Published in final edited form as:

Pediatr Neurol. 2014 September ; 51(3): 398–402. doi:10.1016/j.pediatrneurol.2014.04.028.

Early Neurodevelopmental Screening in TSC: A Potential Window of Opportunity

Tanjala T. Gipson, MD^{1,2,3,4}, Gwendolyn Gerner, PsyD^{1,2,3}, Siddharth Srivastava, MD², Andrea Poretti, MD⁷, Rebecca Vaurio, PhD^{8,9}, Adam Hartman, MD¹⁰, and Michael V. Johnston, MD^{1,2,3,4,5,6}

¹Tuberous Sclerosis Clinic, Kennedy Krieger Institute, Baltimore, MD

²Department of Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, MD

³Clinical Trials Unit, Hugo W. Moser Research Institute, Inc., Kennedy Krieger Institute, Baltimore, MD

⁴Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

⁵Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD

⁶Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD

⁷Section of Pediatric Neuroradiology, Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD

⁸Department of Neuropsychology, Kennedy Krieger Institute, Baltimore, MD

© 2014 Elsevier Inc. All rights reserved.

Address correspondence to: Tanjala T. Gipson, M.D, Neurology and Developmental Medicine, Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, tsclinic@kennedykrieger.org, 443-923-2746.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Contributors' Statements:

Tanjala T. Gipson: Dr. Gipson evaluated the patients, drafted the initial manuscript, edited the manuscript to reflect co-authors' input and approved the final manuscript as submitted.

Gwendolyn Gerner: Dr. Gerner assisted with the patient evaluations, created the developmental trajectories' figure, reviewed the manuscript and provided critical feedback and approved the final manuscript as submitted.

Siddharth Srivastava: Dr. Srivastava reviewed the manuscript, made substantial contributions to the discussion, provided critical feedback and approved the final manuscript as submitted.

Andrea Poretti: Dr. Poretti analyzed the brain MRIs for both patients, selected brain MRI images for publication, reviewed the manuscript, provided critical feedback and approved the final manuscript as submitted.

Rebecca Vaurio: Dr. Vaurio assisted with the interpretation of the patient evaluations, reviewed the manuscript, provided critical feedback and approved the final manuscript as submitted.

Adam Hartman: Dr. Hartman reviewed the manuscript, provided critical feedback and approved the final manuscript as submitted.

Michael V. Johnston: Dr. Johnston reviewed the manuscript, provided critical feedback and approved the final manuscript as submitted.

⁹Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

¹⁰The John M. Freeman Pediatric Epilepsy Center, Department of Neurology, Johns Hopkins University School of Medicine

Abstract

BACKGROUND—Infants born with tuberous sclerosis complex (TSC), 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 TSC and the lack of a gold standard for neurodevelopmental evaluation presents 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 2 age-matched infants with TSC. 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 as confirmed by hypsarrhythmia at 4 months. 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/language therapy. Infant 2 developed complex partial seizures at 1 month. Treatment included levetiracetam, oxcarbazepine and the ketogenic diet. Vigabatrin was initiated upon 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/language therapy.

CONCLUSION—Many risk factors have been associated with intellectual disability and/or autism in individuals with TSC; 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 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

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 manifestations¹. Tuberous Sclerosis Complex (TSC) is one of the leading causes of syndromic autism^{2,3}, and nearly half of the population is affected by intellectual disability⁴; 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 evaluations of infants with TSC as a part of their routine medical care. Here, we highlight the neurodevelopmental profiles as characterized using *Capute Scales*, timing of intervention with vigabatrin for infantile spasms and the early developmental outcomes of 2-age matched infants with TSC during the first year of life.

Case Reports

Infant 1 was the product of a full term uncomplicated pregnancy. Tuberous Sclerosis Complex (TSC) was initially suspected when a cardiac echocardiogram revealed the presence of cardiac rhabdomyomas after a murmur was noticed in the newborn nursery. A brain MRI revealed subependymal nodules (Fig 1). These findings resulted in a clinical diagnosis of definite TSC and were confirmed to be due to a spontaneous, nonsense mutation in *TSC1* (c.2074C>T substitution (p.R692X) in exon 17. A structured neurodevelopmental examination was initiated at 1 month and continued as part of routine care during the first year of life (6, 8 and 12 months). This examination included a structured motor exam to assess primitive reflexes and postural responses and the *Capute Scales: Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS)* to screen for cognitive/visual-motor and language delays^{19,20}. Motor examination did not reveal any areas of concern, and age-expected visual-motor development based on the *CAT* was observed. Language development based on the *CLAMS*, revealed age appropriate gains in language development up to 8 months, with slowed language development between 8 and 12 months, resulting in language delay by 12 months (Fig. 2 and 3). Early intervention to target expressive language development was recommended at 12 months. Infantile spasms developed at 4 months, and treatment with vigabatrin was initiated within 24 hours of witnessed seizure onset. Freedom from seizures was achieved in 41 days without further seizures to date. (Table 1)

