Image of the Month

In most children with Sturge-Weber syndrome (SWS) only one hemisphere of the brain is involved. For Csaba Juhasz, Ph.D., an assistant professor of pediatrics and neurology at Wayne State University in Detroit, and colleagues, this provided an opportunity to use magnetic resonance imaging (MRI) to assess cortical gray matter and hemispheric white matter volumes and any possible relationships with global intellectual function in a prospective study, with the unaffected hemisphere serving as an internal control for each child (Arch. Neurol. 2007;64:1169-74).

The researchers used MRI to study 21 children (13 girls) with SWS plus a history of partial seizures, which are common in this disorder. The children ranged in age from 18 months to 10.3 years (mean age 5.3 years). Most of the children (18) were on daily antiepileptic medication, either mono- or polytherapy with oxcarbazepine, valproate semisodium, levetiracetam, carbamazepine, phenobarbital, and/or topiramate.

The children underwent neuropsychologic testing 1 day prior to scanning. Those aged 18-36 months were assessed using the Bayley Scales of Infant Development, which yielded the Mental Developmental Index. Children aged 3-6 years were assessed using the Wechsler Preschool and Primary Scales of Intelligence, third edition. Children older than 6 years were assessed using the Wechsler Intelligence Scales for Children, third edition. Both indices yielded the full-scale IQ. The Mental Developmental Index and the full-scale IQ are highly correlated. Verbal and nonverbal intellectual functions were available for a subgroup of 15 children. Manual dexterity scores were also obtained using age-appropriate tests.

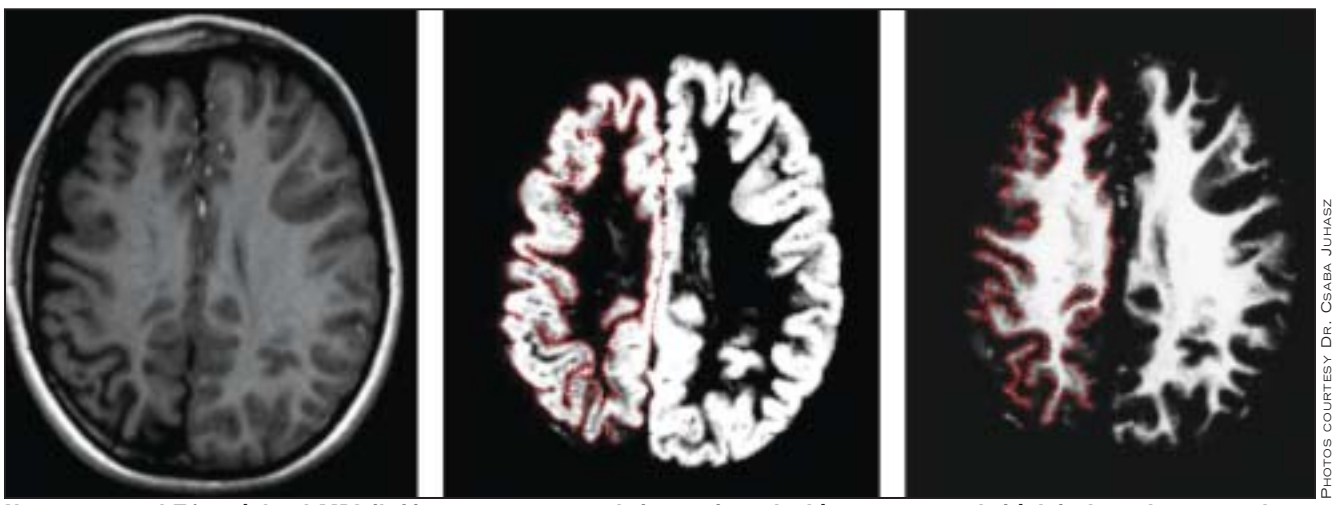
MRI was performed using a 1.5-T scanner. Researchers calculated volumetric measurements using findings from an axial three-dimensional T1-weighted scan.

The volumetric MR images were processed using statistical parametric mapping software. Dr. Juhasz and colleagues created a study-specific template using the brains of the children in this study because most software only includes an adult template. The template is used to spatially normalize the volumetric images of individual children.

By comparing the new template to each child's MRI, researchers produced three new volumetric maps with voxel values between 0 and 1, allowing them to assess volumes of gray matter, white matter, and cerebrospinal fluid.

Left and right hemispheric regions of interest were defined in all supratentorial image planes to derive cortical gray matter and hemispheric white matter volumes. The researchers calculated cortical gray matter and hemispheric white matter volumes for each hemisphere ipsilateral and contralateral to the angioma.

White matter volume in the affected hemisphere was a major predictor of cognitive impairment. Multivariate regression analysis showed a strong correlation between ipsilateral hemispheric white matter volume and full-scale IQ. Age was negatively correlated with full-scale IQ; cortical gray matter volumes showed no link with full-scale IQ. Ipsilateral white matter volumes correlated significantly for both verbal and nonverbal IQ. "The implication is that the white matter has to be preserved or targeted by some kind of treatment in the future," he added. Currently, SWS is treated primarily with seizure drugs. "There is no rational therapy right now to somehow protect or preserve white matter, but it looks like that would be important."



