Special Article

Behavioral and Cognitive Aspects of Tuberous Sclerosis Complex

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ABSTRACT

Tuberous sclerosis complex is a multisystem genetic disorder. Of all the possible manifestations of this complex disorder, the cognitive and behavioral problems represent the area of greatest concern to parents and caregivers. This review outlines the current evidence regarding global intellectual abilities, behavioral problems, psychiatric diagnoses, learning disorders, and specific neuropsychologic deficits for which individuals with tuberous sclerosis complex are at particularly increased risk, and outlines approaches to intervention. Approximately half of individuals diagnosed with tuberous sclerosis complex present with global intellectual impairment and developmental psychopathologies. Those with normal intellectual abilities are also at high risk of specific neuropsychologic deficits and behavioral, learning, and other psychiatric disorders. There is no evidence for an inevitable decline in cognition or behavior, and any such changes should be investigated. The evolving neurocognitive literature suggests that frontal brain systems might be most consistently disrupted by tuberous sclerosis complex–related neuropathology, thus leading to abnormalities in regulatory and goal-directed behaviors. (*J Child Neurol* 2004;19:666–674).

Tuberous sclerosis complex is a multisystem genetic disorder associated with the formation of multiple hamartias and hamartomas throughout the body but particularly in the brain.[1] There is a wide range of structural central nervous system manifestations, including radiologically detectable abnormalities (such as cortical tubers and subependymal nodules)[2] and more subtle fine-grain aberrations of gray and white matter.[3] In addition, there is an extremely high rate of functional central nervous system manifestations, such as the full spectrum of epilepsies,[4] learning difficulties, and behavioral problems,[5] which can, to a greater or lesser extent, be associated with the structural central nervous system features. Of all of the possible manifestations of this complex disorder, however, the cognitive and behavioral problems represent the area of greatest concern to parents and caregivers.[5]

The first cases of tuberous sclerosis complex described by Bourneville in 1880 and 1881 had severe mental retardation, intractable epilepsy, and "sclerose tubereuse" (white potato-like brain growths) on postmortem.[6,7] In 1908, Vogt introduced the classic diagnostic triad for tuberous sclerosis complex: mental retardation, epilepsy, and so-called adenoma sebaceum.[8] These studies predated refinement of diagnostic criteria[1] based on large population-based and clinic samples free of ascertainment biases and predated the incorporation of better imaging and other diagnostic tools.[1–3] The identification of the two genes associated with the disorder further aided to broaden the diagnostic boundaries of tuberous sclerosis complex.[9] These historic changes in the conceptualization of the disorder have led to the identification of individuals who might not necessarily have presented clinically in the past, for example, family members without any overt functional or medical impairments but who are screened for the purpose of genetic counseling. Neither mental retardation nor epilepsy has remained as a diagnostic feature[1] owing to their lack of specificity for the disorder. Contemporary studies report that no more than 30% of individuals with tuberous sclerosis complex seen in clinics today have Vogt's classic triad,[1,10] although, unfortunately, that triad is still presented in many medical textbooks

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Table 1. Common Cognitive and Behavioral Problems in Tuberous Sclerosis Complex: Typical Ages at Presentation and Appropriate Interventions

Age (yr)	*Most Likely Cognitive or Behavioral Problem Presenting at This Age*	*Appropriate Intervention*
0–3	Global intellectual impairment	Individual educational plan
	Autism spectrum disorders	Early intervention programs for autism
3–8	Impulsivity	Provide structure/coaching ± psychopharmacology
	ADD/ADHD	
8–12	Organizational impairment	Provide structure/coaching ± psychopharmacology
	ADD/ADHD	
12–18	Independent living skills	Coaching
	Affect-regulation and judgment	Coaching
	Anxiety disorders and depressive disorders	Cognitive behavioral therapy ± psychopharmacology
18+	Anxiety disorders and depressive disorders	Cognitive behavioral therapy ± psychopharmacology

ADD = attention-deficit disorder without hyperactivity; ADHD = attention-deficit hyperactivity disorder.

and remembered by aspiring clinicians as the hallmark of tuberous sclerosis complex.[11]

