TUBEROUS SCLEROSIS

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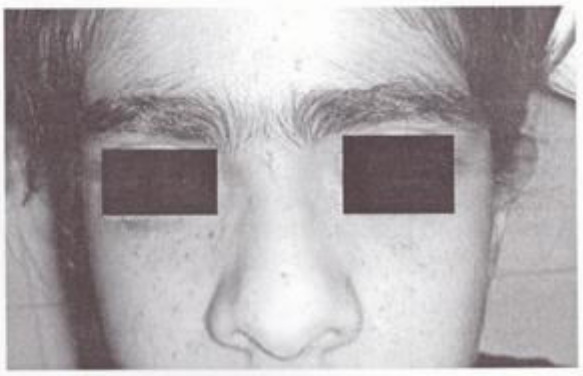
CASE REPORT

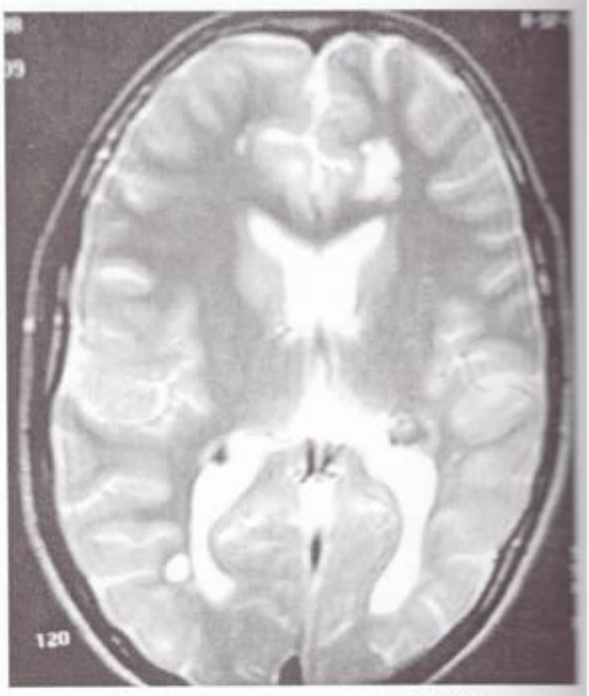
A young girl of about 11 years presented with intractable epilepsy since the age of 8 years. She would scream and grab anyone in front of her and hold on tightly till the attack subsided and then she would fall asleep. During the attack she would be vocalizing words which were incomprehensible and would have excessive salivation at the time. The attack would last anywhere from 30 seconds to a minute and every 8-10 days she would experience this episode. Patient had a normal birth history and was a healthy baby till 6 months of age wherein she started having febrile convulsions wherein she would develop high grade fever following which her face would become red and she would make tight fists. Consultation with a doctor resulted in the patient being started on phenobarbitone and the fits disappeared. She was then gradually weaned off at 5 years of age and till the age of 8 she

Shagreen patch on the nape

remained seizure free. Also the patient was receiving treatment for the lesions on her face and other areas of the body which turned out to be angiofibromas. She had also undergone eye surgery for correction of strabismus and was prescribed spectacles which the patient was using. At presentation, the patient was seizure free. Examination revealed an 11 year old girl of normal mental and physical development. Multiple angiofibromas were present on her face more specifically on the cheeks.

