

Case Report

Infant with infantile spasms: early intervention improves neurodevelopmental outcome

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ABSTRACT

Tuberous sclerosis complex is a multisystem genetic disorder with characteristic skin lesions and variable neurological manifestations like seizures, cognitive impairment and autistic spectrum disorder. Epilepsy and infantile spasms during first year of life are risk factors for mental impairment and Autistic spectrum disorder (ASD). In asymptomatic TSC infants, hypsarrhythmia pattern in EEG suggests early treatment with vigabatrin to improve neurodevelopmental outcome. Early recognition of skin lesions by pediatrician is crucial for timely intervention.

Keywords: Tuberous sclerosis, Ash leaf macules, Hypsarrhythmia, Infantile spasms, Vigabatrin, Neurodevelopmental outcome

INTRODUCTION

Tuberous sclerosis complex (TSC) was described 141 years ago, in 1880 by Desiree Magloire Bourneville. The disease is characterized by formation of hamartomas in multiple organs.

TSC is inherited as autosomal dominant with variable expression.¹ TSC1 and TSC2 are tumour-suppressor genes involved in the disease process. TSC1 gene encodes a protein called hamartin located on chromosome 9q34, and the TSC2 gene encodes tuberlin on chromosome 16p13. The loss of either tuberlin or hamartin protein results in formation of benign tumours (hamartomas). TSC causes epilepsy, learning difficulties and behavioural problems (autism, hyperactivity, and sleep disturbance), renal angiomyolipoma, subependymal giant cell astrocytoma. Thereby, TSC patients need multidisciplinary management. This case is being reported in view of classical clinical and radiological findings of TSC and to emphasise that early recognition and control of infantile

spasms is crucial for improved neurodevelopment and cognitive outcome.

CASE REPORT

A 5 months old girl, born of non-consanguineous marriage of Kerala origin, presented to our hospital with jerky and startle like movements with vacant stare, 3 episodes in the past one-week but multiple episodes since morning. No history of fever, refusal of feeds, lethargy, trauma, or recent vaccination. She was delivered at term, by labour Naturalis with a weight of 2.67 kg and good Apgar score. In the last three-generation pedigree, no other family members had similar complaints. At admission, baby had multiple episodes of jerky movements of the limbs with vacant stare along with intermittent infantile spasms. Examination revealed, multiple hypopigmented lanceolate shaped ash leaf macules on the back (Figure 1) and face (Figure 2). She was alert, afebrile with normal breathing and circulation, systemic examinations were normal. She was treated with IV levetiracetam in view of multiple

episodes of seizures. EEG showed 'hypersarhythmia-pattern' (Figure 3), MRI brain with contrast showed multiple subependymal nodules, cortical and subcortical tubers (Figure 4). Thereby, with 2 major criteria, a diagnosis of TSC was made.

Retinal pigment epithelial depigmented lesions were seen on ophthalmologic examination. Baseline blood, urinalysis, ultrasonography of abdomen, echocardiography, full body MRI were normal. In view of persistent seizures and hypersarhythmia in EEG, she was started on vigabatrin after getting consent from her parents, after which seizures were controlled. She was discharged with oral levetiracetam and vigabatrin in weight dependent doses. She is currently on oral vigabatrin, sodium valproate and clobazam, with normal gross motor and language development, but with limitation in social and fine motor skills. Axial T2 weighted images show well circumscribed areas of high signal intensity involving cortex and subcortical white matter indicating cortical/subcortical tubers. Multiple subependymal nodules are noted along the ventricular surface. Radial bands are also noted as hyperintense straight bands extending from juxtaventricular white matter to cortex.

Axial T1 weighted post contrast image showing strong enhancement of the subependymal lesion at the frontal horn of left lateral ventricle near the foramen of Monro. This needs serial follow up to look for increase in size indicating transformation to subependymal giant cell astrocytoma as well as for development of obstructive hydrocephalus.

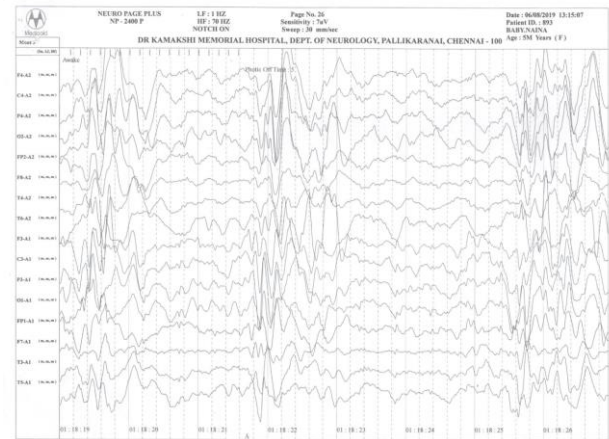


Figure 3: Hypersarhythmia in EEG.

