

A Study of Clinical Manifestations of Tuberous Sclerosis

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Abstract: Although a diagnostic triad has been described, it is not consistently present in all cases. Many cutaneous features have been elaborated in the description of the disease including classical adenoma sebaceum, shagreen patches, white leafy macules and periungual plaques. Other cutaneous manifestations include fibromatous plaques, pedunculated fibromas and poliosis. Males outnumbered females and male: female ratio was 2.3:1. Regarding the clinical spectrum of tuberous sclerosis it was seen that epileptic fits and cardiac complications were seen in 50% patients each, eye abnormalities including retinal astrocytomas were seen in 40% patients, mental retardation was seen in 25% patients followed by astrocytomas and pulmonary disease seen in 20% patients each. Coming to the cutaneous manifestations of tuberous sclerosis adenoma sebaceum was the commonest (95%) cutaneous feature followed by ash leaf macule and shagreen patch each seen in 90% patients followed by koenens tumour seen in 75% patients. Positive family history was seen in 25% patients.

INTRODUCTION

Tuberous sclerosis is characterized by the triad of intractable epilepsy, mental retardation, and adenoma sebaceum; this description (until relatively recently) represented the hallmark of tuberous sclerosis complex (TSC) to most clinicians.¹ Unfortunately, this concept led many TSC is now known to be a genetic disorder affecting cellular differentiation, proliferation, and migration early in development, resulting in a variety of hamartomatous lesions that may affect virtually every organ system of the body.² Less than one third of affected persons fit the classic constellation of symptoms. TSC affects all races without a clear-cut predominance. TSC affects both sexes equally. Some studies have suggested that males are more likely to suffer neurological morbidity, but this has not been demonstrated conclusively. The best-known cutaneous manifestation of TSC is adenoma sebaceum, which often does not appear until late childhood or early adolescence.³ This lesion is an angiofibroma (cutaneous hamartoma) and is not related to excessive sebum or acne. Flat, reddish macular lesions develop first, which can be mistaken for freckles early on. They become increasingly erythematous and papulonodular over time, occasionally with a friable surface that may bleed easily. Facial angiofibromas typically are noted first in childhood and exhibit progression during puberty and adolescence⁴ (Fig 1). Adenoma sebaceum may be disfiguring.

Other skin lesions consist of hypomelanotic (ie, ash leaf) macules (Fig 2), periungual or gingival fibromas (Fig 3), and thickened, firm areas of subcutaneous tissue, often at the lower back known as shagreen patch or forehead and face (fibrous plaques).⁵ Hypomelanotic macules are usually round or oval in shape and vary in size from a few mm to as much as 5 cm in length. Sometimes they have an irregular, reticulated appearance, as if white confetti paper had been strewn over the skin (confetti lesions).⁶ When the scalp is involved, an area of poliosis can result. They may be present at birth, or not show up until later in life. They vary widely in location and number from person to person. Shagreen patches are confined, however, to the subcutaneous tissue and are not associated with dysraphism, osseous lesions, or mass effects on neural structures. Fibromas can occur in the periungual regions, gingivae, or potentially anywhere in cutaneous or mucosal tissues. The underlying tissue may be hypertrophic/hamartomatous.⁷

MATERIAL AND METHODS

Twenty clinically diagnosed cases of tuberous sclerosis were included in our study. Prior approval of hospital ethical committee was taken for the study. Written informed consent of all the patients was taken for the study. In all the patients, a detailed clinical history was taken with reference to age at onset of various cutaneous lesions, infantile spasms, seizures or mental retardation. Family history was taken in all patients, including details of any affected first-degree relative, consanguinity and genetic pedigree. In all patients, thorough dermatological and CNS examination was carried out. Complete ophthalmologic examination was also done in all patients with direct and indirect ophthalmoscopy and funduscopy to detect any retinal hamartomas.

Relevant investigations like routine hematological and biochemical tests, X-rays of the chest, skull, hands and feet; and ultrasound abdomen were performed. These cases were biopsied to confirm the diagnosis of angiofibroma. Patients were also examined for other cutaneous manifestations and when present were biopsied and

subjected to histopathological examination. Computed tomography of brain was performed to find out any CNS lesions. Diagnosis of tuberous sclerosis was made on the basis of the presence of at least one primary feature, which included facial angiofibromas, multiple subungual fibromas, cortical tubers, subependymal nodules or giant cell astrocytomas and multiple retinal astrocytomas.

RESULTS

The data was tabulated and the results were analyzed.

Table 1: Table Showing Age Group of Patients

Sr No	Age distribution	Number	Percentage
1	0-10	4	20
2	11-20	10	50
3	21-30	5	25
4	31-40	1	5
5	>40	20	100

It is clear that the commonest age group (50%) of patients coming to us in our study were between 11-20 years, followed by 25% patients between 21-30 years; 20% patients were in the age group of 0-10 years and 5% patients were between 31-40 years of age.

Table 2: Table Showing Sex Distribution Of Patients

Sr No	Sex distribution	Number	Percentage
1	Male	14	70
2	Female	6	30
	Total	20	100

Males outnumbered females and male: female ratio was 2.3:1.

