CASE REPORT

FAMILIAL TUBEROUS SCLEROSIS: A CASE REPORT

M. Manjukeshwari¹, S. Chidambaranathan²

HOW TO CITE THIS ARTICLE:

M. Manjukeshwari, S. Chidambaranathan. "Familial Tuberous Sclerosis: A Case Report". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 84, October 19; Page: 14731-14735, DOI: 10.14260/jemds/2015/2095

ABSTRACT: Familial tuberous sclerosis is a Neurocutaneous syndrome which runs in family members are less reported in literature. The child presented with recurrent seizure, attention deficit and on examination with neurocutaneous markers (Tuberous sclerosis and ash leaf macule). Hence we suspected for tuberous sclerosis and examined the other family members where the father (Seizure and Adenoma sebaceum) and sibling (Seizure, Adenoma sebaceum and attention deficit) had similar complaints. The neuroimaging of all the three person in the family showed cortical tubers and subependymal calcification. The natural history, investigation and treatment of tuberous sclerosis, are also discussed.

KEYWORDS: Familial Tuberous sclerosis, Adenoma sebaceum, Ash leaf macule.

INTRODUCTION: Von Recklinghausen first described tuberous sclerosis in 1862. Desire Magloire Bourneville (A French physician) coined the term sclerosetubereuse, from which the name of the disease has evolved. Sherlock coined the term EPILOIA encompassing the clinical triad of tuberous sclerosis (Epi: epilepsy, Loi: low intelligence, A: adenoma sebaceum).

CASE REPORT: A 6 year old female child was brought to the Paediatric outpatient department, with history of recurrent generalised tonic-clonic seizures, since one year of age. Each episode was lasting for 5 minutes, involving all the four limbs with up-rolling of eyeballs and bladder incontinence, followed by a brief period of unconsciousness. The child had learning difficulties and Attention Deficit Hyperactive Disorder (ADHD). On examination, child had Adenoma Sebaceum, Ash leaf macule (Fig. 1) and low IQ [2 major criteria – Definitive TSC].

In family history, father had seizure episodes and Adenoma Sebaceum (Fig. 2) over the face. The younger male sibling also presented with recurrent seizure, Adenoma Sebaceum (Fig. 3) and low IQ [2 major criteria – Definitive TSC].

Neuroimaging shows cortical tuber (Fig. 4), subependymal nodules and calcification in the basal ganglia (Fig. 5) which was present in all the three family members. EEG shows abnormal spikes suggestive of seizures and Echo shows normal study in all the three persons. USG reports small cysts in the left kidney of the Index child [minor criteria].

All the three person in the family are diagnosed as Definitive TSC.

The child was treated with anti-epileptics for seizure, Occupational therapy for ADHD and for Daily Activity Living support.

DISCUSSION: The term Tuberous Sclerosis Complex (TSC) is widely used now, an autosomal dominant neurocutaneous syndrome, characterized by the development of benign tumors such as neurofibromas and angiofibromas located anywhere in the body (skin, central nervous system, heart, kidneys, etc.). Patients with TSC present mutations of the TSC1 and TSC2 genes, which intervene in cell cycle regulation.

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This is a dominant autosomal hereditary disease, though 60-70% of all cases are the result of spontaneous mutations.^{1,2} The prevalence of TSC ranges from 1: 6,000 to 1: 10,000 individuals, and the diagnosis is usually established between 4-10 years of age or in puberty.³ It is estimated that nearly one million people are known to suffer from tuberous sclerosis.⁴ It is an underestimated figure as many cases remain undiagnosed due to variegated clinical presentation.

Tuberous Sclerosis shows signs of being carriers of the gene TSC1 gene – located on chromosome 9q34, encodes protein called Hamartin & TSC2 gene – located on chromosome 16p13, encodes protein called Tuberlin for the disease when carefully examined. Tuberous Sclerosis Complex manifests with variable signs and symptoms together with angiofibromas distributed in a characteristic “butterfly” pattern on the face and forehead. The most important neurological problems are mental retardation, seizures, autism and learning difficulties. This neuro-cutaneous syndrome also presents with ash-leaf macules, hamartomas, shagreen patches, periungual fibromas and angiofibromas.⁵ Systemic manifestations include Polycystic kidneys, honey-comb lung, retinal phakomas, rhabdomyomas, hemangiomas of liver/spleen and tubers in the basal ganglia.⁶ Associated congenital defects such as Spina bifida, hare lip, agenesis of corpus callosum, omphalocele.

Pathologically, it is characterised by TS giant cells. Multiple nodules project into the ventricles resembling candle guttering.

The diagnostic criteria of TSC have been divided into major and minor features.⁷ (Table 1).

Table 1. Diagnostic criteria of tuberous sclerosis complex (TSC).

Major Criteria	Minor Criteria
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
Ungual or periungual fibroma (Non-traumatic)	Hamartomatous rectal polyps
Hypomelanotic macules (>3)	Bone cysts
Shagreen patch (connective tissue naevus)	Cerebral white matter migration tracts
Cortical tuber	Gingival fibromas
Subependymal nodule	Nonrenal hamartoma
Subependymal giant cell astrocytoma	Retinal achromic patch
Multiple retinal nodular hamartomas	Confetti skin lesions
Cardiac rhabdomyoma, single or multiple	Multiple renal cysts
Pulmonary lymphangiomyomatosis	Nonrenal hamartomas
Renal angiomyolipoma.	

