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Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex

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BACKGROUND: Behavioral and psychiatric comorbidity are common in tuberous sclerosis complex (TSC), but information regarding psychopharmacologic management is lacking.

METHODS: We reviewed clinical records of patients evaluated over a 20-month period at a large, quaternary referral center specializing in the comprehensive management of patients with TSC. Data were collected regarding psychiatric diagnoses, psychopharmacologic medications used to treat these disorders, and clinical response to treatment at follow-up.

RESULTS: There were 113 encounters by 62 pediatric and adult patients with TSC, which were included in the present analysis. Behavioral and anxiety disorders were most prevalent, as were autism spectrum disorders and attention-deficit/hyperactivity disorder. Antipsychotics, antidepressants, and anticonvulsants with mood-stabilizing properties were the most often prescribed psychoactive medications and were associated with an overall improvement or stabilization of psychiatric symptoms 65% of the time.

CONCLUSIONS: Psychiatric comorbidity, especially behavioral disorders, is very common among patients with TSC. Pharmacologic treatment can be very effective and should be considered for optimal disease management in affected individuals.

KEYWORDS: tuberous sclerosis complex, psychiatric comorbidities, behavior, treatment

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disease with a prevalence of 1 in 6,000 to 10,000, irrespective of sex or race.¹ Disease manifestations are the result of mutation of either *TSC1* or *TSC2*, resulting in dysregulation of mTORC1, an essential intracellular nutrient sensor and regulator of protein translation, cell growth, and differentiation. Multiple organ systems are affected, including the lungs, kidneys, heart, and skin. Neurologic manifestations are the primary cause of disease morbidity in TSC, including early-onset epilepsy (90% of patients), developmental delay (60%), intellectual disability (50%), and autism (25%).²

Psychiatric disorders also are common in TSC, but prevalence estimates vary significantly (40% to 80%).³ Furthermore, beyond prevalence estimates little or no attention has been given to treatment options and outcomes in TSC patients diagnosed with psychiatric disorders. As such, it is readily recognized that psychiatric diagnoses in this patient population often are overlooked, undiagnosed, and left untreated.⁴

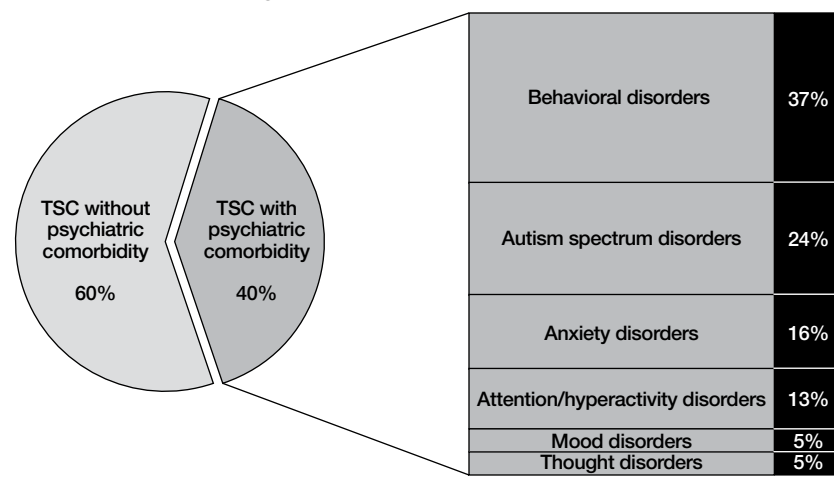
The multidisciplinary TSC clinic at the Cincinnati Children's Hospital Medical Center (CCHMC) includes board-certified specialists in both neurology and psychiatry who diagnose and treat pediatric and adult patients with TSC. Our experience confirms the high prevalence of psychiatric and behavioral disorders in TSC. However, the paucity of evidence-based treatment recommendations and resulting outcomes in this patient population lead us to examine more closely the individual psychiatric diagnoses, pharmacologic treatments utilized, and resulting response to treatment. The results of our analysis are reported here.

METHODS

This is a retrospective review of psychiatric encounters of patients evaluated in the Tuberous Sclerosis Clinic and Research Center at CCHMC between September

FIGURE

Prevalence of psychiatric comorbidity in patients with TSC, by type (primary diagnosis)



TSC: tuberous sclerosis complex.