As detection, diagnosis, and systematic study of tuberous sclerosis complex has progressed, the results have been remarkably consistent in finding that almost 100% of individuals with tuberous sclerosis complex have structural brain abnormalities and that approximately 90% have a history of seizures, but, in marked contrast to initial clinical reports, no more than 50 to 60% of all individuals with tuberous sclerosis complex have global cognitive impairment.[1–4,12] Although these relatively recent studies contradict the previously espoused doctrine of inevitable mental retardation and epilepsy in tuberous sclerosis complex,[13] as yet, little is known about the neurocognitive and behavioral profiles of individuals with tuberous sclerosis complex who do not have global cognitive impairment. Until recently, studies tended to categorize individuals as either "impaired" or "managing independently" based on functional criteria. As more studies started to incorporate standardized clinical testing, findings have begun to confirm that tuberous sclerosis complex renders affected individuals at high risk of a range of specific behavioral and cognitive difficulties that include but are not limited to global mental retardation. Good clinical practice should therefore take these risks into account in diagnostic evaluations across the lifespan, with the aim of identifying and managing those cognitive and behavioral risks appropriately if and as they emerge. Early identification and management is fundamental to avoid or, at least, mitigate the short- and long-term effects of developmental disruptions on a child's subsequent intellectual, behavioral, and social or emotional development.

The focus of this review is to outline the specific behavioral and cognitive problems for which children and adults with tuberous sclerosis complex are known to be at particularly increased risk and to do so within a developmental framework. To that end, the timepoints at which specific difficulties are most likely to emerge will be indicated. The intention is not to assume that those difficulties will necessarily emerge or that they will emerge only at that timepoint. Rather, the goal is to provide information that will allow affected individuals, their families, and their caregivers to anticipate and monitor for these difficulties in an attempt to reduce the lag between the emergence of problems and suitable intervention. The review does not set out to be a detailed research document but rather aims to provide a succinct clinical guide of current evidence. The cognitive and behavioral problems that commonly present in clinical practice are summarized in Table 1. Each is briefly elaborated below with regard to diagnostic characteristics, currently documented frequency, and suggested interventions.

GLOBAL INTELLECTUAL ABILITIES

"Global intellectual ability" is formally defined in terms of performance on standardized measures of both general intelligence and independent living skills. "Mental retardation" is defined in the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)*[14] and the *International Classification of Diseases-10*[15] as a standardized IQ that is 2 SD or more below the population mean (eg, a Wechsler Intelligence Scale for Children [WISC]-IV[16] IQ = 70) combined with an impaired ability to function independently in daily living skills, such as self-care, communication, work, or leisure (formally assessed through an interview with a caregiver using a standardized measure such as the Vineland Adaptive Behavior Scales[17]). A range of other terminologies, such as "learning difficulties" or "global developmental delay", is often preferred to the term "mental retardation". For the purpose of this review, the term "global intellectual abilities or impairment" is used.

A number of studies have investigated global intellectual ability in tuberous sclerosis complex and have shown that, as a rule of thumb, about half of individuals with tuberous sclerosis complex are in the normal or near-normal range of overall abilities.[10,18–25] In the most recent population-based study, 55% of those with the disorder had an IQ > 70, whereas 30.5% had an estimated IQ < 21. Individuals with tuberous sclerosis complex in the normal range of global intellectual abilities showed a normal distribution of IQ but with a mean IQ 12 points lower than their unaffected siblings.[12] Even normally

intelligent individuals with tuberous sclerosis complex without a lifetime history of seizures had mean IQs below those of their siblings without tuberous sclerosis complex.[12]

On closer inspection, global intellectual abilities in tuberous sclerosis complex therefore seem to be distributed bimodally.[12] About 70% of individuals fall on a relatively normal distribution of intellectual abilities (akin to a bell-shaped Gausssian curve), with IQ scores ranging from 20 to 130+. The remaining 30% of individuals with tuberous sclerosis complex have IQ scores that cluster in the profoundly impaired range (IQ < 20). This is an important observation for clinical practice. In the first instance, individuals who fall in the profoundly impaired range are often unable to participate in "formal" standardized testing of their global intellectual abilities. Abilities are therefore typically estimated through characterization of their functional abilities based on structured interview with a parent or caregiver. In contrast, the more able individuals are mostly able to participate in a range of standardized tests to assess their cognitive strengths and weaknesses. Second, the most profoundly impaired children with tuberous sclerosis complex often have arrested development. That is, they do not show developmental gain over time. In contrast, the majority of children with tuberous sclerosis complex will progress in their developmental stages over time, albeit often at a slower rate and lower level than their unaffected siblings.