- Definitive – 2 major or 1 major + 2 minor.
- Probable – 1 major + 1 minor.
- Possible – 1 major or 2 or more minor.

Patients with TSC might have a delay in the diagnosis as some findings might be unrecognized during childhood by medical practitioners and some disease manifestations may not occur until puberty. In the study of Seibert et al, 56% of the patients were diagnosed in adulthood and two-thirds of these patients had symptoms in childhood.⁸ This case report on the family with documented tuberous sclerosis in two generations and discusses the examination and investigation of at-risk family members.

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Patients with Tuberous sclerosis complex (TSC) range from intellectually normal to severely mentally retarded. TSC is often associated with mental retardation (In 70% of cases) and epilepsy (90%). Seizures are the most common neurologic symptom of TSC occurring in 92% of patients.⁹ Children with infantile spasms and hypo arrhythmia are reported to be more severely affected than those with any other form of epilepsy. As multiple organs are involved, there is wide variability in presentation. Arguably the most important hamartomas are cerebral cortical tubers, which are regions of abnormal cortical architecture with distinctive large neuronal cells. Cortical tubers cause some of the most important clinical manifestations of tuberous sclerosis complex syndrome. Neurologic symptoms and complications due to the development of cortical tubers, subependymal nodules and subependymal giant cell astrocytomas (SEGA) are common in patients with TSC.¹⁰ as we found subependymal nodule in a contrast CT scan. The drug of choice for TSC is Vigabartin and ACTH.

Our case reported with mental retardation, epilepsy and cortical tubers in neuroimaging. In addition, multiple behavioural problems including sleep disorder, hyperactivity, attention deficit, aggressiveness and autism have been found in children with TSC.¹¹ the prevalence of learning disabilities varies from 38% to 80%, and when it does exist it tends to be moderate or severe in degree. Intervention programs, including special schooling and occupational therapy may benefit individuals with special needs and developmental issues. Tuberous sclerosis complex is characterized by neurocutaneous manifestations and a careful skin examination of patients suspected to have TSC is mandatory.

Two types of renal lesions occur in patients with tuber sclerosis: angiomyolipomas and renal cysts. They may be found independently or together, they may be unilateral, bilateral, single or multiple. Our case reported with renal cyst in left kidney.

Tuberous Sclerosis may affect the cardiovascular system with Rhabdomyomas – numerous or located at apex of left ventricles, CCF, Arrhythmias, which can be detected with Echocardiography and the pulmonary system with lymphangioleiomyomatosis (LAM), affects women after 20 yrs. of age. Periungual fibroma may present as nodules of skin around fingernails or toenails.

Surgery, including dermabrasion and laser treatment, may be useful for treatment of skin lesions. There is no cure as such for tuberous sclerosis complex. Drug therapy for some of the manifestations of TSC is currently in the developmental stage. Prognosis of the disease depends on the severity or multiplicity of organ involvement. About a quarter of severely affected infants are thought to die before age 10 years, and 75% die before age 25 years; however, the prognosis for the individual diagnosed late in life with few cutaneous signs depends on the associated internal tumors.

CONCLUSION: It is not uncommon for patients with TSC to have symptoms or signs that do not lead to immediate diagnosis. In some cases, diagnosis is delayed for prolonged periods of time because of clinical presentations at various ages. Clinicians including paediatrician, physician, child and adult neurologists, dermatologists, nephrologists and cardiologists should be aware of the myriad potential presenting symptoms and signs of TSC. When we suspect a neurocutaneous syndrome, other family members should be examined. Early diagnosis is very important for thorough clinical and radiological evaluation. Continuous monitoring of symptoms, family planning, genetic counselling and reduction in morbidity and mortality rate.

ACKNOWLEDGEMENT: We would like to thank the child and her parents for their good cooperation. We also thank the department of radiology and dermatology.

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Fig. 1: Ash Leaf Macule- Index Child

Fig. 2: Adenoma Sebaceum- The Father

Fig. 3: The 2 Yr. Old Sibling Child

Fig. 4: Cortical Tuber in the GYRI

Fig. 5: Subependymal Calcification

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AUTHORS:

1. M. Manjukeshwari
2. S. Chidambaranathan

PARTICULARS OF CONTRIBUTORS:

1. Post Graduate, Department of Pediatrics, Rajah Muthiah Medical College and Hospital, Chidambaram.
2. Assistant Professor, Department of Pediatrics, Rajah Muthiah Medical College and Hospital, Chidambaram.

FINANCIAL OR OTHER

COMPETING INTERESTS: None

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. M. Manjukeshwari,
No.12, Swarna Nivas, Cauvery Nagar,
Railady, Mayiladuthurai,
Nagai District-609003,
Tamilnadu.
E-mail: manjukeshwari86@gmail.com

Date of Submission: 22/09/2015.
Date of Peer Review: 23/09/2015.
Date of Acceptance: 08/10/2015.
Date of Publishing: 19/10/2015.