In Africa, One in Four Survivors of Cerebral Malaria Have Long-term Deficits

BY ED SUSMAN

ARTICLE IN BRIEF

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CHICAGO—A study of African children who survived bouts of cerebral malaria indicates that living through the disease — fatal in 15 percent or more — is not the end of the child's problems.

"At two-year follow-up testing, 26.3 percent of children with cerebral malaria had cognitive deficits in one or more areas compared with 12.5 percent of children who had had uncomplicated malaria and 7.6 percent of asymptomatic children in the community," said Michael J. Boivin, MD, professor of neurology at Michigan State University, East Lansing. He described the findings at the AAN annual meeting here in April.

"Basically, one in four Ugandan children under five years of age who develops cerebral malaria is cognitively impaired two years later," he said. "Cerebral malaria may be a major cause of long-term cognitive impairment in children in sub-Saharan Africa."

Dr. Boivin said the differences among children with long-term deficits was statistically significant when compared with children who were asymptomatic or had malaria that had not been complicated by cerebral involvement (p=0.0060). The difference between children with uncomplicated malaria and asymptomatic children in the community, as far as long-term cognition was concerned, did not reach significance (p=0.37).

"Last year in the *Journal of Pediatrics* we reported the results of the first prospective follow-up study of the effects of cerebral malaria on the cognition of children," Dr. Boivin explained. "Here we report the results of our two-year follow-up."

Of the organisms that cause malaria worldwide — *Plasmodium falciparum, P. vivax, P. ovale*, and *P. malariae* — *P. falciparum* is found frequently in Africa and is the most devastating form of malaria. He said that blood cells tend to cluster together in the microscopic blood vessels of the body, particularly in the brain, and the endothelial linings of the cell's wall have a tendency to cluster to these red blood cells as well. This can lead to severe malarial anemia and cerebral malaria. About half the cases of cerebral malaria are seen in children in the sub-Sahara. It is characterized primarily by coma, sometimes by seizures.

STUDY PROTOCOLS

"In exploring the long-term neurocognitive effects of cerebral malaria, we looked at Ugandan children five to 12 years of age, which comprises about a third of the cerebral malaria cases seen," Dr. Boivin said. "Cerebral malaria affects 750,000 African children a year and has a 20- to 25-percent fatality rate."

Dr. Boivin and his research team enrolled children in the study who were treated at Malago Hospital, the national referral hospital in Kampala, Uganda. They enrolled 44 children who had survived cerebral malaria at the time of discharge from the hospital; 54 children with uncomplicated malaria at an outpatient treatment clinic; and 89 healthy children recruited from the homes or the extended families of the cerebral malaria or uncomplicated malaria groups.

The children had neuropsychological tests at discharge and at three months, six months, and 24 months. "We did neuropsychological assessment prior to discharge, usually at day seven if they recovered normally from cerebral malaria," he explained. "We are using neurological assessments we thought could be especially sensitive to some of the attention, memory, and other kinds of learning effects of other parts of the brain that were vulnerable to effects of the blockages caused by blood cells and other types of lymphocytes as well as platelets."

Children who had survived cerebral malaria were compared with matched healthy controls and those with uncomplicated malaria. Disability was defined are performing at two standard deviations below healthy controls in age-matched counterpoints. "We observed that 26.3 percent of cerebral malaria survivors had more frequent cognitive impairment than healthy children (7.8 percent) (p=0.005) in one of the three areas, attention, tactile learning, or memory. For the most part, cognitive impairment occurred in the area of attention."

Considering age, nutritional status, education level, and the quality of home environment, there was a 3.7-fold increase in risk of long-term cognitive deficits in one of these three principal areas — attention, memory, or tactile based learning — for cerebral malaria survivors when compared to community children (p=0.03).

At times from six months to 2 years, the cerebral malaria group was compared to healthy controls and uncomplicated malaria children, and Dr. Boivin found significant differences that persisted for memory and attention. At discharge, the raw memory scores for the cerebral malaria children averaged about 2.7, while the healthy children and the uncomplicated malaria children scored about 3.2 (p=0.001); at six months the differences narrowed with the cerebral malaria children scoring 3.1 on the test compared with the other two groups scoring about 3.3 (p=0.006); at two years the cerebral malaria children were scoring about 3.2, but the other children were at 3.4, still a significant difference (p=0.020), he reported.

"In looking at sub-scales, the memory tests most associated with attention were the ones in which the cerebral malaria children performed the worst," Dr. Boivin said. He said the results should be taken into consideration when therapeutic interventions are developed for these children.

Dr. Boivin said that although the median age for cerebral malaria in Uganda is three years, testing results on children under five were uneven. For that reason the researchers tested children between the ages of five and 12. "That is a limitation of our study," he acknowledged.

"The finding of long-term deficits in these children is not unexpected," said Handojo Surjo, MD, a consultant neurologist at Royal Taruma Hospital, Jakarta, Indonesia. "Any time there is a parasitic invasion in the brain, damage can occur. These are reasonable results."

Dr. Surjo said that cerebral malaria in Indonesia is a relatively rare occurrence but still can be a dangerous condition in children.

Dr. Boivin said his study was supported by the NIH and his Fulbright Regional Research Award. "We have just been funded for a five-year follow-up through the National Institute of Neurological Diseases and Stroke," he said. "The new study may allow for testing of younger children." •

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professor of neurology and anatomy at the University of Wisconsin-Madison; director of the NIH-funded Stem Cell Training Program; and co-director of the University of Wisconsin Stem Cell and Regenerative Medicine Center. Dr. Svendsen said human neuronal stem cells have been isolated from both embryonic stem cells and fetal brain tissue, and can be expanded in culture "without losing the potential to differentiate into both neurons and glia."

Dr. Svendsen said a viable use of stem cells might be the replacement of damaged astrocytes and the delivery of large therapeutic proteins directly to the brain. He said that in animal models of PD and ALS, growth factors such as glial cell-derived neurotrophic factor (GDNF) have had neuroprotective effects. Dr. Svendsen noted that as stem cells migrate and integrate into the damaged CNS, they produce astrocytes and can be genetically modified to release a neuroprotective growth factor. Thus "they are an ideal source of tissue for delivery," he said.

A possible clinical strategy to slow death from a neurological disease might combine the "inherent trophic effects of glia derived from stem cells" with selective gene therapy, he said. "The idea in patients would be to replace the neurons that are sick with human neuronal cells that release GDNF," said Dr. Svendsen. He noted that human trials await the availability of regulated vectors to allow the appropriate dosing of GDNF. He said he is now working on a clinical protocol that involves delivery of neural cells into the spinal cord. "GDNF cannot be given as a pill because it will not enter the brain," he noted.

Asked to comment on Dr. Kerr's and Dr. Svendsen's preclinical research, Dr. Landis said the presentations are about "early work," and "the questions they're asking are much more difficult" than those being asked in use of stem cell therapy for MS. "They're talking about replacing brain cells," she said. "They've set the bar much higher." •

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