Further work will be required to determine whether tuberous sclerosis complex is, indeed, associated with two (or more) distinct cognitive phenotypes based on global cognitive abilities, which, in turn, can be associated with differential developmental trajectories and underlying causal mechanisms.

BEHAVIORAL AND PSYCHIATRIC MANIFESTATIONS

"Behavioral difficulties" are defined as symptoms or problems identified in daily life by parents, caregivers, teachers, or others. A wide range of such difficulties is seen in tuberous sclerosis complex, including aggressive outbursts, severe and persistent temper tantrums, overactivity, restlessness, impulsivity, poor ability to concentrate, other disruptive behaviors, self-injury, anxiety, and depressed mood.[5,10,13,23–30] More than 50% of children with tuberous sclerosis complex are likely to display some behavioral difficulties during development that can be of sufficient degree for parents to seek professional advice.

It is well recognized that individuals with global intellectual impairment are at higher risk of presenting with a range of behavioral problems and psychiatric disorders than those with normal intellectual abilities,[14,15] and individuals with tuberous sclerosis complex are no exception. Between 60 and 70% of children with tuberous sclerosis complex with global intellectual impairment are likely to present with one or more behavioral problems, whereas about 20 to 30% of children with tuberous sclerosis complex with normal global intellectual abilities can have such behavioral difficulties.[23–30] In contrast, about 5 to 10% of children without tuberous sclerosis complex are likely to present with significant behavioral problems.[14,15] Identifying and acknowledging behavioral problems should lead to determining whether any specific psychiatric disorder might be present to investigate the possible causes of the behavioral difficulty and to implement an appropriate management strategy.

"Psychiatric disorders," as defined in the *DSM-IV*[14] or the *International Classification of Diseases-10*,[15] are based on a phenomenologic nosology. That is, disorders are groupings of symptoms into syndromes or symptom clusters without any necessary assumptions about the underlying etiologies or mechanisms of the syndromes. In spite of much debate about how syndromes should be defined, there is clear pragmatic usefulness in making a diagnosis to describe the behavioral profile and to determine the needs of a child, adolescent, or adult with such a psychiatric diagnosis.

Developmental Disorders: Autism and Attention-Deficit Hyperactivity Disorder

Children and adolescents with tuberous sclerosis complex are at high risk of developmental disorders as defined in the *DSM-IV*[14] and the *International Classification of Diseases-10*.[15] Two disorders in particular have been reported in tuberous sclerosis complex at much higher rates than expected. Population-based studies reported classic infantile autism in 25% of cases,[27,30] autism spectrum disorder (also referred to as pervasive developmental disorder) in about 50%,[24,27,30] and attention-deficit hyperactivity disorder (ADHD) and related disorders in more than 50% of individuals with tuberous sclerosis complex.[24,28] Psychiatric diagnoses are significantly higher among those with global intellectual impairment.[23] More than 60% of children with tuberous sclerosis complex with global intellectual impairment can present with autism, autism spectrum disorder, or autistic features that require clinical intervention, in contrast to about 6% in the normally intelligent group with tuberous sclerosis complex.[28] Even though this represents a significant difference within the tuberous sclerosis complex population, an autism rate of 6% among normally intelligent children with tuberous sclerosis complex is a 10-fold overrepresentation in comparison with the prevalence rates of autism spectrum disorders in the normal population.[31] A diagnosis of ADHD is similarly 10-fold overrepresented in normally intelligent children with tuberous sclerosis complex (over 30%) in contrast to their sex-, age-, and IQ-matched peers without tuberous sclerosis complex (about 3–5%).[32]