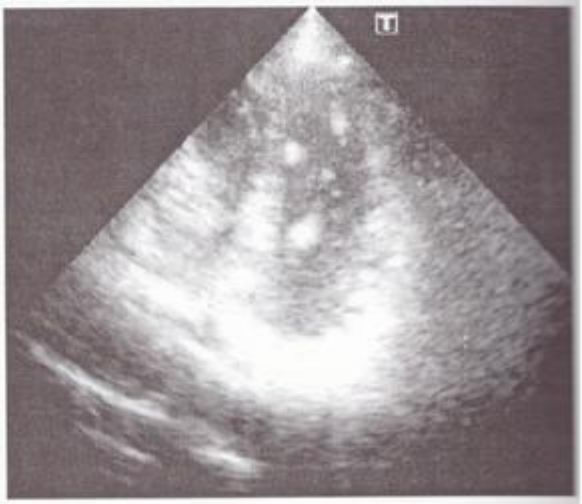


Facial angiofibromas

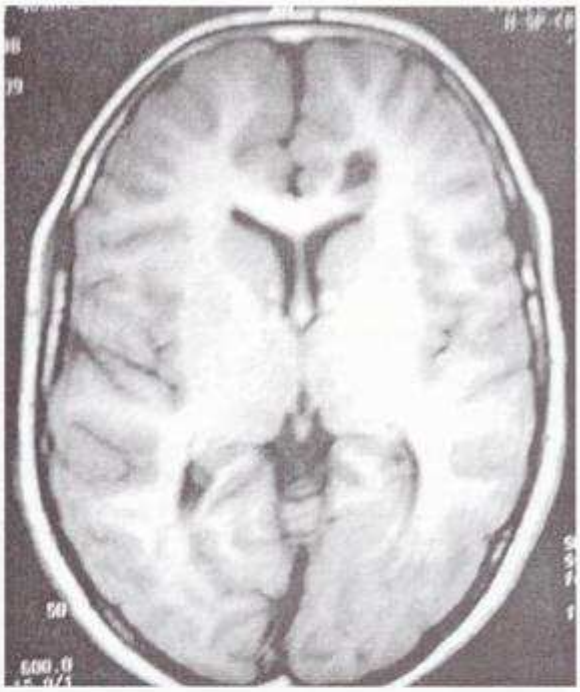


Hyperintense tubers on brain MRI

Examination of the eyes revealed a conjunctival hamartoma.Periungual fibroma was present on the middle toe of right foot. Shagreen patch was present on the nape of neck. A chest X-ray turned out to be normal.



Cardiac rhabdomyomas on Echo



Subependymal tubers on MRI scan

A chest X-ray turned out to be normal. An EEG confirmed the temporal origin of seizures while an MRI scan of the brain revealed subependymal tumors and cortical tubers. An echocardiogram of the heart showed biventricular rhabdomyomas while an ultrasound detected the presence of angiomyolipomas in both kidneys. Both the functional status of the kidneys and the heart fell within normal limits. Subsequently the patient was started on vigabatrin and was advised follow-up.

DISCUSSION

Tuberous sclerosis is recognized as the second most common neurocutaneous disorder.[1,2] Although a childhood disease, the condition can go unrecognized till adulthood. The patient can present with seizures which are the most common manifestation[3] or they can present with the complications arising due to multi organ involvement. Management is aimed at treating the symptoms of the patient and timely identification of complications and their treatment.

EPIDEMIOLOGY

Since its identification in all ethnic groups and no specific predilection for any sex, population studies have identified a live-birth prevalence to be between 10 and 16 cases per 100,000.[4]

PATHOGENESIS

Tuberous sclerosis is an autosomal dominant condition characterized by the appearance of hamartomas in multiple organs. The manifestation results from a mutation in any of the two tumor suppressor genes TSC1 and TSC2.[5] TSC1 located on chromosome 9q34 and encodes for a 130-kDA protein hamartin.[6] TSC2 has been mapped to chromosome 16p13.3[7] and it encodes a 200-kDA protein tuberin.[8] The two proteins interact with each other via their respective coiled-coil domains to form a functional heterodimer (TSC1:TSC2).[9] The two proteins act as tumor growth suppressors, acting as regulators of cellular proliferation and differentiation.[10] Although tuberous sclerosis is an autosomal dominant condition, in 15% of cases mutation cannot be identified. Furthermore, in two-third of the affectees, no parental history can be identified. This signifies a high rate of spontaneous mutation.[11] Also patients with identical mutations exhibit a highly variable phenotype.[12]

