Acta Oncologica Vol. 35, No. 6, pp. 659–663, 1996

PATHOGENESIS OF IRRADIATION-INDUCED COGNITIVE DYSFUNCTION

OLUBUNMI K. ABAYOMI

Neurocognitive dysfunction is a common sequela of cranial irradiation that is especially severe in young children. The underlying mechanisms of this disorder have not been described. The present review describes the role of the hippocampus and the anatomically related cortex in memory function and its marked susceptibility to ischemic and hypoxic injury. Based on studies of animal models of human amnesia and histopathological findings in the irradiated brain, the neurocognitive sequela of cranial irradiation can be seen to be mediated through vascular injury, resulting in ischemia and hypoxia in the hippocampal region. Recognition of the site and mechanisms of this injury may lead to the development of techniques to minimize the risks.

Cognitive dysfunction is a major sequela of cranial irradiation (1–5). Although the prevalence of this injury is difficult to determine, the incidence is substantial and younger children are particularly susceptible (6). This problem is well recognized among children who received cranial irradiation for acute lymphoblastic leukemia and solid brain tumors (7, 8) and has led to changes in the use of radiotherapy in the management of children presenting with leukemia and brain tumors. Furthermore, there are new reports implicating irradiation of extracranial malignancies such as carcinoma of the nasopharynx as a causative factor in the development of cognitive disorders (9, 10).

While cranial irradiation is believed to be the major cause of post-treatment intellectual deterioration, (11–15) the pathogenetic mechanisms of this disorder have not been described. A review of the pathophysiology of memory and learning suggests that the site of injury is the medial temporal lobe cortex and that cranial irradiation-induced vascular damage, characterized by intimal proliferation and narrowing of the lumen with resultant ischemia and hypoxia, results in impairment of memory and learning (16–18).

The purpose of this review is to describe the mechanisms of development of irradiation-induced cognitive dysfunction. An understanding of the pathogenetic mechanisms may make possible the development of techniques of irradiation that will prevent or reduce the incidence and severity of this sequela.

The nature of vascular irradiation damage

The target cells in the walls of blood vessels for radiation effects are the endothelial cells and smooth muscle cells (19). Studies of irradiated vessels have shown that there is at first a dose-dependent reduction in the number of endothelial cell nuclei followed by an attempt at endothelial regeneration (19–22). This is manifested by the appearance of groups of endothelial cells which partially or totally occlude the lumen of the vessel. The other target cells, the smooth muscle cells, also manifest a dose-related atrophy of the muscle cells at varying time intervals following irradiation. This results in hyaline and fibrinoid changes which lead to alterations in the vascular architecture (23). The consequence of these changes is the occlusion or reduction in the luminal diameter of the vessels and a reduction in the size of the capillary bed. These characteristic histopathological changes have been observed in the irradiated brain (24, 25), and have been found to be most pronounced in the hippocampal region, where the vasculo-occlusive changes result in ischemia and hypoxia (23).

Received 5 December 1995.
Accepted 6 June 1996.
From the Department of Radiation Oncology, Howard University Hospital, Washington, D.C., USA.
Correspondence to: Dr Olubunmi K. Abayomi, Department of Radiation Oncology, Howard University Hospital, 2041 Georgia Avenue, N.W., Washington, D.C. 20060, USA.
Fax: (202) 865-1723.

 ISSN 0284-186X

The consequences of vascular damage in the medial temporal lobe

The importance of the hippocampal region for normal memory was first elucidated in 1957 by Scoville & Milner (16). They found that patients who underwent bilateral medial temporal lobe resection, extensive enough to damage portions of the hippocampus manifested a persistent disturbance of memory. There was a correlation between the extent of destruction to the hippocampal complex and the degree of memory impairment. The role of the hippocampus in memory was further confirmed by a study of an amnesic patient who, after an episode of global ischemia, developed severe memory impairment in the absence of other cognitive dysfunction. At autopsy, histological examination of the brain revealed circumscribed bilateral lesions involving the hippocampus. Moreover, investigations of amnesic patients using high resolution magnetic resonance imaging (MRI) have shown that these patients exhibit shrunken and atrophic hippocampal region, thus demonstrating the association of damage to the hippocampus and disorders of memory (26).

