Tuberous Sclerosis and Bipolar affective disorder: A co-morbid association

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ABSTRACT
Tuberous Sclerosis is a genetic, neuro-cutaneous disorder affecting multiple organ systems. Psychiatric manifestations like learning disability, mental retardation, hyperactivity, autism and behavioral problems are common in Tuberous Sclerosis. Mood disorders like depression is also reported with Tuberous sclerosis, however the association of bipolar affective disorder with Tuberous sclerosis is not established due to insufficient data and limited research evidences. In this case report, we present the association of Tuberous sclerosis and bipolar affective disorder in a middle aged lady.

Introduction
Tuberous sclerosis is a autosomal dominant disorder affecting all ages and is characterized by mental retardation, seizure disorder, facial angiofibroma, renal angiomyolipoma and pulmonary lymphangiomyomatosis [1]. Autistic features can be presenting features in Tuberous sclerosis [1]. Mutation of one of the two genes TSC1 and TSC2, which are located in chromosome 9 & 16 and encode for protein hamartin and tuberin respectively, is responsible for the causation of the disease [1, 2]. Tuberous sclerosis affects multiple systems (Brain, eye, kidney, lungs, skin and liver) and diagnosis is mainly based on the clinical features [1 - 3]. Learning disability, mental retardation, behavioral problems, autistic features and hyperactivity are common psychiatric co-morbidities with Tuberous sclerosis [1 - 5]. Other rare psychiatric co-morbidities with Tuberous sclerosis are mood disorders, psychosis and anxiety disorders [5, 6]. The literature supporting association of bipolar affective disorder with Tuberous sclerosis is limited to few case reports [5 - 8]. In a study conducted by Chung et al; in 2011 on patients of Tuberous sclerosis, mood disorder is prominent (primary diagnosis) in approximately 5% patients whereas in 16% of patients mood disorder is secondary to Tuberous sclerosis [9].

Case history
A 30 years old, married, Hindu lady of lower socio-economic status presented with complaints of increased talkativeness, physical restlessness, big talks (talking about having some supernatural power), decreased sleep, irritable mood for approximately 3 months. On further exploration of history, it was revealed that she wanted to marry again and claimed herself, having some extraordinary quality. She had frequent arguments with her family members on trivial issues. She had a similar episode approximately 4 years back. She was also having history of seizure since her childhood, which was treated with high dose carbamazepine (1400mg/day), but she developed double vision for which the dose was reduced to 1000mg/day. In 2009, she became non-compliant to medications and had a manic episode and subsequently developed multiple episodes of generalized tonic-clonic seizure. During 2009, she was treated with carbamazepine 1000mg/day, Risperidone 10mg/day and trihexyphenidyl 4mg/day and was well controlled. Again in 2011, she became non-compliant to medications and had a manic episode and seizures, which was managed with carbamazepine and Risperidone. The current episode was also due to non-compliance to medications. She had also an episode of seizure, one month prior to hospitalization. She had multiple, glistening, oily wart like eruptive lesions in her cheeks and nose and pigmented patches in lower trunk since her birth. She was having a history of very poor scholastic performance and due to repeated failures; she was unable to complete her primary education.

Family history was not contributory. Pre-morbidly she was well adjusted to life. There was no history of any maladaptive personality traits. Her physical and systemic examination did not reveal any abnormality, other than adenoma sebaceum and Shagren patches. On mental status examination, there was increased flow and volume of speech, excessive grooming and make ups. The psychomotor activity was increased. Her attention and concentration was impaired. She was in irritable mood during most part of the interview. She had grandiose ideas and questionables plans for future. Her judgment and insight was impaired.

Routine hematological and urine examination did not reveal any abnormality. Liver function test, renal function test, thyroid function test, blood sugar, serum electrolyte levels were with in normal limits. 24 hour urine protein was 440mg (normal value for adults - <150mg). Ultrasonography of abdomen and pelvis was suggestive of renal parenchymal disease (kidneys were mildly echogenic with poor cortical-medullary differentiation). MRI of the brain showed multiple tubers on the surfaces of lateral ventricles. Her IQ was found to be 68.

On the basis of history, above clinical findings and mental status examination, the diagnosis of “Bipolar affective disorder; current episode manic without psychotic symptoms with mild mental retardation, tuberous sclerosis and seizure disorder” was made. She was started with sodium valproate 1000mg/day which later increased to 1500mg/day, Risperidone 6mg/day and trihexyphenidyl 2mg/day were also added. Despite of above treatment her mood symptoms persisted even after 6 weeks, so lithium was added at a dose of 900mg/day. The patient had shown gradual improvement and reached pre-morbid level of functioning in next 2 months. Currently the patient is well maintained with above medications and in regular follow ups.

Discussion
Non – compliance is a major issue in our patient which led to poor control of seizure as well as frequent relapse of manic episodes. Anti-epileptics are the mainstay of treatment, in the context of such patients where seizure disorder and bipolar disorder coexists.

Diplopia is a common side effect [10] of carbamazepine which limited further dose escalation in our patient to control seizure and hence being replaced by sodium valproate.

Our patient was having Tuberous sclerosis and subnormal intelligence (mild mental retardation) and seizure disorder; which are well known co-morbid associations with Tuberous sclerosis. Though mood disorders are described as psychiatric co-morbidities with Tuberous sclerosis, but depression secondary to Tuberous sclerosis is frequently encountered. There is no strong evidence of association of bipolar affective disorder with Tuberous sclerosis. However, there are case reports suggesting association of Tuberous Sclerosis and bipolar affective disorder and these case reports unable to establish definite association of the two disease entities. The dilemma still exists, whether the
association is just a chance association or a definite co-morbid association.

Bipolar disorder is highly heritable disorder with steady genetic linkage involving multiple genes in different chromosomes like – 1p, 4p, 6q, 12q, 16p, 17q, 18p, 18q, 21q, 22q, Xq [11 – 13]. Tuberous sclerosis and bipolar affective disorder, both involve the chromosome 16. There may be some overlapping or possible linkage between the gene responsible for bipolar affective disorder and gene responsible for Tuberous sclerosis. In such state, it is very difficult to ignore the association of bipolar affective disorder and Tuberous sclerosis as merely a chance association. Further study and genetic exploration in future can establish the fact.

REFERENCE