CLINICAL MANIFESTATIONS

Tuberous sclerosis is a multi organ condition affecting majority organs of the body. However, most patients present with the involvement of dermatological, renal and neurological systems.[5] Neurological symptoms include seizures which are the most common presenting symptoms. Generally seizure presentation occurs very early in life[13] though with aging a change in semiology may be noted.[14,15] Infantile spasms are another common presenting complaint of tuberous sclerosis.[16] These are generalized myoclonic seizures with hypsarrythmias on EEG. They may precede, follow or coexist with other seizure types and often begin between 4 to 6 months of age.[17] Other neurological complaints include neurocognitive dysfunction[18] and pervasive developmental disorders such as autism.[19] Neurological manifestations reflect the underlying structural abnormalities of the brain. These take the form of cortical tubers which are areas of anomalous glial proliferation and migration and are thought to have epileptogenic foci.[20] Subependymal nodules and subependymal giant cell astrocytomas are two other abnormalities found on histopathological examination of brain of a tuberous sclerosis patient. Subependymal nodules are benign proliferative lesions protruding into the ventricular lumen and are usually asymptomatic. In contrast, subependymal giant cell astrocytomas progressively enlarge leading to hydrocephalus and death. Also in 10% patients, subependymal nodules transform into subependymal giant cell astrocytomas.[21] White brain matter migration lines and transmantle cortical dysplasia are two other examples of supratentorial brain lesions.[22] Tuberous sclerosis complex exhibit extensive involvement of the renal system. Collectively, they occur in 50-80% of patients[23-25] and include angiomyolipomas (AMLs), renal cysts, renal cell carcinomas and oncocytoms.[26] Multiple, bilateral AMLs occur in 80% of patients and are the leading cause of mortality second to spontaneous hemorrhage.[26,27] Renal disease commonly manifests as hematuria, flank pain and palpable mass.[27,28] Dermatologic features are found in 96% of

tuberous sclerosis patients and are easily recognizable. Though a common presenting complaint, in a study, they were missed in 9% of cases.[29] Involvement of dermatologic system is age-dependent with hypomelanotic macules by presenting in infancy and childhood serving as first evidence of tuberous sclerosis complex.[30] Facial angiofibromas are present in 80% of patients and usually appear within first two years of life. However, they may not be noted till late adulthood.[31] Shagreen patch, a type of connective tissue nevus appears at the age of 2 years as leathery plaques on the lumbosacral region[31] though may also be present at the nape. It is present in approximately 50% of patients.[31] Other findings include periungual fibromas which develop adjacent to the nail fold and café-au-lait spots. Pits in the dental enamel are a common occurrence in a patient with tuberous sclerosis so much so that they are used as a bedside screening tool for identifying patients. The practice however has been abandoned due to inter-observer variability. Lung involvement is in the form of multifocal micronodular pnuemocyte hyperplasia[32], pulmonary cysts and lymangiomyomatosis[32]. 30-40% of adult with tuberous sclerosis complex present with cystic lymphangiomyomatosis[33-35] and in adults, it is related with a high morbidity and mortality.[33] Cardiac anomalies in the form of rhabdomyomas are detected in 50% of affected infants thought they may undergo involution during the first few years of life.[36] Ocular findings in tuberous sclerosis has both retinal and non-retinal components. Retinal hamartomas are the most common feature of disease involvement of the eye.[37] Non-retinal findings include angiofibromas of the eyelid and strabismus.[38]

DIAGNOSIS

Diagnosis of tuberous sclerosis complex is based on the criteria set forth by the National Tuberous Sclerosis Association of USA.[39] For a definite diagnosis two major or one major and two minor features are needed. A probable one requires the presence of one major and ne minor feature while for possible diagnosis either one major or two or more minor features need to be present. Now since the diagnosis is essentially a clinical one workup of the patient entails identification of organ involvement and assessment of the functional status. Early diagnosis of the individual alongside lifelong monitoring and proactive treatment all help in minimizing the health risks associated with the disease.[40]