Other Psychiatric Disorders

Limited systematic data are available about the rates of other psychiatric disorders in tuberous sclerosis complex. During adolescence and into adulthood, a significant number of individuals with tuberous sclerosis complex develop severe affective symptoms, such as anxiety or depressed mood.[25] In a postal survey of behavioral, psychological, and psychiatric problems in 510 children and adults with tuberous sclerosis complex, 45% reported anxiety symptoms,

whereas 29% had symptoms of depressed mood.[25] Smalley and colleagues suggested prevalence rates of 35% for depressive disorders and 59% for anxiety disorder in a study of adults with tuberous sclerosis complex.[29,33] Mood and anxiety disorders can be extrinsic to tuberous sclerosis complex (eg, secondary to the psychologic impact of having a genetic disorder or as a consequence of seizures or medication). It is, however, not inconceivable that the intrinsic pathophysiologic mechanisms of the disorder can also render individuals at higher risk of mood and anxiety disorders.

Earlier case reports included schizophreniform illnesses or psychosis,[34,35] mania,[36] and Capgras' syndrome,[37] but no clear systematic studies have since been performed. There is, however, an association of temporal lobe epilepsy and psychosis[11] in tuberous sclerosis complex that requires clinical management with appropriate antiepileptic drugs and, potentially, short-term antipsychotic medication.

Taken together, individuals with tuberous sclerosis complex are at high risk of having global intellectual impairment and a range of psychopathologies. The evidence also suggests that even those with normal intellectual development are at a significantly higher risk of behavioral, developmental, and other psychiatric disorders than individuals without tuberous sclerosis complex. Developmental disorders (autism and ADHD) are the most likely diagnoses in childhood and early adolescence, whereas mood and anxiety disorders predominate in late adolescence and adulthood. Behavioral problems (regardless of psychiatric diagnosis) most commonly include symptoms that involve the dysregulation of affect or attention, such as aggressive outbursts, temper tantrums, overactivity, impulsivity, and distractibility. Possible mechanisms for these symptoms and disorders are discussed in subsequent sections.

LEARNING DISORDERS

Learning disorders are diagnosed when an individual's performance on standardized tests of reading, writing, or mathematics shows a discrepancy with the level expected for age, schooling, and global intellectual ability.[14,15] Learning disorders are often referred to as learning difficulties, scholastic difficulties, academic difficulties, or a specific diagnosis, such as dyslexia. Between 2 and 20% of school-aged children can have learning disorders, and the rates are significantly higher in association with specific neurogenetic disorders. These disorders of scholastic skills are often associated with low self-esteem, deficits in social skills, and a general sense of demoralization for the child.

No systematic studies have been performed in tuberous sclerosis complex to date, but anecdotal evidence and feedback from clinicians suggest very high rates of learning disorders in tuberous sclerosis complex, including in children with normal global intellectual abilities. Clinicians are advised to maintain a low threshold for parental concern about a child's scholastic performance and to support appropriate evaluation of and intervention for such potential difficulties.[38,39]

SPECIFIC NEUROPSYCHOLOGIC SKILLS

Neuropsychologic evaluations are used to determine an individual's profile of the strengths and weaknesses of brain-referenced systems.[40,41] Specific neuropsychologic tests and tools are used to measure, for instance, anterior "planning and production" versus posterior "comprehension" systems, left hemisphere "language" versus right hemisphere "spatial" systems, and cognitively "higher-level" cortical versus "lower-level" subcortical functional systems.

Relatively few studies of neuropsychologic profiles in tuberous sclerosis complex have been reported to date. The first study to incorporate specific neuropsychologic assessments examined 23 children in a sequential clinic sample.[42] Among the 7 children with normal global abilities, the authors observed dyspraxia, speech delay, visuospatial problems, memory deficits, and dyscalculia. Among the 10 children with global intellectual impairment without autism, the authors observed linguistic problems and visuospatial difficulties.

