Auditory Processing Delays May Explain Autism

BY PATRICE WENDLING
Chicago Bureau

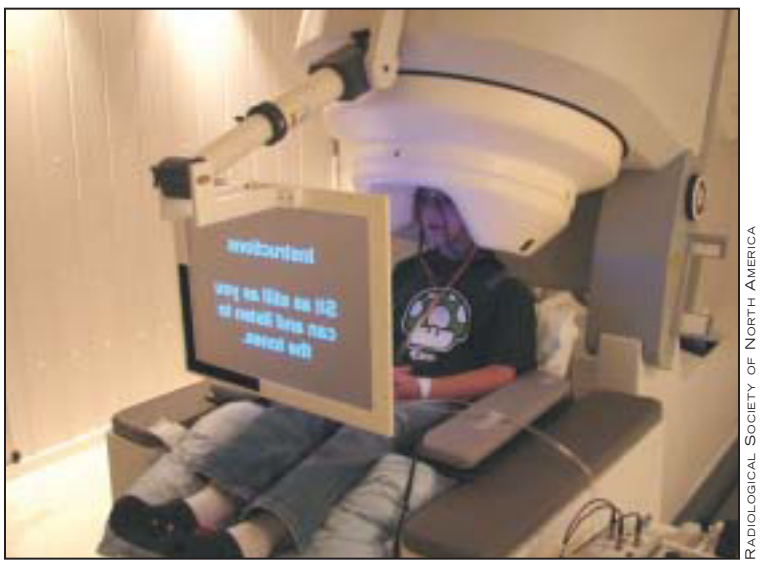
CHICAGO — Researchers have identified delays in auditory processing in the brains of children with autism spectrum disorders.

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 colleagues at Children's Hospital in Philadelphia used magnetoencephalography imaging 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.

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.



Radiological Society of North America

Magnetoencephalography can evaluate the timing of brain activity and the propagation of activity from one area of the brain to another.

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. That is about 1/20 of a second, which doesn't sound like much, except that each syllable of speech lasts only about a 1/4 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 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, 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.

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.

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.

Researchers have made a recording in an 18-month-old, and are 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 by slowing down speech to the affected child.

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 an interview with Dr. Roberts, go to: http://www.youtube.com/familypracticenews. ■

Sodium Valproate Exposure In Utero Linked to Autism Risk

BY ELIZABETH MECHCATIE
Senior Writer

Exposure to sodium valproate early in pregnancy may increase a child's risk for developing an autism spectrum disorder, judging from preliminary results from an ongoing study on the effects of in utero exposure to antiepileptic drugs.

In the study, those children exposed to valproate early in pregnancy were at a sevenfold greater risk of developing autism spectrum disorder (ASD), compared with children whose mothers did not have epilepsy, reported investigators from the Liverpool and Manchester Neurodevelopment Study Group, England (Neurology 2008;71:1923-4).

"The potential risk for autism in this study was substantial for children whose mothers took valproate while pregnant, but more research needs to be done since these are early findings," one of the authors, Gus Baker, Ph.D., of the University of Liverpool (England) said in a statement issued by the American Academy of Neurology, which publishes Neurology. "However, women who 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 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 were 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 3 children was exposed to valproate in combination with lamotrigine (2% of the 51 exposed to polytherapy), 1 child was exposed to phenytoin (11% of the children on exposed to phenytoin), and 1 child exposed 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 and two with Asperger's syndrome).

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

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, they emphasized.

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. 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 that the association between in utero exposure to valproate and ASD has been suspected for awhile. "The present study, being prospective, systematic, and controlled, provides strong evidence for the causative role" of valproate in ASD," he said in an interview. ■

Anyone taking an antiepileptic drug during pregnancy can enroll in the North American AED registry at Massachusetts General Hospital by calling 1-888-233-2334.