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Topical Review

An Updated Review of Tuberous Sclerosis Complex-Associated Autism Spectrum Disorder

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ABSTRACT

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder caused by mutations of either the TSC1 or TSC2 gene. Various neuropsychiatric features, including autism, are prevalent in TSC. Recently, significant progress has been possible with the prospective calculation of the prevalence of autism in TSC, identification of early clinical and neurophysiological biomarkers to predict autism, and investigation of different therapies to prevent autism in this high-risk population. The author provides a narrative review of recent findings related to biomarkers for diagnosis of autism in TSC, as well as recent studies related to the management of TSC-associated autism. Further sophisticated modeling and analysis are required to understand the role of different models—tuber models, seizures and related neurophysiological factors models, genotype models, and brain connectivity models—to unravel the neurobiological basis of autism in TSC. Early neuropsychologic assessments may be beneficial in this high-risk group. Targeted intervention to improve visual skill, cognition, and fine motor skills with later addition of social skill training can be helpful. Multicenter, prospective studies are ongoing to identify if presymptomatic treatment with vigabatrin in patients with TSC can improve outcomes, including autism. Several studies indicated reasonable safety of everolimus in young children, and its potential application in high-risk infants with TSC, before the closure of the temporal window of permanent changes, maybe undertaken shortly.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant, neurocutaneous disorder caused by mutations of either the TSC1 (located on the chromosome 9q34 and encodes for hamartin) or TSC2 (located in the chromosome 16p13.3 and encodes for tuberin) gene. In TSC, the mammalian target of rapamycin (mTOR) pathway, an important regulator of cell metabolism and proliferation, becomes upregulated due to diminished inhibition from the heterodimeric hamartin-tuberin complex. Besides multiorgan and system dysfunction from tubers, various neuropsychiatric features, including autism, are extremely common and debilitating features of TSC.

In 1943, Leo Kanner characterized autistic features for the first time in 11 children.[1] However, the description of autistic features in TSC preceded Kanner's classic description of autism. Critchley and Earl, in 1932, reported about "bizarre attitudes, stereotyped movement, solitary, silent, and apathetic behaviors with sudden, brief outbursts of motiveless excitement" in patients with TSC.[2] Despite the high prevalence of autism in TSC, significant progress has been made in only the last 10 years to prospectively calculate the prevalence of autism in TSC population, to identify early clinical and neurophysiological biomarkers to predict autism, and to investigate different disease-modifying therapies.

Epidemiology

The first operational definition of autism was published in the *Diagnostic and Statistical Manual of Mental Disorders,* third edition (DSM-III), which evolved to the current definition published in the DSM-V.[3,4] Previously reported autism triad of social interaction impairment, communication deficit, and restrictive, repetitive, and stereotyped behaviors now changed to dyad with exclusion of the communication challenges, as wide variability in language

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development is common in autism. The prevalence of autism in the general population is 1% to 2%, and it is four to five times more common in males than females. Autism is a much more common disorder than TSC, and its reported incidence is gradually increasing (1:64) with a change in the case definition, as well as with greater awareness, with diagnostic substitution of other developmental disorders, and possibly due to a true increase in the prevalence.[5] The incidence of TSC is relatively stable at 1:5000 to 1:10,000.[6] A recent, national surveillance study in Germany prospectively estimated the incidence rate of approximately 1:6760 to 1:13,520 live births, using the updated TSC diagnostic criteria of 2012.[7] In addition, there is no male predominance in autism with TSC.[8]

The prevalence rate of autism in TSC in the first several studies was calculated retrospectively. Some studies took into consideration of parental reports rather than based on objective, standardized tests. Hunt and Dennis first systematically studied the association between TSC and autism and found that 46 of 90 children (51%) had autistic traits.[9] Later several other studies assessed the prevalence of autism in TSC and detected a rate of 5% to 61%, using various methodologies (Hunt and Dennis questionnaires, Autism Diagnostic Interview [ADI], Childhood Autism Rating Scale, DSM-III-Revised).[10-15] Recently, more rigorous prospective studies have determined an autism prevalence rate of 40% to 50% in patients with TSC.

