Researchers discover medulloblastoma subtype that responds to less aggressive therapy

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The youngest patients with the brain tumor medulloblastoma are among the most challenging because their rapidly developing brains limit treatment options. Now a team of researchers led by St. Jude Children's Research Hospital have discovered a subtype that responds to a therapy that is less likely to cause long-term cognitive problems.

The report appears today in the journal *Lancet Oncology* and sets the stage for screening medulloblastoma patients to identify those with the subtype.

"This study has important ramifications for treatment of young children with medulloblastoma, a group whose long-term survival rates are stalled at about 50 percent and progression-free survival remains even lower," said first and corresponding author Giles Robinson, M.D., an assistant member of the St. Jude Department of Oncology. "Combination therapy with radiation and chemotherapy has increased survival rates of older children and adolescents, but radiation toxicity has limited its use in younger patients, particularly those less than 3 years old. "Now we have identified a subtype of medulloblastoma that accounts for about 25 percent of infant medulloblastoma and that can be treated successfully with reduced-intensity chemotherapy," Robinson said.

Seventy-five percent of the 21 patients in the newly identified subtype were alive five years after their diagnosis, and their disease had not worsened (progressed).

The rates were even better, 91 percent, for the low-risk patients whose tumor had been completely surgically removed and had not spread.

Medulloblastoma is the most common malignant childhood brain tumor and one of the leading causes of non-accidental death in U.S. children and adolescents. The tumor includes four main molecular subgroups—WNT, sonic hedgehog (SHH), group 3, group 4—each with different clinical and biological characteristics as well as treatment outcomes.

The tumor is diagnosed in about 400 U.S. residents annually, mostly in individuals under 16 years old. With current treatment, which includes surgery, whole-brain and spine irradiation, and chemotherapy, about 70 percent of patients are alive five years after diagnosis. However, brain and spine radiation therapy can be particularly damaging to the developing brain. But long-term survival remains about 50 percent or less when radiation therapy is omitted, reduced or delayed.

The new medulloblastoma subtype is infant SHH-II. It was discovered in a subset of patients with SHH medulloblastoma. The patients were enrolled in a St. Jude-led, 10-year, multi-center phase II clinical trial of risk-adapted therapy for treatment of medulloblastoma patients age 5 and younger. Of the 81 patients enrolled, 65, or 80 percent, were younger than age 3 and were classified as infants.

Patients were assigned to low, intermediate or high-risk therapy based on clinical factors and tumor histology (how tumors looked under the microscope). All patients were treated with chemotherapy. Radiation therapy was limited to intermediate-risk patients who received focal radiation of the tumor bed, not irradiation of the whole brain and spine. No patients received myeloablative regimens that required stem cell transplantation or intrathecal chemotherapy (chemotherapy injected into cerebrospinal fluid).

Researchers used next-generation genomic sequencing and DNA methylation patterns to analyze treatment response based on the patients' molecular subgroups. DNA methylation refers to chemical compounds called methyl groups that attach to DNA and serve as on-off switches to regulate gene expression.

Overall, researchers reported that risk-adapted therapy did not improve progression-free survival. However, analysis of the DNA methylation data revealed distinct subgroups and subtypes of medulloblastoma that were associated with distinct outcomes. First, the researchers noticed that patients with SHH medulloblastoma had higher rates of progression-free survival compared to patients with group 3 or group 4 medulloblastoma. Even more revealing was that the 42 SHH patients evenly divided between subtypes that researchers called iSHH-I and iSHH-II.

Patients with the iSHH-II subtype were less likely to have their disease worsen or return after therapy. The patients were also more likely to survive at least five years when compared to patients with iSHH-I or with group 3 or 4 medulloblastoma.

"While we've understood for some time that medulloblastoma is not a single disease, the results of this molecular analysis are a humbling reminder of differences within medulloblastoma subgroups that influence treatment response," Robinson said. "That is important to keep in mind as the next generation of molecularly driven therapies are designed."