Infant 2 was the product of a full term uncomplicated of pregnancy. At 1 month, multiple seizures described as 2 episodes of staring, followed by a repetitive “swallowing” noise lasting 30–60 seconds prompted an inpatient evaluation. During medical transport, a third event occurred and was described as gaze deviation and stiffening with transient desaturation. These seizures and hypopigmented macules led to clinical suspicion of TSC. Brain MRI revealed subependymal nodules and innumerable cortical tubers. (Fig. 4) Cardiac

rhabdomyomas were also detected. These findings resulted in a clinical diagnosis of TSC and were accompanied by a spontaneous frameshift mutation in *TSC2* (2 base pair duplication at 2185_2186). An EEG at diagnosis did not reveal hypsarrhythmia; therefore, these seizures were not classified as infantile spasms. Levetiracetam was initiated within 24 hours of seizure onset. Oxcarbazepine was added at age 2 ½ months due to intractability. At 3 ½ months, an EEG was obtained after the parents witnessed a new seizure type – recurrent arm extension with leg flexion. Infantile spasms were diagnosed after an EEG revealed hypsarrhythmia, and the ketogenic diet was added. Vigabatrin was added three weeks later and continued for 4 months prior to initiation of a gradual wean. Although there have been seizure-free intervals, freedom from seizures has not been achieved to date (Table 1). A structured neurodevelopmental exam was completed at 1, 6, 8 and 12 months. Motor examination revealed abnormalities at 8 and 12 months, including persistence of primitive reflexes, lack of postural responses, early right hand preference and delayed attainment of motor milestones. Developmental delays in receptive, expressive and visual motor development were detected at all visits after the initial evaluation. Developmental regression in language was observed from age 8 to 12 months. Early intervention to target global developmental delay was recommended at age 6 months (Fig. 2 and 3).

Discussion

Features of epilepsy^{5–8}, neuropathology^{9–12}, genetics^{13,14} as well as the timing and type of mechanism-based medications^{15–18} have been reported as risk factors for intellectual disability and/or autism in individuals with TSC. Many of these proposed risk factors are illustrated in these case reports. Both infants presented with early onset infantile spasms which have been associated with intellectual impairment and were treated with vigabatrin at varying times. Infant 1 received vigabatrin as a first line treatment; whereas, infant 2 received treatment once his EEG revealed hypsarrhythmia. Vigabatrin, an irreversible inhibitor of GABA (γ – aminobutyric acid) transaminase, is considered a mechanism-based treatment in TSC as it targets GABA deficits reported in this population^{21–23}. In the U.S., vigabatrin is FDA approved as first line for infantile spasms; however, European guidelines recommend it as first line for all seizure types in infants with TSC²⁴. Early intervention with vigabatrin has been associated with positive epilepsy and neurodevelopmental outcomes in individuals with TSC^{15,17} suggesting that a delay in vigabatrin treatment in infant 2 may have contributed to the poor neurodevelopmental outcome. Cortical tuber burden, greater in infant 2, has also been associated with poor neurodevelopmental outcome and infantile spasms¹⁸. However, other studies suggest that cortical tuber burden alone is not enough to influence the developmental prognosis¹⁹. The lack of complete myelination until age 2 years is another factor to consider when^{8,12}. Mutation type and location are yet another factor that has been linked to poor cognitive and behavioral outcomes.^{13,14} In these studies, infant 1's mutation type was associated with an increased risk of behavioral difficulties and intellectual disability; whereas, infant 2's mutation type was associated with an increased risk of intellectual disability, learning disability and seizures^{13,14}.

Despite the myriad of risks for poor developmental outcome, few data exist regarding practical clinical tools for early identification of developmental delays in infants with TSC. Here, we present the first reports for use of the *Capute Scales* in infants with TSC as a

component of a structured developmental evaluation. This evaluation was incorporated into our routine clinical care and guided the timing and type of early intervention recommended for these infants. Neurodevelopmental intervention was recommended at 6 months for infant 2 to target delays in multiple streams of development and 12 months for infant 1 to target development of expressive language.