Table 3: Table Showing Clinical Spectrum Of Tuberous Sclerosis

Sr No	Clinical Spectrum	Number	Percentage
1	Epileptic fits	10	50
2	Mental retardation	5	25
3	Astrocytomas	4	20
4	Ocular abnormality (Retinal astrocytomas)	8	40
5	Cardiac arrhythmias with CHF and rhabdomyomas	10	50
6	Pulmonary disease	4	20
7	Renal disease (renal cyst)	10	50
8	Dental anomalies (Dental pits & gingival fibromas)	5	25

Regarding the clinical spectrum of tuberous sclerosis it was seen that epileptic fits and cardiac complications were seen in 50% patients each, eye abnormalities including retinal astrocytomas were seen in 40% patients, mental retardation was seen in 25% patients followed by astrocytomas and pulmonary disease seen in 20% patients each.

Table 4 – Table Showing Cutaneous Signs Of Tuberous Sclerosis

Sr No	Cutaneous Signs	Number	Percentage
1	Adenoma Sebaceum	19	95
2	Ash Leaf Macule	18	90
3	Shagreen Patch	18	90
4	Koenens Tumour	15	75

The above table shows the cutaneous manifestations of tuberous sclerosis and adenoma sebaceum was the commonest (95%) cutaneous feature followed by ash leaf macule and shagreen patch each seen in 90% patients followed by koenens tumour seen in 75% patients.

Table 5 – Table Showing Family History Of Tuberous Sclerosis

Sr No	Family History	Number	Percentage
1	POSITIVE	5	25
2	NEGATIVE	15	75

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Positive family history was seen in 25% patients



Fig. 1 - Facial angiofibromas in a 10 year old child



Fig. 2 - Figure showing ash leaf macule with shagreen patch



Fig. 3 - Figure showing Koenens tumour

DISCUSSION

In our study it was seen that the commonest age group (50%) of patients coming to us in our study were between 11-20 years, followed by 25% patients between 21-30 years; 20% patients were in the age group of 0-10 years and 5% patients were between 31 – 40 years of age. Males outnumbered females and male: female ratio was 2.3:1. Regarding the clinical spectrum of tuberous sclerosis it was seen that epileptic fits and cardiac complications were seen in 50% patients each, eye abnormalities including retinal astrocytomas were seen in 40% patients, mental retardation was seen in 25% patients followed by astrocytomas and pulmonary disease seen in 20% patients each. Coming to the cutaneous manifestations of tuberous sclerosis adenoma sebaceum was the commonest (95%) cutaneous feature followed by ash leaf macule and shagreen patch each seen in 90% patients followed by koenens tumour seen in 75% patients. Positive family history was seen in 25% patients.

Comprehensive diagnostic feature were set out first by Dr. Manuel R. Gomez; they now exist in revised form as set forth in a consensus statement from the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association (USA).¹

• Major features

- Facial angiofibromas or forehead plaque
- Nontraumatic unguinal or periungual fibroma
- Hypomelanotic macules (>3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartoma
- Cortical tuber: When cerebellar cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.^{8,9}
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis: When both lymphangiomyomatosis (LAM) and renal AMLs are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned. As many as 60% of women with sporadic LAM (and not TSC) may have a renal or other AMLs.¹⁰
- Renal AML: When both LAM and renal AMLs are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned (see previous remarks).

• Minor features

- Multiple randomly distributed pits in dental enamel⁵
- Hamartomatous rectal polyps: Histologic confirmation is suggested.
- Bone cysts: Radiographic confirmation is sufficient.
- Cerebral white matter radial migration lines: Radiographic confirmation is sufficient. One panel member felt strongly that 3 or more radial migration lines should constitute a major sign.^{11,12,13}
- Gingival fibromas
- Nonrenal hamartoma: Histologic confirmation is suggested.
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts: Complications of neurological involvement are the most common causes of mortality and morbidity. These are due chiefly to intractable epilepsy, status epilepticus, and subependymal giant cell astrocytoma (SEGA) with associated hydrocephalus. Renal complications are the next most frequent cause of morbidity and death. These usually arise from an enlarging AML, resulting in retroperitoneal hemorrhage. End-stage renal disease can occur, as a result of either destruction of normal renal parenchyma

by an enlarging AML or polycystic kidney disease. Less common are cardiac arrhythmias (which can present with sudden, unexplained death), congestive heart failure, and end-stage lung disease. Cardiac involvement is maximal in infants and exhibits spontaneous regression as the child grows older. Pulmonary disease occurs predominantly in women in the third and fourth decades of life. Various organ systems are affected maximally at different points in life.

