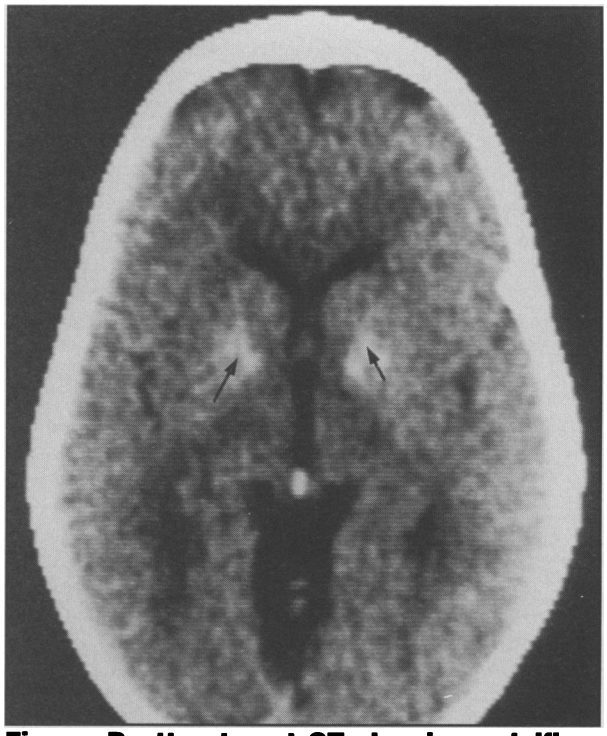

Figure. Posttreatment CT showing calcification in the medial temporal lobe (arrows).

We suggest that development of temporal lobe calcifications and learning disabilities following cranial irradiation are pathogenetically similar. We hypothesize that irradiation-induced vasculopathy results in hypoxia; the resulting injury is most severe in the region of the hippocampus. This injury can be manifested radiographically as cerebral calcification and clinically as impairment of memory and learning. A program to produce data to support this hypothesis has been instituted.

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