Tumor Growth Rates

To The Editor: Such cases as the craniopharyngioma reported by Arginteanu, et al. (Arginteanu MS, Hague K, Zimmerman R, et al: Craniopharyngioma arising de novo in middle age. Case report. J Neurosurg 86:1046–1048, June, 1997) should be published more often so that we may accumulate some information about the early growth characteristics of human neoplasms.

Although craniopharyngiomas develop from a single layer of basal cells, which should establish a linear growth rate, it is not known whether this small layer of basal cells would probably establish a rate approaching the exponential expected of most solid neoplasms. Thus, “de novo in the sixth decade of life” could be refined by assuming some range of error in the magnetic resonance image obtained in January 1994; could a 1-mm pinhead have been missed, or perhaps even a 3-mm one?

Assuming that 10-μm cubic cells allow 20 doublings to produce a 1-ng mass (1 mm³) and 30 doublings to produce a 1-g mass (1 cm³), estimating the craniopharyngioma to be approximately 1.5 cm in diameter (just less than 4 g or 4 cm³ and 32 doublings) in April 1996 allows seven to 12 doublings in the 27-month interval between the two magnetic resonance images, allowing doubling times of 2 to 4 months and 20 to 25 doublings before the “origins” in 1986 (age 45 years) to 1991 (age 50 years).

Of course, we still do not know whether it was originally a congenital malformation, but at least we have some estimate of when it began to grow neoplastically.

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References

Response: We appreciate the interest in our article that Dr. Alvord demonstrated by his insightful comments. We agree with his assumptions regarding the imaging studies and doubling times. We also agree with his conclusion that the mass probably began to grow neoplastically several decades after the patient reached adulthood.

The reason we submitted the article for publication was to point out that a craniopharyngioma does not necessarily grow at a steady rate from intrauterine life. In this case it must have begun its growth during the patient’s adulthood. We believe future research should be directed toward the elucidation of the factor or factors that cause the onset of growth. We hope that this discovery might lead to treatments that would halt or reverse craniopharyngioma growth.

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Radiation-Induced Cavernous Malformation

To The Editor: The report by Larson and colleagues (Larson JJ, Ball WS, Bove KE, et al: Formation of intracerebral cavernous malformation after radiation treatment for central nervous system neoplasia in children. J Neurosurg 88:51–56, January, 1998) on the formation of intracerebral cavernous malformations in six children following radiation to the brain adds to our understanding of the natural history of this lesion and complements the recent work of others.1,3,14,22 It is now hard to deny that therapeutic doses of radiation to the brain following tumor resection play a role in the genesis of these lesions in both the pediatric and adult populations. However, such occurrences must be extremely rare.

In our experience with more than 500 central nervous system cavernous malformations, in both the pediatric and adult populations, we have yet to see a de novo lesion associated with radiation to the brain. We have seen a single de novo cavernous malformation in an adult woman after she underwent resection of an acoustic neuroma.2 However, there was no familial history and she did not receive radiation.

It would be useful to know the approximate number of pediatric patients at the University of Cincinnati who received brain radiation therapy during this study period. This would allow an approximation of the risk of de novo cavernous malformation in the pediatric population following brain irradiation.

It would also be helpful to know whether the authors had screened the patients to rule out the familial form of cavernous malformations, either by careful history or genetic testing.5,6,9,16,23 The de novo formation of cavernous malformations is quite frequent in the familial form of this disease. Zabramski, et al.,2 reported new lesions in six of 21 patients followed up by using serial magnetic resonance imaging for an average of only 2.2 years.

Based on the findings of capillary telangiectasia in resected lesions, the authors suggest that brain irradiation may induce capillary telangiectasia to evolve into a cavernous malformation. The idea of capillary telangiectasias and cavernous malformations as part of a continuum of the same disease is not new.11,17,18,20,22 It seems just as likely that the vascular malformations in these patients arise as a result of radiation-induced genetic mutation. The familial form of cavernous malformations has been linked to an autosomal dominant genetic mutation on the long arm of chromosome 7.3,5,9 The sporadic occurrence of this disease may arise from a similar mutation in a somatic cell line. Support for this concept comes from the finding that similar genetic mutations have been identified in both the hereditary and sporadic forms of hemangioblastomas.12,21 The relatively common occurrence of sporadic cavernous malformations in the general population suggests that the genetic site responsible for this disease is a hot spot for mutational activity.

Hereditary hemorrhagic telangiectasia is a familial form of capillary telangiectasia associated with the delayed
occurrence of high-flow fistulas and arteriovenous malformations but not with cavernous malformations. Hereditary hemorrhagic telangiectasia has been linked to multiple genetic mutations affecting the various receptors for transforming growth factor-β.2 Σomatic cell mutations in the same receptor system may be responsible for the sporadic formation of these lesions, which are frequently seen following exposure to various types of ionizing radiation.