Diagnostic Criteria for Tuberous Sclerosis Complex[39]

Major features

Facial angiofibromas or forehead plaque

Nontraumatic ungual or periungual fibroma

Hvpomelanotic macules (more than three)

Shagreen patch (connective tissue nevus)

Cortical tuber

Subependymal nodule

Subependymal giant cell astrocytoma

Multiple retinal nodular hamartomas

Cardiac rhabdomyoma, single or multiple

Lymphangiomyomatosis

Renal angiomyolipoma

Minor features

Multiple randomly distributed pits in dental enamel

Hamartomatous rectal polyps

Bone cysts

Cerebral white matter "migration tracts""

Gingival fibromas

Nonrenal hamartoma

Retinal achromic patch

"Confetti" skin lesions

Multiple renal cysts

WORKUP

Tuberous sclerosis is a clinically diagnosed disease. Accordingly investigations in such a patient are aimed at identifying organ involvement. These include an EEG to look at seizure types and rule out the presence of infantile spasms which have a characteristic appearance. However, CT scan and MRI of the brain are the most sensitive screening imaging studies when looking for intracranial lesions. MRI is the modality of choice though for identification of calcifications CT scan is preferred.[41,42] Chest radiographs can depict evidence of interstitial fibrosis or honeycombing although CTscan thorax has become the modality of choice when looking for lymphangiomyomatosis LAM. However, Chest x-ray constitutes and good baseline screening tool. Dermatological features can generally be appreciated on observation. Examination under a Wood's lamp should be performed to establish the presence of hypomelanotic lesions that can otherwise be missed. Echocardiography should be ordered to rule out cardiac rhabdomyomas. Additionally it can provide evidence regarding the functional status of the heart. However, ECG is still mandatory to identify arrhythmias that might arise if the conducting pathways are involved. An ultrasound abdomen and pelvis is usually employed as a baseline investigating tool to evidence the presence of renal involvement, though CT scan abdomen supersedes in providing a more accurate picture. Fundoscopy of a tuberous sclerosis patient is essential to delineate any underlying retinal involvement. Molecular diagnosis aids in identifying the involved gene though even in carefully selected cases a negative result does not preclude the diagnosis. Also its role in a screening tool in family members of the affectees is uncertain.

IEATMENT

Management of the patient is multidisciplinary d is aimed at alleviating the symptoms of the tient. For seizure control, drugs commonly advised :

- Vigabatrin
- Topiramate
- Lamotrigene
- Valproate
- ACTH/steroids

Carbemezapine, oxycarbezepine and phenytoin avoided as they result in exacerbation of symp- ns. Agents with sedating properties are avoided over ıg run. Ketogenic diet is another proven therapy in ıtrolling seizures. The diet comprises of fats in a io of 4:1 with 1 part of carbohydrates and proteins mbined. Ketogenic diet is effective in both adults d children and patients can be gradually weaned the diet without any increase in frequency of sei- es. Surgical treatment can be offered in selected ses. These include resection of cortical tubers, cor- s callosotomy, vagus nerve stimulation and tumor ection. Counseling and guidance of the patients and ir attendants is mandatory to aid in helping the pa- nts reach their potential. Newer approach has been introduction of therapy that targets mTOR activa- n and results in its inhibition. Everolimus is the drug t has currently received approval for treatment of ependymal giant cell astrocytomas.

OGNOSIS

Prognosis is greatly improved nowadays. ly diagnosis and timely management leads to re- ced morbidity and mortality. However, patients re- re lifelong follow-up to monitor for disease exacer- ion.

NCLUSION

Tuberous sclerosis is a common neurocutane- disorder. It is easily diagnosed clinically and the nagement is purely symptomatic. Timely interven- is essential to reduce the occurrence of complica- ıs and fatality associated with them.

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