Clinical features of tuberous sclerosis cases

Ayhan Söğüt, Meral Özmen, Serra Sencer, Mine Çalışkan, Nur Aydınlı
Türkan Ertuğrul, Gönül Peksayar

Department of Pediatrics, İstanbul University İstanbul Faculty of Medicine, Çapa-İstanbul, Turkey

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Tuberous sclerosis (TS) is an autosomal dominant, multisystemic and neurocutaneous disease with high spontaneous mutation rate, and it mostly involves the skin, brain, kidneys, heart and the eyes. This study included 35 patients diagnosed with tuberous sclerosis and aged 6 months to 17 years, with a mean age of 6.5±4.8 years. The most frequently observed manifestations were those of the skin (97.1%) and of the central nervous system (seizures 94.2%, mental retardation 51.4%), followed by renal (32.2%), cardiac (25.8%) and ocular (22.5%) manifestations. Among cutaneous manifestations, hypomelanotic macules (94.3%), facial angiofibromas (40%), shagreen spots (20%), fibrous plaques on the forehead (5.7%) and ungula fibromas (5.7%) were observed. Tonic seizures (37.1%) and infantile spasms (21.2%) accounted for majority of seizures. Neurophysiological development was normal in 25.6% of cases, retarded in 51.4% and borderline in 23%. Thirty-four patients had typical pathological findings on magnetic resonance imaging (MRI).

In conclusion, the earliest and most frequent complaint is seizure in cases with TS. Careful investigation for hypomelanotic macules and other skin manifestations typical for TS in cases presenting with convulsion makes early diagnosis possible and obviates unnecessary investigations.

Key words: tuberous sclerosis, seizure, neurocutaneous syndrome.

Tuberous sclerosis (TS), known as Bourneville's disease, epiloia or Pringle syndrome, is a multisystemic and a neurocutaneous disease affecting mainly the skin, brain, kidneys, heart and the eyes. It is usually autosomal dominant, but the rate of spontaneous mutations is also very high[1-3]. The phenotypes vary widely, including seizures, mental retardation, functional abnormalities of the kidneys and the heart and dermatological manifestations[2]. The majority of clinical findings result from the hamartomas in the affected organs[3].

In this paper, we present the clinical features of 35 patients with TS.

Material and Methods

Ninety patients either diagnosed with TS or suspected of having TS presented to the Department of Pediatrics, Division of Pediatric Neurology, İstanbul University between January 1987 and December 1998. Thirty-five patients diagnosed as definite TS according to the criteria shown in Table I[4] who accepted to participate in the study were recruited. Initial complaints, history, type and frequency of seizures and age at the onset were recorded. According to the seizure frequency, patients with seizures every day were classified as having severe TS, those with seizures once a week or less as having moderate TS and those with no seizures for two years, whether they were on anticonvulsive medication or not, as having mild TS. Physical and neurological findings obtained from baseline examinations were compared with those from final examinations, and ophthalmologic examinations were repeated. Neuropsyschological development was investigated using Brune-Lezine (BL) test in children younger than six years old and Wechsler Intelligence Scale for Children-Revised (WISC-R) in older children. IQ or Developmental Quotient (DQ) above 90 was considered as normal, between 71 and 90 borderline, and 70 or lower retarded.

Cranial magnetic resonance imaging (MRI) and electroencephalography were performed in all patients. MRI was performed in the MRI unit with the power of 1 T magnet. T1 weighted (TR: 600, TE: 70 matrix 256 x 256, FOV: 200 cm) axial, sagittal and coronal planes and T" weighted (TR: 3000, TE: 300) spin density (TR: 3000, TE: 17) were used in all cases and multiple sequences in 3 planes in 26 cases following IV gadolinium DTPA (0.2 mg/kg) injection. Thirty-one cases underwent abdominal ultrasonography, echocardiography and retinal examinations.