Aglaia Vignoli et al. performed a study in Northern Italy to identify 42 individuals with TSC.[8] Seventeen (40.5%) of them scored more than 15 in the social communication questionnaire to suggest a diagnosis of autism. Potential risk factors associated with autism were coexistent epilepsy, seizure onset in infancy, TSC2 mutations, cognitive impairment, and sleep dysfunction. Seizure frequency and tuber locations were not associated with autism in this study. However, the authors did not perform the ADI or the Autism Diagnostic Observation Schedule (ADOS) in these patients, the current gold standard for the diagnosis of autism. Jeste et al. prospectively followed patients with TSC for the detection of autism by standardized assessment as well as to formally assess the relationship between intellectual disability and autism.[16] The autism group had a higher rate of intellectual impairment. de Vries et al. have reported the international TOSCA natural history study of 2216 patients with TSC, of which 21.1% had a diagnosis of autism.[17] Owing to the high rate of missing and nonreported data in this cohort, the true prevalence of autism was probably higher. In addition, a higher incidence of autism in children compared with adults in this cohort reflects decreased awareness and testing for autism in the past. Importantly, the autism diagnosis was made very late at the mean age of 7.8 years in this population.

Pathogenesis

Several different models—tuber models, seizures and related neurophysiological factors models, genotype models, and brain connectivity models—have been explored to unravel the neurobiological basis of autism in TSC (Fig 1). However, the role of individual or combination effects of these models has not been systemically studied.

Cortical tuber model

Initially, structural abnormality by cortical tubers has been suspected as the main causative factor for autism. Curatolo et al. hypothesized that high cortical tuber burden over the parietal-temporal region was associated with early-onset autism rather than tubers over the frontal or occipital regions.[18] Bolton and Griffiths reported a similar association of temporal lobe tubers and autism.[19] Seri et al. compared the tuber burden and location between autism and nonautism groups and showed that bilateral cortical tubers were more prevalent in the autism group.[20] Moreover, children with no autistic traits did not have tubers over the left temporal lobe. Huang et al. retrospectively studied 32 patients with TSC and six of whom had a diagnosis of autism.[21] Individuals with autism had a high prevalence of tubers in the insular and temporal regions. The autism group also had a higher prevalence of cystic tubers. The authors hypothesized the role of temporal and insular regions in social perception, language, interoceptive, and affective processes. Interestingly, the autism group also had a higher rate of nonsense mutations of the *TSC2* gene. However, several other studies contradicted temporal tuber-mediated autism hypothesis. One of those studies rather correlated autism with cerebellar tubers.[22] Besides tuber burden and location, Numis et al. also reported that cyst-like tubers could be associated with a higher probability of autism.[23] However, recent research identified structural abnormalities in normal-appearing perituberal tissues also. Ruppe et al. identified mild cellular dysplasia and abnormal mTOR signaling in structurally normal-appearing perituberal cortex by using standard histologic and immunohistochemical labeling.[24] Autism may not directly correlate with tuber burden but may be associated with subtle structural and functional abnormalities involving widespread regions in the brain.

Model related to epilepsy and interictal abnormalities

Epilepsy is one of the most common manifestations of TSC and has been identified as a risk factor for autism. Also, early-onset seizures, particularly infantile spasms, have been associated with a higher risk of developing autism. However, children may develop autism without infantile spasm, and there may not be a causal link between infantile spasms and autism. Besides, it is difficult to associate epilepsy with autism as the prevalence of epilepsy in TSC is very high. However, early-onset seizures with high frequency continue to be associated with autism. *TSC1* mutations were associated with a low prevalence of autism in one study. Numis et al. followed 103 patients with TSC, and 40% had concurrent autism.[23] The autism group had a higher burden of left temporal epileptiform discharges. Aberrant connectivity and myelination problem in the temporal lobe with or without tuber burden in the temporal lobe has been suggested as the risk factor for autism. A trend of increased epileptiform discharges over the left occipital region was also noted in this study.

Besides the evaluation of structural and epileptiform discharges, functional imaging has been utilized to understand neuropsychiatric abnoromalities associated with TSC. Asano et al. performed F-18 fluorodeoxyglucose and α-11C-methyl-L-tryptophan positron emission tomography studies in 26 children with TSC (nine with autism, nine with intellectual disability without autism, and eight with normal intelligence).[25] The authors detected reduced glucose metabolism in bilateral temporal lobes in the autism group. In addition, glucose hypermetabolism in the deep cerebellar nuclei and increased uptake of AMT in the caudate nuclei were associated with stereotypical behaviors. Aberrant GABAergic signaling and alteration in the excitation/inhibition balance have been explored in tuberous sclerosis. Dysfunctional GABAergic neurotransmission has been suggested as a possible factor in the development of autism.[26] The presymptomatic use of vigabatrin, an inhibitor of GABA aminotransferase in patients with TSC, has been investigated to prevent neurocognitive abnormalities.[27,28]

Connectivity model

With the advancement of knowledge in the brain connectivity, the research has been focused on long-range connectivity between

