Inform Women of Possible Risks

Autism *from page 1*

take valproate while pregnant should be informed of the possible risks of autism and are encouraged to discuss them with their doctor[s]. Those who are taking valproate should not stop their treatment without speaking to their doctor[s] first."

The study enrolled 620 women in Liverpool and Manchester between 2000 and 2006 and has collected information on 632 live births. Of these births, 296 of the babies were born to women with epilepsy, including 249 women who were taking antiepileptic drugs (AEDs) at the beginning of their pregnancies (64 were exposed to valproate, 44 to lamotrigine, 76 to carbamazepine, 14 to other monotherapy treatments, and 51 to polytherapy). The remaining 47 babies were born to mothers with epilepsy who were not taking medication.

Neuropsychological tests were done at ages 1, 3, and 6 years; at the end of the study, most—68%—of the children were aged 6 years and older, about 4% were under age 3 years and about 28% were aged 4-5 years).

Of the 632 children, 9 met the DSM-IV criteria for autism spectrum disorders, the authors reported. Another child with a lack of attention, social difficulties, and other ASD features was included in the analyses as a case of ASD. None of the parents of the children with ASD was aware of a family history of autism or another pervasive developmental disorder.

Of these 10 children, 7 had been exposed to an AED during pregnancy (nearly 3% of the 249 children exposed to AEDs). Of these seven children, four had been exposed to valproate (about 6% of the valproate-exposed children).

One of the remaining three children was exposed to valproate in combination with lamotrigine (2% of the 51 exposed to polytherapy), one was exposed to phenytoin (11% of the children on exposed to phenytoin), and one to lamotrigine (2% of the children exposed to lamotrigine).

Of the 336 children who were controls (whose mothers did not have epilepsy), 3 (0.9%) were diagnosed with ASD (one case of autism; two with Asperger's syndrome).

The rate of ASD or features of ASD—6%—in the children exposed to valproate alone during pregnancy was seven times greater than in the controls (0.9%) and is higher than the incidence reported in the general population (6 per 1,000 children).

No conclusion can be made about the risk associated with lamotrigine or phenytoin exposure, based on one case each, they added. Among the limitations of the study is that many of the children were younger than the average age at which ASD usually is detected and diagnosed, and the results are preliminary and need to be confirmed with more prospective studies.

In an interview, Dr. Lewis Holmes, director of the North American AED Registry at Massachusetts General Hospital, Boston, said that it has been clear that, anecdotally and in the published literature, the risk of autism is increased among children exposed to valproate in utero. He said he has seen a few cases of children whose mothers took valproate during pregnancy, whose children "unequivocally" had autism. This increased risk also has been seen in thalidomide-exposed babies.

He added that valproate is associated with many other malformations, a high risk for serious IQ deficits, as well as the link to autism, but physicians often only associate it with a greater risk for neural tube defects.

Dr. Gideon Koren, professor of pediatrics, pharmacology, pharmacy, and medical genetics at the University of Toronto, said in an interview that the association between in utero exposure to valproate and ASD has been suspected for a while. "The present study, being prospective, systematic, and controlled, provides strong evidence for the causative role" of valproate in ASD.

Dr. Koren is director of the Motherisk Program at the Hospital for Sick Children, Toronto, a teratogen information service that also conducts research in this area. Pregnant women and their health care providers who consult Motherisk about valproate are counseled about these risks, "as should any physician caring for women treated with valproate for epilepsy or other conditions," he advised. ■

Any woman taking an antiepileptic drug for any reason during pregnancy can enroll in the North American AED registry at Massachusetts General Hospital by calling 888-233-2334.

Auditory Response Delays May Fuel Language Deficit in Autism

BY PATRICE WENDLING
Chicago Bureau

Chicago — Researchers have identified delays in auditory processing in the brains of children with autism spectrum disorders.

Although the response to various sounds is delayed by only a fraction of a second, this delay may underpin the subsequent language and communication impairment seen in children with autism, principal investigator Timothy Roberts, Ph.D., reported at the annual meeting of the Radiological Society of North America.

Dr. Roberts and his colleagues at Children's Hospital in Philadelphia (CHOP) used a type of imaging called magnetoencephalography to measure the electromagnetic field produced during neuronal activation in 30 children with autism spectrum disorders, with or without concomitant language impairment, and 34 age-matched typically developing controls

Getting children to sit still for any kind of testing can be challenging, with recordings possible in 51 (80%) of the cohort. Their mean age was 10 years and roughly 95% were male.

Recordings were made using a 275-channel whole-head unit while the children were watching a silent movie of their choice without performing any tasks.

When introduced to single tones ranging in frequency from 100 Hz to 1,000 Hz, there was a strong evoked response in typically developing children and a consistent and significant delay of about 20 milliseconds in the response of children with autism.

