INTRODUCTION
Tuberous sclerosis (TSc) is an autosomal dominant multisystemic disorder that manifests with widespread hamartomas and tubers in various organ systems (1). The mutant genes, TSC1 and TSC2, lead to a hyperactivation of the mammalian target of rapamycin (mTOR) signaling cascade that involved in cell growth, proliferation, protein synthesis, and metabolism (1). The central nervous system (CNS) is usually affected in TSc. Structural lesions which are frequently associated with a range of neuropsychiatric signs and symptoms are primarily located in the cortex and subcortex (2). The estimated prevalence of TSc is approximately 1/10,000, and CNS involvement is seen in approximately 85% of the cases, leading to neuropsychiatric entities such as learning disability, epilepsy, cognitive impairment, behavioral...

CASE REPORT
The Occurrence of Psychotic Manifestation Following the Initiation of Everolimus in a Patient with Tuberous Sclerosis: A Possible Involvement of Dysregulated mTOR Cascade
Olcay Senay, Yasin Hasan Balcioglu, Mehmet Cem Ilnem

ABSTRACT
Tuberous sclerosis (TSc) is an autosomal dominant multisystemic disorder. Mutant TSC1 and TSC2 are the responsible genes for the disorder that leading to a hyperactivation of the mammalian target of rapamycin (mTOR), a signaling cascade involved in cell growth, proliferation, protein synthesis, and metabolism. Everolimus and sirolimus, the mTOR inhibitors, are recently offered to restore pathologically up-regulated mTOR pathway in TSc. However, the neuropsychiatric side effects of these drugs are yet to be studied. Here we reported a 22-year-old male patient, with diagnoses of tuberous sclerosis, epilepsy, learning disability, and organic personality disorder without any psychotic manifestations, who was admitted to our outpatient clinic because of disorganized behavior, hallucinations, and delusions with a recent history of hostility and aggression. The aforementioned psychotic manifestations initiated soon after he had undergone on a placebo-controlled double-blind study of everolimus 6 mg/daily for TSc for last four months. Clinical examination, laboratory screening, and magnetic resonance imaging (MRI) of the brain have not revealed any other organic causes of psychosis. His symptoms resolved over the next ten or so days with moderate doses of antipsychotics. The current case is presented in order to discuss possible underlying neuronal signaling mechanisms those may lead psychosis following a short-term mTOR inhibition treatment. Although it would be difficult to allege the direct involvement of short-term everolimus exposure in the development of psychotic symptoms, impaired protein synthesis related to the mTOR inhibition leads to impaired neuronal network and plasticity, and may predispose to the development of psychotic symptoms, consequently.

Keywords: Everolimus, mTOR, neuromodulation, neuronal plasticity, psychosis

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problems, and autism (1). CNS complications are considered as the major cause of the morbidity and mortality in TSc. While existing literature has revealed that TSc has moderate relationship with autism and mental retardation, psychosis has been infrequently reported in TSc cases, without offering satisfying neurobiological basis (2). The prevalence of psychotic disorders is not believed to be increased in TSc compared to the general population which is about 1% (3). Comorbid psychotic symptoms were unconvincingly attributed to the disorganized cortical lamination with loss of gray- and white-matter differentiation relevant to locations of the lesions (4). Besides the fact that management of the disorder is symptomatic, promising mTOR inhibitors everolimus and sirolimus were recently offered to restore pathologically up-regulated mTOR pathway (1). Likewise the unclarified pathogenesis of psychosis in TSc, the literature is ungenerous to recommend specific treatment for such cases. mTOR inhibitors have provided strong treatment strategies in TSc; however, the efficacy and safety aspects of these drugs on neuropsychiatric symptomatology in TSc are yet to be studied. In this case report, we aimed to present a TSc patient who developed prolonged and persistent delusions and disorganized behavior following a short-term everolimus treatment and discuss possible underlying neuronal signaling mechanisms those may lead such condition.