The availability of an animal model of human amnesia has made it possible to carry out systematic investigations of the anatomical structures important for memory (27, 28). Monkeys subjected to global ischemia demonstrated a marked vulnerability of the hippocampus to ischemia and were found to develop bilateral cell loss in the CA1 field of the hippocampus. On tests of memory function these monkeys performed similarly to monkeys with surgically produced damage to the hippocampus (29).

Furthermore, bilateral lesions of the medial temporal lobe that approximate the damage sustained by an amnesic patient have been produced in monkeys (30, 31). On testing, these monkeys exhibited severe impairment on a number of memory tasks. This lesion reproduced many features of memory impairment suffered by the amnesic patient. Other studies employing a direct surgical approach to the hippocampus using a combination of stereotactic neurosurgery and MRI have provided further evidence for the specific role of the hippocampus in memory function (32). These investigations provide a clear demonstration of the importance of the hippocampus as the major component of the medial temporal lobe memory system, and its susceptibility to ischemic damage.

Mechanisms of irradiation-induced cognitive dysfunction

Largely on the basis of studies of irradiated brains and investigations in monkeys and rodents subjected to global ischemia, the hypothesis is presented that postirradiation cognitive dysfunction results from ischemic damage to the hippocampus. Evidence in support of this hypothesis builds on the findings that the irradiated brain manifests histopathological changes that closely mimic those found in the brain following global ischemia (18, 24, 33). These changes are most pronounced in the hippocampal region, an area believed to be crucial for memory and learning. Moreover, patients with hypoxic-ischemic brain injury manifest several neuropsychological features, in common with patients with postirradiation cognitive dysfunction. These similarities suggest very strongly that the pathogenetic mechanisms of postirradiation cognitive impairment are similar to those that follow global ischemia. Studies from a rodent model of global ischemia are also consistent with this view (19).

Indirect evidence suggesting the medial temporal lobe cortex as the site of injury responsible for postirradiation cognitive deterioration has been provided by the observation that some long-term survivors following irradiation for cancer of the nasopharynx manifest intellectual impairment (10, 35). When these patients were given a battery of tests to assess their intellectual function, they showed significant cognitive deficits in recall of general information from memory, impaired comprehension, and impaired analytic and abstract thinking. Some of these patients on follow-up brain computed tomography (CT) manifested hypodense areas in the inferomedial region of the temporal lobe. One of these patients who underwent a post mortem examination demonstrated the characteristic histopathological features of delayed vascular irradiation damage, most prominent in the medial temporal lobe region. On review of the treatment portals for these patients it was found that the common feature among the group of patients manifesting post-irradiation cognitive impairment, was the inclusion of the infero-medial portion of the temporal lobes in the high dose volume. Since none of these patients received chemotherapy and none showed signs of recurrent disease it was concluded that the cause of the sequela of cognitive dysfunction was irradiation damage to the medial temporal lobe.

Furthermore, a study carried out on a cohort of patients treated for carcinoma of the nasopharynx detected CT abnormalities in the temporal lobes of patients whose temporal lobes could not be shielded because of the extent of disease. Some of these patients manifested deterioration of memory and had CT abnormalities that corresponded to the volume of temporal lobe included within the target volume. In contrast, the patients whose treatment techniques did not include the temporal lobes in the high-dose volume did not develop this complication (36).

Clinical implications

As a result of the increasing realization of the severity of neurocognitive sequela of cranial irradiation there has been a major shift away from employing irradiation in the management of brain tumors in children (37). In infants and very young children with medulloblastoma there is a move to delay or omit irradiation (37–39). These children

are treated postoperatively with chemotherapy, and may receive cranial irradiation when they are older and therefore considered less susceptible to radiation-induced neurocognitive impairment. Though chemotherapy has been shown to be effective in treating medulloblastoma, it lacks the long standing track record of efficacy established by irradiation. There is thus a danger that the omission, or delay, in the use of irradiation for medulloblastoma may be detrimental to the treatment outcome in these patients (40, 41).

