Special Article

Autism and Tuberous Sclerosis

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ABSTRACT

The co-occurrence of autism spectrum disorder and tuberous sclerosis complex has been recognized for decades. The prevalence of tuberous sclerosis complex in the autism spectrum disorder population is 1 to 4%, whereas features of autism spectrum disorder are present in 25 to 50% of individuals with tuberous sclerosis complex. The underlying reason for this association might be a nonspecific disruption of brain function owing to tuberous sclerosis complex, including tuber location, seizures and their effect on brain development, cognitive impairment, a disturbance in brain development in regions associated with autism spectrum disorder, or, less likely, a linkage between a *TSC* gene and an autism susceptibility gene. Awareness of the relationship between autism spectrum disorder and tuberous sclerosis complex is important during the evaluation of individuals with either disorder. Better delineation of the association and its causative factors is needed for the development of possible interventions. (*J Child Neurol* 2004;19:675–679).

The autism spectrum disorders encompass a group of developmental disorders with common core features. These include a significant qualitative impairment in socialization, a significant qualitative impairment in communication, and the presence of restricted interests and repetitive behaviors. The label of autistic disorder is given to those children who meet these core criteria and have onset prior to age 36 months. Less severely impaired children can be classified as either Asperger's syndrome when they have normal language development but impairment in the other areas or pervasive developmental disorder not otherwise specified when there is an impairment in socialization plus either an impairment in social communication or the presence of restricted interests and repetitive behaviors. Diagnosis at this time is based on *Diagnostic and Statistical Manual for Mental Disorders-IV* (*DSM-IV*) criteria.[1,2]

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WHAT IS THE RELATIONSHIP BETWEEN AUTISM SPECTRUM DISORDER AND TUBEROUS SCLEROSIS COMPLEX?

The co-occurrence of autism spectrum disorder and tuberous sclerosis complex has been recognized for over 50 years and might predate Kanner's initial description of autism in 1944.[3] Isolated case reports have described the presence of autistic features in children with tuberous sclerosis complex. However, many of these case reports, especially in the 1970s and 1980s, have limited applicability in the determination of the relationship between autism spectrum disorder and tuberous sclerosis complex because of failure to definitively confirm the diagnosis of tuberous sclerosis complex (especially in the absence of neuroimaging studies), the transient presence of features of autism spectrum disorder (which is not the expected natural history for autism spectrum disorder), and inadequate description of the core diagnostic features of either disorder or failure to use recognized diagnostic criteria, such as a validated rating scale or *DSM* criteria.[4–13] Therefore, demonstration of the increased risk of autism spectrum disorder within the tuberous sclerosis complex population awaited investigations targeting larger populations and the use of validated diagnostic tools.

Multiple authors have reported on the prevalence of tuberous sclerosis complex in autism spectrum disorder. An early report in 1963 by Creak described a prevalence of 1 child of 100; in 1967, Lotter reported 1 of 32 children. These findings are limited by failure of an accurate description of

an autistic disorder versus the presence of autistic mannerisms in children with significant mental retardation. However, since that time, reports by Smalley et al, Gillberg, and Fombonne et al have described a small number of individuals with tuberous sclerosis complex in autism spectrum disorder populations (with autism spectrum disorder diagnosis confirmed with validated scales). The reported prevalence is 1 to 4%, depending on the cohort and the presence or absence of associated medical conditions. This is much higher than the described frequency of 0.1 to 0.2% of autism spectrum disorder in earlier years and, more recently, 0.1 to 0.6%.[14–16]