2007 and May 2009. Permission to perform this study was obtained from the institutional review board (IRB) at CCHMC. The CCHMC IRB waived the informed consent requirement in accordance with title 45 CFR 26.116.

Only patients with a definite diagnosis of TSC, either by established clinical criteria⁵ and/or genetic confirmation of disease-associated mutation in either *TSC1* or *TSC2*, were included in the analysis. Data collection included demographic and genotype characteristics, degree of cognitive impairment (by formal neuropsychological testing when available or clinician assessment), psychiatric profile, type and dosing of psychopharmacologic agents prescribed, duration to follow-up, and outcome response. Psychiatric diagnoses were made by a board-certified psychiatrist (D.N.) in accordance with DSM-IV-TR criteria.⁶ When multiple diagnoses were present in a single patient, the initial or most prominent diagnosis was assigned as the primary and any additional diagnoses were classified as secondary.

Outcomes data were subgrouped by diagnosis and treatment. Primary endpoint analysis was treatment response, which was categorized according to parent report and/or clinician assessment as either favorable or unfavorable. Outcome was considered favorable if psychiatric symptoms or behaviors were improved (ie, decreased signs, symptoms, or behaviors compared

with baseline accompanied by improved social, occupational, or other areas of functioning) or stabilized (ie, decreased problematic signs, symptoms, or behaviors compared with baseline but without evidence of accompanying improvement in social, occupational, or other functional areas). All other outcomes were classified as unfavorable, including instances where response was mixed (in patients with multiple diagnoses where some improvement/stabilization might be seen with 1 diagnosis but symptoms worsen in the others) or unclear (insufficient information to determine whether improvement or worsening had occurred). Prevalence of individual diagnosis was calculated by dividing the number of a specific diagnosis by the total number of patients included in the analysis ($n = 62$) and reported as a percentage. Frequency of treatment utilized was calculated by dividing the number of times specific medication was prescribed by the total number of patient encounters. Favorable outcome response was calculated by dividing the number of patients with improved or stable symptoms by the number of patients treated, for which follow-up assessment was available. All calculations were reported as mean $\pm$ standard deviation.

RESULTS

Patient characteristics

A total of 157 individual patients with TSC were evaluated during the 21-month period, of which 62 were formally diagnosed with a psychiatric comorbidity (FIGURE). Some of the 62 patients who were diagnosed with a psychiatric comorbidity were seen by the psychiatrist multiple times, resulting in a total of 113 separate encounters for inclusion in the present study. Four patients were seen once, without follow-up, and therefore could not be included in outcomes analysis. An additional 4 patients returned for follow-up once, but not subsequently, so that outcomes analysis only included the initial visit. In total, outcomes for 105 encounters were able to be determined: 32 patients had 1 full psychiatric assessment, 13 patients had 2 assessments, and 13 patients had >3 assessments. The average length of time from evaluation to follow-up assessment for treatment outcome was 125 ± 81 days.

TABLE 1
Patient characteristics

Age at first visit (years)		15.40 $\pm$ 9.49
Age range (years)		3 to 48
Sex ratio (M:F)		35:27
Genotype (N = 31)	TSC 1	4/31 (12.9%)
	TSC 2	20/31 (64.5%)
	NMI	7/31 (22.6%)
Total number of psychiatric encounters		113
Encounters with follow-up assessment		105/113 (92.9%)
Length to follow-up assessment (days)		125.5 $\pm$ 80.9

NMI: normalized mutual information; TSC: tuberous sclerosis complex.

The average age at time of first encounter was 15.4 ± 9.5 years (range 3 to 48), but most (77%) were age <21 . Sex distribution was fairly equal (56% male, 44% female) (TABLE 1). With regard to baseline cognitive function, 19 of the 62 patients were in the normal or near-normal range ($IQ \geq 80$), 22 were either borderline or mildly disabled ($IQ 60$ to 79), and 30 had cognitive function in the moderate-to-severe range ($IQ 40$ to 59). This pattern follows previous reported distribution of intellectual disability in TSC, with the exception that none in the present cohort had profound intellectual disability that normally comprises up to 30% of patients with TSC.⁷ Genetic testing results were available for 31 patients, with 13% of patients having mutation in *TSC1*, 64% in *TSC2*, and 23% had no mutation identified. Sex and genotype characteristics are consistent with that in the TSC patient population as a whole.⁸⁻¹⁰

