Intractable Seizures as the Initial Presentation of Two Neonates with Genetically Diagnosed Tuberous Sclerosis Complex

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ABSTRACT

Tuberous Sclerosis Complex (TSC) is a genetic disorder that presents in a myriad of clinical manifestations affecting the different organ systems. These manifestations emerge at different times in a patient's lifespan and diagnosis early in the disease can be challenging. Majority of patients with TSC develop epilepsy and is often one of the most difficult to manage. We report two neonates with drug resistant epilepsy with seizure onset on the first day of life and were subsequently diagnosed with Tuberous Sclerosis. These two neonates exemplified the diverse phenotypic expression of TSC.

BACKGROUND

Tuberous Sclerosis Complex (TSC) is a progressive disease with a highly variable manifestation that affects the different organ systems and emerge at different times in a patient's lifespan. Early in the disease and without any clinical features typical of TSC, the diagnosis can be challenging. Epilepsy is present in 90% of patients with TSC and one of the most difficult to manage. We report two neonates with drug resistant epilepsy with seizure onset on the first day of life who were subsequently diagnosed with Tuberous Sclerosis.

CASE PRESENTATION

A fifteen-day-old neonate was brought to our institution due to recurrent focal motor onset seizures on the first day of life. He was delivered full term via normal spontaneous delivery from a 22-year-old primigravid with no known comorbidities. The seizures were described as eyebrow twitching with lip smacking progressing to tonic clonic movements of the left upper extremities with generalization lasting for 30 seconds and occurring multiple times in the day. He was started on Levetiracetam and phenobarbital with poor seizure control, thus he was transferred to our institution. Due to the recurrent seizures, he was intubated and admitted to the Neonatal Intensive care Unit. On the 8th hospital day, hypomelanotic macules (Figure 1) were seen over the trunk and extremities providing the impetus to do diagnostic examinations for TSC. Electroencephalogram (EEG) showed epileptiform discharges coming from the right and left frontal region evolving to become generalized. (Figure 2) Cranial Magnetic Resonance Imaging (MRI) showed Subependymal nodules (SEN) and Subependymal Giant Cell Astrocytoma (SEGA) in the right lateral ventricle. (Figure 3) Cardiac Echocardiogram showed well delineated echogenic non-mobile structures in the right ventricular apex and the chordae of the Mitral Valve in which rhabdomyoma was the primary consideration. The patient was given multiple anti-seizure medications including Phenobarbital, Lacosamide, Carbamazepine and Clonazepam rendering decrease in seizure frequency. Sirolimus was given for the SEGA and cardiac rhabdomyoma. Genetic testing revealed a pathogenic variant in the TSC1 gene Exon 15, c. 1498C>T (p.Arg500*), heterozygous). The patient is being regularly seen at our out-patient clinics.

The second patient is an eleven day old female who was admitted in our

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institution due to focal motor onset seizures on the first day of life. The patient was born full term to a 20-year-old primigravid with no comorbidities. There were no maternal infection or history of perinatal asphyxia. At the fourth hour of life, the patient had focal motor seizures described as right versive gaze, clonic movement of the right upper extremity followed by clonic movement of the bilateral lower extremities for 30 seconds. The seizures persisted at home and occurred multiple times in a day. She developed jaundice and foul smelling umbilical stump prompting consult in another center and was subsequently referred to our institution. The patient did not have any neurocutaneous lesions. She was treated with antibiotics for sepsis and was given on Phenobarbital and Pyridoxine with poor seizure control. Battery of diagnostic examinations were done including cerebrospinal fluid analysis which showed normal results. Cranial ultrasonography which revealed lenticulostriate vasculopathy in the right gangliothalamic region. A prolonged six-hour EEG recording was done showing 71 clinical events and electrographic seizures lasting for 25-35 seconds. There was discontinuity and asynchrony of the background activity with noted 3-4Hz activity. There were frequent sharp and spike discharges over the left frontocentral and left temporal regions with attenuation of the background activity in between bursts of discharges. Comprehensive urine metabolic screening, serum electrolytes, serum lactate, blood gas, ammonia were all normal. Despite the medications, the patient had recurrent seizure episodes occurring in 7 to 19 clusters in a day. The seizures were of varying semiology including focal motor onset seizures, clonic seizures and asymmetric spasms. The patient was managed with an epileptologist and additional anti-seizure medications including Levetiracetam, Topiramate, Phenytoin, Carbamazepine, Lacosamide and Perampanel were subsequently added and adjusted to effect. The patient was also treated with Prednisolone, Lacosamide and Carbamazepine with poor response, hence were discontinued. Genetics referral recommended a whole exome sequencing which revealed a pathogenic variant in the TSC2 gene (C46720>A (p.Clu1558Lys), heterozygous). Cranial MRI showed a probable cortical dysplasia over the left parietal and superior temporal region. His antiseizure medications on discharge were Levetiracetam, Topiramate and Valproic acid. A subsequent 2d-echo at 1-year-old showed an echogenic mass in the apex of the left ventricle measuring 0.64 cm X 0.44 hence sirolimus was given. Currently, the patient has daily brief tonic seizures occurring 3-7 times in a day.

