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Management of Low-Grade Gliomas in Childhood

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In this month's issue of *World Neurosurgery*, Ali et al.¹ present their institutional experience with expectant management for children with incidentally detected presumed low-grade gliomas. Despite a paucity of data in the literature regarding how to manage such children, this is a surprisingly common clinical scenario, and the rarity of reports may well reflect that in the absence of histological confirmation of the identity of the lesion, the diagnosis of a low-grade glioma is inferential at best.

In considering how to apply these results, it is important to bear in mind that low-grade gliomas encompass several histological subgroups of tumors, including pilocytic astrocytomas, which are classified as grade I lesions, and fibrillary and pilomyxoid astrocytomas, which are considered grade II lesions, and that optimal management is influenced by lesion location, size, and mode of presentation. Most childhood low-grade gliomas come to clinical attention because of symptoms, such as seizures or headaches, and are generally sizeable at diagnosis, which contrasts with the incidental detection in the current series. The current management for pediatric low-grade gliomas in general, summarized below, thus differs significantly from the situation considered in this report.

For sizeable, superficial, well-circumscribed lesions in the cerebral or cerebellar cortex, surgical resection remains the treatment of choice. A recent report of a large cooperative group natural history study (CCG9891/POG8930) strongly supported this perspective, demonstrating that the factor most significantly associated with outcome in childhood low-grade gliomas was the extent of surgical tumor removal¹⁶. Five-year progression-free survival was more than 90% in children with low-grade gliomas that had undergone gross total resection, whereas approximately half of children with less extensive resections had disease progression during that interval¹⁶. Accordingly, a number of surgical adjuncts are sometimes used to facilitate tumor removal, such as image-guided tumor localization, functional brain mapping, neurophysiological monitoring, and intraoperative imaging, particularly for deep-seated lesions, such as thalamic tumors¹².

Given the strong association between resection extent and outcome, the existence of an independent association between histology and prognosis has been difficult to establish. Although pilocytic astrocytomas have had a better prognosis than fibrillary lesions in some series, this may reflect that pilocytic tumors, particularly when superficially located, are often better circumscribed and more amenable to gross total resection. Likewise, tumor

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location has a strong impact on outcome in that superficial lesions involving the cerebral and cerebellar cortices have a much better prognosis than deep lesions involving the basal ganglia, optic pathways, diencephalon, or brainstem¹⁶, which reflects that the former tumors are more amenable to gross total resection without excessive morbidity.

Because patients whose tumors have undergone gross total resection have a greater than 90% long-term survival rate, adjuvant therapy is usually not required^{3,4,14}. Such therapies are more commonly warranted for unresectable, deep-seated lesions, such as tumors arising from the hypothalamus and optic pathways, which are usually not amenable to complete removal because of their involvement of critical surrounding structures. Management of such tumors is further complicated by the fact that they commonly arise in young children, who are at high risk of side effects from large-field irradiation. Thus, whereas radiotherapy is a common initial adjuvant management approach in adults, chemotherapy is more often used initially in the pediatric setting, particularly in young children.

During the last two decades, several chemotherapy regimens have been found to have efficacy in delaying or avoiding the need for radiotherapy in children with progressive or incompletely resected low-grade gliomas thought to be at high risk of progression^{2,11}. The recently completed COG A9952 study involved a phase 3 randomized comparison between two active regimens, carboplatin and vincristine versus 6-thioguanine, procarbazine, lomustine, and vincristine, for low-grade gliomas arising in children without neurofibromatosis 1 (NF1) and a single-arm study of carboplatin and vincristine in children with NF1-related low-grade gliomas². Although both regimens had efficacy in delaying tumor progression, the results were slightly better with the lomustine-based regimen and significantly better in patients with NF1², reflecting the often indolent growth of NF1-associated low-grade gliomas. Most children without NF1 in both treatment arms suffered disease progression within five years of initial therapy, which calls attention to the need for new treatment options.

Accordingly, subsequent studies are evaluating other therapeutic approaches for these tumors, including agents such as vinblastine⁸, other combination chemotherapy regimens⁹, and antiangiogenic agents, such as lenalidomide¹⁵. In addition, recent studies have examined the efficacy of three-dimensionally tailored conformal radiotherapy in older children with progressive tumors and younger children who have had disease progression after chemotherapy¹⁰. With the recent discovery that the majority of pilocytic astrocytomas exhibit alterations in the *BRAF* gene, most commonly involving translocations between *BRAF* and *KIAA*, or activating mutations, such as *BRAF*^{v600E}, which induces growth signaling through MAP kinase-related pathways^{5,7,13}, significant interest has been focused on clinical trials of BRAF and MAPK pathway inhibitors, such as AZD6244, which have been launched for children with progressive tumors.

In summary, the management of low-grade gliomas continues to evolve based upon advances in surgery, chemotherapy, radiotherapy, and molecular biology, which highlights the question raised in the series of Ali et al.¹ – is there a drawback to watchful waiting in incidentally detected lesions that *may* be low-grade gliomas in childhood? The common characteristics of the authors' series were that the cases were all small, incidentally detected, nonenhancing, and asymptomatic. Because childhood low-grade gliomas typically have relatively slow growth and rarely transform into higher grade lesions, the risk/benefit profile of watchful waiting versus proactive intervention is somewhat different than in adult gliomas. Whereas a recent study identified a benefit to proactive management in adult low-grade gliomas⁶, which may reflect the greater likelihood of malignant transformation with observation alone, this concern would not apply equivalently to childhood tumors.

It is also important to emphasize that not all incidentally detected, small non-enhancing lesions that *may be* low-grade gliomas actually *are* low-grade gliomas. Some such lesions could represent areas of cortical dysplasia, inflammatory lesions, or higher grade tumors, and the authors indicated the use of advanced imaging techniques in several of the cases to help with their decision-making process. The authors practice at a site where such modalities are available and they emphasize the importance of managing these children in conjunction with a skilled neuroradiology staff and an experienced multidisciplinary neuro-oncology team. In addition, they followed these lesions closely until it was apparent that they were not changing rapidly. This is the approach followed for similar lesions at our center, with the caveats that long-term follow-up is often required to definitively exclude tumor growth and that a small subset of such tumors will enlarge or develop enhancement and in such cases, biopsy and resection are then considered.

Biography

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