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Editorial

Natural history of neurofibromatosis Type 2 tumors

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I have been asked to write a short editorial on the excellent paper on the natural history of intracranial tumors associated with neurofibromatosis Type 2 (NF2) in this issue of the *Journal of Neurosurgery*.[2] Although the study is based on only 17 patients, the duration (mean 9.5 years, range 4–20.7 years) and quality of the follow-up (all patients were followed up with sequential MRIs either done or reviewed at the Clinical Center of the National Institutes of Health [NIH]) make up for the relatively small sample. In addition, as expected, these 17 patients harbored a large number of intracranial tumors, making it possible to separately analyze the rate of growth and the growth pattern of 18 vestibular schwannomas (VSs), 11 nonvestibular cranial nerve (CN) schwannomas, and 135 intracranial meningiomas. From this group's careful analysis, we obtained solid confirmation of some previously suspected concepts, and some new concepts have emerged as well.

The study confirms the previously suspected notion that VSs associated with NF2 behave more aggressively than their sporadic counterparts. While we know that sporadic VSs frequently do not grow over extended periods of follow-up, particularly when they are small,[4] all VSs in the present series grew over the follow-up, and their overall growth rate (0.6 cm^3/year) appears to be at the upper limit of what has been previously reported for sporadic VSs. Neurofibromatosis Type 2–associated intracranial meningiomas also appear to behave more aggressively than their sporadic counterparts. While we know from several previous series in the literature that some meningiomas, perhaps as many as 37%, do not grow,[3] essentially all intracranial meningiomas in the present study grew during the follow-up period. Overall, they do grow at approximately the same rate as their sporadic counterparts. Moreover, the authors' study confirms that, as suspected, female sex and younger age are associated with a more rapid rate of growth in NF2-associated meningiomas. They also confirm that the growth of new intracranial tumors, both meningiomas and schwannomas, occurs in most patients with NF2 followed up for a significant period of time; new intracranial tumors, mostly meningiomas, developed during the follow-up in 64.7% of the patients in their study.

One of the most important previously suspected concepts that this study corroborates is that NF2-associated intracranial tumors, both schwannomas and meningiomas, seem to be less sensitive to stereotactic radiosurgery (SRS) than their sporadic counterparts. All 7 VSs treated with SRS displayed continuous radiographic progression over the follow-up period, and 4 of these lesions required resection for progressive symptomatology. The 2 meningiomas treated with radiosurgery also displayed progressive growth within 4 years, but they did not require surgery since they did not result in progressive symptomatology. As discussed by the authors, several radiosurgical series in the literature have suggested better results, but the follow-up time was shorter. This relative unresponsiveness to SRS is disappointing, because obviously in these patients with multiple intracranial tumors, that treatment modality would appear ideal for small tumors if it were effective.

Some new, previously unsuspected concepts emerged from the current study. The first is that NF2-associated nonvestibular CN schwannomas seem to behave a bit better than their vestibular counterparts. Whereas all VSs in this series grew over the follow-up period, only 9 of the 11 nonvestibular CN schwannomas grew, and they grew at a rate slower than their vestibular counterparts (0.2 vs 0.6 cm^3/year for vestibular tumors). Perhaps the most important new finding from this study is that the majority of these NF2 intracranial tumors grew in a "saltatory" pattern, with periods of growth alternating with quiescent periods (60.9% of meningiomas, 46.7% of VSs, and 55.6% of nonvestibular CN schwannomas in this study exhibited a saltatory pattern of growth). It is interesting that this saltatory growth pattern is also typical of hemangioblastomas associated with Von Hippel-Lindau disease, as has been reported by the NIH group in the past.[1] The clinical implications of this finding are clear. One must exercise caution in interpreting the response rate to therapies such as SRS or external beam radiotherapy over a short period of time since the lack of growth for as long as several years can simply be a part of the natural history of these tumors. Even more importantly, these tumors should not be surgically treated simply because they exist, because they may not grow for considerable periods of time. In a disease characterized by the presence of multiple intracranial tumors, the advice of these authors—to operate only on tumors that are progressively symptomatic—seems particularly appropriate. The authors go further in warning that tumor progression alone, without the development of progressive symptoms, should not be used as an indication for surgery. They calculated that if each tumor that had shown growth in their study had been surgically treated, there would have been an additional 9 unnecessary resections for each patient over the study period.

Finally, this excellent and important study should reinforce the value of careful, disease-specific, NIH-sponsored studies such as this one, in which patients with devastating hereditary conditions, such as Von Hippel-Lindau disease and NF2, are followed prospectively and systematically for long periods of time at the Clinical Center of the NIH. The volume of data obtained by the neurosurgical group at the NIH on Von Hippel-Lindau disease in the past and now on NF2 has contributed greatly to our understanding of these diseases and our ability to provide better care for our patients.

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Disclosure

The author reports no conflict of interest.

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Response

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We appreciate Dr. Heros' insightful comments regarding our study in which we analyzed the long-term natural history of NF2-associated intracranial tumors in a consecutive series of patients. Dr. Heros' editorial highlights the critical biological features of NF2-associated neoplasms found in this patient population, as well as the cardinal differences in managing these tumor types in patients with NF2 as compared with treating patients with histologically similar sporadic tumors.

Most patients with NF2 will harbor multiple tumors of various histological types and locations; therefore, a defined understanding of their spectrum of clinical behavior is requisite to optimizing a management paradigm. A critical feature that impacts the timing of intervention and the assessment of treatment outcome is the saltatory growth pattern associated with most NF2-associated tumors.

Because MRI only illustrates the antecedent growth rate and/or growth pattern of NF2-associated tumors and does not predict future tumor behavior, the need for treatment cannot be substantiated by the identification of a growing tumor alone. Based on our findings, cautious expectant management and resection when early symptoms appear currently constitute the optimal management paradigm for NF2-associated tumors. Prophylactic resection of growing but asymptomatic tumors will lead to additional unnecessary surgeries over a finite period of time. Additionally, the use of radiosurgery to avoid potential cumulative surgical morbidity must be tempered by the facts that this treatment modality appears to be less effective for NF2-related tumors and that many tumors can remain asymptomatic over a patient's lifetime despite radiographic progression.

Because of NF2-related tumor growth characteristics (frequent saltatory pattern of growth characterized by long periods of growth quiescence), outcomes for nonsurgical interventions (chemotherapy or radiosurgery) may need to exceed simple cessation of tumor growth to be considered successful. Further, these therapies will only be best evaluated after long-term follow-up (> 5 years), as extended periods of tumor growth cessation are a hallmark of these tumors.

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