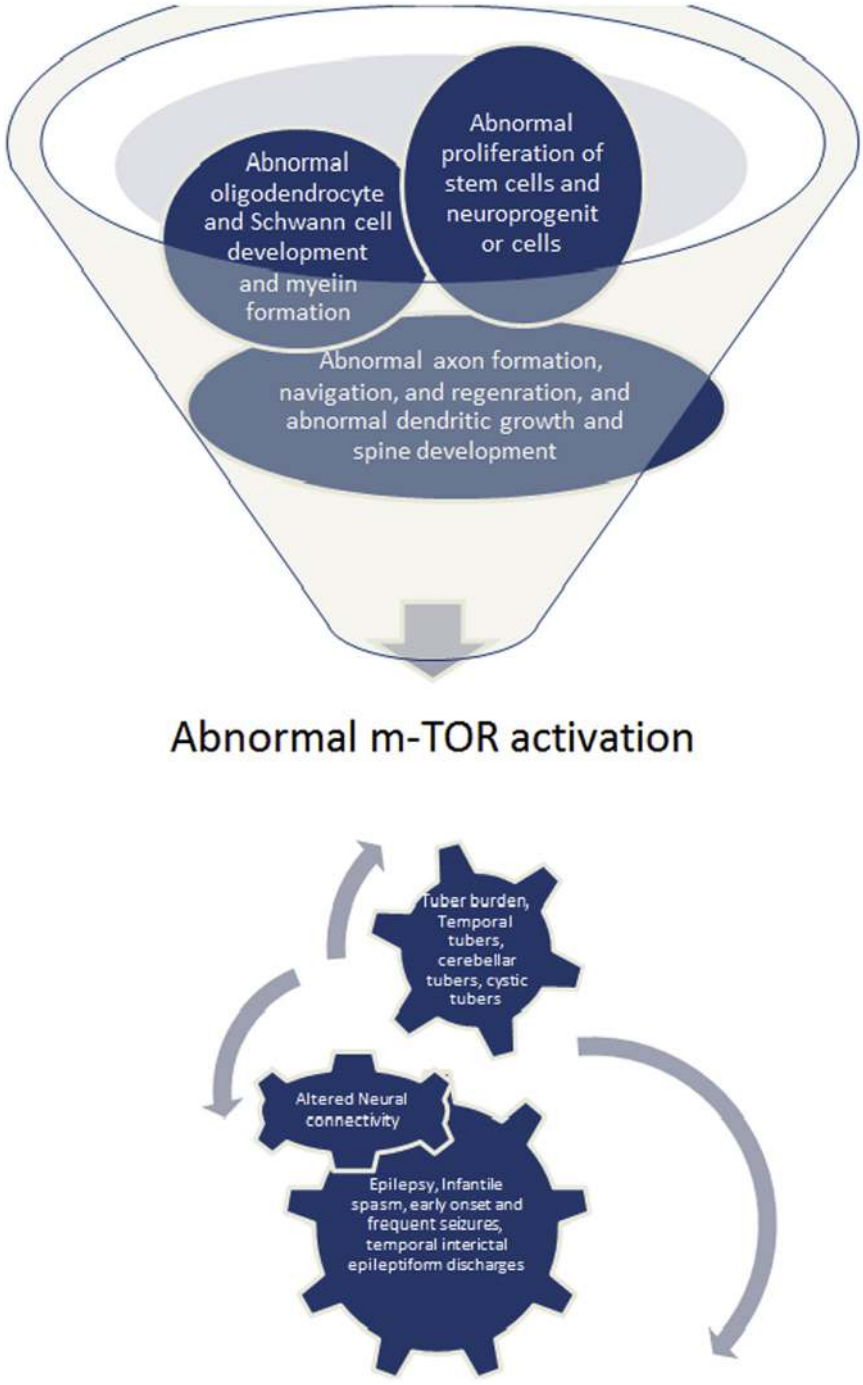

FIGURE 1. Causal and associated factors for tuberous sclerosis complex associated autism. The color version of this figure is available in the online edition.

critical brain regions rather than analysis of tuber burden (number or location in the brain) or epileptiform discharges. Neural connectivity is altered in TSC due to the mTOR pathway's role in the neuronal migration and morphology, synaptogenesis, excitation-inhibition control, and myelination patterns. Jeste et al. demonstrated that children with TSC and autism had longer N290 latency (localized to the ventral temporal cortex) and an absence of hemispheric differences in face processing.[29] The atypical face processing may be indicative of an abnormal neuronal network involving the extrastriate visual cortex, superior temporal sulcus, and lateral fusiform gyrus. The abnormal network may be responsible for poor eye contact and joint attention. The longer latency was not due to low-level processing defects at the striate or extrastriate visual cortex, but due to dysfunctional higher-level processing in the temporal lobe. The absence of the hemispheric asymmetry in the face processing may reflect the abnormal functional organization of the brain. Dickinson et al. compared early network function by high-density electroencephalography (EEG) in 35 infants with TSC and compared with 20 controls at age 12 months.[30] She and her colleagues found that infants with TSC, who would subsequently develop autism, had decreased interhemispheric alpha phase coherence with a more pronounced deficit at age 24 months. Im et al. showed altered interhemispheric connectivity in TSC by doing whole-brain connectivity analysis.[31]