The increased risk of autism and/or intellectual disability is well-known; however, there are currently no predictors or cures. Further, a structured approach to the developmental evaluation and treatment of this at-risk population does not exist. Perhaps pairing early mechanism-based treatment for epilepsy with targeted neurodevelopmental interventions could lead to improved outcomes despite the severity of the TSC phenotype. The Capute scales as a part of a structured neurodevelopmental evaluation may have utility as a screening/monitoring tool in this regard. Evaluation of the utility and generalizability of this approach in a larger population of infants with TSC will be the focus of future research efforts.

Acknowledgments

The authors gratefully acknowledge Rebecca Hinton for assistance with editing the manuscript, Raechel Mattison for assistance with administrative organization as well as Victoria Goode and Ivy Garner for assistance with literature searches and reference formatting.

Funding Sources: Grant 2K12NS001696-11A1 (to Gipson TT) from the National Institute of Neurological Disorders and Stroke; Grant 5T32HD007414-18 (to Gerner G) from the National Institute of Child Health and Human Development.

Financial Disclosure: Tanjala T. Gipson and Michael V. Johnston are participating as investigators in a clinical trial of everolimus developed and sponsored by Novartis Pharmaceuticals. Funds are provided to Kennedy Krieger Institute by Novartis for research costs associated with this trial.

Abbreviations

CAT	clinical adaptive test
CLAMS	clinical linguistic and auditory milestone scale
EEG	electroencephalogram
MRI	magnetic resonance imaging
TSC	tuberous sclerosis complex

References

1. Northrup H, Krueger DA. International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol.* 2013 Oct; 49(4):243–254. [PubMed: 24053982]
2. Gillberg IC, Gillberg C, Ahlsen G. Autistic behaviour and attention deficits in tuberous sclerosis: A population-based study; COMPORTEMENT AUTISTIQUE DE DEFICIT D'ATTENTION DANS LA SCLEROSE TUBEREUSE. UNE ETUDE DE POPULATION. *Dev Med Child Neurol.* 1994; 36(1):50–56. [PubMed: 8132114]
3. Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: A population study. *Dev Med Child Neurol.* 1996; 38(2):146–155. [PubMed: 8603782]

4. Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. *Psychol Med*. 2003; 33(2):335–344. [PubMed: 12622312]
5. Humphrey A, MacLean C, Ploubidis GB, Granader Y, Clifford M, Haslop M, et al. Intellectual development before and after the onset of infantile spasms: A controlled prospective longitudinal study in tuberous sclerosis. *Epilepsia*. 2014 Jan; 55(1):108–116. [PubMed: 24417555]
6. Humphrey A, Williams J, Pinto E, Bolton PF. A prospective longitudinal study of early cognitive development in tuberous sclerosis: A clinic based study. *European Child and Adolescent Psychiatry*. 2004; 13(3):159–165. [PubMed: 15254843]
7. Muzykewicz DA, Costello DJ, Halpern EF, Thiele EA. Infantile spasms in tuberous sclerosis complex: Prognostic utility of EEG. *Epilepsia*. 2009; 50(2):290–296. [PubMed: 18801034]
8. O'Callaghan FJK, Harris T, Joinson C, et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. *Arch Dis Child*. 2004; 89(6):530–533. [PubMed: 15155396]
9. Kaczorowska M, Jurkiewicz E, Domanska-Paketa D, et al. Cerebral tuber count and its impact on mental outcome of patients with tuberous sclerosis complex. *Epilepsia*. 2011; 52(1):22–27. [PubMed: 21204819]
10. Doherty C, Goh S, Poussaint TY, Erdag N, Thiele EA. Prognostic significance of tuber count and location in tuberous sclerosis complex. *J Child Neurol*. 2005; 20(10):837–841. [PubMed: 16417883]
11. Wong V, Khong PL. Tuberous sclerosis complex: Correlation of magnetic resonance imaging (MRI) findings with comorbidities. *J Child Neurol*. 2006; 21(2):99–105. [PubMed: 16566871]
12. Goodman M, Lamm SH, Engel A, Shepherd CW, Houser OW, Gomez MR. Cortical tuber count: A biomarker indicating neurologic severity of tuberous sclerosis complex. *J Child Neurol*. 1997; 12(2):85–90. [PubMed: 9075016]
13. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the united states. *Genet Med*. 2007; 9(2):88–100. [PubMed: 17304050]
14. van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Genotype and cognitive phenotype of patients with tuberous sclerosis complex. *Eur J Hum Genet*. 2012; 20(5):510–515. [PubMed: 22189265]
15. Jozwiak S, Kotulska K, Domanska-Pakiela D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2011; 15(5):424–431. [PubMed: 21507691]
16. Kotulska K, Borkowska J, Jozwiak S. Possible prevention of tuberous sclerosis complex lesions. *Pediatrics*. 2013; 132(1):e239–e242. [PubMed: 23733802]
17. Bombardieri R, Pinci M, Moavero R, et al. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2010; 14(2):146–149. [PubMed: 19369101]
18. O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: Evidence from the united kingdom infantile spasms study. *Epilepsia*. 2011; 52(7):1359–1364. [PubMed: 21668442]
19. Capute AJ, Accardo PJ. The infant neurodevelopmental assessment: A clinical interpretive manual for CAT-CLAMS in the first two years of life, part 1. *Curr Probl Pediatr*. 1996; 26(7):238–257. [PubMed: 8889388]
20. Capute AJ, Palmer FB, Shapiro BK, Wachtel RC, Schmidt S, Ross A. Clinical linguistic and auditory milestone scale: Prediction of cognition in infancy. *Dev Med Child Neurol*. 1986; 28(6):762–771. [PubMed: 3817315]
21. Zhang B, McDaniel SS, Rensing NR, Wong M. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis complex. *PLoS One*. 2013; 8(2):e57445. [PubMed: 23437388]
22. Fu C, Cawthon B, Clinkscales W, Bruce A, Winzenburger P, Ess KC. GABAergic interneuron development and function is modulated by the Tsc1 gene. *Cereb Cortex*. 2012; 22(9):2111–2119. [PubMed: 22021912]