The delay was particularly pronounced at the midrange tones of 300-500 Hz—the frequency range where the bulk of human speech is located, Dr. Roberts said.

"This is a very critical range to be manifesting such a delay in processing sounds," he said. "It's like the signal to have a response simply doesn't get to that part of the brain on time, like when the freeway is clogged up with cars and you can't get to where you're going on time. That delay can have downstream consequences."

When the children were introduced to mismatched tones, there was a significant 35- to 50-millisecond delay in the brains of autistic children to register that one tone was different from another. The delay was most pronounced in the autistic children with language impairment, averaging 40 milliseconds slower than typically developing children.

Forty to 50 milliseconds is about one-twentieth of a second, which doesn't sound like much unless one considers that each syllable of speech lasts only about a quarter of a second, said Dr. Roberts, vice chair of research in the department of radiology at Children's Hospital in Philadelphia.

"To have a 50-millisecond delay in registering that a syllable has changed could be catastrophic," he said. For example, with the word "elephant," he said, "you're still dealing with the 'el' when everyone else has moved on to the 'phant.' You can never catch up, and this could be catastrophic."

As for how the findings might be used in clinical practice, Dr. Roberts said in an interview that they are hoping to use brain activity patterns to establish a "suite of biomarkers" for autism that could be used to improve classification of the disorder and guide treatment.

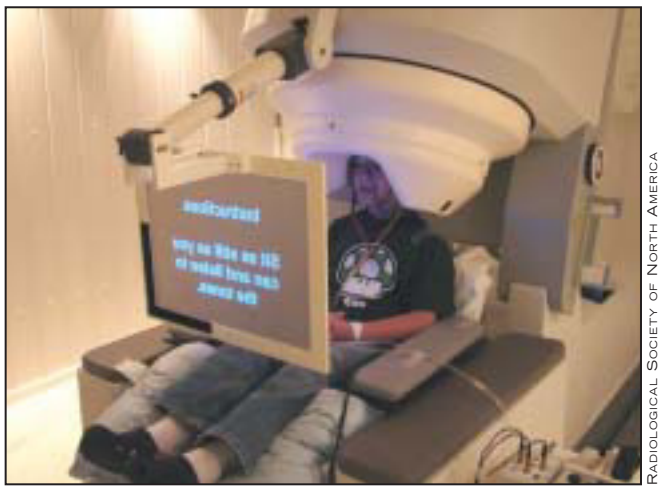
"It may be that we start addressing the heterogeneity of the autistic population by subtyping," he said. "Based on that subtyping, one might triage these patients into different behavioral interventions. It's speculative, but it suggests that if you have an auditory processing deficit that part of your therapy ought to be working on improving auditory processing, whereas if you don't have this particular deficit, then maybe your intervention should target something else."

In a step toward that goal, the investigators used receiver operating characteristic curves to determine if latency responses to various sounds could distinguish study participants with autism from those without the disorder.

What they found was a significant correlation between autism and the response to a single beep tone in the 500-Hz range, resulting in a sensitivity of 82% and specificity of 70%. The correlation was also significant when mismatched tones were used as stimuli, producing a sensitivity of 88% and specificity of 74%, Dr. Roberts reported.

Magnetoencephalography (MEG) has typically been used for epilepsy evaluations, but is emerging as a neurologic/radiologic tool. It lends itself to disorders of connectivity such as autism or Parkinson's disease because of its ability to evaluate the timing of brain activity and the propagation of activity from one area of the brain to another, Dr. Roberts said.

"MEG gives us a reasonable idea of the spatial location of the activity, but gives us a wonderful view of the timing of it," he said. Such split-second measurements are beyond the scope of spatial or locationist modalities like MRI or PET.



Radiological Society of North America

Children with autism had pronounced response delays in the midfrequency ranges that are key to human speech.

The investigators have successfully made a recording in an 18-month-old, and are currently recruiting 100 families to study the use of MEG in neonates and young children. The hope is for early intervention during the crucial stage of language development, possibly in the form of slowing down speech to the affected child.

Unfortunately, there are only 100 MEG machines in the world and two in the U.S. And in a time of global economic slowdown, MEG is an expensive technology, with a price tag of $2 million for the machine alone.

There have been previous reports of MEG in autism, but the research was quite speculative and related autism to its overlap with epilepsy phenotypes, he said.

Future studies may also investigate differences in brain activity between the alpha, beta, and gamma power bands—a phenomenon that has recently been observed in patients with Parkinson's. In the current study, the only significant difference between bands was abnormal patterns of predominantly lower-intensity gamma oscillation in the superior temporal gyrus of children with autism, Dr. Roberts said.

The study was sponsored by the National Institutes of Health and the Nancy Lurie Marks Family Foundation. The investigators reported no conflicts of interest.

To watch a video interview of Dr. Roberts, go to: http://www.youtube.com/watch?v=yoBQ3G3WhiA. ■