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Case Report

Tuberous sclerosis : a rare cause of intellectual disability present with significant behavioral impairment

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Summary

Tuberous sclerosis or Bourneville's disease is a rare multi-system genetic disease, which is clinically characterized by classical Voget's clinical triad such as adenoma sebaceum, low intelligence and epilepsy. It is a Mandelian monogenic disorder which is inherited as autosomal dominant fashion with prevalence rate is approximately I in 6000 live births. In this disease specific genetic abnormality causes benign tumor to grow in brain, kidneys, heart, liver, eye, lungs and skin, which gradually cause significant functional impairment of those organs either in isolation or in combination. This is a case report of 22 years old young man present with aggression with significant behavioral impairment for last 3 years who has history of epilepsy as well as multiple cutaneous manifestations such as adenoma sebaceum, Shagreen patch, peri and subungual fibroma. His IQ was extremely low measured by Wechsler Abbreviated Scale of Intelligence. According to that scale his total IQ score was 53. On systemic enquiry by both clinical and laboratory means we found that he had multiple renal cyst with chronic kidney disease. According to that finding we advised antipsychotics and referred him to National Institute of Kidney Diseases and Urology (NIKDU) for better nephrological evaluation and treatment. Two weeks later on a follow up session we found that he was quiet and calm. His aggression and violence was subsided.

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Introduction

Tuberous sclerosis (TSC) is a rare multi-systemic genetic disease that causes tumors to grow in brain and on other vital organs such as kidney, heart, liver, eye, lung and skin. A combination of symptoms includes seizures, intellectual disability, developmental delay, behavioral problem, skin abnormalities, lung and kidney diseases. TSC is caused by a mutation of either of two genes, TSC 1 and TSC 2, which code for the proteins hamartin and tuberin, respectively. These proteins act as tumor growth suppressors, agents that regulate cell proliferation and differentiation.[1] Now the full name of "tuberous sclerosis" complex is preferred because the disease has manifestations outside the brain. Previously it was mistakenly suspected that this disease is only manifested by involvement of brain.[2] The physical manifestation due to formation of hamartia, hamartomas and very rarely cancerous hamartoblastomas. The effect of these brain leads to neurological symptoms such as seizures, intellectual disability, developmental delay and behavioral problems. Symptoms also include trouble in school and concentration problem. About 50% of people with TSC have learning difficulties ranging from mild to significant.[3]

Case study

A 22-year-old illiterate unmarried muslim young man from lower socioeconomic background was brought to National Institute of Mental Health and Hospital (NIMH), Dhaka on 7th April 2018 by his mother with the complaints of social isolation for 2 years, outgoing tendency for 6 months, violence and aggression to others for 3 months, self injurious behavior for 1 month.

He had history of epilepsy since his 1 year of age, which was manifested by recurrent episodes of seizures. Each episode persisted for 30 to 60 seconds associated with tongue biting and urinary incontinence followed by unconsciousness for 1 to 2 hours. His guardian also reported that episodes of seizure occasionally occurred during sleeping and he couldn't remember the episodes following regaining of consciousness. Sometimes episodes of seizures persisted for 30 to 60 minutes for which he required hospitalization for 3 times previously. But for the last 14 years his epilepsy was controlled with medication (tablet Carbamazepine 400 mg in two divided dose daily).

Since his age of 3 and half years he developed multiple dark brown to blackish spot involving both his malar area which gradually became popular, not associated with any pain, itching or bleedings. Later on the papular lesion became generalized to neck, front of chest and back.

He had no academic involvement since his early life. His intellectual and adaptive functioning was too low to take self care such as bathing, brushing, and toileting. His guardian also reported that he had poor social communication. He was always bullied by his neighbors and some of his close relatives. There was no history of consanguinity of marriage. There was no significant family history of any physical or mental illness in his family. He lost his father when he was 6 years old. His prenatal, natal and post natal history was uneventful. Though his milestones of development were normal, he couldn't carry on his study in early life due to poor intelligence.

He was introverted and shy. But for the last 6 months he developed outgoing tendency without any significant purpose. For the last 3 months he became violent and aggressive toward others without any provocation. For the last one month he developed self injurious behavior without any obvious reason.

On physical examination, he was anaemic. His blood pressure was 140/90 mm of Hg. His height was 5'6" and weight 80 kg. He was obese with dull-looking appearance. There were multiple dark brown sessile papular lesions (adenoma sebaceum) – (Figure- 1), involving both his malar area and nasal bridge, more like butterfly distribution, as well as skin of neck and back. There was a fibrotic nodule in his frontal area of scalp.