Recognition of the site and the underlying mechanisms of the injury responsible for the neurocognitive dysfunction that follows cranial irradiation may lead to the design of treatment techniques that will minimize the risk of this sequela. Thus, treatment fields and techniques can be selected such that the dose to the medial temporal lobe region is reduced. This can be effected by decreasing the dose to supratentorial structures in patients in whom total tumor resection has been achieved while delivering full dose to the posterior fossa. To decrease the late neuropsychometric morbidity associated with cranial irradiation, attempts have been made to exclude the supra tentorial structures from the radiation field or to reduce the dose to this area while maintaining the dose to the posterior fossa. Tomita & McClone (42) reported that a reduction in dosage to the supratentorium in selected patients with medulloblastoma was not associated with increased recurrence. However, other large studies have demonstrated an increase in relapse rates when total neuraxis dose was reduced (43, 44). Thus it appears that the conventional dose to the brain should be maintained while studies are carried out to determine the optimum dose to the supratentorium for tumor control, and the feasibility of lowering the dose without compromising tumor control. There are reports on children who received cranial irradiation for acute lymphoblastic leukemia and primitive neural ectodermal tumors demonstrating dose dependent declines in intelligence quotient (IQ), with children receiving 32–40 Gy to the whole brain manifesting more severe decline in IQ than those who received 18–24 Gy. (45) Furthermore, there is experimental evidence suggesting that the severity and extent of vascular irradiation damage is dose-dependent (23). Partial shielding of the medial temporal lobe to decrease the dose many lower the severity of neurocognitive sequela without increasing the risk for tumor recurrence.

A new technique of treatment suggested for reducing the neurocognitive sequelae of cranial irradiation for childhood medulloblastoma is the use of the partial transmission block which allows the whole brain and the posterior fossa to receive the desired target dose but with reduced fraction size (46, 47). Preliminary results appear promising; whether this technique will result in improved neurocognitive sequelae while maintaining a high tumor control rate remains to be seen.

In the management of other brain tumors, techniques designed to deliver high dose in the tumor volume while sparing the temporal lobe may reduce the incidence of neurocognitive dysfunction. The availability of improved imaging techniques such as high resolution CT and MRI, and the use of conformal radiotherapy techniques should make it possible to deliver the required curative dose to the tumor volume and spare the temporal lobe from the high dose-volume. Moreover, recognition of the susceptibility of the temporal lobe to radiation damage should lead to increased attempts to shield it or exclude it from the high dose volume when irradiating tumors of the pituitary region, the nasopharynx and paranasal sinuses (47).

Summary

Survivors of cranial irradiation manifest severe neurocognitive dysfunction which has a profound effect on the quality of their survival. This has led to a major shift away from using radiotherapy, a modality of proven efficacy in the management of brain tumors. The availability of animal model of human amnesia has made possible investigations of the anatomical structures important for memory. These are located in the medial temporal lobe and consist of the hippocampus together with adjacent anatomically related cortex. Studies have shown that the hippocampus is profoundly sensitive to ischemia and hypoxia. These studies strongly suggest that ischemic damage to the hippocampus impairs memory function in monkeys as it does in humans. Furthermore, there is evidence to suggest that the pathogenetic mechanism of postirradiation intellectual impairment is similar to that following global ischemia and that irradiation damage is mediated through vascular changes which result in ischemia and hypoxia in the hippocampal region. Recognition of the site and mechanism of injury has the potential to lead to the development of techniques that will spare the structures important for memory functions thus reducing the neurocognitive sequela of cranial irradiation. This may lead to a reassessment of policies modifying the role of irradiation in the management of brain tumors in children.

REFERENCES

1. Ellenberg L, McComb JG, Sigel SE, Stowe S. Factors affecting intellectual outcome in pediatric brain tumor patients. Neurosurgery 1987; 21: 638–44.
2. Fogarty K, Volonino V, Caul J, et al. Acute leukemia: Learning disabilities following CNS irradiation. Clin. Pediatr. 1988; 27: 524–8.
3. Moore IM, Kramer JH, Wara W, Halberg F, Ablin AR. Cognitive function in children with leukemia: Effect of radiation dose and time since irradiation. Cancer 1991; 68: 1913–7.
4. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychological performance of children surviving leukemia who received 18 Gy, 24 Gy or no cranial irradiation. J Clin Oncol 1991; 9: 1348–56.

