

Tuberous Sclerosis

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Abstract: Tuberous sclerosis is a rare genetic disorder with a variety of clinically remarkable symptoms and signs, of which seizures, mental retardation and facial angiofibromas (Vogt's triad) are considered classical for the diagnosis. Because of the high frequency with which neoplasms are associated with it and because of the involvement of multiple organ systems, all patients with this disease should be evaluated by a multidisciplinary team. The patients should be followed up based on specific guidelines.

Key words: multi-system involvement, multidisciplinary approach, tuberous sclerosis.

Introduction

Tuberous sclerosis is an inherited neurocutaneous disorder with a variety of multi systemic clinical manifestations. It is also characterized by the presence of numerous benign neoplasms involving multiple organ systems. Diagnosis is mainly clinical. A classic case with review of literature is presented here highlighting the importance of multidisciplinary approach.

Case

A 19 years old boy presented with recurrent uncontrolled generalized tonic-clonic convulsions for three and half years. His prenatal, neonatal and childhood history were not significant. According to his father, he had below-average academic skills but his physical and mental developments were not remarkably slower than his siblings. There was no family history of similar illnesses. For the last three months, he was staying alone, crying at times, and talking to himself and his surroundings.

On examination, he had expressionless face with poor eye contact. He was slow to react but was cooperative and showed signs of mild mental retardation. There were multiple small soft faint-brown papules in the nasolabial region of his face (Fig.1). In his lumbosacral region, there were multiple yellowish thickenings of the skin (Fig.2). There were two hypo-pigmented macules in the front part of his chest

(Fig.3). He also had irregular firm nodule in the nail bed of his left index finger (Fig.4). There were no other significant findings in his systemic review. His CT scan of the head showed multiple calcified sub-ependymal nodules of varying sizes (Fig.5). His chest x-ray, echocardiogram and ultrasonography of abdomen were normal. Based on these findings, a diagnosis of Tuberous Sclerosis was made and a multidisciplinary team involving neurologists, neurosurgeons, psychiatrists, ophthalmologists and dermatologists managed him. On discharge, he was advised for yearly and as required follow up.

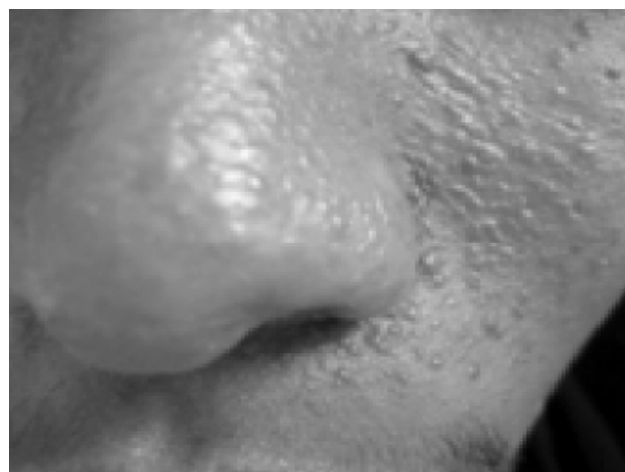


Fig.1. Facial angiofibroma



Fig. 2. Shagreen patches



Fig. 3. Hypopigmented macule



Fig. 4. Subungual fibroma



Fig. 5. Subependymal nodules

Genetics of Tuberous Sclerosis

Tuberous Sclerosis is an autosomal dominant disease with the incidence of approximately 1 in 5000 to 10,000 live births.^{1,2} However, only one third of the cases are familial.³ These non-familial cases represent either spontaneous mutations or mosaicism. Two genes, TSC1 and TSC2, have been identified as affected in the genesis of this disorder. They are located respectively at chromosomes 9q and 16p and encode the proteins hamartins and tuberins. The lack of these proteins causes the cells staying in quiescent stage to enter the cell cycle.^{4,5}

Diagnostic Criteria

The triad of seizures, mental retardation and facial angiofibromas (Vogt's triad) is considered classical for the diagnosis of tuberous sclerosis. However, it occurs in fewer than 50% of patients with tuberous sclerosis.⁶ The Tuberous Sclerosis Consensus Conference in 1998 developed the diagnostic criteria based upon specific clinical features.⁶ According to these criteria, the diagnosis of definite tuberous sclerosis requires two major features or one major and two minor features. Patients with one major plus one minor feature have probable tuberous sclerosis, and those with one major feature or two or more minor features have possible tuberous sclerosis.

