U of T discovery may help children with brain cancer avoid radiation

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(PhysOrg.com) -- A team of scientists from the University of Toronto, the Hospital for Sick Children (SickKids) and The Children's Hospital of Los Angeles have identified a genetic mutation that plays a major role in the outcome of a paediatric brain cancer called choroid plexus carcinoma.

The study also sheds light on why some choroid plexus tumours are more aggressive and reoccur more frequently, and may also provide insight into the treatment of other cancers. The study is published in the March 22 advance online issue of the Journal of Clinical Oncology.

The disease occurs most commonly in the first year of life and accounts for four per cent of all childhood brain tumours. It is usually treated with radiation, chemotherapy and surgeries, with a success rate of only 25 per cent. Patients undergoing radiation often have to cope with long-term side-effects, such as neurocognitive delay and severe growth impairment. For very young patients, the lifelong impact of these radiation-induced toxicities can be even more serious.

"Unfortunately, children with this type of cancer have a very poor survival rate," said Dr. David Malkin, principal investigator of the study and a professor in the Department of Paediatrics at the University of Toronto. "They also often have an inherited condition called Li-Fraumeni syndrome, which predisposes them to develop a spectrum of early-onset malignancies. The aim of our study was to determine how these diseases were related, and to identify ways of improving survival

for patients with choroid plexus tumours," adds Malkin, who is also associate chief of clinical research, co-director of the cancer genetics program, senior staff oncologist and senior scientist at SickKids .

The researchers examined the DNA of 64 patients with choroid plexus tumours and correlated genetic findings to disease outcomes and family histories. They found that most of the tumours had either a mutated tumour suppressor gene called TP53, or mutations in other genes that modify TP53 activity. Patients without a family history of cancer or Li-Fraumeni syndrome were less likely to have TP53 alterations in DNA.

The scientists concluded that the presence of the TP53 mutation determined the expected prognosis. Patients with normal TP53 genes in their tumours had better outcomes, even without aggressive radiation treatment. This suggests these patients can be successfully treated with chemotherapy and surgery in the future, without suffering from the additional effects of radiation.

"This is good news for these very young patients and their families," said Dr. Christine Williams, director of research at the Canadian Cancer Society. "Probably the most significant finding is that radiation is not necessary for some of these children, and so they will no longer have to endure what can be devastating side-effects."

"A big challenge facing physicians and medical specialists is knowing which patients will respond favourably to treatments and which will not," said Dr. Uri Tabori, co-lead author of the study, assistant professor in the Department of Paediatrics at the University of Toronto and staff oncologist and scientist at SickKids. "This is promising news."

As a result of their findings, Malkin and his team are recommending a new approach to managing choroid plexus tumours, and strongly suggest that the TP53 status be determined in patients as well as in their family

members. This information would then be used to select the most appropriate therapy for the patient. In the absence of TP53 testing, however, the study recommends that doctors examine the patient's family and clinical history to determine if Li-Fraumeni syndrome may be a factor.

"Ideally, we would want to screen all patients for their TP53 status, but this is not always practical or possible," said Tabori. "By taking a careful family and clinical history, we can still make a reasonable prediction about the patient's status, and the potential status of other family members, based on an unusually high occurrence of certain types of cancer."

These findings are expected to have a significant impact on patients and their families who are dealing with choroid plexus tumours. The study is also relevant to members of the paediatric oncology community and to scientists who study TP53, as this research may hold important clues for treating other types of cancer.

Malkin and his team are continuing their research by validating their TP53 findings in a larger subset of patients, as well as identifying the other genes that may be disrupted in choroid plexus tumours. "We know that TP53 is not the only gene involved, so we are applying the latest microarray technology to identify other mutations that may also play a more complex role in these tumours," said Adam Shlien, co-first author and a graduate student in Malkin's laboratory. "Understanding the genetic and biological determinants of choroid plexus tumours will have a direct implication for modifying therapy. We intend to see if these findings extend to other forms of cancer as well."

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