Studies have also looked at the prevalence of autism spectrum disorder in the tuberous sclerosis complex population. Fisher et al reviewed data from the North Dakota pervasive development disorder and clinical genetics registry. They found that 4 of 12 children with tuberous sclerosis complex had autism spectrum disorder features, according to *DSM-III* criteria.[17] Hunt and Dennis used a medical records review and a self-developed questionnaire and found that 40 of 69 individuals in their tuberous sclerosis complex population had autistic behaviors. However, they did not specifically state whether these behaviors were of sufficient severity to meet the criteria of autism spectrum disorder.[18] More recently, studies have addressed this question using specific autism spectrum disorder rating scales or *DSM* criteria. Smalley et al used the Autism Behavior Checklist and *DSM-III-R* criteria and found that 7 of 24 individuals had autism.[19] In a later publication, Smalley et al used the Autism Diagnostic Interview and stated that 7 of 13 met *International Classification of Diseases-10* criteria.[14] Gillberg et al used a psychiatric interview, the Autism Behavior Checklist, and the Childhood Autism Rating Scale and identified 17 of 28 children with an autistic disorder and an additional 6 children with autistic-like features.[20] Baker et al used the Autism Behavior Checklist as a screening tool and the Autism Diagnostic Interview for diagnostic confirmation for a cohort of 20 respondents to the study (with 32 invited participants) and identified 4 of 9 children with autism and 12 children showing some features on the screen.[21] Gutierrez et al, using the Autism Diagnostic Interview and the Autism Diagnostic Observation Scale in 28 individuals, found that 8 met the diagnostic criteria for autism and 4 for pervasive development disorder not otherwise specified.[22]

Other studies have used different tools to identify the populations. Curatolo et al used a tuberous sclerosis complex behavioral questionnaire to identify 6 of 23 individuals with features of autism.[23] Using this questionnaire, Jambaqué et al found 2 of 13 with autistic behavior in a cohort treated with vigabatrin for infantile spasm or partial seizures. This questionnaire was not correlated with *DSM* criteria.[24] Hunt and Shepherd used a questionnaire (telephone or mail) and found that, of 21 children, 5 met *DSM-III-R* criteria for autism and an additional 4 met *DSM-III-R* criteria for pervasive development disorder not otherwise specified.[25] Ferguson et al. used a questionnaire format to identify 71 of 138 respondents showing features of social aloofness (interpreted as being an autistic behavior).[26] None of these studies used clinical examination criteria.

In summary, the frequency of autism in individuals with tuberous sclerosis complex in these and other studies is approximately 25%, with about 40 to 50% meeting criteria within the autism spectrum disorders. However, the information from these studies is limited by the sample population (clinic based or responding to a questionnaire), limitations in the type of diagnostic tool being used (whether or not based on *DSM* criteria), the threshold for the diagnosis of autism spectrum disorder, and a lack of consideration for the confounding effects of mental retardation and uncontrolled epilepsy (because the frequency of autistic features rises with an increasing severity of mental retardation and with the presence of an epileptic encephalopathy or uncontrolled epilepsy with frequent daily seizures). Overall, the limited surveys of populations of individuals with tuberous sclerosis complex find that the prevalence of autism spectrum disorder is increased in comparison with the general population.

When the population with autism spectrum disorder and tuberous sclerosis complex is evaluated, it is found that the male-to-female ratio is approximately equal, in contradistinction to the increased male prevalence in the general autism spectrum disorder population. However, even in the general population with autism spectrum disorder, the male-to-female ratio becomes more equal with lower IQ, especially below 50. In the population with combined autism spectrum disorder and tuberous sclerosis complex, a much larger percentage of these individuals show evidence of cognitive impairment, usually severe to profound in nature, in comparison with the overall tuberous sclerosis complex population. In addition, these individuals also have a history of a seizure disorder, especially infantile spasms in the first year of life, which might contribute to the cognitive impairment.[27]

WHY DO AUTISM SPECTRUM DISORDER AND TUBEROUS SCLEROSIS COMPLEX CO-OCCUR?

Several reasons have been proffered for the association between autism spectrum disorder and tuberous sclerosis complex. First, there can be a direct effect of the abnormal *TSC* gene on the development of brain regions that are dysfunctional in autism spectrum disorder. Second, nonspecific brain dysfunction owing to tuberous sclerosis complex, including cognitive impairment, seizures, and tuber location, can cause some individuals to have autism spectrum disorder. Lastly, there can be a linkage between the *TSC* gene and an autism spectrum disorder susceptibility gene.[27,28] There is no support for an association with events during the birth process.[29]

Evidence in support of potential linkage between a tuberous sclerosis complex gene and an autism spectrum disorder susceptibility gene is the genome scan finding that shows a putative location on chromosome 16 of an autism spectrum disorder susceptibility gene. This is in a region similar to that of the *TSC2* gene at chromosome 16p13.[30]

Although this linkage is possible, the equal male-to-female ratio, level of significant cognitive impairment, and frequent presence of poorly controlled seizures argue that the relationship is not usually, if ever, due to gene linkage.