More recently, the neuropsychologic profiles of 44 children between the ages of 6 and 18 years were examined as part of a large-scale clinical study.[43] Consistent with reports from population-based studies, half of the children in this clinic sample showed global intellectual impairments and were not able to complete age-appropriate standardized testing. Twenty-two children did, however, complete a standard protocol that included measures of executive control processes (planning, problem solving), language, memory, and spatial abilities. Data for individual test results were summarized as test performance "within the broad average range" (defined as performance above the 16th percentile) or as "deficient" (defined as performance below the 16th percentile). Deficiencies were most frequent in the domain of attention or executive control processes (with 66% of children showing deficient performance in attentional-executive tasks compared with 19% for spatial, 24% for language, and 38% for memory domains). It was of note that although there was a decline in the frequency of spatial and language deficiencies from the younger age group (6–11 years) to the older group (12–18 years) of children, there was no change in the frequency of executive control deficiencies between the two age groups.[43]

A population-based study of specific attentional skills in children with tuberous sclerosis complex who had normal or near-normal intelligence showed very high rates of selective attention, sustained attention, and attentional switching deficits.[28,44] The children in the study showed most consistent impairment during dual-task performance.[28] Importantly, whereas all of the children in the study who fulfilled the criteria for ADHD showed specific attention deficits, almost all of the children without a diagnosis of ADHD also showed very significant specific attentional deficits. Overall, 17 of the 19 children in the study (89%) had neuropsychologic attention deficits (defined as performance below 2 SD of the population mean) in one or more attentional domains.[28]

No detailed studies of language ability and language impairments had been published at the time of this review. In a survey of 510 individuals with tuberous sclerosis complex, only 28% of families reported normal language development in children and adults with tuberous sclerosis complex.[25] Detailed analysis of 34 children with tuberous sclerosis complex showed that only 30% of children had normal language acquisition and development (Baltaxe CAM, unpublished data, 1994). Among those with normal global intellectual abilities, Baltaxe reported an overrepresentation of difficulties in expressive vocabulary, abstract language skills, and expressive semantic-grammatic difficulties. Language deficits in normally intelligent children with tuberous sclerosis complex therefore more specifically suggested significant problems primarily with production and organization of language. These are predominantly attributed to frontal system difficulties.

Studies of neuropsychologic skills in adults with normal intelligence have shown impairments in planning, self-monitoring, and goal-directed attention.[45–47] In contrast, recognition tasks seemed relatively intact. Similar to the salient features of language abnormalities, the specific deficits so far identified in adults with tuberous sclerosis complex also represent executive processing difficulties, thus supporting frontal systems involvement.

Taken together, research evidence suggests that individuals with tuberous sclerosis complex are at high risk of very specific neuropsychologic deficits in attentional-executive skills, even when their global intellectual abilities are judged to be within normal limits and even when they might not present with sufficient features to fulfill criteria for a psychiatric diagnosis.

ASSOCIATION BETWEEN NEUROPSYCHOLOGIC DEFICITS AND THEIR MANIFESTATIONS IN DAILY LIFE

The term "attentional-executive control" processes can be divided into two main components: first, regulatory mechanisms, such as the regulation and modulation of attention, behavior, and affect, including the ability to sustain attention independently, and second, goal-directed executive mechanisms, such as the ability to plan, organize, execute, and monitor goal-directed activities and to anticipate consequences.[40,41] The general term "attentional-executive control processes" is used to reflect a continuum of functions in which, depending on specific task demands, more regulatory abilities or more executive contributions might be required.[41, 48]

Deficits or reduced strengths in attentional-executive control processes can manifest in various ways in daily life.[40,41,49–51] A child who has difficulty in attentional set-shifting, that is, with shifting attention from one stimulus to another, shifting set can appear to be inflexible, which may manifest as difficulty with managing transitions or sudden changes in rules. If pushed to change a routine unexpectedly, such a child might withdraw or present with disruptive or aggressive behaviors that seem out of proportion to the request. Reduced planning ability can contribute to impulsivity and poor choice of behavior, as well as failure to anticipate the consequences of specific behavior secondary to reduced memory for the future. Because executive control processes are associated particularly with management and organization, children with attentional-executive deficits might have the ability to perform all of the individual parts of a complex task with supervision, for example, when an adult is nearby to prompt each step, but become overwhelmed or disorganized when required to combine elements or to monitor task management independently.

