CASE REPORT

Tuberous Sclerosis with Bipolar Disorder Mania: Genetic Perspective

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ABSTRACT
Tuberous sclerosis or tuberous sclerosis complex (TSC) is a rare multi-system genetic disease that causes non-malignant tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. Non specific psychiatric symptoms occur in substantial number of patients with Tuberous Sclerosis. Tuberous Sclerosis is a rare disorder and most of patients present with behavioural changes, which may be mistaken for variety of psychiatric disorders, though Mania has been rarely reported. Here we report a case of Tuberous Sclerosis with classic radiological findings and manic features. Skin showed typical facial angiofibromas and Ash leaf macules and MRI displayed classic Tubers. There have been very few case reports of Bipolar disorder manic phase and all studies have till now proposed the anatomical relation of tubers in the brain as the underlying mechanism of this psychopathology. The neuroanatomical abnormalities found in this patient could be a possible explanation of his manic symptoms.

Keywords: Tuberous sclerosis, Bipolar disorder, Mania

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. 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] It is readily recognized that psychiatric diagnoses in this patient population are common and are often overlooked, undiagnosed, and left untreated.[3] Mood disorders and thought disorders were encountered but reported as much less prevalent (5%). Behavioral disorders were the most common primary diagnoses (37%), and consisted of intermittent explosive disorder, oppositional defiant disorder, and self-injurious behaviour disorder. Autism spectrum disorders (autism, pervasive developmental disorder, and Aspergers syndrome), anxiety disorders (generalized anxiety disorder, panic disorder, adjustment disorder, posttraumatic stress disorder, obsessive-compulsive disorder, selective mutism, and individual phobias), and attention-deficit/hyperactivitydisorder (ADHD) were frequent.[4]

The revised criteria for diagnosis require the presence of two major or one major and two minor features for a definitive diagnosis of TSC. Among the major features are facial angiofibromas, periungual fibroma, hypomelanotic macules, shagreen patch, cortical tuber, and subependymal nodule; while multiple enamel pits, hamartomatous rectal polyps, bone cysts, cerebral white-matter migration tracts, and gingival fibromas are among the minor features.[5] In infants, the first clue is often the presence of seizures, delayed development or white patches on the skin. The prognosis for individuals with TSC depends on the severity of symptoms, which range from mild skin abnormalities to varying degrees of learning disabilities and epilepsy to severe mental retardation, uncontrollable seizures, and kidney failure. Those individuals with mild symptoms generally do well and live long productive lives, while individuals with the more severe form may have serious disabilities. However, with appropriate medical care, most individuals with the disorder can look forward to normal life expectancy.[6]

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CASE REPORT

A 20 year old Hindu unmarried vegetarian male belonging to a rural background in India, educated till 8th standard and hailing from a lower middle class socio-economic background, was brought by his mother to Teerthanker Mahaveer Medical College and Hospital, India in June 2013 with history of over talkativeness, grandiose ideas, increased sexual desire, irritability, abusive behavior, decreased need for sleep, increased psychomotor activity for one week. Patient never suffered from any psychiatric illness in the past and there was no history of substance use. He never underwent major surgical procedure. There was no history of trauma. There was no history of any psychiatric or neurological illness in the patient's family.

Past history included delayed developmental mile stones as patient started walking at the age of 3 years and speaking at the age of 2 and a half years. He also started having complex partial seizures progressing to generalized tonic clonic seizures at the age of 2 years for which treatment was taken for 3 years. Details of the treatment were not available but the mother reported that the seizures stopped after that.

On examination, the patient had facial angiofibromas (Figure 1). Neurological examination did not reveal any significant abnormality. The patient showed a borderline level of intellectual functioning with IQ of 69 as per WICS Adults[7] and deficits in attention and concentration, recent memory, delayed and immediate recall, and visual retention which are consistent with the reports from earlier studies.[8] The mental status examination revealed a young male who was talking excessively with decreased reaction time, inflated self esteem and delusion of grandiosity, having a poor insight into his illness. Vitals were stable and investigations including haemogram, platelet count, peripheral blood smear, serum glucose, ammonia, liver, renal, thyroid function tests, vitamin B12 level, VDRL, electrolytes and other metabolic parameters were within normal limits.2D Echocardiogram and CT Abdomen showed no significant abnormality. MRI brain (Figure 2,3) revealed cortical tubers and subependymal nodules on T1-weighted images.

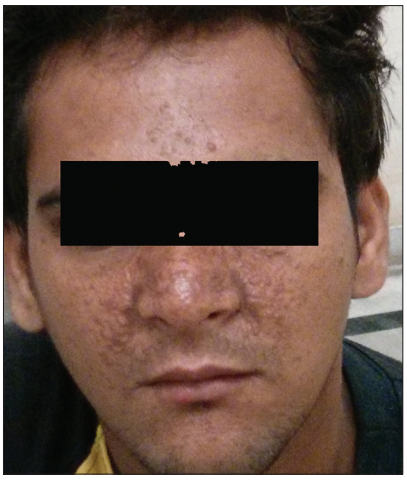

Figure 1: Facial angiofibromas

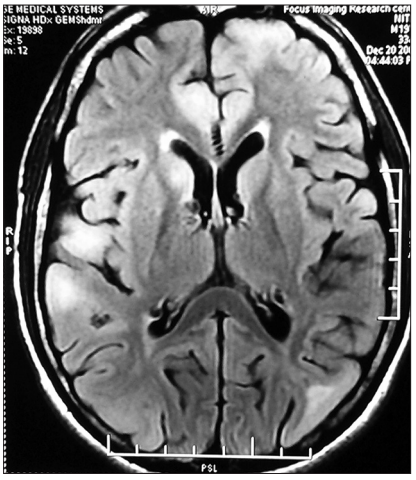

Figure 2: MRI scan showing calcified nodules and subependymal tubers on T1 weighted images

