Characterizing Cognitive, Treatment, and Epilepsy Outcomes in a Sub-Population of Patients With Tuberous Sclerosis Complex and Spasms: Patients With Focal Seizures Preceding Spasms

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th>Citation</th>
<th>MacRae, Rebecca. 2018. Characterizing Cognitive, Treatment, and Epilepsy Outcomes in a Sub-Population of Patients With Tuberous Sclerosis Complex and Spasms: Patients With Focal Seizures Preceding Spasms. Doctoral dissertation, Harvard Medical School.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:41973534">http://nrs.harvard.edu/urn-3:HUL.InstRepos:41973534</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Characterizing cognitive, treatment, and epilepsy outcomes in a sub-population of patients with tuberous sclerosis complex and spasms: patients with focal seizures preceding spasms

Rebecca A. MacRae*, Elizabeth A. Thiele**

* Harvard Medical School
** Pediatric Epilepsy Program, Department of Neurology, Massachusetts General Hospital, 175 Cambridge Street, Suite 340, Boston, MA 02114-2796, USA
Abstract

Purpose: To characterize the cognitive outcomes, epilepsy, and treatment response, specifically to vigabatrin, of tuberous sclerosis complex (TSC) patients with focal seizures prior to the onset of infantile spasms (IS) or epileptic spasms (ES) compared with patients with spasm onset prior to other seizure types.

Methods: The authors retrospectively reviewed the charts of 185 TSC patients with a history of IS or ES and epilepsy. Medical records were assessed for clinical information about gender, age of spasm onset, clinical descriptions, concomitant seizure type, age of concomitant seizure onset, treatment, treatment response, and genetic analyses.

Results: Of the 541 patients with TSC, 185 were diagnosed with IS or ES. A subset of 14 patients received a diagnosis of focal seizure onset prior to spasms onset. A subset of 36 patients received a diagnosis of spasms onset prior to focal seizure onset. The records for 135 patients did not contain detailed documentation regarding the specific onset of spasms and/or focal seizures. Patients with focal seizure preceding spasm onset tend to have lower rates of normal IQ/cognition (7 vs 28%) and higher rates of intellectual disability (93 vs 72%) with a trend of more severe level of intellectual disability (moderate > mild/borderline/normal). They tend to have a less effective response to vigabatrin treatment of spasms (58 vs 82%). These patients also develop significantly higher rates of refractory epilepsy (77% vs 32%).

Conclusions: Compared with TSC patients who present with spasm preceding focal seizure onset, patients with TSC who present with focal seizure preceding spasm onset tend to have more a more severe clinical profile with respect to neurocognitive outcome, response to vigabatrin, and development of refractory epilepsy.
Introduction

Tuberous Sclerosis Complex (TSC) is a genetic multisystem disorder affecting an estimated 1 in 6000 individuals (Osborne et al., 1991). Mutations in the genes TSC1 and TSC2 have been implicated in about 85% of TSC cases (Dabora et al., 2001; Sancak et al., 2005). TSC1 encodes the protein hamartin and TSC2 encodes the protein tuberin. Together these proteins form a dimer involved in the inhibition of the mechanistic target of rapamycin (mTOR) pathway (Astrinidis et al., 2005; Kwiatkowski et al., 2005). Inadequate inhibition of the mTOR signaling cascade results in the formation of benign hamartomas in the brain, skin, kidney, heart, eye, liver, and lung (Crino et al., 2006). With respect to the brain specifically, patients can develop a range of lesions including glioneuronal hamartomas (cortical tubers), subependymal nodules, subependymal giant cell astrocytomas, and white matter heterotopias (Crino et al., 2006; Sabatini, 2006; Goodman et al., 1997). Although the expression of this disease is variable, neurologic manifestations are common and have impactful morbidity and mortality consequences. Natural history studies have shown that about 85% of TSC patients have epilepsy and nearly all TSC patients with a history of seizure will develop epilepsy (Chu-Shore et al., 2010). Seizure frequency, history of infantile spasms (IS), and age of seizure onset has been shown to be correlated with more severe developmental delay (Capal et al., 2017).