It is of great importance to identify such manifestations of specific neuropsychologic deficits in daily life. In the first instance, behaviors can then be viewed as a manifestation of tuberous sclerosis complex rather than as "bad" or "uncooperative" behavior. Furthermore, specific interventions can be implemented under the guidance of, for example, an experienced clinical neuropsychologist. Intervention should aim to anticipate tasks or situations in which a child is likely to struggle and should incorporate structure and appropriate coaching based on the individual's strengths and weaknesses.[49–53]

In summary, the specific neuropsychologic deficits seen in tuberous sclerosis complex can present as significant difficulties in "managing" daily life. These difficulties might not amount to sufficient symptoms to fulfill criteria for a psychiatric diagnosis such as ADHD or autism but should nevertheless be assessed and managed appropriately.

DEVELOPMENTAL TRAJECTORY OF COGNITIVE AND BEHAVIORAL FEATURES IN TUBEROUS SCLEROSIS COMPLEX

Research data about the lifespan progression and outcome in tuberous sclerosis complex were recently reviewed by de Vries and Bolton.[25] The authors commented on the dearth of longitudinal data. A recent study showed that infants with tuberous sclerosis complex who show significant delays in early development relative to their peers without tuberous sclerosis complex remain delayed, and do not catch up later in development.[54] There are suggestions that more able children who do not start off behind their peers early in development can fall behind over time.[28] As highlighted earlier, individuals with profound global intellectual impairment often show developmental arrest and do not show any significant progression from a basic sensorymotor stage. In a follow-up of 23 adults with tuberous sclerosis complex from the age of 5 years to adulthood, little change was observed in the functional abilities of those with severe global intellectual impairment. Behaviorally, whereas symptoms of autism and hyperactivity decreased, the rates of aggressive behavior and self-injury remained unchanged.[55]

In the study of cognition and behavior in tuberous sclerosis complex, it will be important not to make false assump-

tions about the developmental trajectory based solely on studies of the end state, as seen in the study of adults with brain-related disorders. In the context of developmental plasticity, Dennis outlined a model for cumulative cognitive difficulties following early brain insult.[56] She argued that, owing to early disruption, more deficits would emerge over time and that the discrepancy in cognitive and functional abilities between a child with central nervous system abnormalities and their peers would increase. In tuberous sclerosis complex, speculatively, it is possible that the observed tendency for children to fall behind their peers over the course of development could reflect failure in the emergence, development, and establishment of frontal brain systems. Development of these systems is a prerequisite to increased independence in integrating and generalizing skills in the service of novel and complex problem solving.

It is important to note that tuberous sclerosis complex is not associated with inevitable intellectual or behavioral decline (in contrast to slowed gains), as believed at the start of the twentieth century.[13] Any evidence of regression, deterioration, or change should trigger a careful evaluation (see the section on interventions).

POSSIBLE DETERMINANTS OF COGNITIVE AND BEHAVIORAL PROBLEMS IN TUBEROUS SCLEROSIS COMPLEX

There are a number of different levels at which the potential determinants of neurodevelopmental difficulties in tuberous sclerosis complex are investigated. At the genetic level, there are suggestions that individuals with a *TSC2* mutation might be at greater risk of more severe cognitive and behavioral manifestations.[57–60] No specific mutation types have been shown to lead to specific neurodevelopmental manifestations. On the contrary, there is at least one report of nine individuals with the same *TSC* mutation who presented with global intellectual abilities ranging from profoundly impaired to above average.[60]

Progress in the understanding of the cell signaling pathways involving the *TSC* genes[61–64] might shed light on the cellular mechanisms associated with specific learning or behavioral problems in tuberous sclerosis complex. As studies on the psychoneurobiology of tuberous sclerosis complex detail those mechanisms, new avenues might be opened for psychopharmacologic and cognitive enhancers.