Psychiatric diagnoses

A total of 150 psychiatric diagnoses were made in the 62 TSC patients in this cohort, providing a mean of 2.42 ± 1.27 diagnoses per patient (TABLE 2). Behavioral disorders were the most common primary diagnoses (37%), and consisted of intermittent explosive disorder, oppositional defiant disorder, and self-injurious behavior disorder. Autism spectrum disorders (autism, pervasive developmental disorder, and Asperger's syndrome), anxiety disorders (generalized anxiety disorder, panic disorder, adjustment disorder, posttraumatic stress disorder, obsessive-compulsive disorder, selective mutism, and individual phobias), and attention-deficit/hyperactivity disorder (ADHD) also were frequent primary diag-

TABLE 2
Psychiatric diagnoses in patients with TSC
(N = 62)

Number of psychiatric diagnoses per patient, n (%)	2.42 ± 1.27	
1	17 (27.4%)	
2	21 (33.9%)	
3	11 (17.7%)	
4	7 (11.3%)	
5	6 (9.7%)	
Psychiatric diagnosis by category	Primary n (%)	Secondary n (%)
Behavioral disorders (IED, ODD, SIB, impulse-control)	23 (37.1%)	38 (61.3%)
Autism spectrum disorders (autism, PDD, Asperger's)	15 (24.2%)	8 (12.9%)
Anxiety disorders (panic, mutism, adjustment, PTSD, OCD, GAD, phobia)	10 (16.1%)	20 (32.2%)
ADHD (inattention, hyperactivity, mixed)	8 (12.9%)	9 (14.5%)
Mood disorders (MDD, bipolar, dysthymia/cyclothymia)	3 (4.8%)	10 (16.1%)
Thought disorders (schizophrenia, psychosis, delirium)	3 (4.8%)	3 (4.8%)

ADHD: attention-deficit/hyperactivity disorder; GAD: generalized anxiety disorder; IED: intermittent explosive disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; ODD: oppositional defiant disorder; PDD: pervasive development disorder; PTSD: posttraumatic stress disorder; SIB: self-injurious behavior; TSC: tuberous sclerosis complex.

noses (24%, 16%, and 13%, respectively). Mood disorders and thought disorders were encountered but much less prevalent (5%).

As a secondary diagnosis, behavioral disorders remained the most common (61%). Anxiety disorders (32%) and mood disorders (16%) were much more frequently encountered as a secondary diagnosis than as a primary diagnosis, whereas the converse was true for autism spectrum disorders (13%). The frequency of ADHD (15%) and thought disorder (5%) as a secondary diagnosis were essentially the same as that for primary diagnosis.

Pharmacologic treatments and response

As shown in **TABLE 3**, most patients were treated with multiple psychoactive medications (average 2.35 ± 1.38 , range 0 to 5). Overall, medication was much more likely to be initiated or increased (81% of encounters) than decreased (7%) or maintained (30%) in these patients. Upon follow-up, improvement was reported 48% of the time and stabilization of symptoms 17% of the time.

However, in all instances the degree of this favorable response varied significantly for individual patients and some patients reported a mixed response for distinct psychiatric complaints or diagnoses.

Antipsychotic medications with antidopaminergic properties were most frequently prescribed for behavioral disorders, and much less often for thought disorders, in this population (**TABLE 4**). Risperidone was prescribed in 46 of 113 patient encounters (41%) and favorable outcome (improvement or stabilization) was reported at follow-up in 30 encounters (65%). The next most frequently prescribed medication in this class was quetiapine, which was prescribed in 32 patient encounters (28%), which likewise showed a positive benefit for 19 patients at follow-up (59%). Aripiprazole was utilized in only 10 encounters, 7 of which had favorable responses. Other antipsychotics such as haloperidol, olanzapine, perphenazine, metirosine, and pimozide were prescribed too infrequently to assess response.

Selective serotonin reuptake inhibitors (SSRIs) and related medications, such as the norepinephrine/dopamine reuptake inhibitor bupropion, were primarily prescribed for anxiety-related disorders (particularly obsessive-compulsive and adjustment disorders) and, to a lesser extent, mood disorders such as depression or bipolar disorder. Most commonly, escitalopram was utilized (38 of 113 patient encounters) and beneficial 42% of the time. Bupropion was of benefit in 8 of 10 encounters in which it was prescribed. Other SSRIs were prescribed too infrequently to assess response.