**CASE**

A 22-year-old male patient was admitted to our outpatient clinic because of disorganized behavior with a history of hostility and aggression for five days. An overt social isolation existed with an under-eating and insomnia. He was afraid of someone would hurt him. He had a previous diagnosis of TSc, epilepsy, and moderate learning disability with a total intelligence quotient (IQ) score of 60 according to the Wechsler Adult Intelligence Scale (WAIS). He had been following-up by our clinic for five years with the diagnoses of learning disability and personality change due to another medical condition, aggressive type without any psychotic manifestation. There were no history of substance use, family history of TSc and psychiatric disorders. At his mental status examination, cognition was intact. He was irritable and agitated. He was laughing inappropriately during the examination. His speech was slow. Auditory hallucinations, persecution and reference, and grandeur delusions were detected. He had a delusion of being a policeman. Decreased attention and inefficient abstraction presented. He had a lack of insight about his symptoms. Adenoma sebaceum lesions around his nose wings and his abdomen skin presented at his physical examination. Previous and current magnetic resonance imaging (MRI) of the brain demonstrated cortical-subcortical tuberous and hamartomatous hyperintense lesions compatible with TSc without any overt morphological alteration within the time course of the illness (Figure 1). His current prescribed oral medication was topiramate 400 mg/day, oxcarbazepine 1200 mg/day and aripiprazole 15 mg/day with the diagnosis of epilepsy and personality change due to another medical condition.
condition, aggressive type which is primarily based on a persistent personality disturbance predominant with aggressive behavior that is preceded by the diagnosis of tuberous sclerosis. After he went on a placebo-controlled double-blind study of everolimus for the treatment of TSc for last four months, the aforementioned psychotic manifestations initiated and he was hospitalized. Aripiprazole was stopped and intramuscular haloperidol was initiated. Meanwhile, the anticonvulsant treatment has been resumed at the same dosage during the everolimus trial as he remained seizure free for over three years. The trial records we obtained revealed that the patient took 6 mg/daily dose of everolimus for four months during that study and there was grade 1 aggression at the beginning of the study which increased to grade 3 at the end according to the Modified Overt Aggression Scale. The Turkish version of Naranjo Adverse Drug Reactions Probability Scale score was found as six points which represent a probable relationship between the drug and the observed adverse effect (5). Everolimus was stopped following his hospitalization. Also, 40 mg daily dose of propranolol was added to his treatment because of grade 1 hand tremor. His psychotic symptoms and behavioral disturbances resolved over the next ten or so days with parenteral haloperidol 20 mg/daily and biperiden 10 mg/daily medication. His parenteral treatment was tapered off and oral treatment was started with olanzapine 20 mg daily. His Positive and Negative Syndrome Scale score improved to 45 from 107 and he was discharged with oral olanzapine treatment.