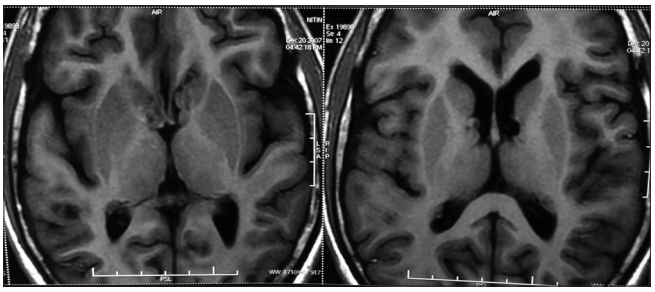

Figure 3: MRI scan showing subependymal tubers on T1 weighted image

DISCUSSION

Tuberous sclerosis complex is an autosomal dominant neurocutaneous disorder with a prevalence of 1 in 6000 to 9000 people.[9] Although a positive family history of tuberous sclerosis complex is frequently observed, spontaneous genetic mutations are common (65-75% of cases). Genetic studies have resulted in the identification of two genes implicated in the disease: *TSC1* and *TSC2*. The gene products of the TSC1 (hamartin) and TSC2 (tuberin) regulate key intracellular growth control pathways, suppress the actions of ribosomal S6 kinase, and inhibit the mammalian target of rapamycin (mTOR). Hamartin and tuberin form a single signaling complex, which is critical for regulating a number of important cellular processes related to cell growth and size.[10]

Definite tuberous sclerosis complex is diagnosed when at least two major or one major plus two minor features

are present. Probable tuberous sclerosis complex includes one major and one minor feature. Possible tuberous sclerosis complex includes one major or two or more minor features. Major features include skin manifestations (ie, facial angiofibromas, ungual fibroma, more than three hypomelanotic macules, and shagreen patch), brain and eye lesions (ie, cortical tuber, subependymal nodules, subependymal giant cell astrocytomas, multiple retinal nodular hamartomas), and tumors in other organs (ie, cardiac rhabdomyoma, lymphangioleiomyomatosis, renal angiomyolipoma). Minor features include multiple randomly distributed pits in dental enamel, rectal polyps, bone cysts, cerebral white-matter migration abnormalities on brain imaging, gingival fibromas, nonrenal hamartomas, retinal achromic patches, confetti skin lesions, and multiple renal cysts. [11]

Epilepsy occurs in 80-90% of all patients, with a positive correlation with subnormal intelligence.[12] Early descriptions of tuberous sclerosis complex emphasized the presence or absence of mental retardation or "delay." Although few studies examine cognition closely, as more patients are identified with tuberous sclerosis complex, it becomes apparent that cognitive outcomes vary more than was previously reported. Studies largely using parent surveys and reports of functional abilities estimate that 37 to 65% of children with tuberous sclerosis complex exhibit mental retardation.[13] The intellectual disability in TSC has been positively correlated with the severity of epilepsy, especially the infantile spasms and the tuber brain ratio.[14] Our patient also exhibited moderate mental retardation with I.Q. scores of 69 on WISC but the moderate range of mental retardation cannot explain the frank manic symptoms of this patient as the patient was maintaining good health until the onset of his manic symptoms compelling us to look for reasons beyond behavioral abnormalities associated with Mental retardation.

Neuropsychologic studies[15] suggest additional deficits in executive functioning and attention in children with tuberous sclerosis complex. In addition, children with tuberous sclerosis complex are at risk of symptoms of autism (≥ 40% of patients) and exhibit an increased risk of disruptive behavior disorders (eg, impulsivity and aggression) and social problems (eg, poor judgment and social awkwardness). Early onset of seizures (< 3 years of age; infantile spasm) and/or intractable seizures appear to be associated with an increased risk of neurodevelopmental and cognitive problems. The case described had no features of autism in his childhood and also successfully completed his primary education and was working as an apprentice in the business of his elder brother and was able to do simple tasks of the work without any difficulties till the development of his manic symptoms. However his early age of onset of seizures could not explain the attentional deficits which were found on the MSE and seem to be more related to his manic state of mind.

There have been very few case reports of Bipolar disorder manic phase and all studies have till now proposed the anatomical relation of tubers in the brain as the underlying mechanism of this psychopathology being reported in TSC cases.[16] Our study also supports this view that the neuro-anatomical abnormalities found in this patient could be a possible explanation of his manic symptoms.

CONCLUSION

Tuberous sclerosis is a multisystem disorder and its associated psychopathological conditions have been rarely reported in adults. This case report aims to add to the prevailing literature and hopes to identify more such psychiatric morbidities in this population of patients, whether this association is a chance one or it has more neuroanatomical correlates is a question on which further research needs to be carried out.

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