Neurobiologic investigations have identified abnormalities of the frontal and temporal regions in individuals with autism spectrum disorder. Tuberin, the *TSC2* gene product, is highly expressed in these areas.[30] A study of individuals with tuberous sclerosis complex and autistic features showed abnormalities in the caudate, cerebellar nuclei, and lateral temporal gyri on positron emission tomographic studies. These findings have been interpreted as evidence of the neurodevelopmental deficits inherent in autism spectrum disorder.[31] This might provide an explanation for the presence of autism spectrum disorder in individuals with tuberous sclerosis complex and normal intelligence and no seizure disorder, although more data are required before a direct relationship is established.

The most likely reason for an association between autism spectrum disorder and tuberous sclerosis complex is a nonspecific consequence of the disruption of brain function in individuals with tuberous sclerosis complex. In those with both autism spectrum disorder and tuberous sclerosis complex, 75% have cognitive impairment, the majority in the severe to profound range. However, autism spectrum disorder features are frequently present in individuals with severe to profound mental retardation, irrespective of the etiology of the mental retardation.[27,30]

Similarly, 75 to 100% of individuals with autism spectrum disorder and tuberous sclerosis complex have a history of a seizure disorder. Seizure onset is usually within the first few years of life, including a frequent association with a prior occurrence of infantile spasms. The seizure focus is usually frontal or temporal, similar to findings described in individuals with autism and abnormal electroencephalograms (EEGs). The features of autism spectrum disorder can appear in association with the initial onset of seizures or fluctuate in severity or manifestation in conjunction with the presence or absence of seizure control. Therefore, the presence of features of autism spectrum disorder might be related to a functional disruption of brain processes owing to an underlying epileptic encephalopathy or, possibly, a disturbance of central nervous system organization owing to early and persistent seizure activity.[28,32–38]

Lastly, multiple studies have shown an association between localization of tubers and the presence or absence of autism spectrum disorder features (independent of the presence or absence of mental retardation). Most studies suggest the presence of tubers in the temporal lobe as a predisposing feature, whereas isolated studies have suggested an association with frontal lobe and posterior tubers or with the presence of tubers in the cerebellum. Curatolo et al described two populations: one with onset before age 2 years with parietal and temporal tubers and one with onset from 3 to 5 years with frontal and posterior tubers. More than 8 tubers were found in 5 of 6 children with tuberous sclerosis complex and autism spectrum disorder but in only 6 of 17 children without features of autism spectrum disorder.[23] Bolton and Griffiths localized tubers in individuals with autism spectrum disorder to the temporal lobes, with a greater number of tubers in those with both autism spectrum disorder and tuberous sclerosis complex.[39] In a later report of a larger series, they stated that risk factors for autism spectrum disorder were temporal lobe tubers associated with temporal lobe epileptiform activity, early onset, and ongoing spasms.[37] Seri et al also described temporal lobe localization in those with autism spectrum disorder but found no difference in the total number of tubers.[40] Jambaqué et al examined 23 children with tuberous sclerosis complex and identified 6 with autism spectrum disorder, mental retardation, seizures, and bifrontal and posterior tubers.[41] Weber et al evaluated data on 29 individuals with tuberous sclerosis complex and found a positive correlation between higher scores on the Childhood Autism Rating Scale and the number of cerebellar tubers.[42] Two studies have suggested that there is no relationship with any supratentorial tubers.[31,43] Overall, the evidence suggests a relationship with tuber localization, although interpretation of the data in some studies is limited by the use of computed tomography, which can underidentify the number of tubers, and the effect of intractable seizures on the features of autism spectrum disorder.

In summary, although no definitive reason has been determined for the association between autism spectrum disorder and tuberous sclerosis complex, it is most likely that autism spectrum disorder features in this population are present as a consequence of a nonspecific disruption of brain function related to the complications of tuberous sclerosis complex (including seizures, mental retardation, and tuber localization). Less likely, although possible, is abnormal brain organization owing to the adverse impact of a tuberous sclerosis complex gene, perhaps in conjunction with an autism spectrum disorder susceptibility gene. At present, there are no data to support a linkage between the *TSC* gene and an autism spectrum disorder susceptibility gene.

