Medulloblastoma

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Introduction and clinical presentation

Central nervous system (CNS) tumors, which consist of tumors of the brain and spinal cord, are the most common type of solid tumor in pediatric patients and the second most common type of malignancy in children overall. Medulloblastoma, a type of childhood brain tumor, occurs in approximately 1:100,000 pediatric patients. An embryonal tumor, medulloblastoma normally presents in the posterior fossa of the brain and is 10 times more common in children than adults (Image 1). This tumor type has a slight male predominance similar to other pediatric brain tumors. In general, medulloblastomas are spontaneous tumors; however, some patients may have underlying genetic syndromes.

Patients with medulloblastoma may present with headache, nausea and vomiting, especially with changing positions or first thing in the morning, as well as lethargy, or changes in balance and coordination. Tumor blockage of cerebrospinal fluid (CSF) flow causes a buildup leading to increased pressure and subsequent symptoms. On ophthalmologic evaluation, these patients may have papilledema or swelling of the optic disc consistent with increased intracranial pressure. These tumors can spread to other parts of the brain, the spinal cord and into the CSF in up to 10-40 percent of patients; however they rarely spread outside the CNS axis. Therefore, all patients should have imaging of the entire brain and spinal cord, and lumbar puncture to evaluate tumor cells in the CSF as part of the diagnosis and staging.

Figure 1

MEDULLOBLASTOMA GROUPS AND ASSOCIATED RISKS

	WNT	SHH	Group 3	Group 4	Other
Low Risk	<16y	–	–	All of the following: • Non-metastatic • Chr 11 loss	–
Standard Risk	–	• TP53 wt (somatic or germline) • No MYCN amplification • Non-metastatic	All of the following: • No MYCN amplification • Non-metastatic	All of the following: • Non-metastatic • No Chr 11 loss	–
High Risk	–	One or both: • Metastatic • MYCN amplification	–	• Metastatic	–
Very High Risk	–	TP53 mutation (metastatic or non-metastatic)	Metastatic	–	–
Unknown	Metastatic	–	Non-metastatic with MYC amplification Significance of anaplasia Isochromosome 17q	Significance of anaplasia	Melanotic medulloblastoma Medullomyoblastoma Boundary between Group 3/4 Definition of MYC & MCYN amplification

New classification system

Medulloblastomas were originally classified by histologic subtype based on microscopic features. Classic medulloblastoma was the most common type and correlated with standard risk disease. Desmoplastic/nodular medulloblastomas (small blue cells with pale islands) portended a favorable prognosis, while anaplastic (abnormal appearing nuclei) portended a poor prognosis. In recent years, more has become understood about the molecular features of medulloblastomas and they are now categorized into four main groups based on these molecular characteristics (Figure 1).

There are four groups of medulloblastoma with distinguishing histologic features and distinct genetic mutations. They are referred to as: WNT-activated medulloblastoma (11 percent of cases), Sonic Hedgehog (SHH-activated) medulloblastoma (28 percent of cases), group 3 medulloblastoma (28 percent of cases) and group 4 medulloblastoma (33 percent of cases). The group that a patient falls into is very important as we have learned that these groups are also associated with differences in overall

outcome and risk. Some groups, such as group 3, have a higher chance of being metastatic, relapsing or not responding to therapy whereas the WNT group has been shown to have excellent overall cure rates.

Treatment

Initial treatment focuses on surgical resection, recognizing that the best outcomes are achieved when the tumor can be completely resected. Beyond surgical resection, adjuvant therapy has focused on a combination of radiation to the brain and spinal cord, as well as systemic chemotherapy. To determine the optimal treatment, patients are stratified into these risk groups: low risk (LR), standard risk (SR), high risk (HR), and very high risk (VHR). Risk groups are based on the degree of tumor present after surgery, the presence of metastasis, histology of tumor cells, and specific cytogenetic analysis.
The intensity of therapy increases with the degree of risk.

Overall survival varies based on risk group, as well as the underlying molecular group. For low risk disease, including patients that fall into the WNT subgroup, overall survival exceeds 90 percent. Standard risk patients have an overall survival of about 80 percent (75-90 percent). The more aggressive subtypes fall under high risk and very high risk with survival rates of 50-65 percent and less than 50 percent, respectively. Infants tend to do very poorly due to the inability to receive radiation therapy, leading to outcomes closer to 30-50 percent survival, regardless of risk group.

While survival is good, morbidity from treatment can be a significant issue. Patients may have treatment-related learning difficulties, endocrine abnormalities and growth issues. Most patients have some degree of hearing loss requiring hearing aids. Therefore, current therapeutic trials are working to identify treatment for the high risk groups which will improve outcomes and minimize treatment-related side effects in the lower risk groups.

Experience at Akron Children's Hospital

We reviewed our experience treating patients with medulloblastoma over an 11-year period from January 2005 to December 2015. During that time, 16 new cases were diagnosed, comprising about 8 percent of the total number of CNS tumors we saw during that period. This is significantly lower than the incidence of approximately 20 percent of childhood CNS tumors reported by SEER data. Similar to that data, most of our patients presented with tumors of the fourth ventricle and there was a slight male predominance (53 percent).

Of our cases, a majority (14) was standard risk, which is consistent with general data. Overall survival was 86 percent for standard risk patients (n=14) and 50 percent for high risk patients (n=2) (Figure 2). This compares to published overall survival rates for all patients with medulloblastoma (approximately 80 percent for standard risk and 50-75 percent for high risk.) A majority of these patients were diagnosed and treated prior to the more recent advent of molecular diagnostics and classification, so they cannot be classified into the current molecular groups, which may also alter the outcome data overall. Currently, all patients with medulloblastoma undergo evaluation for subgroup classification. As a member of the Children's Oncology Group (COG), our patients are eligible for open COG clinical trials based on subgroup classification.

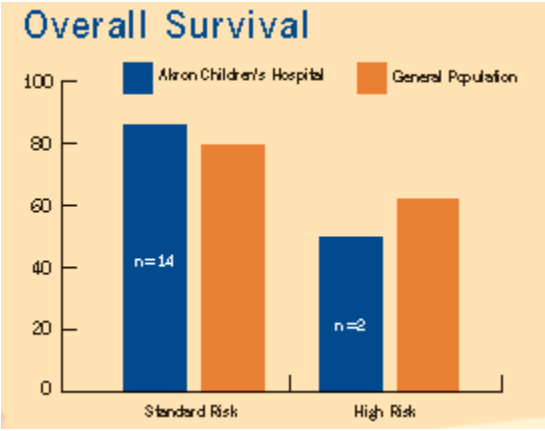

Figure 2

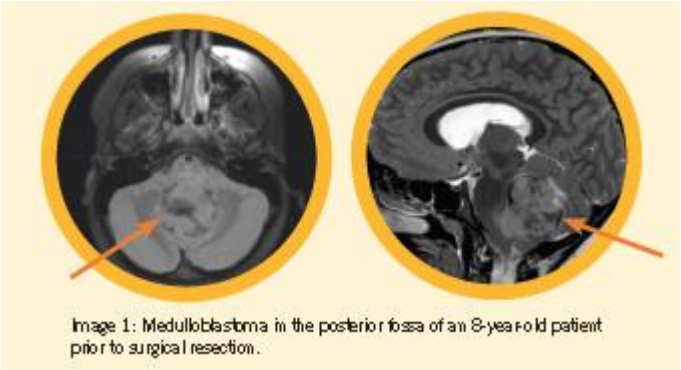

Image 1: Medulloblastoma in the posterior fossa of an 8-year-old patient prior to surgical resection.