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Autism: Electroencephalogram Abnormalities and Clinical Improvement With Valproic Acid

Autism is a severe disorder of social and communicative development. Although there are a number of biomedical causes of autistic symptoms,[1] a cause has not been identified for the majority of children with this condition. There is a much higher prevalence of epilepsy and electroencephalographic (EEG) abnormalities in autistic children as compared with controls.[2,3] However, it is not clear whether autistic children with epileptiform abnormalities on EEGs (spikes and/or sharp waves) who have never had seizures would benefit from anticonvulsants. In a comprehensive review of autism, Minshew et al[4] mentioned nonconvulsive seizures as a possible association with autism but recommended further testing and anticonvulsants only in those children with clinical indications of possible epileptic phenomena. More significantly, in a recent review of autism, Rapin[5] wrote: "There is little evidence to suggest that seizure-free children with rare spikes or other paroxysmal EEG discharges will benefit from anticonvulsants."

In my report, I describe three children with autism who had no clinical suggestion of seizures. Each child had epileptiform findings on EEGs. Each significantly improved with the use of valproic acid.

Report of Patients. *Patient 1.* A boy, aged 5 years 2 months, was seen for assessment of speech delay and autistic symptoms. The pregnancy was without complications. Labor was full term and started spontaneously. Because the labor failed to progress, he was delivered by cesarean section at a birth weight of 3.9 kg. There were no complications at the time of birth and his postnatal course was unremarkable. His only past medical problem was recurrent otitis media. His gross motor developmental milestones were normal. He started saying his first words at 4 years of age. Owing to delayed development of language, he underwent a speech therapy assessment at 4 years of age. His receptive language skills were from 14 to 16 months of developmental age and expressive language skills, 13 to 15 months. Results of formal hearing and opthalmologic assessments were normal. There was no relevant family history, and he was taking no medications. There was no history of seizures or of any events that could have been interpreted as being potentially ictal or episodic in nature.

At the time when he was first seen, his only spoken words were yes and no, besides fairly continuous babbling sounds with no communicative intent. He would not engage with peers in any activities and displayed no imaginative use of toys. He would place toys in lines and would not use them appropriately. His head circumference was 52.0 cm (50th percentile). His general physical

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examination only revealed one café au lait spot on the dorsum of his left wrist. His neurologic examination did not reveal any abnormalities. He qualified for the diagnosis of autism by satisfying the following *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*)[6] criteria for autism: A1, A4, A5, B1, B3, B4, B5, and C5.

Results of additional laboratory testing that included screening for thyroid functioning, levels of serum amino acid, lactate, and pyruvate, complete blood cell count, blood chemistry studies, and chromosome analysis, including cultures for fragile X, were normal. During sleep, the EEG revealed single and short runs of spike discharges from the right frontal-temporal area, with phase reversals at T_4. A computed tomographic scan of the head was normal.

At the age of 5 years 3 months, he started valproic acid therapy, 125 mg three times a day. Within a month his language and social skills started to improve significantly. When he was seen for a reevaluation at the age of 5 years 8 months, he was freely speaking in four- to five-word sentences, he knew his telephone number and address, he made inquiries about friends and relatives, and he had made strides in socially interacting with peers and adults. He technically no longer qualified for the diagnosis of autism since the following *DSM-III-R*[6] criteria for autism no longer applied to him: A1, A4, A5, B1, B3, B4, and B5. He has maintained his clinical improvement and has remained clinically stable for 11 months.

Patient 2. A 3-year-old girl was seen for assessment of speech delay. The pregnancy was without complications. Labor was full term and started spontaneously. She was born of a vaginal, vertex presentation at a birth weight of 3.4 kg. There were no difficulties at the time of birth or subsequently. Her only medical history was an episode of mild croup at 1 year of age, one bout of bronchi-

tis, and several episodes of otitis media. Her developmental milestones were entirely normal, with independent walking and speaking of words (mommy, bye-bye, and bad boy) at 1 year of age. Between the ages of 1 and 2 years, there was a gradual change. She lost interest in talking and started to use hand gestures. She became much more withdrawn and disinterested in her toys and peers. She started to line up toys by size or color and not use them appropriately. She would engage in no imaginative activities. She enjoyed watching spinning objects and would spin herself uncontrollably. Her personality became very rigid, and she insisted that objects be placed in the house exactly as she liked them. She would have temper tantrums when things were disturbed. The family history was unremarkable, and she was taking no medications. There was no history of seizures or of any events that could have been interpreted as being potentially ictal or episodic in nature.

On examination, her head circumference was 51.0 cm (75th percentile). She did not generate any words other than babbling sounds. She responded to noises but not to her name being called. She lined up toys but did not use them in an appropriate fashion. She displayed no social interactions and maintained poor eye contact. Her general physical examination did not reveal any abnormalities. There were no abnormalities detected on neurologic examination. She qualified for the diagnosis of autism by satisfying the following *DSM-III-R*[6] criteria for autism: A1, A3, A4, A5, B1, B2, B3, C1, C2, C4, and C5.

Results of additional laboratory testing that included levels of serum amino acid, lactate, pyruvate, and serum lead, screening for thyroid functioning, complete blood cell count, blood chemistry studies, and chromosome analysis, including cultures for fragile X, and results of audiometric screening were all normal. During sleep the EEG revealed independent, sharp waves in both frontal regions.

