Antiepileptic Adherence Trajectories Described

BY ESTHER FRENCH

FROM JAMA

VITALS

Major Finding: Nonadherence rates for antiepileptic medication reached 58% in the first 6 months after epilepsy diagnosis.

Data Source: A 6-month, single-center study of 124 children with newly diagnosed epilepsy.

Disclosures: The study was funded by a grant from the National Institutes of Health. Dr. Modi disclosed that she has been a consultant for Novartis Pharmaceuticals. Another study author disclosed speaker and adviser relationships with companies that manufacture antiepileptic drugs.

Some level of nonadherence to antiepileptic drug monotherapy was apparent in four of five adherence trajectories described in a single-center study of 124 children with newly diagnosed epilepsy.

Based on these findings, "clinicians should consider routinely assessing adherence to antiepileptic drug therapy in all children with epilepsy. Self-report measures of adherence have recently been developed for children with epilepsy and could be used in routine clinical care," wrote Avani C. Modi, Ph.D., and her co-authors at Cincinnati Children's Hospital Medical Center.

They reported that the five trajectories included "severe early nonadherence" for 13% of patients, "severe delayed nonadherence" for 7% of patients, "moderate nonadherence" for 13%, "mild nonadherence" for 26%, and "near-perfect adherence" for 42%. The authors described the study as the first to examine adherence trajectories for children with epilepsy.

According to this group-based trajectory modeling, almost 60% of the patients were nonadherent for the first 6 months of treatment. This was a "surprising" figure, given the results of the investigators' previous study, which found a nonadherence rate of 20% in the first month of treatment, they wrote (JAMA 2011;305:1669-76).

Prior cross-sectional studies of children with epilepsy have described self-reported nonadherence rates of 12%-35%, but they had "major methodological problems," according to the authors.

The children in the current study had a mean age of 7.2 years (range of 2-12 years) and 64% of them were male. The cohort was 76% white, 17% black, 7% biracial or multiracial, and 1% Asian; 3% were Hispanic. Nearly half of the cohort had idiopathic localization-related epilepsy (48%), and others had idiopathic generalized epilepsy (19%), idiopathic unclassified epilepsy (15%), cryptogenic localization-related epilepsy (8%), cryptogenic generalized epilepsy (5%), symptomatic localization-related epilepsy (5%), or symptomatic generalized epilepsy (1%).

A majority of the patients (60%) received carbamazepine, and others received valproic acid.

An electronic monitoring system measured adherence rates by recording when the medicine bottle was opened or closed. During follow-up appointments at 1 month post diagnosis and every 3 months thereafter, a pediatric epileptologist or pediatric epilepsy nurse practitioner recorded seizure frequency, adverse events, and any change in medication for controlling seizures or reducing intolerable adverse events.

Dr. Modi and her associates found no effect on adherence rates by other variables such as age, sex, caregiver marital status, seizure type and frequency, initial and total number of antiepileptic medications, frequency of adverse events, and who first observed the child's seizure.

The five adherence groups exhibited significant intra- and interpatient variability, according to the investigators. Children who had severe early nonadherence "took between one-quarter and one-half of their antiepileptic drug doses in the first month of therapy and then became completely nonadherent over time, suggesting 'volitional' nonadherence, wherein parents may have actively decided that their children should not take antiepileptic drugs based on reasoned decisions."

Children in the severe delayed nonadherence group initially had about 90% adherence, but that gradually declined to about 20% after 6 months. This decline "may reflect caregivers who occasionally missed giving antiepileptic drug doses with no major health consequence (e.g., seizure) and, thus, made decisions to discontinue antiepileptic drugs."

Dr. Modi and her coauthors said that those two groups are the children and families in greatest need of "adherence interventions focused on discussing the family's beliefs regarding epilepsy and antiepileptic drugs and providing education about treatment misconceptions."

Children in the moderate nonadherence group, which averaged taking about 70% of their doses, may have missed taking their medication in blocked periods of time such as on vacations and during weekend sports, and "would benefit from problem-solving regarding barriers to adherence and instituting general behavioral and organizational strategies."

