

## A Patient with Tuberous Sclerosis Complex and Spinal Muscular Atrophy; A Case Report

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### Abstract

#### Background

Tuberous Sclerosis Complex (TSC), and Spinal Muscular Atrophy (SMA) are two inherited disorders while they are genetically independent. TSC is characterized by the formation of multiple hamartomas in nearly all organs. SMA is a destructive neurological disorder leading to progressive muscular weakness and atrophy.

#### Case Presentation

The patient was an Iranian (Urmia, East Azerbaijan Province, Iran) 11-year-old daughter of non-consanguineous parents. She developed seizures as an infantile spasm at three months old. She had a delay in motor development. At 11 years old, the patient had proximal muscle weakness resulting in a characteristic waddling gait and Gowers' sign, which was suspected of SMA. The SMA was then confirmed using molecular analysis. Clinical examination of the patient revealed angiofibromas, shagreen patch, and hypopigmented spots on the skin; cortical tubers, subependymal nodules, and subependymal giant cell astrocytoma in the brain; angiomyolipomas in the kidneys; and retinal hamartoma, which fulfilled the diagnostic criteria of TSC.

#### Conclusion

Although TSC and SMA are genetically independent disorders, they may rarely occur together in an individual, simultaneously. Further studies required to find the patterns of genetic inheritance of these diseases among the reported patient.

**Key Words:** Child, Genetic disorders, Spinal muscular atrophy, Tuberous sclerosis complex.

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## 1- INTRODUCTION

Tuberous Sclerosis Complex (TSC) is an autosomal dominant inherited multisystem disorder (1). TSC is characterized by the formation of multiple hamartia (non-growing lesions leading abnormal tissue) and hamartomas (benign growth tumors) in nearly all organs, prominently in the skin, brain, kidneys, heart, eyes, and lungs (1, 2). This disorder can affect both males and females in all ethnic groups with incidence rates of 1/6,000-1/10,000 among live births and a population prevalence of about 1/20000 (1, 3). Von Recklinghausen initially noticed this condition in 1862 that recognized hamartomas in the brain and heart of patients with seizures and mental retardation. However, the term "sclerose tubereuse" was firstly used by Bourneville, who described the syndrome and found the correlation between the cutaneous features with other clinical manifestations in 1880 (2, 4). The diagnostic criteria of TSC are now based on major and minor clinical features (4, 5).

The significant features are Sub-Ependymal Nodules, Sub-Ependymal Giant cell Astrocytoma (SEGA), shagreen patch, hypopigmented macules, angiofibromas (fibrous cephalic plaque), unguis fibromas, cardiac rhabdomyoma, multiple retinal hamartomas, cortical dysplasia, lymphangiomyomatosis, angiomyolipomas. The minor features are nonrenal hamartomas, confetti lesion, intraoral fibroma, enamel pits, retinal hypopigmented macule, and multiple renal cysts. The precise diagnosis is carried out when two major clinical features or one major plus two minor criteria are present. A probable diagnosis can also be carried out with one major feature, or two or more minor features are present (4, 5). Overall, TSC has profoundly variable clinical manifestations with a full onset age ranging from infancy to adulthood. However, it commonly does not cause