The microstructure of the white matter in the brain is highly altered in patients with TSC and autism. Peters et al. demonstrated by diffusion tensor imaging that patients with TSC with autism had significantly lower fractional anisotropy of the corpus callosum compared with patients with TSC without autism or normal controls.[32] This tractography abnormality suggests significantly more white matter microstructural changes in patients with autism. In a further study using *ex vivo* high-resolution diffusion imaging and histopathology in different tissue types, Peters et al. demonstrated that diffusion abnormalities in the imaging correlated with myelination.[33]

Although TSC mutations impact brain structure before birth, changes in the functional connectivity are dynamic. The alpha range signal coherence (alpha phase coherence)—active alpha frequency activity with a consistent phase relationship over a period of time in spatially separated regions—provides precise information about global network processing by showing consistent and coordinated activity between the underlying brain regions producing these similar signals. With increasing age, alpha power increases in the normal population, but not in the intellectually impaired children. Alpha coherence and increased alpha power correlate well with axon growth and maturation of the myelination. Autism is associated with disrupted long-range connectivity, computed by the high-density EEG techniques. Despite general consensus about the difference of coherence pattern between individuals with and without autism, the exact difference and significance of the individual pattern remain unknown.[34] Dickinson et al. reported a cohort of 17 (55%) children who developed autism in a cohort consisting of 31 children with TSC.[30] Although there was no difference in different parameters of alpha oscillations between autism and nonautism groups at 12 months, the autism group showed decreased long-range alpha phase coherence at age 24 months.

Local circuit hyperconnectivity evident in functional magnetic resonance imaging (MRI) has not been conclusively proved by methods that use higher temporal resolution such as EEG and magnetoencephalography.[35] Functional connectivity in the brain is dynamic and age-dependent. Moreover, assessment of functional connectivity can be difficult in TSC as tubers may disrupt functional connectivity measurement. Surface Laplacian transform can be utilized to avert this technical difficulty. In addition, behavioral issues during the recording, presence of antiepileptic drugs and seizures, and the ubiquity of interictal EEG abnormalities may hinder the accurate estimation of the functional connectivity. More importantly, as many studies were performed in older children, adolescents, and adults, these might fail to capture early changes in the connectivity. The neural communication between different lobes can be assessed using brain signals with narrow bandwidth, such as alpha oscillations from EEG and magnetoencephalography. These brain activities can be relevant to task-specific activities such as during face processing, but waveforms during the resting state and sleep can also be utilized. Granger causality and directed transfer method can better assess causality and directionality of the information transfer from one brain region to others, such as from the frontal cortex to the language areas.[36] However, these latter methods are computationally more complex than coherence analysis. Reduction of both short- and long-range connectivities in alpha-gamma phase-amplitude coupling in the young adult with autism was noted in the fusiform areas of the brain, as well as in connectivity with other brain regions, during a face-viewing task.[37] Although this global hypoconnectivity was not concordant with local hyperconnectivity regarded in earlier studies, increased proximal hyperconnectivity in earlier childhood may evolve to global hypoconnectivity. In addition, the phase lag index has demonstrated that early hyperconnectivity in the alpha frequency during video-watching in 14-month-old children may predict a diagnosis of autism at age 36 months.[38]

Sophisticated functional studies should be done in early infancy with longitudinal follow-up to validate the ability of the study to predict autism and show dynamic changes in response to disease-modifying therapies. Display of the path length and clustering coefficient using graph theory is needed between autism and nonautistic patients with TSC to prove if patients with autism have an inefficient network compared with an efficient small-world network present in patients without autism.[39]

mTOR pathway model

Rather than secondary causes such as cortical tubers or epilepsy, recent research has focused on the role of the mTOR pathway to cause autism directly. Abnormal mTOR activation has been found not only in TSC but also in other syndromic and nonsyndromic autism.[40] Walter et al. showed in a mouse model of *TSC2* haploinsufficiency that genetic mutation itself could induce social deficits in mice.[41] However, autistic behaviors increased when seizures were induced by using kainic acid to suggest that epilepsy might have an additive effect to induce autistic traits. Rosina et al. have demonstrated increased protein levels related to mTOR and mitogen-activated protein kinase signaling pathways, isolated in the nonneuronal peripheral mononuclear blood cells in idiopathic autism, which correlated with the severity of autism.[42] However, further studies of protein levels are needed in TSC with longitudinal follow-up and potential changes following precision therapies.