IS are a well-recognized, common symptom of TSC affecting about one third of children with TSC (Fukushima et al, 1998; Curatolo et al., 2002). IS were originally described by Dr. West in 1841 in his own son as “slight bobbings of the head forward” increasing in frequency (West, 1841). Classically, spasms manifest as clusters of abrupt flexion jerks of the neck, trunk, and extremities. Extension of the extremities can also be seen. These jerks typically last for about 1 -2 seconds and can occur at any time during the awake period, but most often occur during the sleep-wake period (Hrachovy, 2002). Spasms most commonly have onset between the ages of 4 – 8 months (Hrachovy, 2002). When spasms occur after the first year of life or later, beyond the infantile period, they are often described as epileptic spasms (ES). Although the diagnosis of spasms can be made clinically, EEG findings of hypsarrhythmia, a chaotic, high-voltage interictal abnormal pattern, are pathognomonic for spasms (Gibbs, 1954). In addition to TSC, there
are a number of other etiologies that are associated with spasms, including cortical
dysplasia, genetic anomalies, and hypoxic ischemic injury (Paciorkowski et al., 2011).
However, studies have shown that specifically within the population of patients with TSC who develop IS, vigabatrin (VGB) is more efficacious (95% vs 54% patients had
cessation of spasms) than in infants with spasms, but without TSC (Hancock and
Osborne, 1999). Thus, VGB should be used as first-line treatment for patients with
spasms and TSC (Hancock and Osborne, 1999). This finding highlights the importance of
characterizing the differences among patients with spasms of different etiologies in order
to optimize treatment and long-term outcomes.

The association between IS in TSC and high risk for poor developmental outcome
is well supported in the literature. In 2010, Chu-Shore et al. published a retrospective
chart review of patients with TSC to characterize the natural history of epilepsy in TSC
(Chu-Shore et al., 2010). They found that 37.8% of TSC patients had a history of
infantile spasms (Chu-Shore et al., 2010). In TSC patients with infantile spasms, 74.4%
were cognitively impaired compared with 39.2% without a history of infantile spasm
(Chu-Shore et al., 2010). They also characterized the relationship between genotype and
infantile spasm, reporting that patients with a TSC2 mutation were more likely to have a
history of infantile spasms compared with patients with a TSCI mutation (56.1% vs.
10%) (Chu-Shore et al., 2010). Additionally, they found that patients with TSCI were
more likely to have a history of infantile spasms compared with no mutation identified
(NMI) (Chu-Shore et al., 2010).

In 2013, Vignoli et al. looked at epilepsy variability and severity in an Italian
cohort of TSC patients (Vignoli, 2013). They used intelligence quotient (IQ) to stratify
the cognitive profile and intellectual disability of patients in different epilepsy severity
groups (Vignoli, 2013). They looked within the infantile spasms group to stratify
intellectual disability and similarly found that there was a significant correlation between
infantile spasms and intellectual disability (Vignoli, 2013). In 2013, van Eeghen et al.
calculated the absolute and relative risks for infantile spasms for various mutation classes
(van Eeghen et al., 2013). Looking within the TSC2 population, they found that missense
mutations located in the central region of TSC2 were associated with a significantly
reduced incidence of IS and with a less severe cognitive profile (van Eeghen et al., 2013).
This finding provides evidence for variant phenotypes of sub-populations of patients with TSC.

Sub-populations of patients with TSC and IS have rarely been studied. In 2013, Hsieh et al. published a retrospective chart review of one sub-population characterizing epileptic spasms occurring in TSC patients after the age of two years (Hsieh et al., 2013). They found that epileptic spasms occur concurrently with refractory epilepsy with other seizure types (Hsieh et al., 2013). Genetic analyses resulted that 93% of TSC patients with epileptic spasms had a pathological TSC2 mutation (Hsieh et al., 2013). Importantly, they found that VGB was not as efficacious a treatment for spasms in this subset of patients as for the general TSC population (Hsieh et al., 2013). Hsieh et al. provide evidence for variant cognitive outcomes, treatment response, and epilepsy prognoses for sub-populations of patients with TSC and IS.

Focal seizure onset precedes spasm onset in about one third of children with TSC who develop spasms (Curatolo et al., 2001; Curatolo et al., 2002). This study aims to characterize the cognitive outcomes and treatment responsiveness of this sub-population of patients with TSC and spasms: patients with focal seizure onset preceding spasm onset.

**Student Role**

The student queried the MGH TSC database (n=520), a database with all clinical data of TSC patients evaluated at the Herscot Center for TSC, to gather phenotypic data (age of spasm and focal seizure onset, spasm description, seizure semiology, cognitive profile information, autism diagnosis, epilepsy outcome), treatment data (spasm treatments, AED treatments, other seizure control treatments), and genetic data (TSC1, TSC2, NMI mutation type). Cases were stratified based on age of onset for spasm and focal seizure, cognitive disability severity, spasm response to VGB, and epilepsy outcome. The student performed statistical analysis with R statistical software.
Materials and Methods

Patients: We retrospectively reviewed the medical records of 541 patients seen in the Herscot Center for Tuberous Sclerosis Complex at the Massachusetts General Hospital between January 2002 and January 2018. All patients had a clinical diagnosis of TSC (Roach and Sparagana, 2004). Spasms were defined by the semiology of a sudden flexion or extension or both of the trunk or upper limbs, lasting less than three seconds, and most often occurring in clusters. A record of EEG with hypsarrhythmia was not required for the diagnosis of spasms. Epilepsy was defined as at least 2 clinical seizures, not including spasms. Refractory epilepsy was defined continued seizures uncontrolled by two or more antiepileptic drugs (AED). Patients were considered seizure free if they had no clinical seizures within at least 1 year using the last clinic seizure status documentation as the end-point of follow-up. Patients were considered lost to follow-up if there was no clinic documentation within 5 years.