The investigators wrote that the "often intrinsic link between socioeconomic status and education" makes it plausible that the limited financial resources of many of the families of children that fell into groups with mild or worse rates of nonadherence affect tangible aspects of poor adherence, such as the inability to pay for medications, as well as the intangible aspects, such as parental supervision. ■

Maternal Autoantibodies Appear to Be Linked to Autism

BY DOUG BRUNK

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

HONOLULU – Certain maternal autoantibodies are associated with development of autism spectrum disorders, results from a large ongoing analysis demonstrate.

The finding lays the groundwork for an eventual diagnostic test for autism, said Judy Van de Water, Ph.D.

"Currently there is no biologic marker for autism," said Dr. Van de Water, an immunologist at the University of California, Davis. "It's completely defined by behaviors."

The maternal immune response in autism is of interest to researchers because of its role in neurodevelopment. "Maternal IgG isotype antibodies readily cross the placenta and are known to persist for up to 6 months postnatally in the child," Dr. Van de Water said. "In addition, maternal antibodies have been shown to cause changes in fetal development in several known autoimmune disorders, such as SLE."

In 2002, Dr. Van de Water and her associates began to collect blood samples from families as part of the Childhood Autism Risk from Genetics and the Environment (CHARGE) study.

They sampled the study population from three groups of children aged 2-5 years: children with autism (currently includes more than 800 families); typically developing children without autism or other developmental disabilities selected from the general population (currently 600 families enrolled); and children with developmental disabilities without autism (currently 220 families enrolled).

In the original experimental design, Western blots against human fetal brain protein were performed with 61 mothers of children with autism (36 regressive and 25 early onset), 40 mothers of children with developmental delay, and 62 mothers of typically developing children (Neurotoxicology 2008;29:226-31).

The investigators found that seven mothers of children with autism (12%) had IgG reactivity to fetal brain proteins at bands 37kDa and 73kDa. "We did not see this pattern in the typically developing controls or in the developmentally delayed population, so this seemed to be very specific for autism," Dr. Van de Water said.

VITALS

Major Finding: IgG reactivity to fetal brain proteins at bands 37kDa and 73kDa was significantly associated with diagnosis of full autism; reactivity to proteins at bands 39kDa and 73kDa was significantly associated with diagnosis of the broader autism phenotype.

Data Source: Western blots against human fetal brain protein performed in 204 mothers of children diagnosed with autism, 71 mothers of children diagnosed with an autism spectrum disorder, and 183 mothers of typically developing children.

Disclosures: Dr. Van de Water has received personal compensation for activities with Pediatric Bioscience as a consultant, and holds stock and/or stock options in the company. She has also received royalty payments from the University of California, Davis.

Analysis of autoantibody profiles of an additional 458 mothers – 204 mothers of children diagnosed with autism, 71 mothers of children diagnosed with an autism spectrum disorder, and 183 mothers of typically developing children – continues to yield highly significant associations between the presence of IgG reactivity to fetal brain proteins at bands 37kDa and 73kDa and a diagnosis of full autism.

Dr. Van de Water and her associates also discovered an association between the 39kDa and 73kDa bands and a diagnosis of the broader autism phenotype, "though this pattern is less frequent in the full autism group," she said.

"We think we may have a very interesting biomarker, but is there a pathologic significance to these antibodies?" she asked. To find out, the researchers analyzed behavioral characteristics associated with maternal antibodies to fetal brain proteins.

Children of mothers who demonstrated reactivity at bands 37kDa and 73kDa had less expressive language. Similar results were seen in children of mothers who demonstrated reactivity at all three bands. In contrast, children of mothers who demonstrated reactivity at bands 39kDa and 73kDa had higher scores on the Aberrant Behavior Checklist irritability subscale.

A pilot study in monkeys conducted by Dr. Van de Water and her associates demonstrated behavioral changes in offspring following passive transfer of maternal IgG during the late first and early second trimesters (Brain Behav. Immun. 2008;22:806-16). Subsequent studies have confirmed that passive transfer of these antibodies into an animal model can recapitulate some behaviors characteristic of autism. More confirmatory studies are underway. ■