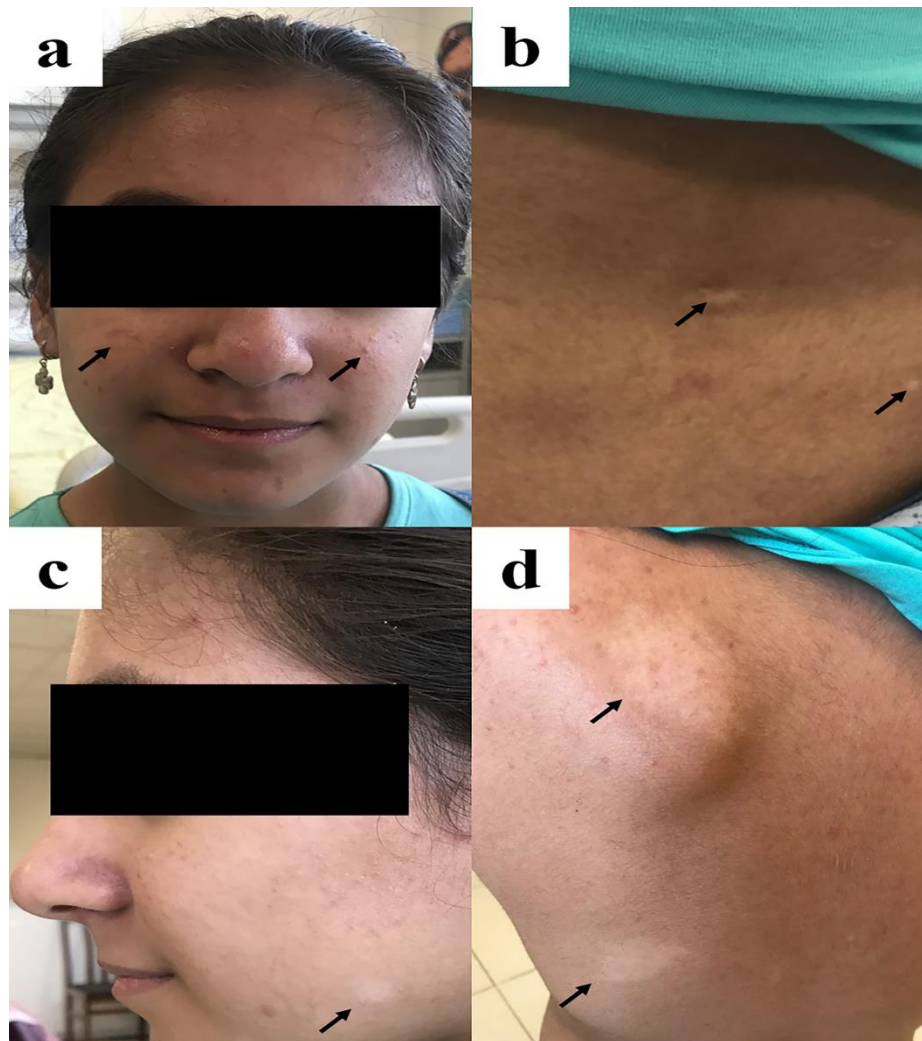
motor neuron loss leading to muscular weakness and atrophy that can be mainly observed in Spinal Muscular Atrophy (SMA). Spinal Muscular Atrophy (SMA) is a destructive neurological disorder characterized by the degeneration of lower motor neurons in the spinal cord and brainstem, leading progressive muscular weakness and atrophy (6-8). It is considered as the most common genetic cause of infant mortality with a prevalence of one in 6000-10,000 live births and a carrier frequency of one in 40-60 adults (6, 8). Hoffmann and Werdnig initially described the condition in the 1890s who independently reported children with muscular atrophy and progressive paralysis (7, 9). The clinical manifestations of SMA often present in childhood; however, it has a wide range of onset time with various symptoms and severity from a fetus with joint contractures, an infant with congenital arthrogryposis needing a ventilator, to adults with leg weaknesses (6, 10). Overall, TSC and SMA are entirely two distinct, independent, and rare disorders with no genetic relationship. Here, we report a sporadic case suffering from TSC and SMA simultaneously.

## 2- CASE REPORTS

The patient was an Iranian (Urmia, West Azerbaijan Province, Iran) 11-year-old daughter of non-consanguineous parents referred to Tabriz Pediatric Hospital, Iran. She was born as a result of the first pregnancy by vaginal delivery at 36 weeks. She developed seizures as infantile spasms at three months old that was then properly controlled using Vigabatrin (Sabril) until four years old. She had a delay in reaching motor milestones. She started crawling after the first year of age and stand and walk without assistance in 2.5 years old (30 months old), according to her mother's. Afterward, no improvement in her walking was observed by the parents. The patient had motor retrogression at the time of

referring to the hospital. She had waddling gait, difficulty in climbing stairs, and getting up from a chair. The patient had no DTR, positive Gowers' sign, and reduced muscle strength with strength 3/5 in lower limbs according to the subsequent clinical examination. Electromyography and Nerve Conduction Velocity (EMG / NCV) was carried out and revealed that the patient might suffer from SMA type III as the initial diagnosis. The diagnosis of SMA was confirmed by Polymerase Chain Reaction (PCR) based molecular analysis detecting the deletion of exons 7 and 8 of the SMN gene. The subsequent clinical

examination revealed facial angiofibromas and shagreen patches on her back. She also had hypopigmented spots on her face, back, and abdomen (**Figure. 1**). Renal angiomyolipomas were detected using the ultrasonography and retinal hamartomas using the fundoscopy. Additionally, the multiple hyperdense subependymal nodules, cortical tubers, and SEGAs were reported using the brain CT-scan eventually fulfilled the diagnostic criteria of Tuberous Sclerosis Complex (TSC). Therefore, the genetic test (molecular analysis) was not carried out for the TSC diagnosis.



