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Clinical Observations

The Utility of Surveillance Electroencephalography to Guide Early Antiepileptic Drug Therapy in Infants With Tuberous Sclerosis Complex

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ABSTRACT

BACKGROUND: Seizures are a common early presentation in infants with tuberous sclerosis complex (TSC) and can be preceded by electrographic changes on electroencephalography (EEG) before clinical seizure onset. A limited number of studies have addressed the initial EEG findings in TSC and the outcome of early treatment with antiepileptic medication prior to clinical seizure onset. **METHODS:** We describe two infants with tuberous sclerosis complex whose surveillance EEG showed focal seizures that were not previously recognized by caregivers. We review previously reported patients with TSC with early EEG findings. Our patients were started on vigabatrin after the onset of focal seizures with the aim of preventing seizure recurrence, halting the possible progression to infantile spasms or focal seizures, and preventing neurodevelopmental decline. **RESULTS:** Both patients remain seizure free and have reached appropriate developmental milestones. **CONCLUSIONS:** We recommend early serial EEG monitoring once a diagnosis of TSC is suspected or confirmed in infants. Additional prospective studies are needed to assess the long-term outcome of early antiepileptic drug initiation as soon as electrographic seizure activity is detected.

Keywords: electroencephalography (EEG), tuberous sclerosis complex (TSC), infantile spasms, epilepsy, surveillance, vigabatrin
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Introduction

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome with variable genetic expression and is characterized by the presence of multiple benign hamartomas in several organs including the brain, eyes, lungs, kidneys, heart, liver, and skin.[1,2] TSC is inherited in an autosomal dominant manner, and between 60% and 70% of cases result from sporadic mutations.[2] Mutations in the genes *TSC1* and *TSC2*, which code for hamartin and tuberin, occur in 85% of individuals with TSC and are the only genes known to be responsible for TSC.[2]

Approximately 80% to 90% of patients with TSC develop neurological complications including epilepsy, which is often refractory to therapy.[2] The peak onset of epilepsy is in the first year of life, a critical time in neurodevelopment.[2] Infantile spasms is the most common epilepsy syndrome and occurs in up to 69% of TSC patients.[3] The presence of infantile spasms in children with TSC has been associated with cognitive impairment and the development of refractory epilepsy. The early identification and treatment of epilepsy is therefore crucial.[4]

A limited number of studies have addressed early electroencephalography (EEG) screening in children with TSC.[5-9] It is postulated that early detection of EEG abnormalities and early seizure control may prevent the development of an epileptic encephalopathy and therefore improve cognitive/behavioral outcomes in children with TSC.[5,10] Philippi et al.[11] demonstrated that three to six weeks before the clinical and

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electrographic onset of infantile spasms, the EEG can show predictable findings, which are characterized by abnormal background activity with diffuse sharp waves lasting more than 50% of nonrapid eye movement EEG recording time. In 2012, recognizing the significant impact that early onset epilepsy can have, a European TSC expert committee recommended early EEG monitoring before clinical seizure onset in affected individuals. Early antiepileptic treatment before clinical seizure onset was also recommended in the first 24 months of life in the presence of EEG ictal discharges regardless of clinical seizures.[12]

Given the limited number of reports of early EEG screening in individuals with TSC, we aim to further demonstrate its importance through the description of two infants with TSC who had early EEG monitoring. The initial EEG findings, their progression over time, timing of epilepsy onset in relation to EEG findings, and the outcome after early treatment initiation with antiepileptic drugs are discussed. We reviewed the previously reported examples of TSC with early EEG monitoring (Table) and reference is made to these patients throughout.

Methods

Consent was obtained from both patients' families in accordance with the policy for publication of case reports at the Hospital for Sick Children, Toronto, Ontario, Canada.

Patient One

This one-year-old girl was born at term to nonconsanguineous parents. Her prenatal ultrasound had shown large echogenic areas within the heart. The delivery was uncomplicated. A neonatal echocardiogram completed at ten days of life confirmed the presence of multiple cardiac rhabdomyomas with no cardiac obstruction. Given the presence of rhabdomyoma, TSC was suspected. Subsequent genetic testing for the *TSC1* and *TSC2* gene mutations revealed a heterozygous mutation in the *TSC2* gene (exon 30 c.3593T>C, p.Leu1198Pro) of uncertain significance. The family history was negative for TSC. Magnetic resonance imaging (MRI) of the brain at age six weeks showed multiple tubers in both hemispheres and subependymal nodules within the walls of the lateral ventricles. At age three months, she had a normal eye examination and a renal ultrasound, which showed small cortical cysts in the left kidney. The neurological examination was normal. On dermatological examination, she had two small hypopigmented macules on her back/thigh and confetti macules over the right abdomen.

At age four months, she underwent a routine surveillance EEG during which multiple electroclinical seizures were observed. The family did not report any clinical seizures. The seizures were characterized by left head and eye deviation and jerky movements of the right arm and leg. The child was assessed to be in focal status epilepticus because of the presence of near-continuous electrographic seizures. The seizures were characterized by rhythmic 4 to 5 Hz theta activity over the left posterior temporal head region with spread to the mid-temporal, mid-central, and parietal head regions (Fig 1). The background rhythm consisted of delta and theta frequencies, and sleep features were normal.

Given the presence of new-onset focal seizures and the clinical findings of TSC, the infant was started on vigabatrin (100 mg/kg/day). After commencing vigabatrin, the seizures stopped. Follow-up EEG at age five months showed no epileptiform discharges.

A repeat EEG at age eight months showed normal background activity with no seizures or interictal abnormalities. A repeat EEG at almost 12 months of age showed occasional spike and wave discharges over the right frontal head region. To date, the child has attained appropriate milestones without developmental concerns and remains seizure free on vigabatrin therapy.

TABLE.
Summary of the Included Studies in the Literature Review

Study	Study Type	No. of Included Patients	Age Population	No. of Patients who had Electrographic Seizures or Abnormal EEG Before Clinical Seizures	Average Age at First Abnormal EEG (Range)	Average Age at Clinical Seizure Onset	Time Interval From Abnormal EEG to Clinical Onset of Seizure
Wu et al.[7]	Prospective multicenter observational study	40	Infants	14	4.2 months (1.2-9 months)	6.7 months (2-20 months)	1.9 months (median), 2.8 months (mean)
Ikeno et al.[8]	Case report	1	Neonate	1	13 days of life	1.5 months	1 month
Domanska-Pakiela et al.[6]	Prospective unicentral observational study	5	Neonate and infants	4	2.6 months (17 days of life to 5 months)	2.6 months (17 days of life to 5 months)	1-8 days
Kotulska et al.[9]	Retrospective chart review	21	Neonates	21	Not reported	12.6 days (1-28 days)	Not reported
Jozwiak et al.[5]	Prospective open label trial	45	Infants	10	4 months (median)	5-5.5 months (median) (2-17 months)	Not reported

Abbreviation:
EEG = Electroencephalograph