The following are considered major clinical features of tuberous sclerosis:

- Facial angiofibromas or forehead plaques
- Shagreen patch (connective tissue nevus)
- Three or more hypomelanotic macules
- Nontraumatic ungula or periungual fibromas
- Lymphangioleiomyomatosis (also known as lymphangiomyomatosis)
- Renal angiomyolipoma
- Cardiac rhabdomyoma
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodules
- Subependymal giant cell astrocytoma
- The following are minor features:
- Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules)
- Gingival fibromas
- Multiple randomly-distributed pits in dental enamel
- Hamartomatous rectal polyps

- Multiple renal cysts
- Nonrenal hamartomas
- Bone cysts
- Retinal achromic patch
- Cerebral white matter radial migration lines

The presence of seizures is not a diagnostic criterion because of poor specificity for tuberous sclerosis.⁶

Natural History

Tuberous sclerosis is a progressive disorder. Individual features have different natural histories. It is difficult to predict the extent to which a patient with newly diagnosed disease is affected due to the variability of expression of the disease among patients and within families.

All of the clinical features of tuberous sclerosis may not be apparent in the first year of life. Thus, a child with initial possible or probable diagnosis of tuberous sclerosis will be definite tuberous sclerosis when additional features are identified later.

The main causes of morbidity in young people with tuberous sclerosis are complications in major organ systems and they also contribute to an increased incidence of early deaths.⁷ A report published by the Mayo clinic found that neurological complications, including sub-ependymal giant cell tumors and status epilepticus, were the most common causes of death.⁸ Renal disease, including renal cell carcinoma, hemorrhage into angiomyolipoma and renal failure, was the next most common cause of death. Other causes of death included pulmonary disease from lymphangiomyomatosis and bronchopneumonia.

Recommendations

Patients suspected of having tuberous sclerosis should be evaluated by a multidisciplinary team that should include geneticist, neurologist, ophthalmologist, nephrologist, dermatologist, neurosurgeon and plastic surgeon. The patient should be evaluated according to the guidelines published by the Tuberous Sclerosis Consensus Conference.^{6,9}

The developmental and academic history should be reviewed. A detailed family history is mandatory. Parents and siblings, if possible, should be examined for typical signs. A thorough clinical examination is necessary. Ophthalmic evaluation should be done to detect intraocular lesions. CT head or where possible, MRI should be performed to detect intracranial benign or malignant lesions. Renal ultrasonography is indicated to evaluate for the presence of renal angiomyolipoma or cysts.

If problems are not encountered by the patients, they should be followed up every year. Visits should include physical examination, ophthalmic evaluation, growth measurement, developmental assessment and review of school progress. Neuropsychologic evaluation may identify cognitive deficits early so that academic support can be provided in time. Children with cardiac rhabdomyoma should be evaluated and followed by a pediatric cardiologist.

Imaging Recommendations⁹

- Renal ultrasonography should be performed every one to three years. If malignant transformation or the development of large angiomyolipomas is detected, abdominal CT or MRI should be performed to further evaluate the abnormalities.
- Cranial CT or MRI (preferably) should be performed every one to three years.

Conclusion

Tuberous sclerosis has widespread physical and mental ailments frequently associated with the disease and can be stressful not only to the patient but also to the family. It should be managed by a multidisciplinary team of specialists in various fields of medical science. The management of this disease can be challenge in a resource poor developing country like ours.

References

1. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci* 1991; 615:125.
2. Levy M, Feingold J. Estimating prevalence in single-gene kidney diseases progressing to renal failure. *Kidney Int* 2000; 58:925.
3. Rose VM, Au KS, Pollom G et al. Germ-line mosaicism in tuberous sclerosis: how common? *Am J Hum Genet* 1999; 64:986.
4. Soucek T, Yeung RS, Hengstschlager M. Inactivation of the cyclin-dependent kinase inhibitor p27 upon loss of the tuberous sclerosis complex gene-2. *Proc Natl Acad Sci USA* 1998; 95:15653.
5. Soucek T, Pusch O, Wienecke R et al. Role of the tuberous sclerosis gene-2 product in cell cycle control. Loss of the tuberous sclerosis gene-2 induces quiescent cells to enter S phase. *J Biol Chem* 1997; 272:29301.
6. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 1998; 13:624.

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7. Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. J Urol 2002; **168**:1315.
8. Shepherd CW, Gomez MR, Lie JT et al. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc 1991; **66**:792.
9. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol 1999; **14**:401.