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Original Article

Early Neurodevelopmental Screening in Tuberous Sclerosis Complex: A Potential Window of Opportunity

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ABSTRACT

BACKGROUND: Infants born with tuberous sclerosis complex, a genetic condition resulting from a mutation in *TSC1* or *TSC2*, are at increased risk for intellectual disability and/or autism. Features of epilepsy, neuropathology, genetics, as well as timing and type of mechanism-based medications have been proposed as risk factors. Neurodevelopmental outcomes have been reported among these studies; however, few include data about the individuals' early neurodevelopmental profile, a factor that may contribute significantly to these outcomes. Further, there is no clinical standard for the neurodevelopmental assessment of these infants. The paucity of data regarding the natural history of neurodevelopment in infants with tuberous sclerosis complex and the lack of a gold standard for neurodevelopmental evaluation present a significant challenge for clinicians and researchers. **METHOD:** During the first year of life, we tracked the onset of infantile spasms, the type and timing of antiepileptic treatments, and the associated response of two age-matched infants with tuberous sclerosis complex. We also employed *Capute Scales* as a part of a structured neurodevelopmental evaluation to characterize and compare their neurodevelopmental profiles. **RESULTS:** Infant 1 developed infantile spasms with confirmed hypsarrhythmia at 4 months of age. Treatment with vigabatrin was initiated within 24 hours with near immediate cessation of seizures and no further seizures to date. Expressive language delay was detected at 12 months and treated with speech and/or language therapy. Infant 2 developed complex partial seizures at 1 month. Treatment included levetiracetam, oxcarbazepine, and the ketogenic diet. Vigabatrin was initiated on detection of hypsarrhythmia after 4 months. Intractable epilepsy persists to date. Global developmental delay was evident by 8 months and treated with physical, occupational, and speech and/or language therapy. **CONCLUSION:** Many risk factors have been associated with intellectual disability and/or autism in individuals with tuberous sclerosis complex; however, few data are available regarding practical clinical tools for early identification. In our case series, inclusion of the *Capute Scales* as a part of routine medical care led to the identification of developmental delays in the first 12 months of life and selection of targeted neurodevelopmental interventions. Development of a risk-based assessment using this approach will be the focus of future studies as it may provide a potential window of opportunity for both

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research and clinical purposes. In research, it may serve as an objective outcome measure. Clinically, this type of assessment has potential for informing clinical treatment decisions and serving as a prognostic indicator of long-term cognitive and psychiatric outcomes.

Keywords: development, tuberous sclerosis, vigabatrin, everolimus, sirolimus, cognition, Capute Scales, mTOR inhibitors
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Introduction

Tuberous sclerosis complex (TSC) is a genetic condition resulting from either a familial or de novo mutation in *TSC1* or *TSC2*. Although it is classically considered a neurocutaneous syndrome, it may be better described as a lifelong disease with multisystem manifestations. Clinical diagnosis of this condition is based on the presence of specific numbers and types of these manifestations.[1] TSC is one of the leading causes of syndromic autism,[2,3] and nearly half of the population is affected by intellectual disability[4]; however, the predictors and causation are unknown. Features of epilepsy,[5-8] neuropathology,[9-12] genetics,[13,14] as well as timing and type of mechanism-based medications[15-18] have been linked to developmental outcomes. However, none of these studies have reported details about the individuals' infant presentation making it difficult to fully interpret the results. Further, there is no clinical standard for developmental

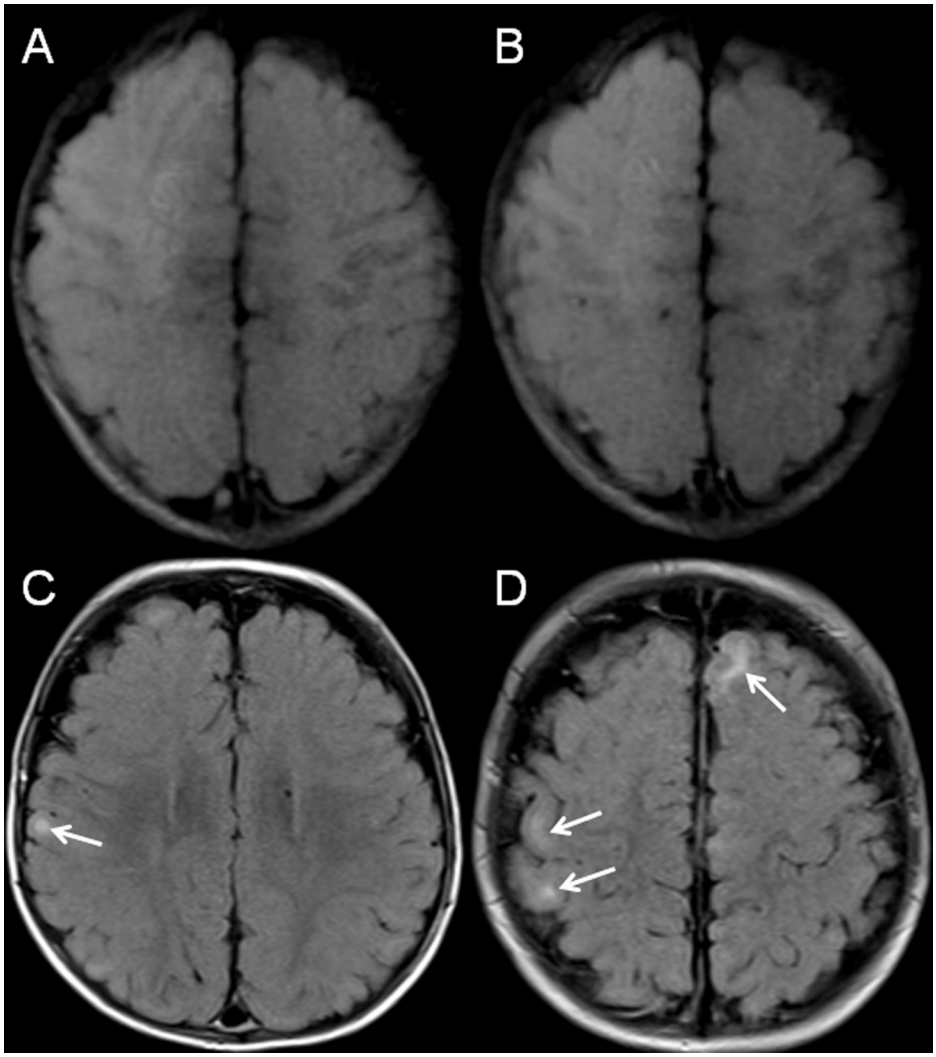

FIGURE 1.
(A and B) Axial FLAIR (Fluid attenuated inversion recovery) images of a 3-day-old neonate with tuberous sclerosis complex reveal a normal signal intensity of the depicted supratentorial gray and white matter structures. Magnetic resonance images revealed multiple calcified subependymal nodules lining the lateral ventricles and T_1-hyperintense and T_2-hypointense radial migration lines (not revealed). (C and D) Matching, axial FLAIR images of the same child at 12 months of age demonstrate new FLAIR-hyperintense lesions representing tubers and involving the cortical subcortical white matter of the right frontal and parietal lobe (white arrows in C and D) and right parasagittal frontal lobe (white arrow in D).