Table I. Diagnostic criteria for TS according to tuberous sclerosis (TS) complex consensus conference (1998)

Major features	Minor features
1. Facial angiofibromas or forehead plaque	1. Multiple, randomly distributed pits in dental enamel
2. Cardiac rhabdomyoma, single or multiple	2. Hamartomatous rectal polyps
3. Nontraumatic ungual or periungual fibroma	3. Bone cysts
4. Hypomelanotic macules (three or more)	4. Radial migration lines in the cerebral white matter
5. Shagreen patch (connective tissue nevus)	5. Gingival fibromas
6. Multiple retinal nodular hamartomas	6. Nonrenal hamartoma
7. Cortical tuber	7. Retinal achromic patch
8. Subependymal nodule	8. 'Confetti' skin lesions
9. Subependymal giant cell astrocytoma	9. Multiple renal cysts
10. Lymphangiomyomatosis of the lungs	
11. Renal angiomyolipoma	

Definite TS complex : Either two major features or one major feature plus two minor features.
Probable TS complex: One major plus one minor feature.
Possible TS complex : Either one major feature or two or more minor features.

Results

This study consisted of 35 patients (22 boys, 13 girls) with a mean age of 3.1±3.2 years on baseline examination and of 6.6±4.8 years on final examination. Clinical manifestations included those of the skin, central nervous system, kidney, heart and the eyes, in order of decreasing frequency. Thirty of 35 cases (97.1%) had dermatological manifestations. Hypomelanotic macules and facial angiofibromas were the most common dermatological findings. Other cutaneous findings were shagreen patches, fibrous plaques on the forehead, ungula fibromas, light brown patches, skin tags and hemangiomas (Table II). On the final examination, the frequency of hypomelanotic macules, facial angiofibromas and shagreen patches increased.

The most common presenting symptom was seizures (94.2%) and they began within 18.3±29.2 months on average; 62.5% of cases had seizures beginning before their first birthday. Generalized seizures affected 72.7% of cases, whereas 27.3% suffered from partial seizures (Table III). The most common generalized seizures were of tonic type in 37.1% of cases and of infantile spasm type in 21.2%. Seizure frequency was mild in 34.2% of cases, moderate in 42.8% and severe in 23%.

Neuropsychological development of patients was retarded in 51.4% of cases, borderline in 23% and normal in 25.5%.

Abdominal ultrasonography was performed in 31 cases, of which five (16.1%) were found to have renal angiomyolipoma and another five (16.1%) renal cysts. None had cardiac complaints, but of 31 cases, seven (22.5%) patients had rhabdomyomas and one patient had mitral and aortic insufficiency on echocardiography. Six patients (19.3%) had retinal hamartomas and one patient (3.2%) iris coloboma on retinal examinations.

Table II. Skin lesions in our cases

	First exam		Last exam	
Lesion	n	%	n	%
Hypomelanotic macules	30	(85.7)	33	(94.2)
Facial angiofibromas	5	(14.2)	14	(40.0)
Shagreen patches	3	(8.5)	7	(20.0)
Fibrous plaques on the forehead	2	(5.7)	2	(5.7)
Ungual fibroma	2	(5.7)	2	(5.7)

Table III. Types of seizures

Type	No. of cases	%
Generalized	24	72.7
Infantile spasm	7	21.2
Tonic	13	39.4
Clonic	3	9.1
Atonic	1	3.0
Partial	9	27.3

Thirty-four cases were found to have pathological findings on cranial MRI. Thirty-four (97.1%) had cortical tubera, 34 (97.1%) subependymal nodules, 19 (54.2%) white matter involvement such as radial glial bands and heterotypes, and three cerebellar lesions. Since in nine patients subependymal nodules were localized in the foramen Monro and uptake of contrast medium was positive, they were suspected of giant cell astrocytoma.

Cortical tubera were counted in 26 of 34 cases who had pathological findings on MRI: 15.5% of cases were found to have less than 5, 53.8% of cases 5-10 and 30.7% of cases more than 10. The diameters of the tubera were less than 1 cm in 15.4% of cases, 1 2.5 cm in 50% of cases and more than 2.5 cm in 34.6% of cases. The tubera were found most often in the parietal region (58%) and least often in the median/ parasagittal region (50%).

Discussion

Clinical findings of TS, first described by Frederich Daniel von Reckinghauson in 1862[1], vary with age and manifest over the years. Dermatological signs, especially hypomelanotic macules, and central nervous system signs are commonly seen within the first year of life. Cardiac rhabdomyomas are usually seen in the newborn, but signs of disorders of the eyes and kidneys generally manifest after 2-3 years of age[5].