Photos courtesy Dr. Csaba Juhasz

Nonsegmented T1-weighted MRI (left), gray matter mask (center), and white matter mask (right) show the same plane in the same child: The red dots delinate the 39% loss of gray and 48% loss of white matter in the right hemisphere.

Given the findings, abnormal development or loss of white matter may be a critical factor of cognitive decline in SWS. It may be that incomplete maturation or disruption of fiber tracts that connect various cortical and subcortical structures may lead to loss of functional connectivity, impaired efficiency of information processing, and abnormal cognitive development.

The researchers are also using diffusion tensor imaging (DTI) to view tracts of fiber. Susceptibility-weighted imaging (SWI) allows for visualization of small vessel abnormalities. In SWS, vessel abnormalities typically start in the parietal and occipital regions. The frontal lobe becomes involved as the disease progresses. Preliminary DTI appears to show more extensive diffusion changes than would be expected from conventional MR images, said Dr. Juhasz.

"We are trying to figure out why for many of these children their brain involvement looks quite limited on conventional MR imaging but the neurocognitive outcomes are very variable," said Dr. Juhasz.

Mismatch between the brain's large metabolic demands in the first few years of life and the limited blood supply in children with SWS may provide one answer. Dr. Juhasz and Dr. Harry T. Chugani, (director of the PET center at the Children's Hospital of Michigan, Detroit) and their colleagues also recently studied children with SWS using [18F]-2-fluoro-deoxy-D-glucose (FDG) PET imaging. They showed major metabolic progression in children with SWS occurs in the first 3-4 years of life, coinciding with a huge increase of metabolic demand as the brain develops.

A major aim of the larger (MRI and PET) longitudinal study is to find imaging markers to flag children with SWS who need aggressive therapy. Currently, there are not many treatment options. Aspirin is sometimes used; it may diminish the effects of ischemia. "The bottom line is that it only works if we can catch the patients early," he said.

These findings are part of a longitudinal study that is continuing to recruit patients for neuroimaging. With a larger population—on the order of 30-40 patients—researchers can start looking at the effects of age, gender, and side of the angioma along with focusing on brain regions rather than hemispheres.

Dr. Juhasz noted that once progression has started, it is not always a bad thing if the angioma destroys the affected hemisphere very, very early. "The only plausible explanation is that they undergo a reorganization to the other hemisphere."

"We use the contralateral hemisphere assuming that it is basically a healthy, normal hemisphere. But actually in some cases where this happened very early, the other hemisphere is not just normal but I would say 'supernormal,'" he said.

Neurologists wishing to enroll their SWS patients in Dr. Juhasz's longitudinal study should contact him directly at juhasz@pet.wayne.edu.

—Kerri Wachter

FDA Approves FluMist for Use in Children Aged 2-5 Years

BY ALICIA AULT
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The Food and Drug Administration approved the nasal influenza vaccine FluMist for children aged 2-5 years, which could help push up childhood vaccination rates.

FluMist manufacturer MedImmune Inc. said that it anticipated shipping the vaccine to physicians and health care providers almost immediately.

The Centers for Disease Control and Prevention (CDC) currently recommends that all children aged 6 months to 5 years be vaccinated against influenza. The trivalent FluMist vaccine has previously been approved only for healthy children over age 5 years and for adults aged 18-49 years.

Dr. Sarah Long, chief of infectious diseases at St. Christopher's Hospital for Children in Philadelphia, said that the new FluMist approval is likely to spur higher vaccination rates. But, she added, physicians probably will not widely use the vaccine in young children until the CDC's Advisory Committee on Immunization Practices recommends it for the approved populations. Without an ACIP endorsement, insurers are reluctant to reimburse for a vaccine, Dr. Long, a member of the American Academy of Pediatrics committee on infectious diseases, said in an interview.

That recommendation is likely to come at ACIP's next meeting in late October, as FluMist's likely approval for use in young children had been discussed at its last meeting, Dr. Long said.

The AAP and the CDC agree that children of all ages are vastly undervaccinated. The CDC just issued vaccination statistics on children age 6-23 months. Overall, only 21% of children under the age of 2 years received full vaccination coverage—that is, two doses—in the 2005-2006 flu season, said Dr. Jeanne M. Santoli, deputy director of the Immunization Services Division in the CDC's National Immunization Program, at a press briefing on the upcoming flu season convened by the National Foundation for Infectious Diseases that occurred as the FluMist approval was granted.

FluMist joins two other vaccines currently approved for use in young children. Sanofi Pasteur's Fluzone is indicated for anyone over 6 months of age, and Novartis' Fluvirin for anyone aged 4 years or older. "This approval also offers parents and health professionals a needle-free option for squeamish toddlers, who may be reluctant to get a traditional influenza shot," said Dr. Jesse L. Goodman, director of the Food and Drug Administration's Center for Biologics Evaluation and Research in a statement.

The approval was based on a pivotal study of 4,000 children aged 2-5 years who received the live attenuated vaccine during the 2004-2005 flu season. According to MedImmune, there was a 54% reduction in influenza in children given FluMist, compared with those who received a traditional injection.

The FluMist vaccine is contraindicated in those with asthma, children under age 2 years, and children under age 5 years who have recurrent wheezing because there is an increased risk of exacerbation of that symptom. It also should not be given to children receiving concomitant aspirin, or therapy containing aspirin, according to MedImmune, which will charge $17.95 per dose this flu season. ■