5. Suc E, Kalifa C, Brauner R, et al. Brain tumors under age of three: The price of survival. A retrospective study of 20 long-term survivors. Acta Neurochir (Wien) 1990; 106: 93–8.
6. Jannoun L. Are cognitive and educational development affected by age at which prophlactic therapy is given in acute lymphoblastic leukemia? Arch dis Child 1983; 58: 953–8.
7. Eiser E. Intellectual abilities among survivors of childhood leukemia as a function of CNS irradiation. Arch Dis Child 1978; 53: 391–5.
8. Twaddle V, Britton PG, Craft AC, Noble TC, Kernahan J. Intellectual function after treatment for leukemia or solid tumors. Arch Dis Child 1983; 58: 949–52.
9. Lee AWN, Ng SH, Tse VK, Chin HM, Thaw MYO. Bilateral temporal lobectomy for necrosis induced by radiotherapy for nasopharyngeal carcinoma. Acta Oncol 1993; 32: 343–7.
10. Woo E, Lam K, Yu YL, Ma J, Wang C, Yeung RTT. Temporal lobe and hypothalamic—Pituitary dysfunctions after radiotherapy for nasopharyngeal carcinoma: A distinct clinical syndrome. J Neurol Neurosur Psychiatry 1988; 51: 1302–7.
11. Hoppe-Hirsch E, Renier D, Lellouch-Tubiana A, Sainte-Rose C, Hirsch JF. Medulloblastoma in childhood: Progressive intellectual deterioration. Childs Nerv Sys 1990; 6: 60–5.
12. Packer RJ, Sutton LN, Atkins TE, et al. A prospective study of cognitive function in children receiving whole brain radiotherapy and chemotherapy: 2 years' result. J Neurosurg 1989; 70: 707–13.
13. Raimondi AJ, Tomita T. The disadvantages of prophylactic whole CNS postoperative radiation therapy for medulloblastoma. In: Paoletti P, Walker MD, Butti G, Knerich R, eds. Multi-disciplinary aspects of brain tumor therapy. Amsterdam: Elsevier/North Holland Biomedical Press, 1979: 209–18.
14. Riva D, Pantaleoni C, Milani N, Belani FF. Impairment of neuropsychological functions in children with medulloblastomas and astrocytomas in posterior fossa. Childs Nerv Syst 1989; 5: 107–10.
15. Cousens P, Waters B, Said J, Stevens M. Cognitive effects of cranial irradiation in leukemia. A survey and metanalysis. J Child Psychol Psychiatry 1988; 29: 839–52.
16. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiat 1957; 20: 11–7.
17. Squire LR, Zola-Morgan S. The medial temporal memory system. Science 1991; 253: 1380–6.
18. Volpe BT, Hirst W. The characterization of an amnesic syndrome following hypoxic ischemic injury. Arch-Neurol 1983; 40: 436–40.
19. Van Der Kogel AJ. Radiation induced damage in the central neurous system: An interpretation of target cell responses. Br J Cancer 1986; 53 (Suppl. VII): 207–17.
20. Hopewell JW, Wright EA. The nature of latent cerebral irradiation damage and its modification by hypertension. Br J Radiol 1970; 43: 161–7.
21. Myers R, Rogers MA, Hornsey S. A reappraisal of the roles of glial and vascular elements in the development of white matter necrosis in irradiated rat spinal cord. Br J Cancer 1986; 53 (Suppl. VII): 221–3.
22. Yeung TK, Hopewell JW. Histological and physiological studies on rat heart following irradiation with single doses of x-rays. Br J Cancer 1986; 53 (Suppl. VII): 196–8.
23. Hopewell JW, Campling D, Calvo W, Reinhold HS, Wilkinson JH, Yeung TK. Vascular irradiation damage: Its cellular basis and likely consequences. Br J Cancer 1986; 53 (Suppl. VII): 181–91.
24. Woo E, Chan Y, Lam K, Lok ASF, Y, Huang C. Apoplectic intracerebral hemorrhage: An unusual complication of cerebral radiation necrosis. Pathology 1987; 19: 95–8.
25. Crompton MR, Layton DD. Delayed radionecrosis of the brain following therapeutic x-radiation of the pituitary. Brain 1961; 84: 85–101.
26. Press GA, Amaral DG, Squire LR. Hippocampal abnormalities in amnesic patients revealed by high resolution magnetic resonance imaging. Nature 1989; 341: 54–7.
27. Mishkin M, Spiegler J, Saunders RC, Malamut BJ. Toward a treatment for Alzheimers Disease. In: Corkin S. Davis KL, Crowdon JH, Usdim EJ, Wurtman RJ, eds. New York: Raven Press 1982: 235–47.
28. Mishkin M. Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. Nature 1978; 273: 297–98.
29. Volpe BT, Pulsinelli WA, Tribuna J, Davis HP. Behavioral performance of rats following transient forebrain ischemia. Stroke 1984; 15: 558–62.
30. Zola-Morgan S, Squire LR, Mishkin, M. Neuroanatomy of amnesia: Amygdala-hippocampus vs temporal stem. Science 1982; 218: 1337–9.
31. Zola-Morgan S, Squire LR. Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. Behav Neurosci 1985; 99: 22–34.
32. Alvarez-Royo P, Clower RP, Zola-Morgan S, Squire LR. Stereotactic lesions of the hippocampus in monkeys: Determination of surgical coordinates and analysis of lesions using magnetic resonance imaging. J Neurosci Methods 1991; 38: 223–32.
33. Squire LR, Amaral DG, Press GA. Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. J Neurosci 1990: 3106–17.
34. Deck MDF. Imaging techniques in the diagnosis of radiation damage to central nervous system. In: Crilbert HA, Kagan AR, eds. Radiation damage to the central nervous system: A delayed therapeutic hazard. New York: Raven Press 1980: 107–27.
35. Lee PWH, Hung BKM, Woo EKW, Tai PTH, Choi DTK. Effects of radiation therapy on neuropsychological functioning in patients iwth nasopharyngeal carcinoma. J Neurol Neurosurg Psychiatry 1989; 52: 488–92.
36. Leung SF, Kreel L, Tsao SY. Asymptomatic temporal lobe injury after radiotherapy for nasopharyngeal carcinoma: Incidence and determinants. Br J Radiol 1992; 65: 710–4.
37. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 1993; 328: 1725–31.
38. Loeffler J, Kretschmar SC, Sallan SE, et al. Preirradiation chemotherapy for infants and poor prognosis children with medulloblastoma. Int J Radiat Oncol Biol Phys 1988; 15: 177–81.
39. Geyer R, Zeltner P, Finlay J, et al. Chemotherapy for infants with malignant brain tumors. Report of the children cancer study group trials CCG 921 and CCG 945. Proc Am Soc Clin Oncol 1992; 11: 1259.
40. Brunat-Mentigny M, Bernard J, Tron P, et al. The treatment of medulloblastoma with surgery, chemotherapy, and radiation therapy limited to the posterior fossa and the spinal cord. Proc International Soc Pediatric Oncology 1986; 58–9.
41. Attard-Montalto S, Plowman N, Breatnach F, Saha V, Eden OB. Is there a danger in delaying radiotherapy in childhood medulloblastoma? Br J Radiol 1993; 66: 807–13.
42. Tomita T, McClone DG. Medulloblastoma in childhood:

Results of radical resection and low dose neuraxis radiation therapy. J Neurosurg 1986; 64: 238–49.
43. Deutsch M. Thomas P. Boyett J, et al. Low stage medulloblastoma. A childrens cancer study group (CCSG) and pediatric oncology group (POG) randomized study of standard versus reduced neuraxis irradiation (Abstr). Proc Am Soc Clin Oncol 1991; 10: 124.
44. Gnekow AK, Bailey CC, Michaelis J, et al. SIOP/GPO medulloblastoma trial II. Medical 84 Annual Status Report. Med Pediatr Oncol 19, 435 (Abstr.).
45. Silber JH, Radcliffe J, Peckham V, et al. Whole brain irradiation and decline in intelligence: The influence of dose and age on IQ score. J Clin Oncol 1992; 10: 1390–6.
46. Plowman PN, Doughty D. An innovative method for neuraxis radiotherapy using partial transmission block technique. Br J Radiol 1991; 64: 603–7.
47. Plowman PN. Partial transmission block radiotherapy technique for childhood medulloblastoma. Br J Radiol 1993; 66: 91–92.
48. Glass PJ, Hwang T, Leavens ME, Libshitz HI. Cerebral radiation necrosis following treatment of extracranial malignancies. Cancer 1984; 54: 1966–72.