Both neonates did not have a family history of TSC and we did not elicit any family member with neurocutaneous lesions, cardiac or neurologic findings that is consistent with Tuberous Sclerosis. Both cases were managed using a multidisciplinary approach including Child Neurology, Neurosurgery, Cardiology, Hematology-Oncology and Neurodevelopmental Pediatrics.

DISCUSSION

Tuberous sclerosis complex (TSC) is a genetic disorder that is inherited in an autosomal dominant pattern and characterized by growth of hamartomas that occur in various organ systems, including the brain, heart, kidneys, lungs, skin and eyes. The incidence is approximately 1 in 5,000–6,000 live births. Approximately 70%–85% of those diagnosed with definitive TSC have mutation in one of the two genes, TSC1 or TSC2.[1] The protein products of these genes form a heterodimer (TSC1–TSC2 complex) that inhibits the mammalian target of rapamycin (mTOR) signaling cascade. Inadequate suppression of the mTOR pathway results in dysgenic lesions in multiple organ systems including the developing fetal brain.[2]

Involvement of the central nervous system (CNS) is invariably present.[3] The prevalence of epilepsy in TSC is high at 90%.[3] Early onset epilepsy initially presents as focal motor onset seizures and can

Figure 1. Neurocutaneous lesions. Hypomelanotic macules on the trunk

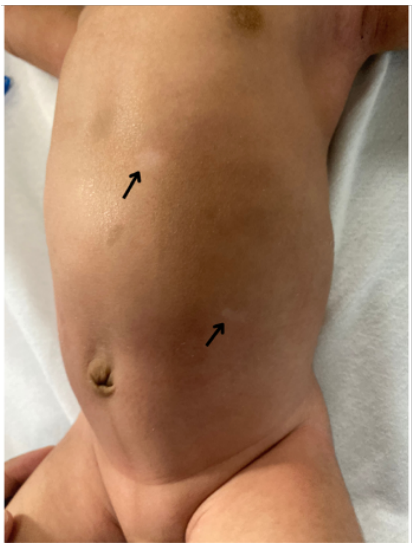


Figure 2. Electroencephalogram showing focal epileptiform discharges from the right and left frontal region with generalization

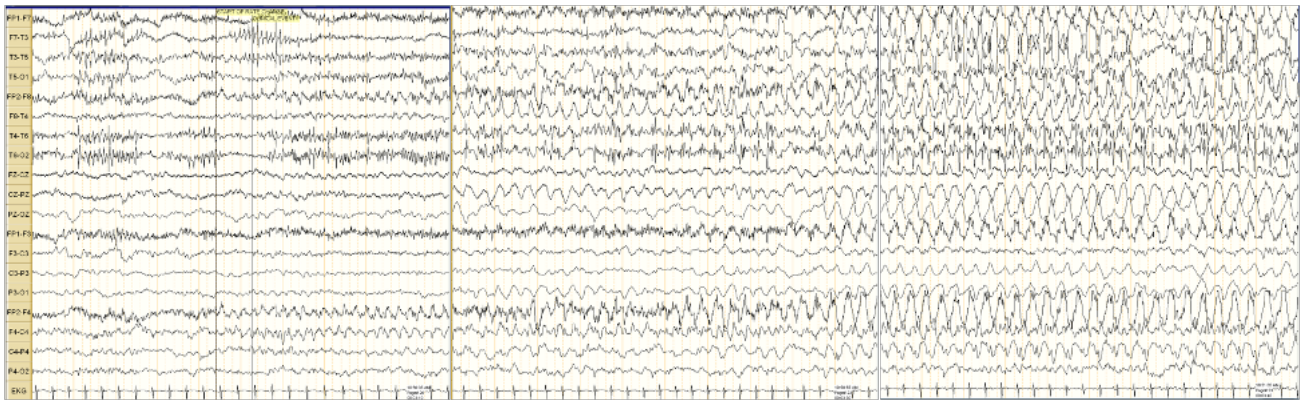
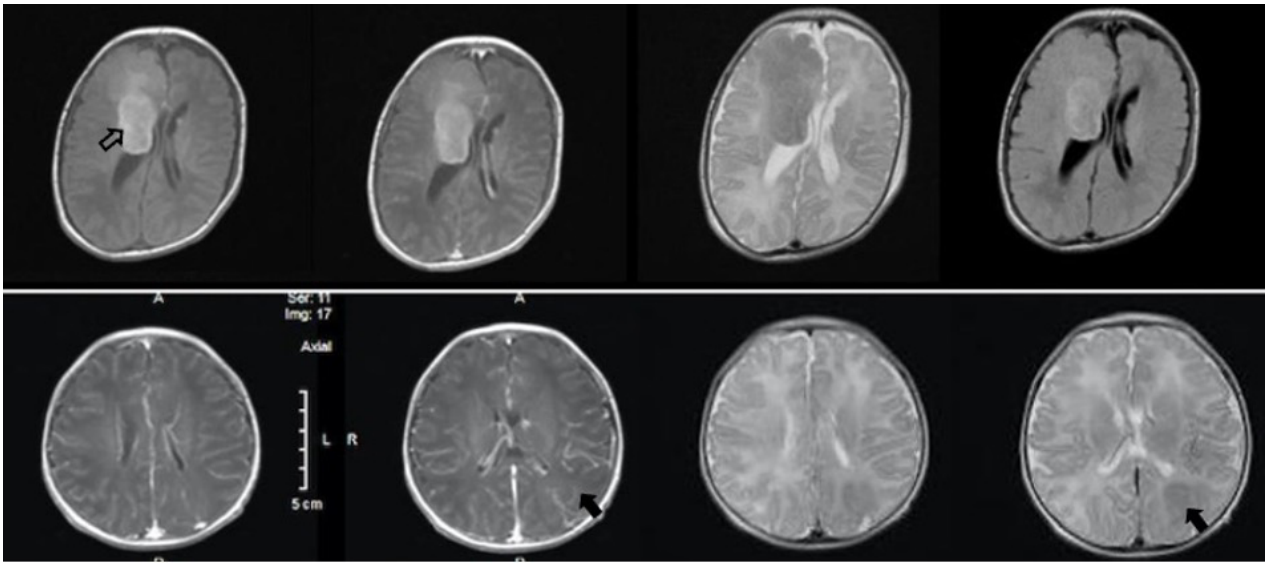


