

IMAGE OF THE MONTH

“Cerebral palsy is not really the diagnosis. It is a descriptor of the child’s motor function ... the real push is to understand the factor or factors underlying the development of cerebral palsy,” said Alexander H. Hoon Jr., M.D., director of the Phelps Center for Cerebral Palsy and Neurodevelopmental Medicine at the Kennedy Krieger Institute in Baltimore.

Cerebral palsy falls into broad etiologic groups: disorders of early brain formation, injury associated with prematurity (periventricular leukomalacia), neonatal encephalopathies, and a heterogeneous group of postnatal disorders. Approximately 30% of cerebral palsy cases are associated with brain malformations, 40% with prematurity, 20% with neonatal encephalopathies, and 10% with postnatal causes—with some regional epidemiologic variability.

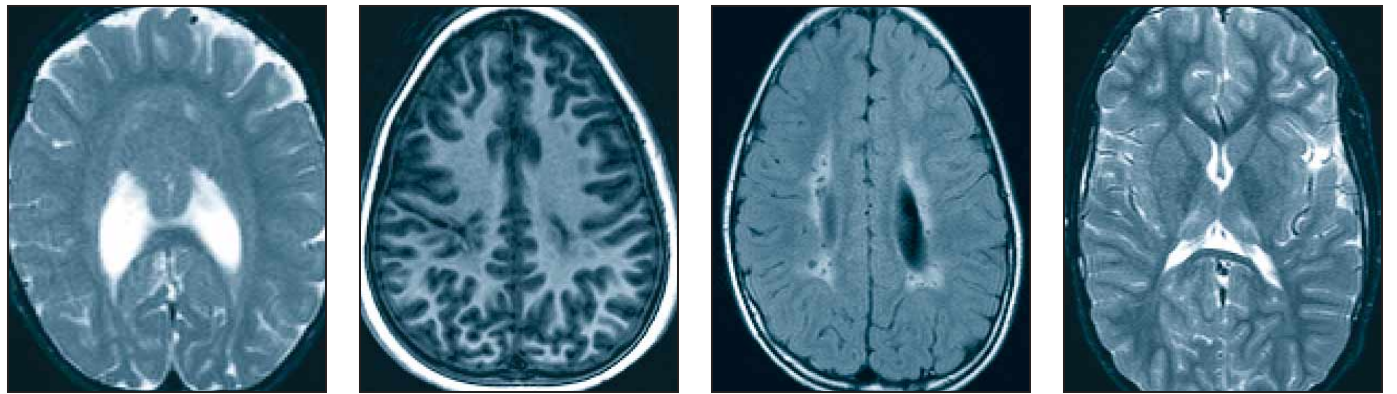
Conventional MR imaging and diffusion tensor imaging (DTI) can be used together to establish an etiology and to refine the classification of cerebral palsy. “The importance of establishing an etiology is to use this information to refine therapy, and improve understanding of prognosis and recurrence risk,” said Dr. Hoon. MRI established the diagnosis of periventricular leukomalacia in the child evaluated for spastic quadriplegic cerebral palsy. The DTI images—acquired under a research protocol to refine understanding of pathogenesis and classification—revealed abnormalities in both motor and sensory pathways.

Significant delays in the acquisition of motor skills make clinicians suspect cerebral palsy. For a child with severe cerebral palsy, the disease is usually evident within the first 6-12 months of life; and for a moderately affected child by 1-2 years of age, said Dr. Hoon. For a mildly affected child, clinicians typically wait as long as possible to see if the child develops independent ambulation.

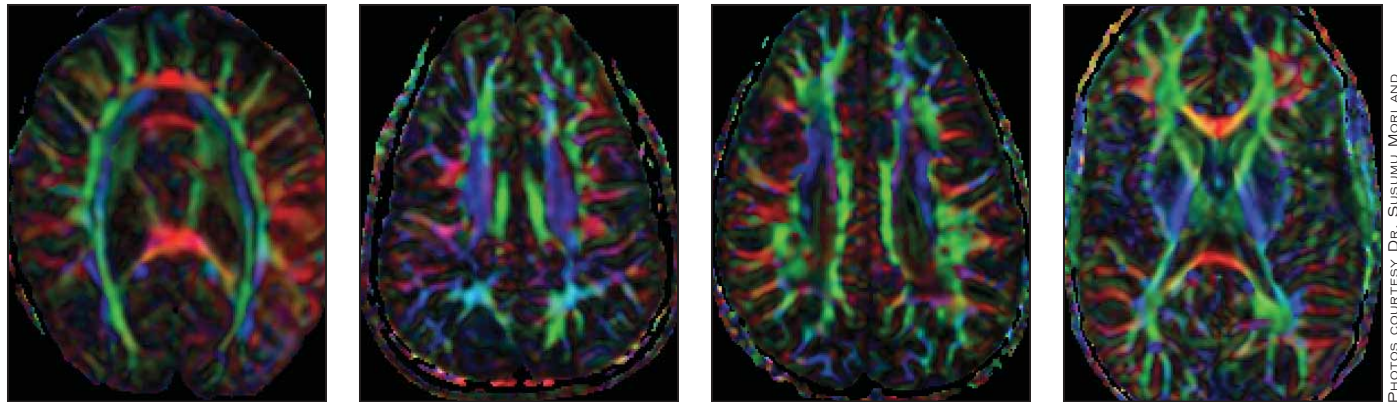
Any child with cerebral palsy should be imaged, he said. Once the diagnosis of cerebral palsy is established, conventional MRI is part of the routine work-up to classify children with cerebral palsy more precisely than by clinical exam. By pinpointing the cause, clinicians can make certain inferences about recurrence risk, and to some extent prognosis, said Dr. Hoon.