DISCUSSION

This case illustration intended to gather attention regarding occasional neuropsychiatric adverse effects of immunosuppressive agents through the inhibition of mTOR, one of the major neural signaling cascade in the CNS. Structural lesions in TSc are the results of abnormal mTOR function that leads to inappropriate protein synthesis and tissue formation. mTOR is a serine/threonine kinase that in the brain; mediates several critical physiological functions such as neuronal proliferation, neuronal migration, synaptic plasticity, and neurotransmission, and also seems to be involved in pathogenesis of numerous neurological, neurodegenerative, developmental, and cognitive disorders (6). As our patient manifested, mental retardation and epilepsy are the most characteristic domains of the disorder and their origins are attributed to epileptogenic tuberous foci and abnormal synaptic connectivity with deficient long-term potentiation (LTP) in the brain (2). In recent years, mTOR pathway interactions in neurobiological processes of behavior and cognition have been drawing the attention of the authors. Evidence from animal studies has shown that some behavioral and cognitive deficits may be related to aberrant molecular mTOR signaling (2). Cunningham et al. have discussed the down-regulated mTOR signaling to affect the mitochondrial oxygen oxidative function via decreased gene expression of mTOR cascade components that leads insufficient cellular respiration and resilience, and neuronal damage consequently (7). Disruption of mTOR pathway has been considerably implicated in the pathophysiology of cognitive disorders in experimental animal models. Inhibiting mTOR pathway with rapamycin and its analogues has been associated with decelerated hippocampal neurogenesis with the development of cognitive and behavioral disturbances in rodents (8). On the other hand, improvement in affective symptoms, anxiety and behavioral disturbances accompanying neurological diseases were documented under mTOR inhibition treatment (9). Rare and indirect reports have been published regarding mTOR related mechanisms in psychotic disorders. For instance, rapamycin has significantly decreased depressive and anxiety-like behaviors in mice (10), possibly by stimulating major monoamine pathways in the brain that may be implicated in the development of psychosis through increased dopamine release. Glutamate is the main excitatory neurotransmitter in the brain, and glutamatergic dysfunction is a well-known culprit in the neuropathology of schizophrenia (11). Experimental animal models indicated that rapamycin-inhibited
hippocampal dendritic protein synthesis in mice neurons has been induced by the activation of glutamate receptors, particularly NMDA and metabotropic receptors (12). Additionally, reelin and brain-derived neurotrophic factor (BDNF), the key proteins in synaptic plasticity and maintenance of neural networks which are recruited by mTOR signaling cascade, were reported to be down-expressed in schizophrenia (13). In spite of the implications on the depressed mTOR signaling in the pathogenesis of schizophrenia, the role of overactivated mTOR was also mentioned. The mutation of disrupted-in-schizophrenia 1 (DISC1) gene was associated with the development of schizophrenia and DISC1 was asserted to negatively regulate mTOR signaling cascade (14). In addition, overactivity of 5-HT6 receptors was found to be associated with enhanced mTOR signaling in schizophrenia which leaded cognitive deterioration (15). This contradiction has probably been a result of the supposition that mTOR signaling and sensitivity to its pathological effects are varied in different brain regions. Indeed, overactivation of signaling may be considered as a compensatory response in selected models.

One can postulate that interactions in drug metabolism may play a role in the emergence of de novo psychosis. This assumption comes from the fact that cytochrome P450 enzymes possess a major involvement in the metabolism of the drugs the patient has received. For instance, oxcarbazepine induces CYP3A4 (16), while everolimus is metabolized by CYP3A4 (17). However, in this situation, it is expected that the serum level of everolimus would be reduced and it would be harder to observe the manifested adverse effects in consequence. Another alternative explanation for the occurrence of psychotic manifestation is a possible relationship between mTOR inhibitors and posterior reversible encephalopathy. mTOR inhibitor-related neurotoxicity usually presents with confusion, dizziness, agitation, and tremor; however, psychotic symptoms such as perception and thought disorders have not been precisely linked with these immunosuppressive agents (18).

In the present case, psychotic symptoms have emerged following a short-time exposure to everolimus. Everolimus is an orally-administered rapamycin analogue that selectively inhibits mTOR signaling pathway. Everolimus was pointed superior to cyclosporine with less neurotoxicity and other side effects; however, no clear correlations have been established yet between the use of everolimus and development of central side effects (e.g., depression, anxiety, cognitive impairment or other psychiatric conditions) (19). Impaired protein synthesis related to the inhibition of mTOR leads to impaired neuronal network and plasticity and may predispose to the development of psychotic symptoms (Figure 2). Nevertheless, it would be difficult to allege the direct involvement of short-term everolimus exposure in the development of psychotic symptoms. It would be better to regard the fact that schizophrenia is a multifactorial disorder and combination of predisposing circumstances would take a bigger part in the explanation of etiopathogenesis of schizophrenia. TSc with its relation to impaired neurodevelopmental processes should be studied, and discussed in terms of liability for psychotic disorders in larger groups. This report may widen the insight over impaired mTOR pathway in schizophrenia. Advanced studies on this topic would offer novel pharmacological options in the treatment of psychotic symptoms.
schizophrenia. Patients should be carefully monitored for their psychiatric/neurological profiles in any clinical situation where a mTOR inhibitor will be used (e.g., cancer treatment, TSC or immunosuppression).

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REFERENCES