

SEARCHING FOR AUTISM SYMPTOMATOLOGY IN CHILDREN WITH EPILEPSY—A NEW APPROACH TO AN ESTABLISHED COMORBIDITY

The Prevalence of Autistic Spectrum Disorder in Children Surveyed in a Tertiary Care Epilepsy Clinic

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It is well documented that children with autistic spectrum disorder (ASD) have an increased prevalence of seizures; however, studies have not been done to evaluate the prevalence of ASD in children with epilepsy. This comorbidity is important to define as early diagnosis and intervention in some children with ASD has been shown to improve outcome.

METHOD: Children with epilepsy seen in a tertiary care epilepsy clinic were evaluated using validated autism screening questionnaires (ASQ). In addition, questions about sleep-related disorders, behavior, seizure characteristics, antiepileptic agents, and body mass index (BMI) were requested. An attempt was then made to determine if there was a correlation between the factors identified and ASD.

RESULTS: Of the 107 questionnaires returned, 97 ASQs were properly completed and used in this study. Approximately 32% of children fit the ASQ criteria for having ASD. Most children had not been previously diagnosed. Worst behavior and daytime sleepiness was seen in those at greater risk ($p < 0.01$). Seizures also occurred earlier (approximately 2 years) in children at risk of having ASD.

CONCLUSION: Though confirmatory diagnostic evaluations are needed, this questionnaire-based study suggests that children with epilepsy are at greater risk of having ASD, and illustrates the need for more clinical vigilance. Behavioral difficulties and daytime sleepiness identified in these children could potentially affect their ability to learn. It is of interest that the age of seizure onset identified in those at greater risk corresponds with the approximate age of regression identified in some children with ASD.

COMMENTARY

Autism is a disorder of neurodevelopment characterized by core deficits in three major domains: social interaction, communication, and restricted interests, with repetitive behaviors. Because of these shared features, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines autism as a spectrum disorder (1), encompassing autistic disorder, pervasive developmental disorder not otherwise specified (PDDNOS), Asperger's syndrome, childhood disintegrative disorder, and Rett syndrome. The number of observed cases is escalating rapidly, with up to 1 in 166 children affected. It remains unclear whether the rise is due to better or earlier detection; to an increased incidence resulting from environmental, genetic, autoimmune, or other factors; or to both increased detection and incidence. Although the popular perception of autism is one of a socially withdrawn child, in his or her "own little world," the spectrum of autism includes individuals of varying intelligence (mental retardation to superior intelligence),

language abilities (limited expressive language to fluent speech, with difficulty understanding colloquial expressions), and social skills (withdrawn to gregarious, with socially awkward behavior). Neurologic and psychiatric comorbidities associated with autism include anxiety, rigidity, and epilepsy (2,3). How these comorbidities are related to autism—cause, result, or association based on common neuropathology—awaits further study.

The relationship between epilepsy and autism spectrum disorder (ASD) has captured the attention of neurologists for decades, although many areas for ongoing debate exist. Epilepsy is more common in ASD patients than in the general pediatric population, with the prevalence rates estimated at 2% to 3% among all children compared with 30% in ASD. Even in children with ASD who have normal intelligence, no family history of epilepsy, and no other risk factors, such as cerebral palsy, perinatal disorders, or other medical disorders, the prevalence of epilepsy is still two to three times higher than in typically developing children, supporting an association between the two disorders (3). In the absence of a history of clinical seizures, interictal epileptiform discharges (IEDs) also are more prevalent in ASD patients. Investigators studying nonautistic populations have debated whether transitory cognitive impairment or behavioral disorders may result from IEDs (4). Given the disabling

behaviors associated with autism, this debate takes on greater relevance. However, IEDs may simply reflect underlying cortical dysfunction rather than be causal for cognitive or behavioral alterations. Study of the relationship between IEDs and behavior/cognition in this population is complicated further because epileptic seizures may mimic autistic features, such as repetitive behaviors or failing to respond to verbal stimuli.