- Cardiac involvement occurs during the intrauterine or neonatal period.
- Rhabdomyomas tend to regress over time.
- Epilepsy, autism, and developmental delays manifest themselves from infancy to adolescence.
- Polycystic kidney disease usually is apparent in infancy or early childhood.
- AMLs may develop at any time from childhood into adult life.
- Lymphangiomyomatosis typically presents in the third or fourth decade of life

• Diagnostic criteria

- **Definite TSC** - Either two major features or one major feature plus two minor features
- **Probable TSC** - One major plus one minor feature
- **Possible TSC** - Either one major feature or two or more minor features

History should focus upon identification of specific signs and symptoms suggestive of or consistent with TSC.¹⁴ Particular symptoms occur at various points in the life span, and this serves as a framework for history taking. Cardiac involvement is maximal in prenatal life or infancy. Seizures, autism, and developmental delays present in infancy or childhood. Seizures are often not intractable, and many adult patients may no longer suffer from them or require anticonvulsants. Many will have been told that they had febrile convulsions or an age-related epilepsy syndrome. Cutaneous manifestations such as ash leaf macules are often present from birth but frequently are unrecognized.¹⁵ More obvious lesions such as angiofibromas or shagreen patches usually appear in childhood to early adolescence. Renal lesions can present as hypertension and renal failure in the case of polycystic kidney disease, usually in infancy or early childhood. AMLs manifest as flank pain, hematuria/retroperitoneal hemorrhage, or abdominal masses from childhood throughout adult life. Pulmonary involvement typically occurs in the second or third decade, with dyspnea, pneumothorax, or chylothorax. It often is misdiagnosed as emphysema, particularly in those with a history of smoking. Persons with dental involvement may have had their teeth sealed or bonded for pitting, or a gingival fibroma resected. Family history should center on identification of one or more of these manifestations in first- or second-degree relatives. Abnormal neurological findings result from the location, size, and growth of tubers and the presence of subependymal nodules. Tubers are noted most commonly in the cerebrum, without clear predilection for any particular lobe. They occur in the cerebellum as well, where they may be apparent only on microscopic examination. Rarely, they have been noted in the brain stem and spinal cord. Depending on the location of tubers, neurological findings can include abnormalities in cognition (either global delays or specific location-related deficits like language delays), cranial nerves, focal motor/sensory/reflexes abnormalities, cerebellar dysfunction, or gait abnormalities. At least 50% of patients have ocular abnormalities; some studies have reported prevalence as high as 80%. These lesions are in fact retinal astrocytomas that tend to become calcified over time. They appear as rounded, nodular, or lobulated areas on funduscopic examination, becoming whitish in color as they calcify.

REFERENCES

1. Gomez MR. Tuberous sclerosis. In: Gomez MR, editor. *Neurocutaneous diseases*. Butterworths: Boston; 1987. p. 30.
2. Kwiatkowski DJ, Shori MP. Tuberous sclerosis. *Arch Dermatol* 1994;130:349-54.
3. Monaghan HP, Kravchik BR, MacGregor DL, Fitz CR. Tuberous sclerosis complex in children. *Am J Dis Child* 1981;135:912-7.
4. Nijhawan A, Lyon VB, Drolet BA. Paediatric dermatology Cutaneous markers of malformations and selected syndromes - what do you see, when do you see it and how do you find it? *Curr Probl Dermatol* 2001;13:249-300.
5. Paller AS, Goldsmith LA. Tuberous sclerosis complex. In: Freedberg IM, Eisen AZ, Wolff Klaus, Austen KF, Goldsmith LA, Katz SI, editors. *Fitzpatrick's dermatology in general medicine*. 6th Ed. McGraw Hill: New York; 2003. p. 1822-5.
6. Nordberg H. Tuberous sclerosis complex: genetic aspects. *J Dermatol* 1992;19:914-9.
7. Harper JL. Genetics and Genodermatoses. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors. *Textbook of dermatology*. 6th Ed. Oxford Blackwell Science.
8. Krishnan SG, Yesudian DP, Jayaraman M, Janaki VR, Raj Boopal JM. Tuberous sclerosis. *Indian J Dermatol Venereol Leprol* 1996;62:239-41.
9. Anisyo-Nisanth AV, Satischandra P, Nagaraja D, Swamy HS, Jayakumar PN. Spectrum of epilepsy in tuberous sclerosis. *Neurol India* 2004;52:210-2.
10. Arhiser JJ, Boat D, Hunter S, D'Armentio J, Henske EP, Arhiser ZK, et al. Tuberous Sclerosis-associated lesions of the kidney, brain and skin are angiogenic neoplasms. *J Am Acad Dermatol* 2002;46:376-80.
11. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: A population study. *Br J Dermatol* 1996;135:1-5.
12. Kumar P, Brindha S, Manimegalai M, Premalatha S. Tuberous sclerosis with interesting features. *Indian J Dermatol Venereol Leprol* 1996;62:122-4.
13. Jeevan KB, Thappa DM, Narasimhan R. Cutaneous features of tuberous sclerosis: A hospital based study in South India. *Indian J Dermatol* 2000;45:149-53.
14. Roach ES. Introduction. In: Roach ES, Miller VS, editors. *Neurocutaneous disorders*. Cambridge University Press: Cambridge; 2004. p. 1-3.
15. Fitzpatrick TB, Szabo G, Hori Y, et al. White leaf-shaped macules. Earliest visible sign of tuberous sclerosis. *Arch Dermatol* 1968;98:1-6.