Of the 62 patients with psychiatric comorbidity, 57 (92%) reported past or current history of seizures, which is typical for TSC.² Of those included in the present study, 72% were prescribed antiepileptic drugs (AEDs) at the time they were evaluated by the psychiatrist. While almost exclusively being used to prevent seizures in this population, these medications also can have significant effect on various psychiatric and behavioral conditions.¹¹ As shown in **TABLE 4**, valproic acid (20%) and lamotrigine (16%) were most often prescribed, followed by benzodi-

azepines (15%) and oxcarbazepine (12%). Levetiracetam, topiramate, phenytoin, carbamazepine, gabapentin, zonisamide, phenobarbital, and vigabatrin were each utilized <10% of the time. Although in the majority of cases these medications were associated with a favorable outcome, in most instances they were unchanged from assessment to follow-up (data not shown). Clinical improvement was thought to be more likely the result of adjustment in other psychoactive medications. However, this does not exclude the possibility that these medications may have had an adjunctive role in the treatment of psychiatric comorbidities in these patients.

For ADHD, methylphenidate and dexamethylphenidate were more often of benefit than not (9 of 12 reported improvement or stabilization of symptoms), whereas the alpha-adrenergic agents guanfacine and clonidine were the opposite (7 of 10 reported worsening or mixed response).

No specific pharmacologic treatments were utilized to target autism spectrum disorders or personality disorders directly. Rather, medications were prescribed irrespective of whether these disorders were present to treat associated symptoms or comorbid psychiatric disorders as above.

Finally, there is significant interest in the impact pharmacologic inhibitors of mTORC1 (sirolimus, everolimus) might have on cognitive function and psychiatric comorbidity in this population,¹² but no clinical experience with these agents in this regard have been reported. Therefore, we feel it important to report the response of 3 patients treated with these medications in this group. Patients were age 10, 18, and 19, and were diagnosed with intermittent explosive disorder (patient 1) and adjustment disorder NOS (patients 2 and 3). Everolimus was added to the regimen of patients 1 and 2 and sirolimus to patient 3. Upon follow-up 1 to 4 months later, each reported improvement in psychiatric symptoms.

DISCUSSION

Here we report the prevalence of psychiatric comorbidity in patients with TSC evaluated and treated by a board-certified psychiatrist within the multidisciplinary clinic at the quaternary referral center of the CCHMC. Behavioral disorders, autism spectrum disorders, anxiety disorders, and ADHD were found to occur in the highest frequency in this group.

TABLE 3
Psychoactive medications prescribed in patients with TSC (N = 113)

Psychiatric medications prescribed per encounter, n (%)	2.35 ± 1.38
0	11 (9.7%)
1	18 (15.9%)
2	38 (33.6%)
3	21 (18.6%)
4	16 (14.2%)
5	9 (8.0%)

TSC: tuberous sclerosis complex.

Previous estimates of psychiatric comorbidity and symptoms in patients with TSC have been highly variable, likely attributable to the different patient populations and research methodologies employed. For example, postal questionnaire responses from parents of 300 patients with TSC found aggressive behaviors and related difficulties in >56% of patients, including aggression, tantrums, noncompliance with caregivers, and self-injury.¹³ Behaviors associated with autism spectrum disorder, including social impairment and obsessive/ritualistic activities, ranged from 25% to 43%, and hyperactivity was reported in 28% of these patients. Another review of published case series of autism and TSC found that the 2 disorders coexisted in 17% to 58% of cases.¹⁴ More recently, neuropsychological assessment tools and patient or parent report of psychological symptoms have been employed, but with inconsistent results: anxiety disorders ranging from 5% to 56%, affective disorders ranging from 4% to 43%, and thought disorders ranging from 1% to 43%.¹⁵⁻¹⁹

In contrast to these earlier studies, the current analysis was limited to patients evaluated and diagnosed by a board-certified clinical psychiatrist with experience and familiarity with TSC. The importance of clinical expertise in diagnosing psychiatric disorders in patients with TSC cannot be overemphasized; there is inherent difficulty in distinguishing psychiatric illness from other central nervous system (CNS) aspects of TSC, including intellectual disability, epilepsy, and autism. Furthermore, many treatments, particularly for epilepsy, can cause deterioration or alteration of CNS function such that psychiatric illness is masked or mimicked. On a similar note, AEDs may exert a favorable impact on psychiatric disorders and symptoms.¹¹

