

IMAGE OF THE MONTH

Diffusion-based magnetic resonance images are sensitive to water motion in the brain. Diffusion tensor imaging (DTI) provides information on microarchitecture of the brain's white matter that reflects changes in axonal myelination processes and, therefore, the integrity of organized tissue microstructures.

"The part that we can pick up is the water motion that is in the sulci next to the gray matter [in the cerebrospinal fluid]. This is very easy to measure," said Manzar Ashtari, Ph.D., a senior neuroscientist in the radiology department of the Children's Hospital of Philadelphia.

Dr. Ashtari used a DTI measure called the apparent diffusion coefficient (ADC) to measure cerebrospinal fluid (CSF) changes in the sulci as a surrogate for gray matter changes. The ADC is an average measure of the diffusion of water in all directions in a single voxel. ADC is greatest in CSF and least in coherent, healthy white matter. The idea that ADC could be a surrogate marker is based on the observations that cortical brain atrophy is associated with a corresponding increase in sulcal and ventricular CSF, meaning that CSF may be considered a tracer for detecting cortical gray matter reductions.

ADC rises with increasing CSF volume, which may represent gray matter volume loss. "We are basically saying that if you look at the water motion in the cerebrospinal fluid that is in the sulci, whatever changes that happen to the CSF could be a surrogate for the gray matter right next to it," said Dr. Ashtari.

Dr. Ashtari used the new technique to look for potentially subtle differences in gray matter volume in high-functioning autism or Asperger syndrome patients.

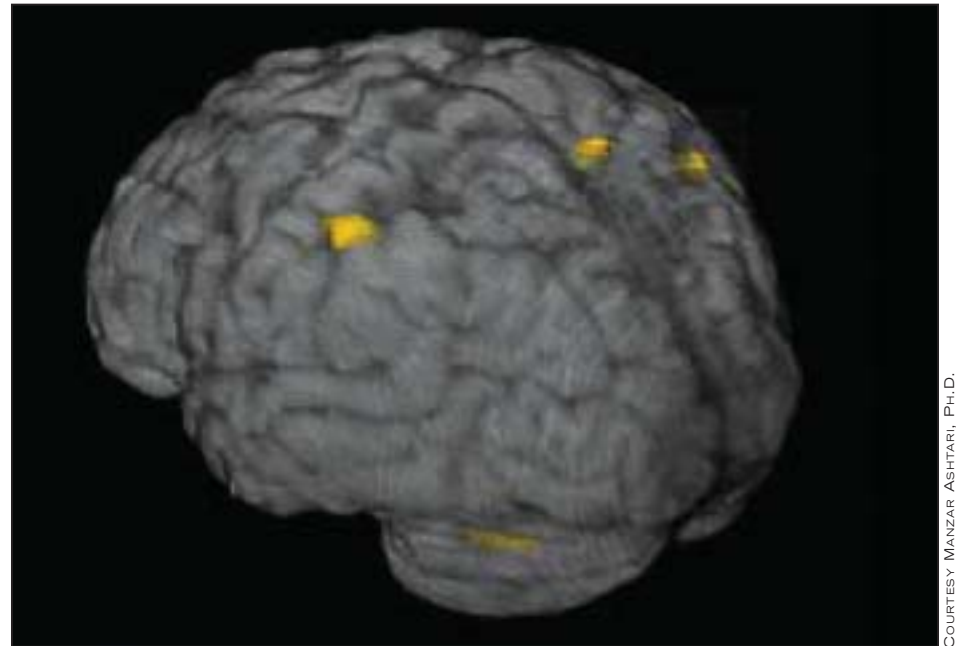
The autism imaging literature on white, gray, and whole-brain volumes is very confusing in part because imaging findings vary by age, she said.

The brains of autistic children appear not to go through normal growth processes, as compared with the neuronal development of healthy children. Although autistic children start with larger brain volumes, eventually normal children catch up with and pass their autistic counterparts in terms of gray or white matter volume.

In her study, Dr. Ashtari looked only at preadolescent boys (average age 11 years for both controls and autistic children). Autism most often affects boys, by a 4:1 ratio. She specifically looked at a preadolescent population because previous work of hers showed a big spurt of myelination during adolescence in healthy participants (Neuroimage 2007;35:501-10).

Quite unexpectedly, "We found increased gray matter [decreased ADC values] in several areas of the cortex," in autistic preadolescents. "I don't want this study to be generalized. I'm not claiming that if you look at [autistic] adults, this is what you'll see," said Dr. Ashtari.

The areas of abnormality occurred most often in the parietal lobe, which has a strong connection with the prefrontal region. "I concluded that I'm looking at mirror neuron abnormalities in autistic kids," she said. Mirror neurons are thought to fire both when an animal acts and experiences an emotion or sensation and when the animal observes the same action, emotions, and sensations in others. They mirror the behavior of another animal, as though the observer were acting itself. These neurons have been directly observed in primates and are believed to exist in humans.



Apparent diffusion coefficient–based morphometry revealed clusters of increased gray matter (highlighted) in the right and left parietal cortex of an autistic boy.