**Fig.1.** CXR showing cardiomegaly in the thorax. CXR: Chest x-ray.

### 3- DISCUSSION

In the present study, an 11-year-old girl was suffered from two wholly distinct and independent disorders, TSC and SMA, simultaneously. TSC is an autosomal dominant inherited disorder that is caused by defects in the genes *TSC1* and *TSC2*. The *TSC1* is located on chromosome 9 (9q34) and *TSC2* on chromosome 16 (16p13.3), which are responsible for the expression of Hamartin and Tuberin proteins, respectively. The complex of Hamartin-Tuberin as a tumor suppressor could inhibit the mammalian Target of Rapamycin (mTOR) through the phosphatidylinositol 3-kinase signaling pathway. The mTOR pathway, as a cell apoptosis inhibitor, can enhance cellular proliferation. Therefore, loss of the Hamartin-Tuberin complex because of any defect in *TSC1* and/or *TSC2* causes the permanent activity of mTOR and uncontrolled cell cycle that can eventually lead to forming hamartomas in multiple body organs (1, 2, 4). As mentioned, these lesions were identified as angiofibromas, shagreen patch, and hypopigmented spots on the skin; cortical tubers, subependymal nodules, and SEGA in the brain; angiomyolipomas in the renal; and retinal hamartomas. Neurologic complications are considered as the most prominent causes of low-quality life and mortality among TSC patients. Seizure with a prevalence of 75-90% of TSC patients is the most common neurologic complication, which in some cases may accompany mental retardation. The earlier onset of the seizure, the more the risk of mental retardation (2). Tubers are abnormalities in the brain, which can cause seizures and epilepsy by harming the layers of the cerebral cortex in TSC patients (5). Kandt et al. (11) showed that the number of cortical tubers was correlated with seizure severity and cognitive impairment among TSC patients. They seem to be not associated with oncological growth

potential (12). Subependymal nodules are small accumulations of cells (hamartomas) on the walls of the cerebral ventricles that may grow and develop into SEGA (12). Santos et al. (13) demonstrated that there was no relationship between the number of subependymal nodules and the severity of TSC clinical symptoms. SEGAs are prevalent among children, which can cause hydrocephalus. However, this can be apparent after 20 years old (12). In a population-based study by O'Callaghan et al. (14), it was shown that the incidence of SEGA was 5.6% among TSC patients. Among the neurologic complications, the formation of brain tumors is rare among TSC patients. The frequency of brain tumors has been estimated as 2-10% of TSC patients and 1.1-1.4% of all pediatric brain tumors (5). Skin lesions are another prevalent complication among TSC patients. Shagreen patch is a skin lesion resulted from collagen accumulation, which can typically be observed in the lumbosacral region of TSC patients.

This lesion can be found in 20-30% of the patients; however, it is rare among young children (2). Renal complications are the second most common cause of mortality among TSC patients that usually appear as angiomyolipomas. This lesion is a benign tumor composed of blood vessels, adipose tissue, and immature smooth muscle cells that can be detected in 75-80% of TSC children older than ten years, more apparently in females. Although small angiomyolipomas have no symptoms, those larger than 4 cm in diameter can increase the risk of severe hemorrhages, hypertension, and chronic renal diseases. Renal cysts are the second most frequent renal lesions that were not detected in our reported case (2, 12). According to the present study, about 30-50% of TSC children suffer from retinal hamartomas (12). It has been revealed that the number and size of the congenital lesions are not correlated with age. Therefore, they

remain stable in TSC patients over time (12). Retinal hamartomas do not cause visual impairment in the majority of TSC patients; therefore, a regular retinal examination is not necessary unless ophthalmic complications such as squint, coloboma, or papilloedema are present (5, 12). Retinal hypopigmented macules can also be observed in TSC patients (5). However, they were not detected in the reported case. Although most body tissues can be affected by TSC, this disorder is not usually associated with motion disabilities. Our patient had no DTR, delay in reaching movement milestones, positive Gowers' sign, and reduced muscle strength. She also had waddling gait, the difficulty in climbing stairs, and getting up from a chair. Subsequently, clinical and paraclinical examinations revealed that the patient was also suffering from SMA III simultaneously. According to the onset and the disease severity, SMA has been commonly divided into five subtypes. Type 0 is the prenatal type of the disease with no fetal movement, arthrogryposis, and joint contractures.

Type I or Werding-Hoffman disease is the most common form of the disease (60-70% of cases), which causes acute muscle weakness and Hypotonia. The patients are not able to sit or walk and often die due to respiratory failure before two years old (15). Rudnik-Schoneborne et al. (16) showed that 75% of the patients with SMA I had coronary artery complications. Type II is the intermediate form of SMA and usually occurs before 18 months old. The affected children can sit upright but are not able to walk without assistance. The patients are prone to suffer from pulmonary complications but maybe survive until adulthood. Type III or Kugelberg-Welander disease is usually apparent after two years old. The affected children can walk without assistance before the disease progresses and typically can survive until adulthood. Type IV is the