Finally, it appears that radiation-induced cavernous malformations represent a subset of these lesions demonstrating a more aggressive behavior than that of cavernous malformations in patients who have not received radiation therapy. In the series of 145 patients with intracerebral cavernous angiomas reported by Pozzati and colleagues,13–15 18 patients exhibited especially aggressive lesions. Of this subgroup, six were documented de novo lesions, with five attributed to previous irradiation of the brain. In the present paper by Larson and coworkers, the study group was small; however, the rate of symptomatic hemorrhage could be used to buttress this argument. If the assumption is made that all lesions were present from the time of birth (the classic assumption)8,9,10,19 and that full brain irradiation led to the induction of a clinically symptomatic lesion, the calculated risk of hemorrhage was 3.6% per year. If the assumption is made that all lesions occurred de novo at the time of radiation therapy, the risk of hemorrhage increases to 6.7% per year. If they formed later, which is the likely scenario, the hemorrhage rate would be even greater. Regardless of formulation, these values are higher than the 0.25 to 0.7% per year risk of hemorrhage cited in the literature.19

References


RESPONSE: We appreciate the comments of Drs. Detwiler, Porter, Zabramski, and Spetzler concerning our report on cavernous malformations. Their work in this area is well recognized.2

The occurrence of a de novo cavernous malformation following brain irradiation is a rare yet significant problem. We cannot calculate its exact incidence because not all of the patients in our series received radiation treatment at the University of Cincinnati. Some patients were referred to our institution after undergoing radiation treatment at another institution.

All patients in our series were screened carefully to rule out a family history of cavernous malformations. Genetic testing was not performed. It is our understanding that there may be genetic heterogeneity among cerebral cavernous malformations, as demonstrated by varying linkage patterns among kindreds.1

The clinical dilemma of a de novo lesion in a child who has been treated with radiation therapy for central nervous system neoplasia lies in the diagnosis and treatment of these lesions. The possibility of a cavernous malformation as well as that of a neoplastic process must be considered.
Surgical resection of such a lesion or close observation with follow-up magnetic resonance imaging studies is recommended. Detwiler, et al., are accurate in pointing out our finding that radiation-induced cavernous malformations represent a subset of these lesions with an aggressive behavior. In our series, there was an increased risk of clinically significant hemorrhage in the radiation-induced cavernous malformations compared with cavernous malformations in patients who had not received radiation treatment. This observation may lend support to the surgical treatment of lesions that have a more aggressive natural history.

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References

Medullary Compression and Hypertension

TO THE EDITOR: We read with great interest the recent article by Colón, et al. (Colón GP, Quint DJ, Dickenson LD, et al: Magnetic resonance evaluation of ventrolateral medullary compression in essential hypertension. J Neurosurg 88:226–231, February, 1998). In this report, the authors conducted a blinded prospective study in which magnetic resonance (MR) imaging was used to evaluate the role of lateral medullary compression in essential, or neurogenic, hypertension. Thirty patients with hypertension and 45 controls underwent thin-slice MR imaging of the posterior fossa and skull base for comparison by four blinded, independent reviewers. The authors concluded that although there was a tendency toward left vertebral artery dominance in the group with hypertension, no differences between the two groups were observed regarding brainstem compression or rotation.

As the authors point out, these results differ from other series in the literature. Morimoto and colleagues1 demonstrated a 74% rate of medullary compression detected by thin-slice MR imaging. Naraghi and colleagues2 demonstrated even higher rates of brainstem compression in neurogenic hypertensive patients at 83% and 91%, respectively. Despite these studies, we concur with the criticisms by Meaney, et al.,3 concerning the sensitivity of MR imaging in which 3-mm slices are used. Medullary compression due to smaller vessels, such as the posterior or anterior internal carotid artery, may be missed by using this technology. Furthermore, as Colón, et al., maintain, medullary compression is a matter of degree, and conventional MR technology at present may be insufficiently sensitive to detect only marked brainstem compression.

In their paper, Colón, et al., suggest “perhaps only large associated deformities result in hypertension,” and that “subtle vascular contiguity or compression is not the culprit.” Based on our operative experience, we cannot agree with this hypothesis. We are reporting on 12 patients with severely uncontrolled, medically refractory neurogenic hypertension (without any other cranial nerve rhizopathies) treated with microvascular decompression of the left lateral medulla.3 All 12 patients had preoperative MR imaging of the brain, with special attention to the posterior fossa and skull base. Although all patients had clear intraoperative demonstration of medullary compression, only three (25%) had preoperative MR demonstration of medullary compression. The vertebral artery was the offending vessel in two of the patients, and a large posterior internal carotid artery was the offending vessel in the third. For the remaining nine patients, preoperative MR imaging demonstrated dolichoectatic basilar arteries in two patients, severe vertebrobasilar artery tortuosity and displacement in two patients, and was unremarkable in the remaining five patients. However, left medullary compression by one or more arteries was clearly seen intraoperatively in all 12 patients.

We are not surprised by findings such as those of Colón, et al., and Watters, et al., because we too were only able to show a 25% rate of medullary compression in a severely hypertensive (mean peak systolic pressures 212 mm Hg) population with intraoperative evidence of medullary compression. Our operative experience agrees with their conclusions that thin-slice MR imaging is not a good screening tool to identify patients with neurogenic hypertension. Symptomatic compression, however, is not limited to only the large brainstem deformities evident on thin-slice MR imaging. Furthermore, patients with subtle vascular compression detectable only by thin-slice MR imaging or surgical exploration may be the most promising candidates for improvement following microvascular decompression. Only with prospective investigation and rigorous outcome criteria will we be able to identify the population who can benefit most from microvascular decompression of the lateral medulla. We have recently embarked on such a study.

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