There was multiple firm, variable sized nodular growth involving his fingers of both upper limbs as well as toes of both lower limbs suggestive of subungual and periungual fibroma or KÖenen tumors (Figure- 2). Multiple well defined roughened hypermelanotic patches were noted on his back of chest, torso and buttock showing an orange peel appearance suggestive of Shagreen patch (Figure- 3). His oral evaluation revealed there was nodular fibroma at dorsum of tongue, enamel hypoplasia with multiple pit at both sided 2nd premolar, 1st and 2nd molar teeth of upper jaw with gingival hypertrophy. On physical examination of abdomen, respiratory, cardiovascular as well as nervous system revealed no abnormality.

Mental state examination revealed he was cooperative but shouting during examination. His speech and mannerism were age inappropriate. There were no evident hallucinations or delusions. He had poor attention. His memory, ability to do simple calculations, comprehension, judgment and overall intelligence were all impaired. He had immobile facial features. He was self-centered and stubborn. Occasionally he was impulsive, destructive and aggressive. He had no insight about his problem and its possible solution.

His important laboratory investigation revealed Hb%: 10 gm/dl, Serum creatinine: 2.1 mg/dl. CT Scan of head revealed several nodular calcifications of different sizes bilaterally distributed under the ependyma of the lateral ventricles (Figure- 4). USG of whole abdomen showed multiple cyst of variable size involving both kidneys. There was poor corticomedullary differentiation in both kidneys suggestive of evidence of chronic kidney diseases (Figure- 5). His cardiovascular, respiratory, opthalmological, odontological as well as orthopaedic laboratory as well as radiological evaluation revealed no abnormality. Then he was treated with tablet Haloperidol 15 mg in three divided doses daily, tablet Procyclidine 15 mg in three divided doses daily and referred to National Institute of Kidney Disease and Urology for nephrological evaluation as well as better management and advised for follow up after 2 weeks.

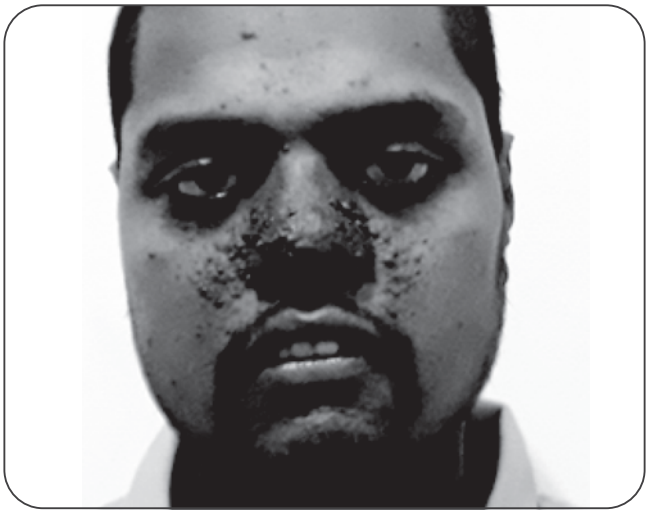

Figure- 1: Adenoma sebaceum over the both malar and nasal area (indicated by white arrow).

Figure- 2: Periungual fibroma at right middle finger (indicated by white arrow).

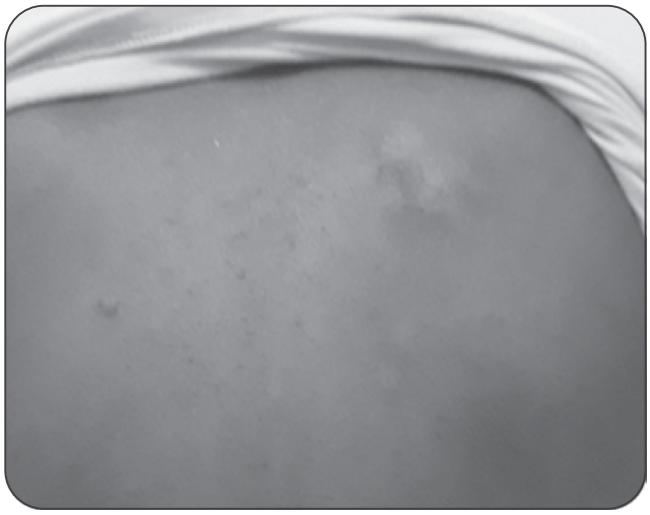

Figure- 3: Shagreen patch at skin over the right shoulder (indicated by white arrow).