Among sings of central nervous system impairment, the most common and earliest one is seizures[1,6]. In our cases, the first complaint and presenting symptom was seizures in 94.2% of cases. Two newborns had been referred from the Cardiology Department due to cardiac rhabdomyomas.

The skin and the brain are the most frequently affected organs in TS[1,3,7,8]. Sings of skin impairment, including hypomelanotic macules, facial angiofibromas, shagreen patches fibrous plaques on the forehead and periungual fibromas may be seen in 96% of cases[1,9].

Hypomelanotic macules are the most common skin manifestation[1,10] and are seen in 80-100% of cases[1,11,12]. They may be detected at birth and they may disappear later in life[9]. Hypomelanotic macules may also be seen in normal individuals; for the diagnosis of TS, more than two lesions must be present[4]. In our cases, frequency of hypomelanotic macules was 94.2%. Frequency of facial angiofibromas is reported as 42-90%[1,2,9,13]. These lesions' are not present at birth and they appear at any time between five years and adolescence[14]. Their frequency increases with age[9]. The frequency in our cases was comparable to those reported in the literature and also increased with age.

Shagreen patches appear after puberty. They are diagnostic of TS and their frequency is between 20-54%[1,3,9,15]. Like facial angiofibromas, they become more common with increasing age[9]. The frequency in our cases was 20%, increasing with age.

Fibrous plaques on the forehead are usually seen in the newborn and in the early infancy period[1,4]. Their frequency ranges from 19-25%[13,16], but was 5.7% in our cases.

Rate of periungual fibromas ranges between 15% and 50%, and they usually appear after puberty[1,3,14]. However, it was 5.7% in our cases, which may be attributable to our cases being prepubertal.

Frequency of seizures in TS is about 80-92%[1,3,17,18]. Seizures may occur at any age but they usually begin within the first year of life[8,19]. They were the first presenting symptom in 94.2% of our cases and had begun within the first six months of life in 57.5% of cases.

Mental retardation is seen in 38-65% of TS cases[1,17]. In our cases, 51.4% had mental retardation, 17.3% had borderline IQ and 31.3% were considered normal. Jozwiak et al.[16] reported that in mentally retarded cases, the risk of seizures increased significantly within the first six months and was almost two and a half times higher than that in normal individuals. In our study, the seizures had started within sixmonths in six (33.3%) of 18 mentally retarded cases.

Cardiac rhabdomyomas (RM) are seen in 30-60% of TS cases[13,16]. RM may be detected in the prenatal or neonatal period[20]. Since these tumors may regress in time, they are usually treated in a conservative manner and followed by echocardiography[21]. RM in our cases also shrank in time. On the other hand, opthalmologic and renal signs may increase in time and, since the most common cause of mortality is renal pathology, these cases should be followed up carefully[22]. In our cases, rates of involvement of the eyes and the kidneys were very low, which was probably due to the younger ages of our cases.

Cortical tubera and subependymal nodules are typical lesions of TS. The rate of cortical tubera is about 88-95% and that of subependymal

nodules 80-95%[27-30]. The subependymal nodules in the foramen Monro region and holding contrast material need to be investigated for giant cell astrocytomas[26]. Rate of giant cell astrocytomas in TS is about 5-8.5%[5,26]. Rates of intracranial lesions in our series were comparable to those reported in the literature. However, rate of suspected giant cell astrocytoma (25.7%) was higher than that expected; the actual rates will be known only after the follow-up.

In conclusion, TS is a multisystemic disease affecting mainly the skin and the brain. The earliest and most frequent complaint is seizure. Therefore, investigation of TS specific skin lesions, especially in cases presenting with seizures, makes early diagnosis possible and obviates unnecessary investigations.

