Date Received : 22 June 2022 | Accepted: 22 February 2023
**Indian Journal of Developmental & Behavioral Pediatrics**
(Official Journal of IAP Chapter of Neurodevelopmental Pediatrics)


# A case of Tuberous Sclerosis with Behavioral Problems and Poor Scholastic Performance

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## ABSTRACT

**Background:** Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with variable and heterogeneous expression. Prevalence is of 1 in 6,000 newborns affecting both sexes equally. TSC1 and TSC2 genes are tumor-suppressor genes, either of which when lost causes formation of hamartomas. Although there has been great progress in the identification and treatment of many of the physical features, the neuropsychiatric manifestations remain highly under identified and undertreated.

**Case Presentation:** An 8 years old, male, studying in second grade of an English medium school, only child of a non-consanguineous marriage, was brought with behavioral issues namely inattention and hyperactivity, reported from school and home settings with poor scholastic performance since beginning of schooling. No history of seizures was reported. Family history was not significant. There was initial speech and language delay. Other developmental domains were age appropriate. General examination revealed multiple hypomelanotic macules with normal systemic examination. His intelligence quotient (IQ) indicated low average intelligence. He could not perform corresponding to his grade in battery of psychoeducational and scholastic assessments. MRI brain had findings suggestive of TSC.

**Management:** Multidisciplinary holistic intervention plan with goals tailored according to child's needs were formulated and regular multidisciplinary follow-ups were planned.

**Conclusion:** TSC runs a progressive course and can lead to various systemic complications. Early diagnosis by clinical diagnostic criteria, timely management and regular surveillance is crucial.

**Keywords:** Tuberous sclerosis complex, hamartoma, poor scholastic performance, behavioral issues, hypomelanotic macules, case report

## Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with variable and heterogeneous expression affecting multiple organs, with a prevalence of 1 in 6,000 newborns [1] affecting both sexes equally [2]. Spontaneous genetic mutations occur in 65% of the cases. TSC1 gene, located on chromosome 9q34 which encodes protein hamartin and TSC2 gene, located on chromosome 16p13 which encodes protein tuberin, are two identified foci for TSC. Overall in 85% of TSC cases, 31% have TSC1 mutation (hamartin gene) and 69% have TSC2 mutation (tuberin gene) [1, 2]. TSC1 and TSC2 genes are tumor-suppressor genes, which when lost cause formation of hamartomas [1, 3].

Although there has been great progress in the identification and treatment of many of the physical features of TSC, including subependymal giant cell astrocytoma (SEGA), the neuropsychiatric manifestations remain highly under identified and undertreated [4].

## Case Presentation

An 8 years old, male, studying in second grade in an English medium school, only child of a non- consanguineous marriage delivered at term/ vaginally with birth weight of 1.5 kg (intra-uterine growth restriction), cried at birth with NICU stay for 12 days for low birth weight care and neonatal hyperbilirubinemia, was brought by his parents for behavioral issues in the form of inattention and hyperactivity reported from school and home settings and poor scholastic performance since beginning of schooling. There was no history of seizures. Family history was not significant.

*Developmental History*

1. Gross motor development: Age appropriate
2. Fine motor development: Age appropriate
3. Cognitive development: Understood complex commands
4. Social communication development: Age appropriate
5. Speech and language: Initial delay reported; Could narrate with unclear articulation
6. Academics: Concerns reported since early schooling in comprehension and writing, needed repetition of instructions
7. Behavior: Poor attention span with hyperactivity reported from home and school settings

***Examination***

- Anthropometry (according to IAP growth charts)
    - Weight: 23 kg (25th-50th percentile)
    - Height:122.8 cm (10th-25th percentile)
    - Body Mass Index (BMI): 15.45 kg/$m^2$ ($50^{th}$ percentile)
- General examination: multiple (08) hypomelanotic macules over chest (2), abdomen (2), back (3) and right thigh (1) each measuring approximately ≥ 7 mm.
- Systemic examination: Normal

***Summary of Psychoeducational Assessments***

- IQ was 88 (low average intelligence)
    - Verbal IQ was 82
    - Performance IQ was 93

**Table 1: IQ Assessment**

| Verbal Scale | | Performance Scale | |
|---|---|---|---|
| Domain | IQ | Domain | IQ |
| Information | 80 | Picture completion | 70 |
| General comprehension | 90 | Block design | 125 |
| Arithmetic | 80 | Object assembly | 62 |
| Analog and similarity | 90 | Coding | 94 |
| Digit span | 67 | Mazes | 113 |
| Vocabulary | 85 | | |

Social maturity by Vineland Social Maturity Scale was adequate (Social Quotient=95)

- He could not perform corresponding to his grade in battery of reading and spelling, graded reading and listening comprehension tests, graded mathematical test and expressive language.

**Table 2: Battery of Scholastic Performance Tests**

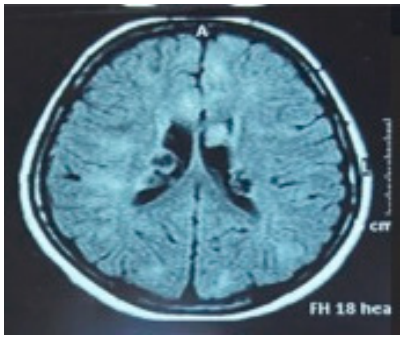
| Test | Result | Inference |
|---|---|---|
| Schonell's Graded Word Reading Test | Reading Age (RA) = 6 years 10 months | 1 year 2 months below chronological age (CA) |
| Schonell's Graded Word Spelling Test | Spelling Age (SA) = 5 years | 3 years below CA |
| Graded Reading Comprehension Test | Below the level of grade I | Not grade appropriate |
| Graded Listening Comprehension Test | Below the level of grade I | Not grade appropriate |
| Expressive Language | Not grade appropriate | Not grade appropriate |
| Graded Math Achievement Test | Not grade appropriate | Not grade appropriate |

- Conners-3 ADHD rating scale reported by parents showed moderate to severe dysfunction in domains of Inattention, Hyperactivity/Impulsivity, Learning problems, Executive functioning, Defiance/ Aggression with normal scores in peer relations.