mild form of the disease and usually does not appear before adolescence or adulthood (6, 7, 15). SMA is a genetic disease like TSC, unlike it is inherited autosomal recessively. It is caused by the lack or deficiency of the Survival Motor Neuron (SMN) protein. This protein is mainly (80-90%) expressed by the *SMN1* gene located in the telomeric region of chromosome 5q13. A fewer amount of this protein is also represented by *SMN2* located in the centromeric region of chromosome 5. The only difference between these two genes is a cytosine (C) to thymine (T) transition in exon 7 of *SMN2* (840 C>T) (15, 17). Although this single nucleotide difference does not alter the amino acid composition of the SMN protein, it changes the splicing pattern, which eventually decreases the SMN protein expression (18). SMN protein interacts with various proteins and has associations with a variety of cell processes, including endocytosis, ribonucleoprotein formation, ubiquitin homeostasis, and cytoskeleton dynamics. Loss of this protein can affect all these cellular processes, and therefore, different amounts of this protein caused by various mutations in the *SMN1* and *SMN2* leads to various clinical signs and explains different disease severity and age of onset of SMA (19).

#### 4- CONCLUSION

In conclusion, TSC and SMA are two inherited diseases with relatively low incidences. Although they are genetically distinct, and completely independent disorders, they may rarely occur together in an individual, simultaneously. Further studies are needed to obtain the patterns of genetic inheritance of these diseases in the reported patient.

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## 7- REFERENCES

1. Almobarak S, Almuhaizea M, Abukhaled M, Alyamani S, Dabbagh O, Chedrawi A, et al. Tuberous sclerosis complex: Clinical spectrum and epilepsy: A retrospective chart review study. *Translational neuroscience*. 2018;9(1):154-60.
2. Leung AK, Robson WLM. Tuberous sclerosis complex: a review. *Journal of Pediatric Health Care*. 2007;21(2):108-14.
3. Cao Y, Zhang H, Wang F, Zhu D, Liao M. Case Report Radiological appearance of tuberous sclerosis complex: a case report and review of literature. *Int J Clin Exp Med*. 2017;10(5):8282-7.
4. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNPd, Rivitti-Machado MCdM. Tuberous sclerosis complex: review based on new diagnostic criteria. *Anais brasileiros de dermatologia*. 2018;93(3):323-31.
5. Rosset C, Netto CBO, Ashton-Prolla P. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. *Genetics and molecular biology*. 2017;40(1):69-79.
6. Farrar MA, Kiernan MC. The genetics of spinal muscular atrophy: progress and challenges. *Neurotherapeutics*. 2015;12(2):290-302.
7. Faravelli I, Nizzardo M, Comi GP, Corti S. Spinal muscular atrophy—recent therapeutic advances for an old challenge. *Nature Reviews Neurology*. 2015;11(6):351.
8. Shorrock HK, Gillingwater TH, Groen EJ. Overview of current drugs and molecules in development for spinal muscular atrophy therapy. *Drugs*. 2018;78(3):293-305.
9. Oskoui M, Kaufmann P. Spinal muscular atrophy. *Neurotherapeutics*. 2008;5(4):499-506.
10. Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*. 2005;57(5):704-12.
11. Kandt RS. Tuberous sclerosis complex and neurofibromatosis type 1: the two most common neurocutaneous diseases. *Neurologic clinics*. 2003;21(4):983-1004.
12. Ng K, Ng S, Parker A. Annual review of children with tuberous sclerosis. *Archives of Disease in Childhood-Education and Practice*. 2015;100(3):114-21.
13. Santos C, Miller V, Roach E. Tuberous sclerosis. *Neurology in clinical practice*. 2004:1867-73.
14. O'Callaghan FJ, Martyn CN, Renowden S, Noakes M, Presdee D, Osborne JP. Subependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population-based study. *Archives of disease in childhood*. 2008;93(9):751-4.
15. Carré A, Empey C. Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. *Journal of genetic counseling*. 2016;25(1):32-43.
16. Rudnik-Schöneborn S, Heller R, Berg C, Betzler C, Grimm T, Eggermann T, et al. Congenital heart disease is a feature of severe infantile spinal muscular atrophy. *Journal of medical genetics*. 2008;45(10):635-8.
17. Omrani O, Bonyadi M, Barzgar M. Molecular analysis of the SMN and NAIP genes in Iranian spinal muscular atrophy patients. *Pediatrics International*. 2009;51(2):193-6.
18. Prior TW, Nagan N. Spinal muscular atrophy: overview of molecular diagnostic approaches. *Current protocols in human genetics*. 2016;88(1):9.27. 1-9.. 13.
19. Groen EJ, Talbot K, Gillingwater TH. Advances in therapy for spinal muscular atrophy: promises and challenges. *Nature Reviews Neurology*. 2018;14(4):214.