While most studies examining the relationship between epilepsy and ASD have focused on identifying seizures and abnormal EEGs in cohorts of individuals with ASD, Clarke and colleagues have taken a novel approach: they examined a group of children with epilepsy (ages 2–18 years) for features of ASD. Using the Autism Screening Questionnaire (5), they found that 32% of children exhibited autism symptomatology. One third of these children were not previously diagnosed with ASD or any other developmental disability. Limitations of this study include a low (approximately one third) response rate on the screening questionnaire. Selection bias is likely, in that parents concerned about their children's behavior may have been more motivated to return the questionnaire. The study also used a screening tool for symptoms associated with ASD, rather than a gold-standard instrument for diagnosing autism, such as the Autism Diagnostic Interview-Revised or the Autism Diagnostic Observation Scale (6,7). However, the Autism Screening Questionnaire has demonstrated high convergent validity with the Autism Diagnostic Interview-Revised and therefore may be a useful screening tool for autism symptomatology.

Clarke and colleagues' findings are provocative. They implore us to search for autism in children treated for epilepsy, rather than attributing their disabling behaviors to the effects of seizures or antiepileptic drugs. This search for autism symptomatology becomes even more compelling given emerging data that early detection of ASD and initiation of behavioral interventions in the first few years of life appear to improve cognitive and behavioral outcomes (8). It will require further study to determine whether the subset of children with ASD and coexisting epilepsy will benefit to the same degree, or possibly more, from such behavioral interventions, as compared to children with epilepsy who do not demonstrate autism symptomatology. In addition, unraveling the relationship between epilepsy and ASD has implications for advancing the knowledge of both disorders, including the identification of genetic markers for autism. One approach to help delineate the genetics of autism is to focus on phenotypic subsets of autism as opposed to considering autism as a single diagnosis (9). When the clinical phenotype of ASD is combined with seizures, common etiologies underlying autism and epilepsy can be explored. For example, autism susceptibility genes on chromosome 15q11-q13 have been associated with several neurodevelopmental disorders. Deletions within this chromosomal segment have been associated with Prader-Willi or Angelman syndrome. Inverted duplications within this

region have been associated with a syndrome of autistic behavior, developmental delay, and seizures (10). Identification of children with both autism and epilepsy will allow for a more focused search of chromosomal structural abnormalities and genetic polymorphisms.

Clarke and colleagues also emphasize sleep-related problems in children with epilepsy at risk for having ASD. Those patients testing positive on the Autism Screening Questionnaire were reported to have significantly more difficulty falling back to sleep after arousals, early morning wakings, and teacher-reported daytime sleepiness. Parental reports regarding sleep latency, sleep duration, nocturnal arousals, and sleep-disordered breathing did not differ between children screening positive on the Autism Screening Questionnaire and those who did not. Follow-up studies using gold-standard assessments for autism as well as objective measures of sleep (e.g., polysomnography and actigraphy) would be of interest to extend these findings. Sleep, epilepsy, and autism form a rich interrelationship filled with possibilities for future investigational work. The most common sleep disturbance in children with ASD is insomnia, which may have a variety of biological and behavioral causes, ranging from neurotransmitter and circadian abnormalities, to anxiety, to poor sleep habits (11). Furthermore, epilepsy can disrupt sleep as well as contribute to daytime sleepiness, although some of the newer antiepileptic drugs may actually have a beneficial effect of sleep consolidation and daytime functioning (12). In turn, disordered sleep may facilitate seizure activity and exacerbate the disabling daytime behaviors observed in both autism and epilepsy (13). Therapeutic interventions aimed at improving sleep in children with autism and epilepsy may have beneficial effects on seizure control and ameliorate adverse daytime behaviors.

In summary, Clarke's work is novel in approaching the identification of autism from a different angle—through the dimension of epilepsy. Although deciphering the relationship between autism and epilepsy will not be straightforward, the end result of such work will be a deeper understanding of the etiologies of both of these neurological disorders as well as more effective treatment strategies for affected individuals.

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