The exact pathogenesis of mTOR-mediated autism is unclear and subject to active research.[43] The mTOR pathway is the key regulator of the neural stem cells and neural progenitor cells. Abnormal proliferation of stem cells may occur in TSC due to hyperactivation of mTORC1 with increased neuronal production and megalencephaly, a clinical finding that can be seen in patients with autism.[44] Dysfunction in the neuronal migration and differentiation may also be partially responsible for the pathogenesis of autism.[45] Moreover, mTOR signaling is necessary for axon formation, axonal navigation, and axonal regeneration.[46] Similarly, dendritic growth and dendritic spine development are dependent on the mTOR pathway.[47] Functional MRI studies have shown, by using the cross-correlation method, reduced long-range connectivity between key distal cortical areas with increasing connectivity between proximal brain regions.[48] It is currently unknown if the changes in axonal or dendritic processes can produce this aberrant connectivity pattern. In addition, the dysfunctional mTOR pathway modifies synaptic plasticity with alternation of both excitation and inhibition in a cell-type-specific manner.[49] Impaired plasticity has been demonstrated by transcranial magnetic stimulation in patients with autism.[50]

As mTOR signaling is key for oligodendrocyte and Schwann cell development and myelin formation, abnormal myelination pattern is recognized in TSC.[51] Patients with TSC with autism showed lower fractional anisotropy to reflect impairment in the white matter structure. Autophagy (recycling of macromolecules in lysosomes) is important for postmitotic cells such as in neurons to balance metabolic status. The mTOR pathway regulates autophagy, and impairment of the autophagic process has been demonstrated in TSC.[52] However, a comparison of autophagic dysregulation between autism and nonautism groups in patients with TSC has not been performed.

The complex interplay of genetic abnormality, mTOR pathway dysregulation, dysfunction in the connectivity, tuber count and location, prevalence and location of epileptiform discharges, and presence of epilepsy and infantile spasm may need to be further explored using sophisticated modeling and analysis to able to

predict a future diagnosis of autism in infants with TSC. Although group-level knowledge of 50% risk of autism is helpful, individual-level prediction of neuropsychiatric profile and severity needs to be established.

Clinical features

Autism, a serious and heterogeneous neurodevelopmental disorder, is characterized by dysfunctional social communication and social interaction, and restrictive, repetitive behaviors with a wide range of clinical symptoms.[53] Although symptoms of impaired social communication and abnormal behaviors are more apparent by age two years, earlier features may be present in early infancy (Supplementary Table 1). Family members may become concerned about social and language skills months or years before the formal diagnosis of autism. Frequent tantrums or intolerance to change can be noticed very early. Autism is commonly associated with intellectual disability and language impairments. Several common features associated with social-emotional reciprocity, nonverbal and pragmatic communication behaviors, a problem in developing and sustaining friendships, as well as restricted and repetitive behaviors, interests, and activities are detailed in Supplementary Table 1. Other features such as motor deficits and macrocephaly have been reported in autism in general, as well as autism in association with TSC. Rather than autistic regression, developmental stagnation with divergence from the age-based norm is noted in TSC-associated autism. However, autistic regression has been reported in association with seizure onset in infants with TSC.

Although most patients with autism have definitive symptoms by age two years, diagnosis is usually made approximately at age three to four years. However, several studies recently prospectively evaluated early features of autism in patients with TSC. EPISTOP study enrolled 101 infants aged less than four months, between 2013 and 2016 in 10 cities from Europe and Australia, before the development of epilepsy to prospectively track epileptogenesis.[54] A total of 82 children had assessments with the Bayley Scales of Infant and Toddler Development every six months from age six months to two years. Children with nonverbal mental age greater than 12 months and independent walking ability were assessed by the ADOS—20 children at 12 months, 45 at 18 months, and 69 at 24 months—using five modules to estimate social affect and restricted and repetitive behaviors. DSM-V clinical criteria for autism were used to evaluate other children. At age two years, 25 of 82 children (30%) were diagnosed with autism; 14 of these 25 had concomitant developmental quotient less than 70. Interestingly, children with epilepsy did not have a higher incidence of autism. Poor fine motor skills at six months were associated with a higher risk of autism diagnosis at two years, and cognitive, motor, and language impairments at one year similarly predicted later autism diagnosis at age two years. Early developmental delay at six months persisted during later assessments at 12 and 18 months and was associated with autism diagnosis at age 24 months. No patient with normal development at age 12 months later developed autism. In two-year-old children with autism, atypical social communication was more prevalent than repetitive, restrictive behaviors. Other common features of autism, such as poor eye contact, joint attention, and social engagement, were highly prevalent in children with TSC-associated autism.