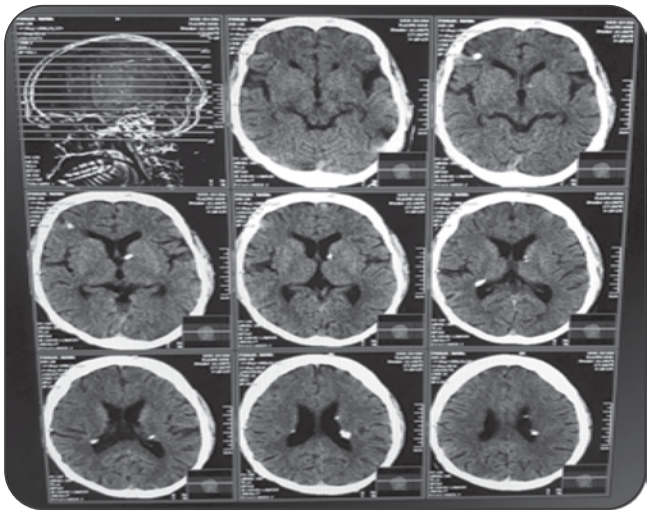

Figure- 4: Multiple subependymal nodule at both lateral ventricles (indicated by white arrow).

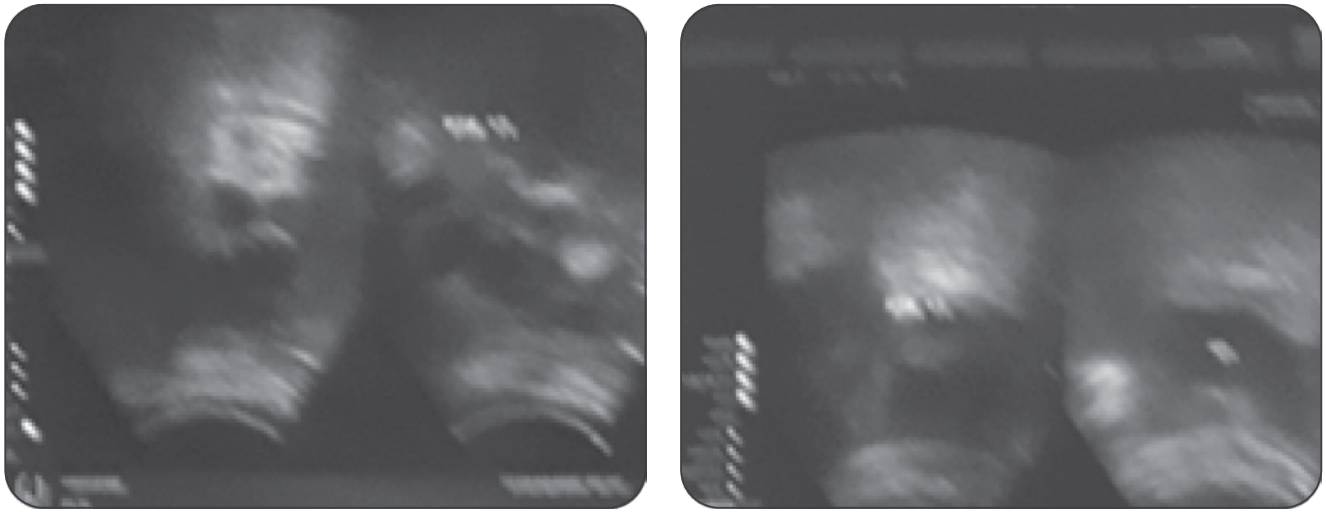

Figure- 5: Multiple renal cyst in both kidneys (indicated by white arrow).

Two weeks later on follow up session he was quiet and calm and cooperative with examiner. His violence and aggression was subsided. His sleep and appetite were improved. An IQ test was done by Weschsler Abbreviated Scale of Intelligence and it revealed his total IQ score was 53 which suggested that his IQ was extremely low. He was referred to Social Welfare and Occupational Therapy Department of NIMH for his better integrated medical and psychological management including social rehabilitation.