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REFERENCES

1. Gomez MR. Tuberous sclerosis. In: Gomez MR (ed). Neurocutaneous Diseases. Boston: Butterworth Publishers; 1987: 30-52.
2. Van Slegtenhorst M, Verhoef A, Tempelaars A, et al. Mutational spectrum of the TSC1 gene in a cohort of 225 tuberous sclerosis complex patients: no evidence for genotype-phenotype correlation. J Med Genet 1999; 36: 285-289.
3. Roach ES. Neurocutaneous syndromes. Pediatr Clin North Am 1992; 39: 591-600.
4. Roach ES, Gomez MR, Northup H. Tuberous Sclerosis Complex Consensus Conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13: 624-628.
5. Menor F, Marti-Bonmati L, Mulas F, Poyatos C, Cortina H. Neuroimaging in tuberous sclerosis: a clinicoradiological evaluation in pediatric patients. Pediatr Radiol 1992; 22: 485-489.
6. Williams R, Taylor D. Tuberous sclerosis. Surv Opthalmol 1985; 30: 143-154.
7. Shepherd CW, Houser OW, Gomez MR. MR findings in tuberous sclerosis complex and correlation with seizure development and mental impairment. AJNR Am J Neuroradiol 1995; 16: 149-155.
8. Curatolo P, Ousmi R, Cortesi F, ;Chiron C, Jamboqué I, Dulac O. Neuropsychiatric aspects of tuberous sclerosis. Ann NY Acad Sci 1991; 615: 8-16.
9. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol 1996; 135: 1-5.
10. Avellino AM, Berger, MS, Rostomily RC, Shaw CM, Ojeman GA. Surgical management and seizure outcome in patients with tuberous clerosis. J Neurosurg 1997; 87: 391-396.
11. Bell DG, King BF, Hattery RR, Charboneau JW, Hoffman AD, Houser OW. Imaging characteristic of tuberous sclerosis. AJR 1991; 156: 1081-1086.
12. Braffman BH, Bilaniuk LT, Zimmerman RA. The central nervous system manifestations of the phakomatoses on MR. Radiol Clin North Am 1988; 26: 773-800.
13. Fryer AE, Chalmers AH, Osborne JP. The value of investigation for genetic counselling in tuberous sclerosis. J Med Genet 1990; 27: 217-223.
14. McGrae JR, Hashimoto K. Unilateral facial angiofibromas-a segmental form of tuberous sclerosis. Br J Dermatol 1996; 134: 727-730.
15. Vanderhooft SL, Francis JS, Pagon RA, Smith LT, Sybert VP. Prevalence of hypopigmented macules in a healthy population. J Pediatr 1996; 129: 355-361.
16. Jozwiak S, Schwartz RA, Janiger CK, Michalowich R, Chmielik J. Skin lesions in children with tuberous sclerosis complex: their prevalence, natural course, and diagnostic significance. Int J Dermatol 1998; 37: 911-917.
17. Kotagal P, Rothner AD. Epilepsy in the setting of neurocutaneous syndromes. Epilepsia 1993; 34: 71-78.
18. Wippold FJ, Baber WW, Gado M, Tobben PJ, Bartnicke BJ. Pre and post contrast MR studies in tuberous sclerosis. J Comp Assist Tomography 1992; 16: 69-72.
19. Brett EM. Neurocutaneous syndromes. Pediatr Neurol 1996; 599-618.
20. Barkovich AJ. Pediatric Neuroimaging (2nd ed). New York: Raven Press; 1995: 786-790.
21. Distefano G, Sciacca P, Mattia C, Tornambenen G. Cardiac involvement in tuberous sclerosis in the first months of life: physiopathologic and clinical aspects of cardiac rhabdomyoma. Pediatr Med Chir 1998; 20: 29-32.
22. Shepherd CW, Gomez MR, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc 1991; 66: 792-796.
23. Houser OW, Sheperd CW, Gomez MR. Imaging of intracranial tuberous sclerosis. Ann N Acad Sci 1991; 615: 81-93.
24. Inoue Y, Nemoto Y, Murata R, et al. CT and MR imaging of cerebral tuberous sclerosis. Brain Dev 1998; 20: 209-221.
25. Osborn AG. Diagnostic Neuroradiology. (Chap 5). St Louis, Missouri: Mosby-Year Book Inc; 1994: 93-98.
26. Atlas SW. Magnetic Resonance Imaging of the Brain and Spine (2nd ed). Philadelphia: Lippincott-Raven Publishers; 1996: 296-304.