At the age of 3 years 2 months, she started valproic acid therapy, 125 mg twice a day, with subsequent therapeutic blood levels of 62 μg/mL. She was seen for a reassessment at age 3 years 5 months. By that time, she had completely stopped spinning, had stopped flapping her hands and fingers, had started to say understandable words, had started to use toys appropriately (eg, would dress and undress dolls), had started to engage in imaginative activities (eg, acting out scenes between dolls), had improved her eye contact and social interactions, and had even picked out videotapes that she was interested in viewing. She technically no longer qualified for the diagnosis of autism since the following *DSM-III-R*[6] criteria for autism no longer applied to her: A1, A3, B1, B2, B3, C1, C2, and C5. She has maintained her clinical improvement and remained clinically stable for 11 months.

Patient 3. A girl, aged 4 years 5 months, was seen for assessment of speech delay. The pregnancy was without complications. Labor was full term and was induced with oxytocin citrate. She was born of a vaginal, vertex presentation at a birth weight of 3.1 kg. There were no difficulties at the time of birth or postnatally. She had no significant medical history. Her gross motor developmental milestones were entirely normal, with crawling at 7 months of age and walking at 12 months of age. She said the word mama at 6 months of age, but there was no further development of language until the age of 2½ years. Results of audiometric screening were normal. There were two maternal uncles and two aunts who were believed to have learning disabilities. She was taking no medications. There was no history of seizures or of any events that could have been interpreted as being potentially ictal or episodic in nature.

At the time when she was first seen, she had no imaginative activities. She would not use toys appropriately but would compare them, stack them, or line them up. She had a fixation for putting balls of hair or dust on objects. She had no involvement with or interest in peers. She was able to speak in sentences, but much of her speech was echolalic. When asked her name, she would repeatedly say her sister's name. She did not identify her mother. She was not able to understand one-step commands. She had very minimal eye contact. Her head circumference was 50.0 cm (50th percentile). Her general physical examination revealed one café au lait spot on her left thigh. Her neurologic examination did not reveal any abnormalities. She qualified for the diagnosis of autism by satisfying the following *DSM-III-R*[6] criteria for autism: A1, A3, A4, A5, B2, B3, B4, B5, and C5.

Results of additional laboratory testing that included levels of serum amino acids, lactate, and pyruvate, screening for thyroid function, complete blood cell count, blood chemistry studies, and chromosome analysis, including cultures for fragile X, and results of audiometric screening were all normal. The EEG revealed the presence of independent, sharp waves in both the frontal and central regions when the patient was asleep.

At the age of 4 years 7 months, she started valproic acid therapy, 125 mg three times a day, with subsequent therapeutic blood levels of 60.6 μg/mL. When she was seen for reevaluation 1 month later, she had made a substantial improvement. She was speaking appropriately and would identify herself and her mother by name. She would play with dolls appropriately and would carry on conversations between them. She easily followed one-step commands. She expressed sadness and loneliness at the absence of an expected relative. She would apologize for misconduct when reprimanded. She technically no longer qualified for the diagnosis of autism since the following *DSM-III-R*[6] criteria for autism no longer applied to her: A1, A3, A5, B3, B5, and C5. She has maintained her improvement and has remained clinically stable for 7 months.

Comment. All three children satisfied *DSM-III-R*[6] criteria for autism, had no other identified biomedical expla-

nation for their autistic symptoms, and had epileptiform findings on their EEGs. Within 1 month of starting valproic acid therapy, each child had a significant improvement in language and social skills. Although their autistic symptoms had not fully resolved, each one technically no longer qualified for the diagnosis of autism.

Two patients with autism with abnormal findings on EEGs and a positive response to anticonvulsants have been described.[7] However, in both of these cases the patients had clinically described staring spells that suggested an ongoing seizure disorder. None of the three patients described in my report had any suggestion of ictal or episodic events.

Acquired aphasia in children with epileptiform abnormalities on EEGs, with or without clinical seizures, is a well-recognized neurologic disorder (the Landau-Kleffner syndrome).[8] However, at the time of onset of their language disturbance,[8] and even with long-term follow-up,[9] these children do not qualify for the diagnosis of autism. Thus, the children described in my report are distinctly different from those with acquired epileptic aphasia.

The incidence of epileptiform abnormalities on EEGs in children without epilepsy has been reported to be 3.5% (in a study of 3726 schoolchildren)[10] and 4% (in a study of 50 children).[11] In comparison, in a series of 139 autistic children without epilepsy but with EEG recordings, 8% (11 children) had epileptiform abnormalities.[3] This report does not state whether the EEG tracings were obtained with the patients awake or asleep. In all three children in my report, the epileptiform abnormalities were recorded only during sleep. It is possible that in the retrospective study,[3] a significant proportion of EEGs were obtained when the patients were awake. Thus, epileptiform abnormalities during sleep may have been missed, and the actual incidence of EEG abnormalities would have been decreased. Nevertheless, it appears that none of the 11 children were treated with anticonvulsants.[3]

Of significance is the fact that all three children in my report were first seen and their conditions were evaluated in an outpatient child neurology clinic over a 6-month period. Over this same period, only two other autistic children were seen who did not have EEG abnormalities and who were not treated with anticonvulsants. This finding suggests that the incidence of epileptiform abnormalities on EEGs in autistic children may be more common than previously reported.[3]

It should be noted that the three children in my report were young (age range, from 3 to 5 years) when treatment was started.

The fact that all three children significantly improved strongly suggests that a prospective study of young autistic children should be undertaken in which EEGs would be obtained when the children are awake and asleep. Those children who have epileptiform abnormalities on EEGs should then undergo detailed, standardized, behavioral tests and should be treated with a trial of anticonvulsants. Valproic acid could be compared with carbamazepine. Clinical effectiveness should be monitored using a defined protocol.

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