Next, Dr. Ashtari looked for possible correlations between increased gray matter and specific autism behaviors. To do this she used the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule.

They also measured the children's IQs. She plotted the inverse of the ADC (which represents gray matter changes) against the measures of stereotyped behavior/restricted interest. She found that the greater the gray matter values, the poorer the performance (correlation factor of 0.6; P value of .04). She also plotted gray matter changes against measures of abnormalities in social interactions. Greater gray matter volume trended toward greater abnormalities in social interaction (correlation factor 0.5; P .08). Next, she plotted gray matter volume

against IQ for both normal children and those with autism. She found that normal children have increased IQ with increased gray matter but there was no correlation in children with autism and IQ. In fact, the trend was the reverse; with increased gray matter, children with autism showed a decreased IQ.

"The conclusion I made was that this increased gray matter is nonfunctioning gray matter," said Dr. Ashtari.

"There was one other area of abnormality that we found and that was deep inside, not really on the cortex ... basically around the right amygdala area," said Dr. Ashtari. The amygdala is a center for emotional processing. The researchers found decreased gray matter in the right amygdala of children with autism.

—Kerri Wachter

C. immitis Meningitis Can Present Without Hydrocephalus

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Hydrocephalus is an easy clue to potential *Coccidioides immitis* meningitis, but a subacute course of the disease can make it much more difficult to pin down the diagnosis, Dr. Parvin Azimi said at the annual meeting of the American Academy of Pediatrics.

She described two cases of chronic meningitis that illustrate different manifestations of *C. immitis*.

The first patient, a 16-year-old African American boy, had a history of exposure to soil in endemic areas, the likely source of his fungal infection, said Dr. Azimi, director of infectious diseases at Children's Hospital and Research Center, Oakland, Calif.

The patient presented with a 5-week history of headache, vomiting, and decreased energy, with no response to treatment with oral amoxicillin. He had a fever higher than 100° F with a stiff neck, flat affect, and lethargy.

A spinal tap showed that the cerebral spinal fluid (CSF) had a high protein level (148 mg/dL) and a low glucose level (15 mg/dL). The RBC count was 3/mcL and the WBC count was 380/mcL with 25% polymorphonuclear leukocytes (PMNs), 66% lymphocytes, and 9% monocytes. Gram stain and culture were negative for bacteria.

"Obviously, the spinal fluid findings look very much

like TB," so clinicians did a work-up for tuberculosis, she said. A purified protein derivative (PPD) skin test for tuberculosis produced no induration, although "that doesn't mean the patient doesn't have TB," she acknowledged. Chest x-ray, cranial CT scan, and EEG were all normal.

The teenager had been traveling to Corpus Christi, Tex., where he collected insects and played with his pet tarantula and puppy during his visit. He sought help for his symptoms at a Texas hospital and was sent home to California with a diagnosis of viral meningitis.

The headaches and vomiting continued. A repeat spinal tap 3 weeks after the first one showed that the CSF protein level had increased (176 mg/dL) and the glucose level decreased (9 mg/dL). The RBC was 1/mcL and the WBC was 737/mcL with 33% PMNs, 51% lymphocytes, 15% monocytes,

and 1% macrocytes.

Infectious disease consultants were called in at this point. They ordered fungal, parasitic, and acid-fast bacilli studies and started the patient on empiric therapy for presumed TB meningitis pending results of cultures.

The CSF was negative for cryptococcal antigen and amebic trophozoites, ruling these out of the differential diagnosis, Dr. Azimi said. An HIV test was negative.

Finally, the CSF and sera were found to be reactive to *C. immitis* antibodies.

Fewer than 1% of cases of *Coccidioides* infection become disseminated, but half of disseminated cases have central nervous system involvement.

In the second case described by Dr. Azimi, a 19-month-old Filipino-Latino boy from Antioch, Calif., presented with a 6-month history of decreased activity, clinging behavior, and poor growth. In the past 6 days, he'd had lethargy, frequent falls, and difficulty walking. On physical exam, he was mildly feverish and irritable, and refused to stand or walk.

A head CT scan showed hydrocephalus "that was significant enough that it prompted surgeons to place a shunt quickly" to provide decompression, she said. Hydrocephalus is a well-known complication of *Coccidioides* meningitis.

The patient's CSF showed highly elevated protein (319 mg/dL) and low glucose (25 mg/dL). The RBC was 340/mcL and the WBC was 117/mcL with 65% lymphocytes and 4% PMNs, among other findings. CSF Gram stain and cultures were negative, as were a chest x-ray and PPD skin test for TB.

As in the first patient with subacute disease, this patient's CSF and sera were reactive for *C. immitis* antibodies.

Fewer than 1% of cases of *Coccidioides* infection become disseminated, but half of disseminated cases have CNS involvement, Dr. Azimi said. Dissemination is more likely in males, Filipinos, African Americans, and people with deficient cell-mediated immunity.

Oral fluconazole is the treatment of choice, continued for life. Stopping therapy risks a recurrence in 35% of cases. Itraconazole or amphotericin has been used as an alternative to fluconazole in some cases.

"This is a very, very difficult disease to treat," Dr. Azimi said. Meningitis is fatal without treatment. ■