Jeste et al. demonstrated that atypical social communication, especially visual behaviors, was evident by age six months.[29] Atypical fine motor behaviors might be the first early sign of autism. The authors calculated that an ADOS score of greater than 8 at 12 months was associated with a 50% probability of autism and these children should receive early intervention.[29] On the contrary, a score of less than 8 indicated an 83% probability of not developing autism. The authors commented that the latter group might need only surveillance for the development of any worrisome symptoms and signs, without any formal intervention for autism. However, it remains unknown if the total ADOS score or the score specifically related to social affect at 12 months should be used to predict later development of autism.

In another report, Jeste et al. described a cohort of 40 infants with TSC, followed from age less than three months to up to 36 months.[55] A total of 22 (55%) children developed autism. Children with autism developed early nonverbal deficits, especially in visual reception (visual tracking and disengagement of attention versus babbling or orientation to name) and fine motor function, before the more global delay was evident by age nine months. By age one year, these children showed a significant cognitive deficit. These children continued to have a decline in nonverbal intelligence quotient (IQ) between age one and three years. The autism group had earlier-onset epilepsy with more frequent seizures and required a higher number of antiepileptic drugs. Surprisingly, the nonverbal decline was more evident than the expected verbal IQ impairment typically associated with autism.

As the ADOS cannot be administered in many children between age 12 and 18 months, Capal et al. administered the Autism Observation Scale for Infants (AOSI) in 79 patients with TSC at mean age 12 months.[56] When these children were tested by ADOS-2 and the ADI-Revised at mean age 24 months, it was noted that higher AOSI score at 12 months significantly associated with later diagnosis of autism. The AOSI is a semistructured assessment tool for six- to 18-month old children to evaluate sensory, emotional, and motor behaviors, attention, and visual tracking. A score equal or higher than 13 at age 12 months was noted to be 88.6% specific for a later autism diagnosis. In addition, multiple individual items such as name orientation, action imitation, social smile and interest, attention engagement, and shared interest were noted to be predictive of later autism diagnosis. However, coexistent developmental disabilities can erroneously produce a higher score, and judicious clinical assessments over a long period are always necessary to detect heterogeneous developmental trajectory and expert appraisal between social languages versus cognitive language impairments. McDonald et al. followed 23 infants with TSC from age 12 months.[57] The authors noted that the children who would develop autism had deficient social referencing, eye contact, social contact, and shared enjoyment. Several other features, such as impaired name orientation, social babbling, and motor control, were noted at age 12 months, as well as unusual “sticky attention.” As discussed in the previous section of identifying biomarkers to predict the risk of autism, early identification of individual clinical risk factors is also very important in every single infant with TSC.

Management

Now early diagnosis of TSC is increasingly possible prenatally or in early infancy before the development of autism. Owing to high-quality prenatal ultrasound and availability of fetal MRI, cardiac rhabdomyomas or cortical tubers can be detected very early in life with an opportunity for intervention to prevent emergence of neuropsychiatric manifestations. Infants with TSC have one of the highest risks of developing autism, higher than even siblings with familial autism. Every child with autism should receive behaviorally oriented therapeutic programs from early in life with careful long-term and periodic follow-up to determine the effectiveness of the intervention. Moreover, psychoactive medications are necessary for some patients with careful monitoring of side effects. As with the advancement of knowledge in the pathogenesis of TSC-associated autism, disease-modifying therapies may be utilized in early or presymptomatic high-risk children (Fig 2).