TABLE 4
Medication response in TSC patients
with psychiatric comorbidity

CLASS	Favorable response (improvement or stabilization)
Antipsychotics	n (%)
Risperidone	30/46 (65.2%)
Quetiapine	19/32 (59.4%)
Aripiprazole	7/10 (70.0%)
Haloperidol	0/1 (0.0%)
Olanzapine	2/3 (66.7%)
Perphenazine	1/1 (100.0%)
Metirosine	0/1 (0.0%)
Pimozide	1/2 (50.0%)
Antidepressants	
Escitalopram	16/38 (42.1%)
Bupropion	8/10 (80.0%)
Citalopram	2/2 (100.0%)
Fluoxetine	3/5 (60.0%)
Venlafaxine	0/2 (0.0%)
Amitriptyline	7/10 (70.0%)
Trazodone	0/1 (0.0%)
Doxepin	0/1 (0.0%)
Imipramine	1/1 (100.0%)
Mood stabilizers	
Lithium	2/2 (100.0%)
Lamotrigine	14/18 (77.8%)
Oxcarbazepine	11/14 (78.6%)
Valproic acid	16/23 (69.6%)
Stimulants	
Methylphenidate	6/8 (75.0%)
Dexmethylphenidate	3/4 (75.0%)
Alpha-adrenergic agonists	
Guanfacine	2/5 (40.0%)
Clonidine	1/5 (20.0%)
Anxiolytics	
Lorazepam	10/14 (71.4%)
Clonazepam	0/2 (0.0%)
Chlordiazepoxide	0/1 (0.0%)
Other	
Naltrexone	2/2 (100.0%)
Sirolimus	1/1 (100.0%)
Everolimus	2/2 (100.0%)
TOTAL (includes combined treatment)	73/113 (64.6%)

TSC: tuberous sclerosis complex.

Although certainly more subjective than many alternative approaches, the clinical assessment utilized in the present study does provide an opportunity for separating psychiatric diagnoses from the important and unavoidable confounders present in people with TSC. This approach is also more likely to represent actual practitioner experience.

An obvious limitation of the methodology used here is the referral bias that was unavoidably introduced. Even though the CCHMC has a psychiatrist present in clinic, not all patients with TSC were able to be evaluated and treated by the psychiatrist because of time and availability constraints. As a result, overall prevalence estimates herein likely underestimate the true prevalence in patients with TSC. However, those included largely represent the most symptomatic and severely affected psychiatric patients, and thus the reported treatments utilized and responses thereof become all the more relevant.

Only one study to date has reported on the prevalence of psychiatric disorders in patients with TSC, using evaluation by a clinical psychiatrist as in the present study.³ A study by Muzykewicz et al³ included 43 patients with an average age of 19 (range 2 to 49 years). Of these, 98% received a psychiatric diagnosis and 33% had features of autism spectrum disorders, similar to our findings here. Specific psychiatric disorder frequencies also were consistent with our findings. The study, however, limited analysis and discussion of treatment to only 12 patients treated with citalopram for anxiety or mood disorders and risperidone for aggressive behaviors.

The present study expands significantly on pharmacologic management of comorbid psychiatric disorders in patients with TSC. Specific dosing practices at our center have been published previously.¹ In the present analysis, favorable treatment responses were observed with risperidone, quetiapine, and aripiprazole for aggressive behaviors 59% to 70% of the time. Benefit with escitalopram and bupropion was observed 42% to 80% of the time for treatment of anxiety symptoms, compulsive thoughts and behaviors, and mood disorders. Similarly, methylphenidate and dexmethylphenidate were effective in the treatment of ADHD symptoms.

All 3 patients treated with mTORC1 inhibitors demonstrated clinical improvement in psychiatric symptoms. The mechanism responsible for this improvement is not known, but could represent a novel strategy for the treatment of psychiatric disorders and other neuropsychiatric conditions associated with TSC, as current treatments

almost exclusively target neurotransmitter release and uptake. In contrast, a variety of mechanisms have been postulated which could impact CNS function at the molecular and neuronal level, including changes in neuronal dendrite structure, synaptic plasticity, surface receptor expression, and long-term potentiation and depression.^{12,20,21}

CONCLUSIONS

Psychiatric comorbidity is highly prevalent and should not be overlooked in the comprehensive management of patients affected with TSC. Treatments are readily avail-

able and effective for the treatment of psychiatric symptoms in these patients. ■

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