The role of structural abnormalities in cognition and behavior has received some focus.[65–69] At present, there is, however, no convincing evidence that tuber count and tuber load are useful markers of global cognitive abilities in tuberous sclerosis complex. Earlier suggestions that a tuber count over 6, for example, suggests severe global cognitive impairment are potentially clinically misleading. It is not uncommon to see children with 20 or more tubers who have normal intellectual abilities. Magnetic resonance imaging is an important assessment tool but should not be considered a substitute for thorough cognitive and behavioral assessment. There are no biomarkers of cognitive abilities or behavioral problems that are currently of predictive value in the clinic. Reports suggesting a complex interaction between temporal lobe tubers and infantile spasms as causal mechanisms of autism[30,70] are discussed in a separate article focusing on autism in tuberous sclerosis complex in this issue.[71]

There is no doubt that epilepsy is an important factor in relation to cognitive and behavioral features[72] and in relation to the developmental trajectory of children and adolescents with tuberous sclerosis complex.[73] Infantile spasms and severe intractable seizures are highly correlated with global intellectual impairment, but not inevitably so.[4,12,30] Although most individuals with profound global intellectual impairment have a history of seizures, many of those with a history of seizures have normal or above-average global intellectual abilities.[12] Absence seizures can impair a child's ability to learn and progress academically.[11,74] Partial seizures can manifest as disruptive, repetitive, or aggressive behaviors.[11] Nighttime behavioral disturbance and sleep disorders should, in particular, raise the possibility of seizures.[10,23] The side effects of antiepileptic drugs can hinder a child's ability to learn or can lead to behavioral disturbances.[11,75] Accurate identification and appropriate treatment of seizure disorders are therefore paramount. The management of epilepsy in tuberous sclerosis complex is discussed elsewhere in this issue.[4]

Taken together, there are a number of pathways to the psychopathologies and cognitive difficulties associated with tuberous sclerosis complex. From a clinical perspective, seizures and seizure control, as well as monitoring for the emergence of a subependymal giant cell astrocytoma,[1,2] require careful attention. It is, however, important to be mindful that neither seizures nor cortical tubers are necessary and/or sufficient to explain the cognitive and behavioral risks associated with tuberous sclerosis complex, nor are they predictive of individual outcomes.

INTERVENTIONS FOR NEURODEVELOPMENTAL DIFFICULTIES IN TUBEROUS SCLEROSIS COMPLEX

There are no specific or unique interventions for the cognitive or behavioral problems associated with tuberous sclerosis complex, and no studies have been performed in tuberous sclerosis complex to investigate the effectiveness or side effects of interventions used to address similar problems in individuals without tuberous sclerosis complex.

Assessment

The first step toward intervention is to perform comprehensive age-, and developmentally appropriate assessments at key timepoints. Consensus clinical guidelines have recently been drawn up by an international panel of psychiatrists, neuropsychologists, clinical psychologists, pediatricians, pediatric neurologists, special education experts, service users, and caregivers.[76] These guidelines included two main recommendations. First, the panel advocated

routine assessments in infancy, preschool, early school years, middle school years, adolescence, and adulthood. The purpose of these periodic assessments is to identify cognitive and behavioral problems as they emerge rather than to wait until severe clinical problems have become established. The second recommendation was to perform urgent assessments whenever evidence of regression in cognitive skills or a change in behavior occurs. A change in a child's behavior can sometimes be the only sign of a developing subependymal giant cell astrocytoma. Assessment should therefore include a comprehensive physical and neurologic review plus appropriate special investigations to identify the likely underlying causes of the cognitive or behavioral change.[76]

In the context of the multisystem nature of tuberous sclerosis complex, it is prudent to adopt a hierarchical approach to evaluating the potential causes of cognitive and behavioral difficulties.[25] Physical factors pertaining to the central nervous system, such as seizure control, change of seizure type, and the possibility of a subependymal giant cell astrocytoma, should be considered first. Non–central nervous system factors should next be examined, for example, renal failure, electrolyte disturbances, or the effect of medication. Next consider the role of an emerging developmental disorder or other psychiatric disorders. Finally, environmental factors, such as change, unpredictability, life events, or inconsistent management, can all play important roles, particularly when behavioral changes are observed.[25,76]

Multi-agency, Multidisciplinary Work

Once the cognitive and behavioral profile of the individual has been assessed, information should be integrated into an overall formulation of the needs of that person.