23. Mori K, Mori T, Toda Y, et al. Decreased benzodiazepine receptor and increased GABA level in cortical tubers in tuberous sclerosis complex. *Brain Dev.* 2012; 34(6):478–486. [PubMed: 21959128]
24. Curatolo P, Jozwiak S, Nabbout R. TSC Consensus Meeting for SEGA and Epilepsy Management. Management of epilepsy associated with tuberous sclerosis complex (TSC): Clinical recommendations. *Eur J Paediatr Neurol.* 2012; 16(6):582–586. [PubMed: 22695035]

Figure 1.

(**A, B**) Axial FLAIR images of a 3-day-old neonate with TSC show a normal signal intensity of the depicted supratentorial gray and white matter structures. MR images revealed multiple calcified subependymal nodules lining the lateral ventricles and T1-hyperintense and T2-hypointense radial migration lines (not shown). (**C, 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, D**) and right parasagittal frontal lobe (white arrow in **D**).

Figure 2.

Line graph of the visual motor developmental age equivalent obtained using raw scores of the Cognitive Adaptive Test from *The Capute Scales*.

Figure 3.

Line graph of the language development age equivalent obtained using raw scores of the Clinical Linguistic and Auditory Milestone Scale from *The Capute Scales*.

Figure 4.

(A, B) Axial FLAIR images of a 1-month-old infant with TSC reveals multiple FLAIR-hyperintense lesions representing tubers and involving the cortical and subcortical white matter of the bilateral frontal and parietal lobes. Additionally, multiple subependymal nodules were seen in the body of the lateral ventricles as well as the left foramen of Monro (not shown). (C, D) Matching, axial FLAIR images of the same child at 14 months of age

show again multiple cortical and subcortical FLAIR-hyperintense tubers within the bilateral frontal and parietal lobes (white arrows in **C**, **D**).

Table 1

Epilepsy characteristics and treatment

	Age at TSC Diagnosis (days)	Seizure Onset (months)	EEG results	Vigabatrin (interval from seizure onset to initiation in days)	Interval to 150 mg/kg/day VGB (days)	Seizure type	Other Antiepileptic Treatments (interval from seizure onset to initiation in days)	Seizure Outcome
Infant 1	2	4	Hypsarhythmia	1	48	Infantile spasms	None	Resolved 41 days Hospital: ED - 2 Admit -1 ICU - 0
Infant 2	33	1	Multiple: Sharp waves; hypsarrhythmia; spikes	88	90	Multiple: Complex partial; Infantile spasms	LEV - 1 OXC - 79 KD -100 VGB - 121	Intractable Hospital: ED - 6 Admit - 5 ICU - 1

Abbreviations: KD - ketogenic diet; LEV - levetiracetam; OXC - oxcarbazepine; VGB - vigabatrin