In Africa: Evaluating the Neuropsychological Effects of Cerebral Malaria in Ugandan Children

November 10, 2004

Michael J. Boivin (front, second from left) was a Fulbright scholar to the department of pediatrics at Makerere University in Kampala, Uganda. Seen here at a farewell dinner with his research team and family, Boivin is also professor of psychology at Indiana Wesleyan University, and an adjunct research investigator in the department of psychiatry at the University of Michigan.

I spent a year at Makerere University in Kampala, Uganda as a Fulbright researcher on the Regional African Research Program. Although I am a professor of psychology at Indiana Wesleyan University, primarily teaching courses in experimental and biological psychology, my appointment at Makerere was with the department of pediatrics, and my principal Ugandan collaborators were pediatricians. My project focused on the neurological and neuropsychological effects of pediatric cerebral malaria, and my Ugandan colleagues and I pursued this study in the department of pediatrics and at Mulago Hospital, the national referral hospital serving the poor of Uganda. Cerebral malaria, or CM, is associated with at least 2.3 million deaths annually, from an estimated 400 million yearly cases of malaria worldwide, and is the leading cause of hospitalization, mortality, and morbidity of children under age five in sub-Sahara Africa. In East Africa alone, malaria-related annual mortality stands at 70,000 to 110,000 under-five deaths, making it the leading cause of death in this age group.

I arrived in Uganda with my wife Grace and two children (Matthew, 14, and Marjorie, 16) in mid-August 2003 and stayed until the end of July 2004. We were joined in December by our oldest daughter, Monique, who did an internship in public health management of HIV/AIDS anti-retroviral drug treatment programs in Kampala.

This was actually our second time as a Fulbright family in Africa. My wife grew up the daughter of medical missionaries in Congo, which inspired me to apply for a research Fulbright award that allowed the family to spend a year in DR Congo (formerly Zaire) at a small medical mission near Kinshasa in 1990. While there, I evaluated the neuropsychological effects of treatment for anemia from intestinal parasite infection, chronic malaria, and iron-poor anemia in school children. Later that year, I also did a preliminary study in the cognitive effects of pediatric HIV infection.

I was the last Fulbright scholar to go to DR Congo before the program was suspended in 1991 due to the chaos and civil war that ensued six weeks after we left. I returned to Africa in the summer of 1997 on a two-month fellowship from the West African Research Association to do a preliminary study on the neuropsychological effects of cerebral malaria in Senegalese children. That set the stage for my research

proposal to return to Uganda as a Fulbright researcher to continue this work, and for our subsequent proposal to the National Institutes of Health.

The day after arriving in Uganda I hired a research assistant, Paul Bangirana, who had just completed his master's degree in clinical psychology at Makerere University. Justus Byarugaba, a pediatric neurologist, and I planned the medical side of the study and were joined later by Opika Opoka, who had just returned to Mulago after completing a master's in medicine program in China. Opoka was the principal clinical care pediatrician for our study children, while Byarugaba oversaw the neurological assessments.

The brain effects of CM have been generally thought to be based on hypoxia – an absence of oxygen resulting from blockages of small blood vessels in the brain caused by parasitic red blood cells. But there is also evidence of widespread rupture of small blood vessels and blood/brain barrier compromise, perhaps leading to a strong immuno-reactive component damaging the white matter in the brain and spinal cord. This damage can lead to persistent neurological and neuropsychological deficits. However, no conclusive clinical research in humans testing this theory has yet been published.

Despite the fact that CM is one of the biggest killers of children in the tropics, we do not really know how severe malaria progresses to cerebral malaria, nor do we fully understand the principal mechanism for subsequent brain damage and the neurological and neuropsychological sequelae. With this issue in mind, we gathered both blood serum and cerebral spinal fluid from our CM study children for later cytokine analysis, as a means of assessing the immuno-reactive profile of the children during their neurological and neuropsychological recovery from the disease, particularly at three- and six-month follow-ups. We also compared serum cytokine levels of our study children to their healthy control siblings and children admitted to Mulago Hospital with uncomplicated malaria before and after treatment.