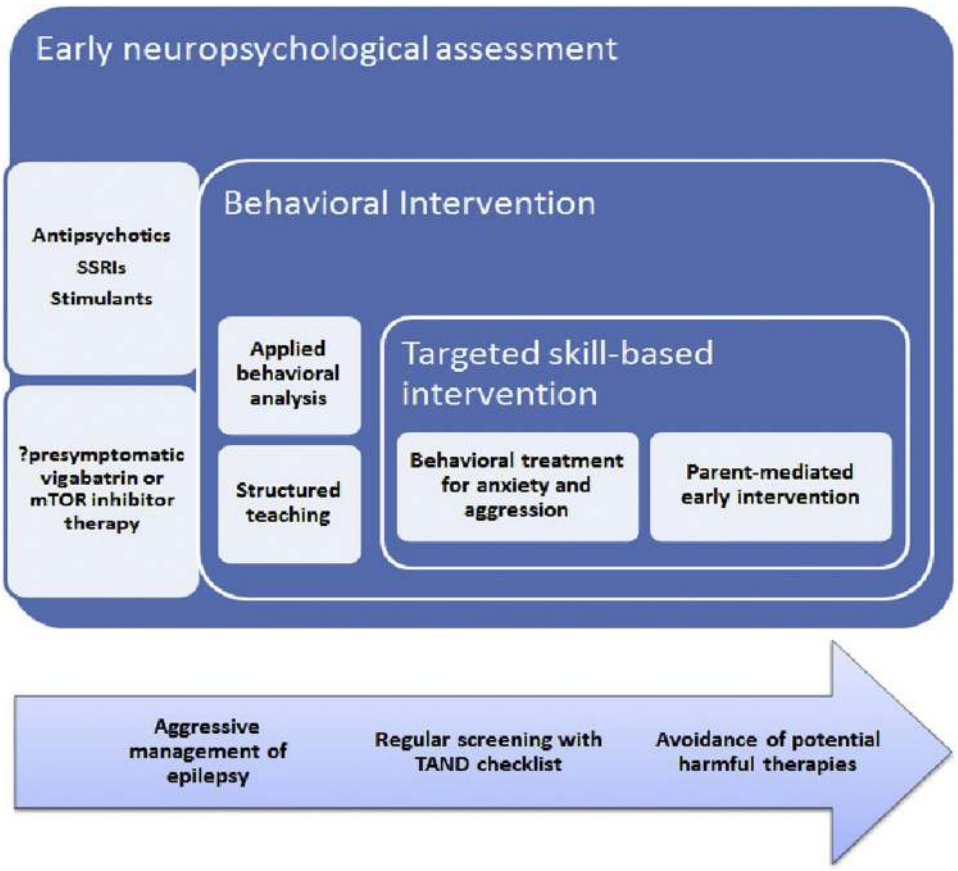

FIGURE 2. Behavioral and pharmacologic management approach in tuberous sclerosis complex-associated autism. The color version of this figure is available in the online edition.

Behavioral intervention

A randomized, blinded trial of parent-mediated social communication intervention between age nine and 14 months in presymptomatic patients with familial autism showed reduced overall severity of autism at the age two years.[58] Later intervention to improve social communication can provide short-term improvement without lasting benefit. However, several studies showed benefit from early intervention, particularly with the utilization of family-focused intervention.

Several behavioral interventions have been studied for the treatment of autism, but none specifically for autism secondary to TSC.[59] Moreover, randomized controlled studies to estimate outcomes from the behavioral intervention are severely lacking. Young children aged less than five years can benefit from early behavioral intervention or more comprehensive intervention with combined behavioral, developmental, and relationship-based approaches. Applied Behavior Analysis (ABA) principles are integrated into these approaches, as well as self-management, social interaction, response to cues, and motivation, and many other pivotal areas for optimum development.[60] A particular type of ABA, Discrete Trial Training, has been used extensively to change behavior by rewarding good behavior and ignoring inappropriate behavior related to a particular task.[61] On the other side, Pivotal Response Treatment, a play-based therapy also derived from ABA, focusses on general pivotal areas of child development rather than few target specific behaviors.[62] Older children can be exposed to structured teaching programs such as the TEACCH (Treatment of Autistic and Related Communication Handicapped Children) program.[63] This program provides a structured environment to use children's strength in visual skills to compensate for another weaker skill. Children initiate communication and focus on self-learning in this program. For nonverbal children, the Picture Exchange Communication system can be useful to foster communication.[64] Older children can be exposed to social skill training, training in living skills and autonomy, and vocational training.

Targeted cognitive-behavioral therapy is useful for anxiety and aggression, in which concrete, practical instructions are useful rather than heavy focus on introspection. Parent-mediated early intervention can be practical and convenient as it can be applied at home and increases parents' confidence, but evidence of its efficacy is low.

Symptomatic pharmacotherapy

For challenging or repetitive behaviors, several antipsychotics have been used, with moderate efficacy noted from risperidone and high efficacy from aripiprazole.[65,66] However, the risk of adverse effects is high, including weight gain, sedation, extrapyramidal symptoms, and hyperprolactinemia. Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine) have been used to reduce repetitive behaviors, but no high-level evidence exists to support effectiveness.[67] Stimulants can be used to counteract attention-deficit/hyperactivity disorder behaviors. Some supplements such as vitamins, omega-3 fatty acids, and a gluten-casein-free diet are frequently used in these patients without strong evidence of efficacy. However, chelation therapy, hyperbaric oxygen therapy, and antimicrobial agents should be avoided due to the high risk of adverse effects and paucity of scientific evidence of efficacy.