It will soon become apparent to clinicians who work with children, adolescents, and adults with tuberous sclerosis complex that their complex needs can rarely be assessed and managed by a single professional or discipline. Appropriate management will almost undoubtedly require multi-agency, multidisciplinary work, including educational, medical, therapeutic, and social service agencies.

Interventions as appropriate to non–tuberous sclerosis complex should be implemented. For instance, a child with an autism spectrum disorder should be linked with an appropriate early intervention program designed for children who have primary social communication disorders. Children with global or specific cognitive deficits should receive statutory assessment of their educational needs, and individual educational plans should be implemented. Many children might require regular follow-up by a psychologist, psychiatrist, or behavioral neurologist or pediatrician to monitor their behavior and educational progress. Clinical psychologists and/or learning disability specialists can play an extremely important role in performing functional analysis of behaviors and in the implementation of a behavior management or modification plan. These are often particularly useful for repetitive behaviors, self-injury, eating difficulties, and sleep disturbances. In some instances, psychopharmacologic interventions might be useful. It is, however, essential that psychotropic drugs be used with great care and consideration in the context of the multisystem nature of tuberous sclerosis complex.

Psychoeducation and Support

Cognitive and behavioral problems are often the most worrying of all of the tuberous sclerosis complex manifestations to parents and carers.[5] Clinicians should therefore not underestimate the impact of the disorder on families. Parents need clinicians to listen to their concerns, to identify their child's needs through careful assessment, and to build a therapeutic alliance with them. The needs of individuals with tuberous sclerosis complex will remain lifelong; therefore, families need clinicians who will be able to maintain a long-term relationship that affords consistent support and perspective.

Families with tuberous sclerosis complex are very fortunate to have the support of an excellent network of nonprofit organizations, such as the Tuberous Sclerosis Association (UK) and the Tuberous Sclerosis Alliance (USA). Both the Tuberous Sclerosis Association and the Tuberous Sclerosis Alliance provide excellent information and fact sheets through their Web sites (<www.tuberous-sclerosis.org> and <www.tsalliance.org>). An umbrella organization, Tuberous Sclerosis International, provides a very useful initial source of international contact details for professionals or families (<www.stsn.nl/tsi/tsi.htm>).

FUTURE DIRECTIONS

In contrast to the explosion in research related to the molecular genetics and biochemical pathways associated with tuberous sclerosis complex, very little is known about the cognitive and behavioral manifestations of the disorder. In broad terms, longitudinal studies of developmental trajectories, studies of the mechanisms that underlie cognitive and behavioral deficits, intervention studies, and further searches for biomarkers of cognitive and behavioral disorders are essential. Developmental models to explain the variability of expression and efforts to integrate the behavioral, cognitive, structural, and biochemical levels of investigation hold great promise but will require collaborative work.

Based on the current evidence regarding the patterns of strengths and weaknesses presented here, the findings point with remarkable consistency toward frontal systems involvement in tuberous sclerosis complex. The convergence of attentional-executive neuropsychologic deficits,[24,25,28,43–47] high rates of developmental disorders,[24,27,28,30] and replicated neuroradiologic findings that highlight fine-grain abnormalities in the thalamus, basal ganglia, and frontostriatal white matter[3] raises the possibility that the *TSC* genes, independent of the role of cortical tubers or subependymal nodules, might impair the functional development and integrity of the basal forebrain, thus leading to deficits in the emergence, development, and establishment of attentional-

executive skills, subserved by the frontostriatal networks.[77] These aberrant networks present with specific neuropsychologic deficits[78] associated with impaired development of widespread networks required for complex attention and executive control processes. These deficits, in turn, could be predicted to impede the development of social cognitive and metacognitive skills, thus contributing to the risk of developing a range of psychiatric disorders (including ADHD), behavioral disorders, and social communication disorders.[78]

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