Research assistant Paul Bangirana does a cognitive test on a child patient with cerebral malaria. Bangirana and Boivon studied 80 cerebral malaria patients.

For our study from the Acute Care Unit at Mulago Hospital, we recruited children 4- to 12-years-old who were admitted for cerebral malaria, typically in coma and often with seizure activity. After medical officers stabilized the child's breathing and vital signs, and after we obtained consent for study participation from the parents, we then did blood draws; blood slides for malarial parasite density counts; lactic acid, glucose, and Hemoglobin strip tests; a lumbar puncture; a cerebral spinal fluid draw to evaluate for meningitis; administered IV quinine and glucose along with seizure management medication as needed; and resuscitated if respiratory distress occurred. We also transfused if the child was severely anemic. If all went well, the child was usually transferred to our study ward in pediatrics within 12 to 24 hours following admission.

In addition to continued IV quinine treatment and close-care monitoring by the study nursing staff, we did an EEG and additional blood draw 72 hours after admission, took a stool specimen for intestinal

parasite infection, and completed a detailed neurological and neuropsychological evaluation prior to discharge from the hospital. While the child was in the hospital, we also did an interview with the principal caregiver to evaluate the home environment, which was later verified by medical officers who visited the home. This allowed us to control for quality of home environment in evaluating the impact of cerebral malaria on neuropsychological recovery and cognitive ability performance.

Parents were then scheduled to return with a healthy control child (without a history of cerebral malaria or other comatose state) who is a sibling to the CM child. They were also encouraged to bring the CM child back if there were any continuing problems in recovery (e.g., seizure activity, recurring fever, loss of appetite). When the parents brought the healthy control sibling, we did a blood smear for malaria and a blood draw for a complete blood count, stored blood serum for later cytokine analysis, and did a physical exam along with stool specimen analysis. We also did a complete neuropsychological assessment. Both the healthy sibling and the CM study child returned at three months and at six months for neuropsychological assessments, after which the study protocol was completed.

In all, ours was a very ambitious protocol involving coordination among specialists in acute care, pediatrics, microbiology, EEG and neurology, immunology, and our fledgling neuropsychology unit at Mulago. Despite the challenges of coordinating these various programs at a large, complex national referral hospital such as Mulago, we managed to recruit 80 cerebral malaria patients and progressed up through the three-month evaluation and healthy control recruitment with about 60 of them.

Our initial results have shown that the most pronounced effects of cerebral malaria pre-discharge compared to healthy and uncomplicated malaria groups seem to be with respect to sequential-processing working memory tasks. Furthermore, performance recovery for these tasks at the three-month follow-up is predicted by severity of anemia, coma depth, and duration at admission, as well as white blood cell levels in the initial treatment stage. We are anxious to see what the cytokine analysis will reveal on our stored serum and cerebral spinal fluid specimens in the months ahead as the results from this phase of our analysis come in.

Because of the lack of medical supplies and equipment at Mulago Hospital and the need to supplement the very low government salaries for our study personnel, the cost of mounting this cerebral malaria project was much higher than I originally anticipated. Fortunately, we received a small NIH grant to continue the study, in response to an NIH John E. Fogarty International Center request for applications to study brain injury across the life span in the developing world. It was very encouraging to see our study concept make it to this level and to be in the same league as “the big dogs” from Yale and Oxford, who we know are doing similar neuropsychology research in Africa at places like Kilifi, Kenya, Malawi, and Zambia.

Despite the many challenges and struggles along the way, my Ugandan colleagues and I performed important neuropsychological research, and established the foundations for a severe malaria research center at Mulago and a neuropsychological assessment component (previously non-existent at Makerere/Mulago). We also provided medicines, supplies, and a quality of care to our project kids at a significantly better level than what might otherwise have been available to them. Finally, we integrated neuropsychological science with the clinical medical care of children within the context of an important public health problem, which will hopefully make a difference for future generations of children in Africa in malaria-endemic regions.