In summary, formal neuropsychologic assessments of infants with TSC may be beneficial from age six months, and parents need to be educated about early symptoms and signs of autism for earlier diagnosis in this high-risk group. From the beginning, targeted intervention to improve visual skill, cognition, and fine motor skills should be started, with later addition of social skill training.

Disease-modifying therapies

Several research groups showed reversal of autistic traits such as social deficits in *TSC1* and *TSC2* mouse models by using mTOR inhibitors.[68,69] Sato et al. noted an improvement in the social behavior following everolimus treatment in TSC mutant mice.[70] Schneider et al. also assessed the behavioral impact of status epilepticus secondary to intraperitoneal injection of kainic acid in Eker *TSC2* mutant rats. These rats developed impaired social interaction and social cognition compared with the wild-type controls. The researches then treated these rats with everolimus for one week and noted a complete reversal of abnormal behaviors.[71] Kilincaslan et al. reported a response to everolimus in four patients with severe autism with TSC in an open-label retrospective study.[72] Three of four patients had marked improvement in the social interaction, speech, and verbal response, and one patient had improvement in the stereotypical behaviors. However, autism diagnosis of these patients was made by Childhood Autism Rating Scale and DSM-IV criteria rather than using the gold-standard ADOS. More importantly, these changes were based on parenteral reports rather than objective assessment.

Krueger et al. performed a prospective randomized controlled phase II study to assess neurocognitive changes following everolimus treatment.[73] Among 47 patients (mean age of 12.7 years) in the cohort, 16 had a diagnosis of autism. After six months of everolimus treatment, no significant difference was noted in socialization and behavior between everolimus and placebo groups. Everolimus was also not noted to be associated with the worsening of neuropsychiatric functions. Although everolimus can improve behavior by controlling epilepsy better, the study participants had well-controlled seizures at baseline. Other than the delayed use of everolimus concerning the neuropsychiatric abnormalities, these patients also did not receive any behavioral intervention, which might be essential adjunctive treatment with mTOR inhibitor therapy.

Overwater et al. reported a randomized, double-blind, everolimus versus placebo-controlled trial among 32 children (aged four to 17 years).[74] The primary outcome was to determine the change in full-scale IQ. Autistic behavioral assessment by the ADOS was done as a secondary measure. Of 15 children exposed to everolimus, six had autism. After 12 months of the study period, seven children showed signs of autism to demonstrate that the everolimus might not reverse cognitive and behavioral impairments, including autistic features if used in children older than four years. This poor efficacy is not likely due to lower doses, and maintenance of a higher trough level is not practical in most situations due to adverse effects. Although everolimus can improve behavior by controlling seizures better, prevention of autistic behavior might only be possible, if at all, with earlier use of pharmacotherapy, preferably between age six and 12 months. Early signs of autism, such as dysfunctional visual behavioral or fine motor skills, may be relevant to identify these high-risk infants and the use of modifying agents before the closure of the developmental window.

Jozwiak et al. had demonstrated that the use of vigabatrin at the onset of epileptiform discharges but before seizure onset in TSC reduced the risk of severe epilepsy and intellectual disability at age two years and minimum age of five years (median eight to nine years).[27,28] Although this study did not specifically assess for autism, autism is closely linked with intellectual impairment. Large-scale studies EPISTPOP and Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) trial are currently ongoing to evaluate the role of presymptomatic therapy with vigabatrin.

Conclusion

Presymptomatic changes in the brain, such as cortical surface area growth, increased extra-axial cerebrospinal fluid (CSF), impaired white matter connectivity, and altered functional connectivity may be increasingly utilized in the next decade as biomarkers for earlier diagnosis of autism.[75] However, clinical judiciousness should not be minimized as autism is a highly heterogeneous disorder with the potential for atypical or unusual manifestations. With significant advancement in the knowledge of the mTOR pathway and availability of disease-modifying therapies, TSC will be used as an ideal model for targeted treatment in autism. As TSC is one of the most common monogenetic causes of autism and associated with the widest variability of autistic symptoms closely mimicking idiopathic, nonsyndromic autism, knowledge accumulated from structural and functional connectivity will get broader applicability in autism. Increasingly well-characterized cellular and network dysfunction in TSC-related autism may need to be further refined to link individual core features of autism with specific functional network dysfunction.

Further research to identify any association among prenatal inflammation/immune activation, autism, and mTOR pathway upregulation should be conducted to understand the role of inflammation in autism. In the United States and Europe, multicenter, prospective studies are ongoing to identify if presymptomatic treatment with vigabatrin in patients with TSC can improve outcomes, including autism. Several studies indicated reasonable safety of everolimus in young children, and potential application of mTOR inhibitors in high-risk infants with TSC, before the closure of the temporal window of permanent changes, may be undertaken in the near future.[76]

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2020.03.008.

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