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Researchers find novel signature in the brains of children with cerebral malaria

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Cells associated with inflammation and blood clotting accumulate in the brain blood vessels of children affected by a potentially fatal form of malaria called cerebral malaria (CM), potentially contributing to the disease process, an international team of researchers has found, and HIV can exacerbate this development. The work was published this week in *mBio*, an online open-access journal of the American Society for Microbiology.

In autopsied brain tissue from over 100 African children, researchers observed that children with CM had more than nine times the amount of white blood cells called monocytes, which help scavenge dead tissue, and platelets, which promote blood clotting, compared to children who did not have malaria. Accumulation of these cells was twice as high in HIV-positive children compared to those who did not have HIV.

"Our study clearly shows that HIV exacerbates the disease process in cerebral malaria and also leads to some really interesting insights into what may be going on with children who are dying of cerebral malaria, which has been very controversial," said senior study author Kami Kim, MD, professor of medicine, pathology, and microbiology and immunology, and director of the Training Program in Geographic Medicine and Emerging Infections at Albert Einstein College of Medicine in the Bronx, N.Y. "Children who are HIV-positive and at risk for malaria may benefit from targeted anti-malaria drugs, and adjunctive therapies that target inflammation or blood clotting may improve outcomes from CM."

CM, one of the most severe complications of malaria that can lead to behavioral problems, seizures, coma or death, is mainly seen in children under five years old living in sub-Saharan Africa. While CM is fairly rare, affecting about 2 percent of children with the disease, says Kim, it is thought to be responsible for half of malaria deaths, "so it's a big deal. The more we know about CM, the more that we can theoretically do something either to better treat or prevent it." Even with appropriate treatment, 15-20 percent of children affected with CM die.

In an ongoing study of pediatric CM in Blantyre, Malawi, researchers enrolled more than 3,000 participants and completed 103 autopsies in those who died from either CM or other causes of coma. HIV prevalence was higher than expected and led to higher mortality in CM patients, researchers found. The prevalence of HIV was 14.5% in children enrolled in the study vs. 2% in the general Malawi pediatric population. Twenty-three percent of HIV-positive children died while and 17% of those without HIV died. Twenty percent of autopsy cases were HIV-positive.

Researchers also noted that HIV-infected children with CM were older than children without HIV (an average of 99 months vs. 32 months) and were not severely immunocompromised, and that monocytes and platelets were significantly more prevalent in HIV-positive children with CM than neutrophils, white blood cells that are among the first responders for many infections.

"We identified a unique and pervasive pathology pattern in pediatric CM, marked by monocytes and platelets, which is more severe in HIV-positive children," Kim says. "It doesn't prove that these cells cause clinical disease but the fact that they're there in huge abundance when there's a lot of parasites is pretty strongly suggestive evidence that they're doing something. We never see that in healthy brain tissue."

Additional studies of children with varying severities of malaria are necessary in order to design better treatment algorithms, Kim says.

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