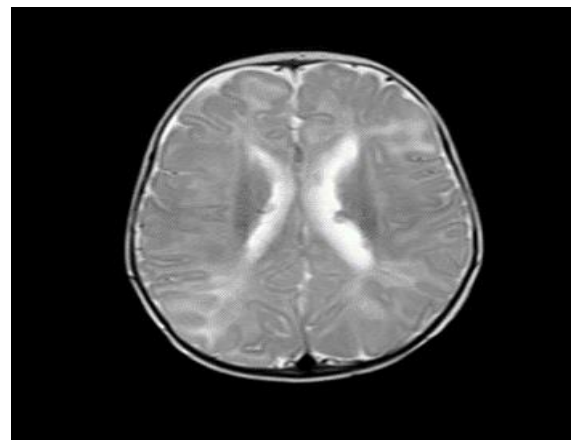


Figure 4: Subependymal nodules in axial T2 weighted image.



Figure 1: Hypomelanotic macules in the trunk.



Figure 2: Hypomelanotic macules in the face of our 5-months-old infant.

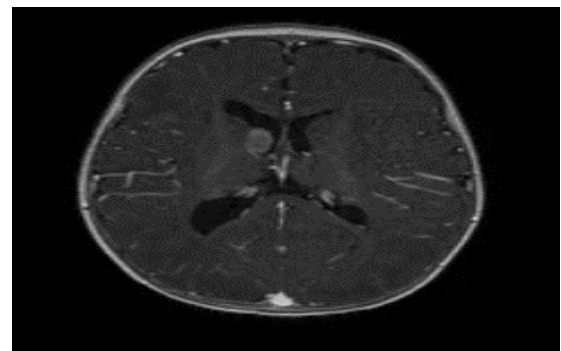


Figure 5: Contrast enhanced axial T1 weighted image showing subependymal lesion at the frontal horn of left lateral ventricle.

DISCUSSION

Despite advances in genetic diagnosis of TSC, it is important to make a secure clinical diagnosis. Definite TSC is diagnosed when at least 2 major or one major plus 2 minor clinical criteria for diagnosis of tuberous sclerosis features are present.¹

Major features

It includes- (a) cortical tuber; (b) subependymal nodule; (c) subependymal giant cell astrocytoma; (d) facial angiofibroma or forehead plaque; (e) ungual or periungual fibroma (non-traumatic); (f) hypomelanotic macules (>3); (h) Shagreen patch; (i) multiple retinal hamartomas; (j) cardiac rhabdomyoma; (k) renal angiomyolipoma; and (l) pulmonary lymphangioleiomyomatosis

Minor features

It includes- (a) cerebral white matter migration lines; (b) multiple dental pits; (c) gingival fibromas; (d) bone cysts; (e) retinal achromatic patch; (f) Confetti skin lesions; (g) conrenal hamartomas; (h) multiple renal cysts; (i) hamartomatous rectal polyps

To exclude TSC, a full clinical examination with Wood's lamp, funduscopy and cranial imaging is mandatory.

Manifestations of TSC

The unique skin lesions develop early even before neurologic symptoms, which aids prompt diagnosis with early treatment and appropriate follow-up.

Hypomelanotic macules are the earliest and most frequently reported cutaneous finding, which are more conspicuous under Wood lamp. Medium to large (1-12 cm in diameter) hypopigmented patches occur in 50% of patients at birth and in all by 2 years. These patches are referred to as 'ash-leaf' spots because they resemble the leaf of the eastern mountain ash tree.²

Confetti-like skin lesions are hypomelanotic macule 1-3 mm in diameter seen in 2.8-28% of patients and spread symmetrically over distal extremities.

Facial angiofibromas or adenoma sebaceum, are pink-brown symmetrical smooth papulonodules with glistening surface over the face seen in 75% of patients in first 2-5 years of life.³ They start small and gradually increase in size, with growth augmentation by puberty.

Shagreen patches are seen in 50% of patients. They are asymmetric pink-brown plaques with an orange peel-like texture, over dorsal surfaces, back and lumbosacral regions.

Periungual or subungual fibromas are red-skin colour lesions near proximal nail fold of toenails and sometimes near fingernails in 15% of patients during early adolescence.