Figure 3A Top: [Left to right: T1-weighted, Contrast Study, T2- Weighted image, Dark fluid] Cranial MRI: Subependymal nodules and Subependymal Giant Cell Astrocytoma **3B** Bottom: [Left to right: Contrast Study, T2- Weighted image] Cortical Dysplasia Left Parietal and superior Temporal region



coexist or evolve into infantile spasms[4] and is usually observed between the 4th and the 6th month of life.[5] Only 5% have epilepsy onset in first 28 days of life.[6] The onset of infantile spasms is highest between 3 months to 9 months, focal seizures at 21 months and other seizure up to 26 months.[3] Both our patients presented with focal motor seizures on the first day of life. Among these seizure types, infantile spasm is a negative prognostic factor for development of refractory epilepsy.[4]

Patients with TSC2 mutations are associated with a more severe neurologic phenotype presenting with early onset and more severe disease including earlier onset and more active epilepsy, lower cognition index and more tubers than those with TSC1 mutation.[5,7,8] The hallmark of CNS involvement in TSC is represented by the cortical tubers, subependymal nodules (SEN),subependymal giant cell astrocytomas (SEGA) and radial glial lines. The genotype/phenotype correlation of individuals diagnosed with TSC showed that patients with TSC2 protein truncation mutation are more likely to have subependymal nodules.[7] Dabora et al. also showed that seizures, average cortical tuber number and SEN are more frequent or severe in patients with de novo TSC2 mutations.[9] However, Alsowat et al. showed on brain MRI that tubers were seen at similar frequencies between TSC1 and TSC2 mutation. Although SEGA were found in 67% of TSC2 mutation and 63% of TSC1 mutation, there was no significant statistical difference in the presence of tubers, SEN and SEGA between the two mutations.[10]

Although many features of TSC do not appear until later in life, most infants with TSC present early with cardiac rhabdomyomas and hypomelanotic macules. We emphasize the importance of careful skin examination in neonates presenting with seizures. A thorough skin examination and echocardiography are important non-invasive methods that can aid in the early identification of TSC patients.[3] As in our first case, the recognition of the hypomelanotic macules heralded the initiation of diagnostic tests leading to the diagnosis of TSC.

The presentation of our patients are not consistent with previous data stated in literature and shows the diversity of phenotypic expression of TSC mutations. The first patient with TSC1 mutation presented with more severe disease including earlier onset of drug resistant seizures, subependymal giant cell tumors and cardiac rhabdomyoma in contrary with the second case with TSC2 mutation who presented with intractable seizures and cardiac rhabdomyoma on subsequent testing. The early recognition and early management of seizures is of utmost importance in the prevention of subsequent epileptic encephalopathy and intractable epilepsy. Early management of epilepsy reduces the cognitive and the neuropsychiatric consequences associated with Tuberous Sclerosis. With the advent of genetic testing, early diagnosis of TSC gives the opportunity to treat even before the onset of clinical seizures or other neurodevelopmental disorders which may greatly impact the neurologic outcome of patients through close surveillance of the sequelae of TSC.[3]

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