ASSESSMENT AND INTERVENTION

Because of the co-occurrence of autism spectrum disorder and tuberous sclerosis complex, evaluation of individuals with one disorder requires a heightened awareness for the other condition. All of those with autism spectrum disorder should be examined for clinical features of tuberous sclerosis complex, including the presence of skin lesions, and, if necessary, with the use of a Wood's lamp. Routine magnetic resonance imaging is not warranted unless there are clinical features, such as significant cognitive impairment, seizures, or skin lesions, to support this testing. In individuals with tuberous sclerosis complex, ongoing monitoring for features of autism spectrum disorder is warranted. In young children, one must be careful not to confuse autism spectrum disorder features with those of severe to profound cognitive impairment, because, with age, the latter population will manifest more appropriate social skills and a relative absence of repetitive behavior or restricted interests. In

the tuberous sclerosis complex population, the occurrence of an autistic regression should raise the question of an underlying seizure disorder and lead to an appropriate evaluation, including an EEG that includes sleep. Given that the features of autism spectrum disorder can wax and wane in relationship to the control of seizures, it might be more prudent to use the label of an epileptic encephalopathy rather than true autism spectrum disorder in this circumstance. Evaluators should remember that the clinical features of autism spectrum disorder can have different underpinnings in the tuberous sclerosis complex population in comparison with those individuals with "idiopathic" autism spectrum disorder.

Intervention for this population is dependent on cognitive level and, indirectly, on autism spectrum disorder features. All children require appropriate educational and behavioral programming, although it should be noted that the response to an autism spectrum disorder–based program might not be as robust in this population, especially those with more severe cognitive impairment, in comparison with the idiopathic autism spectrum disorder population. However, this type of programming might lead to an improvement in overall behavioral functioning.[44] Early and aggressive management of seizures can lessen a theoretical adverse impact on central nervous system function and organization and lessen the overall level of seizure-related cognitive impairment or autism spectrum disorder features. The presence of an unexplained regression should lead to an evaluation for a seizure disorder, central nervous system tumor or the occurrence of increased intracranial pressure or hydrocephalus owing to a giant cell astrocytoma.

Lastly, challenging and disruptive behaviors require appropriate medical and behavioral management. This includes identification of the reason for the behavior and implementation of necessary interventions. Evaluation and treatment should use strategies found to be effective in other populations with similar problems.[44, 45]

FUTURE DIRECTIONS

Despite many publications on autism spectrum disorder and tuberous sclerosis complex, our knowledge about the relationship is still limited. Areas for future investigations include the following:

1. Better definition of the neurobiologic basis for autism spectrum disorder in tuberous sclerosis complex, including the use of functional neuroimaging; determination of the exact relationship between tuber localization, disruption of function, and development of autism spectrum disorder; the relationship between autism spectrum disorder and epilepsy in the tuberous sclerosis complex population; the impact of the neurodevelopmental effects of the abnormal *TSC* genes on brain development and autism spectrum disorder; and the relative contributions of the type of *TSC* gene (*TSC1* or *TSC2*) toward an autism spectrum disorder predisposition
2. Epidemiologic studies of tuberous sclerosis complex cohorts more representative of the community tuberous sclerosis complex population, including segregation into *TSC1* and *TSC2* groupings, to provide more meaningful prevalence data
3. Use of well-defined autism spectrum disorder screening and diagnostic instruments for identification of affected individuals to allow comparison of data between different tuberous sclerosis complex populations
4. Differentiation between those with autism spectrum disorder owing to a functional brain impairment caused by difficult to control epilepsy, which can remit with successful seizure management, and those with autism spectrum disorder related to a structural abnormality, which will persist over time, although the intensity of clinical features might lessen with age
5. Determination of the efficacy of recommended interventional strategies for idiopathic autism spectrum disorder in children with tuberous sclerosis complex and autism spectrum disorder and the relationship of treatment response to other factors, such as intelligence and seizure frequency
6. Exploration of the possibility of the existence of subgroups within the combined autism spectrum disorder and tuberous sclerosis complex population that have independent or interrelated causes of autism spectrum disorder, such as the level of cognitive impairment, age at onset and type of seizure, tuber localization, and close proximity of the *TSC* gene to an autism spectrum disorder susceptibility gene

Studies to date have begun to define the relationship between autism spectrum disorder and tuberous sclerosis complex. Future work should better delineate these features and their underpinnings and define the types of intervention that will be most effective.

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