Treatment options includes topical mammalian target of rapamycin (mTOR) inhibitors, vascular laser surgery, cryotherapy or surgical excision. Tubers can be identified since foetal period and may persist throughout life. They

do not increase in number after birth, although may become more visible on MRI as the brain myelinates in the first 2-3 years of life. Patients may present with epilepsy, infantile spasms, signs of raised intracranial pressure, hydrocephalus during any age group. Increased intracranial pressure is due to Subependymal giant cell astrocytoma (SEGA), which characteristically arises at foramen of Monro from a subependymal nodule and typically enhances after contrast on CT or MRI. If it grows large enough to obstruct one or both foramina of Monro it causes hydrocephalus. Indications for surgical removal are progressive ventricular enlargement or symptoms of raised intracranial pressure. The giant cell astrocytoma can be surgically removed with a minimal chance of recurrence. Tuberous sclerosis associated neurological disorders are autism, depression and anxiety. There are many cases reported with normal intelligence even in the presence of many tubers and infantile spasms.⁴

The seizure type in TSC varies from Infantile spasms, focal or generalized seizures. Vigabatrin, an inhibitor of γ -aminobutyric acid transaminase is considered as the drug of choice for infantile spasms and in some as an alternative to ACTH.⁵ The principal side effect of vigabatrin is retinal toxicity seen in almost 30%, with resultant visual field defects despite withdrawal of the drug. Vigabatrin is currently been suggested in asymptomatic patients with Hypsarrhythmia in EEG as it results in better neurodevelopmental outcomes.⁶ Behavioural and occupational therapy are provided for the same.

Tubectomy is considered in case of intractable seizures when major seizure activity arises from a single tuber. When seizures are intractable in spite of medical or surgical interventions; ketogenic diet, corpus callosotomy, or vagus nerve stimulation are considered.

Rapamycin (sirolimus) and its analogues (e.g. everolimus) inhibit the mTOR complex and impede mTOR overactivation, they shrink existing lesions and prevent tumour growth associated with TSC. Oral everolimus has been evaluated in several studies in patients with SEGA, renal angiomyolipomas, lymphangioleiomyomatosis (LAM) and epilepsy associated with TSC. Oral everolimus and oral sirolimus both are currently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of certain TSC-associated illness.⁷ The effect of oral everolimus on skin lesions was evaluated prospectively as a secondary endpoint in two pivotal phase III studies, EXIST-1 and EXIST-2 and from these trials, oral everolimus has proved to improve cutaneous TSC lesions. Rapamycin (sirolimus) is a lipophilic compound which is used as topical for the cutaneous lesions.

Although, thought to be effective in treating cutaneous TSC manifestations, oral mTOR inhibitors are currently reserved for patients whose internal disease warrants systemic treatment.

Paediatrician role in management of TSC

Paediatricians should be knowledgeable about the diagnostic criteria and cutaneous signs of TSC in order to facilitate timely diagnosis. Also, because TSC-related manifestations can change during the course of a patient's illness, ongoing surveillance is important to account for the potential emergence of new or progressing sequelae.

A consensus guideline recommendation for baseline assessment and ongoing monitoring is recommended- (A) skin: detailed dermatological examination annually; (B) brain: (a) MRI to identify tubers, subependymal nodules, migrational defects and SEGAs and then every 1-3 years if asymptomatic, screen for Tuberous sclerosis associated neurological disorders (TAND), (b) perform baseline EEG; if abnormal, follow-up with 24-hour video EEG to assess for subclinical seizure activity and consider starting vigabatrin, and (c) educate parents on infantile spasms and importance of treatment during infancy; (D) kidney: (a) measure blood pressure to screen for hypertension; (b) measure GFR to assess renal function, and (c) MRI of the abdomen to identify angiomyolipoma and renal cysts, then every 1-3 years; (E) heart: (a) if rhabdomyomas are identified prenatally, consider echocardiography after birth to assess risk for heart failure; (b) ECG to identify conduction defects and every 3-5 years if asymptomatic; (c) echocardiography in patients ≤ 3 years and every 1-3 years in asymptomatic paediatric patients until cardiac rhabdomyomas regress; (F) lung: (a) clinical screening (exertional dyspnoea) at each visit for LAM, (b) baseline HRCT and then every 5-10 years in absence of lung cysts or every 2-3 years in presence of lung cysts, and (c) baseline pulmonary function testing, 6 min walk test if at risk for LAM (typically women ≥ 18 years) and annually if lung cysts present; (G) eye: ophthalmological evaluations annually

Prognosis of the disease depends on the severity and multiplicity of organ involved. The skin manifestations of TSC are the clinical hallmark and helpful in diagnosing this disorder. Unfortunately, no specific prenatal test is available. Genetic counselling should be offered to families with affected members, even though accurate counselling remains difficult because of the variability of gene expression and mutation.⁸ Genetic testing is recommended in view of newer modalities of mTOR inhibitors which can be used for treatment options and for establishing recurrence risk.

CONCLUSION

Ash leaf macules are the earliest lesions found since neonatal period in TSC. Early epilepsy and infantile spasms are important risk factors for neurodevelopmental outcome. Routine EEG is indicated even in asymptomatic TSC infants for early initiation of vigabatrin in case of hypsarrhythmia, for better neurodevelopment outcome. Genetic testing is recommended for establishing recurrence risk and to use newer modalities like mTOR inhibitors for treatment.

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