Discussion

TSC is a rare genetic disorder with an autosomal dominant pattern of inheritance, variable expressibility and incomplete penetrance.[4,5] Classical intracranial manifestation of TSC include subependymal nodules and cortical or sub-cortical tubers.[6] There is no pathognomic clinical signs for TSC complex. Many signs are present in individuals who are healthy or who have another disease. In order to meet diagnostic criteria for TSC complex, an individual must either have:

1. Two or more major criteria; or
2. One major criteria alone with two or more minor criteria (according to major and minor criteria adopted by International Tuberous Sclerosis Association, April 2002)

Major criteria		Minor criteria	
1	Facial angiofibroma (adenoma sebaceum)- at least 3 in number.	1	At least 3 randomly distributed pits in dental enamel.
2	Non traumatic subungual and periungual fibroma- at least 2 in number.	2	"Confetti" skin lesions, 1 to 2 mm hypomelanotic papules.
3	Hypomelanotic macules (Ash leaf macule)- at least 3 in number not less than 5 mm in diameter.	3	Intra oral fibromas.
4	Shagreen patch.	4	Non renal hamartoma.
5	Brain cortical dysplasia.	5	Retinal achromic patch.
6	Subependymal nodules.	6	Multiple renal cyst.
7	Subemendymal giant cell astrocytoma.		
8	Multiple retinal nodular hamartomas.		
9	Cardiac rhabdomyoma.		
10	Pulmonary lymphangioleiomyomatosis.		
11	Renal angiomyolipoma.		

In infants, the first clue is often the presence of seizure, delayed development or white patches on the skin.[7,8] About 50% of people with TSC have learning difficulties ranging from mild to signiticant,[3] and studies have reported that between 25% and 61% of affected individuals meet the diagnostic criteria for autism, with an even higher proportion showing features of a broader pervasive developmental disorder.[9] Other behaviors and disabilities such as ADHD, aggression, behavioral outbursts and OCD can also occur. Lower IQ is associated with more brain involvement on MRI.[6]

A 2008 study reported self-injurious behavior in 10% people with TSC.[10] Between 60 and 80% of TSC patients have benign tumors of the kidney called angiomyolipomas frequently causing haematuria. About 20 to 30% of people with TSC have renal cysts. However 2% may also have autosomal dominant polycystic kidney disease.[11] Some form of dermatological manifestation is present in 96% of individuals with TSC. Most causes no problem, but are helpful in diagnosis. The most common skin abnormalities include angiofibroma (adenoma sebaceum) that appear on nose and cheeks in a butterfly distribution consisting of blood vessels and fibrous tissue, potentially socially embarrassing rash start to appear during childhood, peri and subungual fibromas in hand and feet. Hypomelanotic macules may appear anywhere in the body, forehead plaque, Shagreen patch (one type of connective tissue nevus) appears as thick leathery skin that dimpled like an orange peel. Usually found on lower back, nape of neck or scattered across the trunk or thigh. Seizure is present in about 80 to 90% of patient which begins during the first year of life; varies from subtle focal seizure, infantile spasm to generalized seizures.[12,13]

According to diagnostic criteria adopted by the International Tuberous Sclerosis Association our patient has 4 major criteria such as

1. Adenoma seabaceum > 3 in number

2. > 2 sub and periungual fibroma in both upper and lower limb
3. > 3 Shagreen patch at torso and buttock whose diameter > 5 mm
4. On CT Scan of head shows multiple subependymal nodules

and 3 minor criteria such as

1. > 3 randomly distributed pits in dental enamel
2. Intraoral fibroma
3. Multiple renal cyst (as a consequence he developed chronic kidney disease with hypertension)

Conclusion

Tuberous sclerosis is a multi-systemic genetic disease which manifest with multiple physical and mental signs, symptoms and complications. This syndromes as well as complications are an important cause of significant morbidity as well as mortality for the affected person. They are also a significant source of stress for both caregivers as well as patient. In this case our patient was suffering from intellectual disability with significant behavioral impairment and multiple renal cysts in both kidneys with chronic kidney disease with hypertension. For that reason we prescribed antipsychotic for his psychiatric problem and referred to him NIKDU for better management of his physical complications where the patient was prescribed antihypertensive, iron, calcium and vitamin D supplementation. After 2 weeks on a follow up session his both mental and physical problems were well controlled. Later on he was included in Social Welfare Service for rehabilitation. Integrated holistic approach such as combined physical and mental treatment as well as rehabilitation services is the best option for such type of patient.

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