***Other Investigations***

- Ophthalmological evaluation- Normal fundus examination; No evidence of retinal hamartoma
- Audiological evaluation- Pure tone audiometry was within normal limits
- Magnetic Resonance Imaging (MRI) of brain was done in view of the hypopigmented macules to look for TSC and the findings were consistent with findings suggestive of TSC.

Figure 1: MRI brain Axial T2-weighted image showing cortical tubers with subependymal nodules




- A genetic diagnostic testing was offered to the patient but they could not do it for economic reasons.

***Management***

Multidisciplinary intervention plan with goals were counseled to parents constituting

1. remedial teaching for academic issues
2. speech and language therapy for misarticulation
3. occupational therapy for graphomotor issues
4. behavioral therapy with the child and his parents (medication plan for ADHD/ behavioral issues had been kept for later plan)

Regular follow up with developmental pediatrician (to monitor and review goals for the intervention 3 monthly), pediatrician, neurologist and ophthalmologist (to follow up and monitor features and progression for the TSC) was advised.

Discussion

TSC was first observed by Von Recklinghausen in 1862, but the first clear description of TSC was given by Desire-Magloire Bourneville in 1880, who recognized the pathological features of white tumors or tubers and areas of sclerosis of cerebral gyri at post-mortem in patients with epilepsy and mental retardation [2, 5].

The cognitive and behavioral problems are of greatest concern to parents and caregivers.

Approximately 50% of the individuals diagnosed with TSC present with epilepsy, cognitive impairment and developmental psychopathologies including autism spectrum disorder. Those with normal intellectual abilities are also at high risk of specific neuropsychologic deficits, behavioral, learning, and other psychiatric disorders [1, 4]. Average IQ is observed in 40–50% patients with TSC [4]. The characteristic brain lesion is a cortical tuber. Subependymal nodules found along the wall of lateral ventricles which calcify latter by 2nd decade of life and project into ventricular cavity (candle-dripping appearance) which can later grow into SEGAs and can cause obstructive hydrocephalus [1].

Retinal lesions consist of hamartomas and white depigmented patches found in 50% to 80% patients [5]. Other retinal findings include retinal pigmentary disturbance ranging from hyperpigmented areas to "punched out" hypopigmented areas at the posterior pole or mid periphery. Non-retinal findings include angiofibromas of the eyelids, coloboma of the iris, lens and choroid, strabismus, poliosis of eyelashes, papilloedema and sector iris depigmentation [5].

Hypomelanotic patches over trunk and extremities are found on 90% of patients. Shagreen patch in lumbosacral region is also a hallmark of TSC. About 15-20% of TSC cases may develop small fibromas or nodules around fingernails or toenails during adolescence. Facial angifibromas develop by 4 to 6 years of age [1].

Approximately 50% children with TSC have cardiac rhabdomyomas which may cause congestive cardiac failure or arrhythmias. In children older than 10 years of age, angiomyolipomas may develop in kidneys in 75-80% cases, which by third decade may cause lumbar pain, hematuria or rarely, retroperitoneal bleeding [1].

**Table 3: Diagnostic Criteria of TSC**

Definite TSC diagnosed when at least two major or one major plus two minor features are present [1, 5].

| Major Features of TSC | Minor Features of TSC |
|---|---|
| 1. Cortical tuber | 1. Cerebral white matter migration lines |
| 2. Subependymal nodule | 2. Multiple dental pits |
| 3. Subependymal giant cell astrocytoma (SEGA) | 3. Gingival fibromas |
| 4. Facial angiofibroma or forehead plaque | 4. Bone cysts |
| 5. Ungual or periungual fibroma (non-traumatic) | 5. Retinal achromatic patch |
| 6. Hypomelanotic macules (>3) | 6. Confetti skin lesions |
| 7. Shagreen patch | 7. Non-renal hamartomas |
| 8. Multiple retinal hamartomas | 8. Multiple renal cysts |
| 9. Cardiac rhabdomyoma | 9. Hamartomatous rectal polyps |
| 10. Renal angiomyolipoma | |
| 11. Pulmonary lymphangioleiomyomatosis | |

Our patient had three major features of TSC with low average IQ, behavioral issues and academic difficulties.

## Conclusion

Multiple systemic involvement renders regular follow ups and screening by developmental pediatrician, neurologist, ophthalmologist and dermatologist. A brain MRI in every 1-3 years, renal imaging in every 1-3 years and neurodevelopmental testing annually with regular follow ups to monitor progress is needed in all patients with TSC [1, 2].

The surveillance and management recommendations for TSC (2012) advise to screen and assess behavioral and neuropsychiatric symptoms under the terminology TAND, proposed to describe interrelated functional and clinical manifestations of brain dysfunction common in TSC-including aggressive behaviors, autism spectrum disorders, intellectual disabilities, psychiatric disorders, neuropsychological deficits and school and occupational difficulties [6]. These include the behavioral level (such as sleep problems or aggressive behaviors), the psychiatric level (DSM/ICD defined psychiatric disorders such as autism spectrum disorders or attention deficit hyperactivity disorder, the intellectual level [intellectual ability as defined by intelligence quotient (IQ)-type tests], the academic level (learning disorders, e.g., reading or mathematics difficulties), and the psychosocial level (e.g., self-esteem, family difficulties) [4].

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