MRI also can be useful for children in a gray zone—for whom it’s uncertain whether they will develop cerebral palsy. If the MRI appears normal, parents can be reassured, with the caveat from the neurologist that ongoing follow-up is important. It’s less clear whether to image children with milder delays but who appear clinically to have a good prognosis.

On MRI, clinicians look for evidence associated with



Shown are axial MRIs of children with, left to right, holoprosencephaly (brain malformation), schizencephaly (brain malformation), periventricular leukomalacia (prematurity), and hypoxic-ischemic encephalopathy (neonatal encephalopathy).



Axial diffusion tensor images of the same children as above, in the same order as above, reveal white matter tracts oriented in the plane of the image (shown in blue), up and down (shown in green), and left to right (shown in red).

brain malformation, white matter disorder associated with prematurity, injury that occurred in a term infant, or postnatal causes including genetic or metabolic disease. Up to 70%-90% of children with cerebral palsy will have an abnormal MRI. “It’s a very helpful diagnostic test,” said Dr. Hoon. For example, cerebral palsy with a normal MRI would suggest other possible causes, including a treatable disorder called dopa responsive dystonia.

DTI reveals abnormalities in white matter tracts by using the diffusion of water along the longitudinal direction of the axons in the tracts. Within white matter, water moves parallel to tracts. Conventional MRI can distinguish white from gray matter but can provide very little detail about the white matter; MRI cannot reveal or quantify specific fiber tract directions.

DTI relies on the principle that water diffusion—or brownian motion—is affected by the properties of the medium in which it occurs. Diffusion within biologic tissues reflects tissue structure and architecture at the microscopic level. DTI allows researchers to look at brain structures that were previously not visible *in vivo*, he said.

At the Kennedy Krieger Institute, DTI is used in research to evaluate 26 brain white matter tracts in much greater detail to look for abnormalities—small size or ab-

sence. Visualizing individual tracts of white matter is only part of the problem. At the moment, researchers don’t know exactly what normal tracts look like nor do they know how function correlates with specific tracts.

Dr. Hoon and his colleagues are currently studying the white matter tracts of 30 children born prematurely at various gestational ages, with the goal of correlating tract abnormalities with clinical measures of the child’s motor and sensory function. “We’re at the very beginning of this process,” said Dr. Hoon.

Once function can be correlated with specific tracts, researchers would then be able to use DTI to establish specific therapies for abnormalities associated with each tract. While DTI is still largely a research tool for cerebral palsy, many MRI scanners have the capacity to perform DT scans.

MR and DT imaging do not pose any risk to children, but there is some risk associated with anesthesia. Young children are typically sedated with chloral hydrate or intravenous sedation to minimize movement in the MR machine and generally do well. In older children with more significant movement, anesthesia may be necessary, which poses some risk, said Dr. Hoon.

—Kerri Wachter

Tolterodine’s Safety Profile in Children Remains Reassuring

BY ELIZABETH MEHCATIE
Senior Writer

ROCKVILLE, MD. — No new safety concerns were raised in a review of pediatric adverse event reports for the muscarinic receptor antagonist tolterodine, according to the Food and Drug Administration.

Tolterodine is marketed as Detrol and Detrol LA (the extended-release formulation). Among the drug’s indications is treatment of overactive bladder in both neurologically impaired and neurologically intact children.

Dr. Larry Grylack, a medical officer in the FDA’s division of pediatric drug development, Rockville, Md., presented data

before the FDA’s Pediatric Advisory Committee from pediatric exclusivity studies in neurologically impaired and intact children with overactive bladder, as well as data from other studies by Pfizer.

The three 12-week, open-label studies of neurologically impaired children enrolled 34 patients aged 1 month to 15 years, who received different doses of Detrol immediate release syrup or Detrol LA capsules. The urodynamic data were inconsistent within and across trials, and there was a “lack of dose response trends” across studies, Dr. Grylack told the panel. The two phase III studies of neurologically intact patients with overactive bladder, aged 5-10, found no significant differences in the number of weekly incontinence episodes

during waking hours in the 486 children on Detrol LA (2 mg/day), compared with the 224 on placebo.

In these and the other Pfizer studies, of 917 pediatric patients taking tolterodine, 20 patients reported 24 serious adverse events, including four lower urinary tract infections (UTIs) and three cases of pyelonephritis. There were no deaths. There also were reports of aggressive and/or abnormal behavior in 18 patients, which were called nonserious adverse events, Dr. Grylack said. The Detrol LA label already includes information on the excess number of UTIs and episodes of abnormal behavior in patients treated with tolterodine, compared with those on placebo, he noted.

The adverse event reporting system database entries from 1998, when Detrol was approved, through February 2005 included 29 unduplicated pediatric adverse event reports (25 for Detrol and 4 for Detrol LA). Nine were anticholinergic events, including lethargy, urine retention, constipation, dry mouth, and blurred vision, as listed on the labels. But events also included overheating, confusion, and flushing.

There also were eight reports of CNS stimulation: These included reports of aggression and hyperactivity, which are not listed in the Detrol label but are on the Detrol LA label; and irritability and insomnia, which are not on either label. There were two reports of UTIs, three of medication errors, and five classified as “other.” ■