Data Collection: Medical records were reviewed to collect clinical information about gender, age of onset of IS, clinical descriptions, concomitant seizure type, age of onset of concomitant seizure, treatment, treatment response, and genetic analyses. Genetic mutation was assessed when information was available and designated as either mutation in TSC1, TSC2, or no mutation identified. Treatment data was reviewed for concurrent AEDs at the onset of spasms, in addition to spasm treatment and response. Treatment response was based on the medical records and parent report. An effective response was defined as near complete or complete cessation of spasms. A partially effective response was defined as greater than 50% reduction in spasms.

Psychomotor development was assessed with formal neurocognitive testing when available. Patients had one of four types of formal neurocognitive testing: Wechsler Intelligence Scale for Children (WISC), Stanford-Binet, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Bayley Mental Scales (BMS). Cognitive impairment or global developmental delay was defined by a developmental quotient or intelligence quotient (IQ). Per DSM-V classifications of intellectual disability, score classifications were defined as: borderline for IQ 70 – 79, mild for IQ 55 – 70, and moderate for IQ 40 –
54, severe for IQ 25 – 39, and profound for IQ less than 25 (American Psychiatric Association, 2013). Formal neurocognitive testing used was dependent on the examiner and the individual patient. For patients who did not have formal neurocognitive testing, patient charts were reviewed for clinical assessment and description of standard age milestones.

Statistical analyses were performed using Fisher’s exact test due to sample size and Mann-Whitney U test. All reported p-values used two-tailed tests of significance with α set at 0.05.

The investigational review board of the Massachusetts General Hospital approved this protocol.

Results

Patient Characteristics (Figures 1 – 4)

Group 1: Of the 14 patients who were diagnosed with focal seizure prior to spasm onset, 6 were female and 8 were male with a median age of 10 years (range 1 - 21 years) at the time of the study. Clinical spasms were described as flexor spasms for 7 patients, extensor for 0 patients, mixed for 4 patients, and not specifically described for 3 patients. Spasm onset in these patients ranged from 3 to 36 months of age with a median of 11 months and standard deviation of 11.3 months (Figure 1). Spasms occurred in the setting of concurrent seizure types in all patients. Seizure types were typically mixed. Descriptions of seizure type included: focal with impaired awareness, focal with preserved awareness, focal clonic, focal tonic, focal hyperkinetic, GTC, generalized atonic, generalized myoclonic, behavior arrest, automatisms. Focal seizure onset in these patients ranged from 0.5 to 24 months old with a median of 3.5 months and a standard deviation of 6.0 months (Figure 2). The average time between seizure onset and spasm onset was 7.5 months. None of the patients had had epilepsy surgery/tuberectomy prior to the onset of spasms or seizures.

Group 2: Of the 36 patients who were diagnosed with spasms prior to focal seizure onset, 22 were female and 14 were male with a median age of 14 years (range 2 -
50 years) at the time of the study. Clinical spasms were described as flexor spasms for 6 patients, extensor for 6 patients, mixed for 4 patients, and not specifically described for 20 patients. Spasm onset in these patients ranged from 1 to 15 months of age with a median of 5 months and a standard deviation of 3.4 months (Figure 3). Descriptions of seizure type included: focal with impaired awareness, focal with preserved awareness, focal clonic, focal tonic, GTC, generalized atonic, generalized myoclonic, behavior arrest, automatisms. Focal seizure onset in these patients ranged from 2 to 156 months old with a median of 11.5 months and a standard deviation of 45.7 months (Figure 4). The average time between spasm and seizure development was 5.5 months. None of the patients had epilepsy surgery/tuberectomy prior to the onset of spasms or seizures.

Relationship of Group to Age of Seizure and Spasm Onset: Histograms of spasm and seizure onset results are shown in Figures 1 through 4. Mann-Whitney U test found significant difference in spasm onset between Group 1 and Group 2 (p = 0.014). Figure 5 shows the box and whisker plot for spasm onset in Group 2 and Group 1.

Genetic Analyses (Table 1)

Group 1: Of the 14 patients who were diagnosed with focal seizure prior to spasm onset, 8 patients had genetic mutation analyses. Of the patients with available genetic results, 6 patients had a pathological mutation in TSC2 (75%) and 2 patients had a pathological mutation in TSC1 (25%). No patients had results of no mutation identified (NMI).

Group 2: Of the 36 patients diagnosed with spasms prior to focal seizure onset, the majority of patients had genetic mutation analyses (27 patients). Of the patients with available genetic results, 23 had a pathological mutation in TSC2 (85%), 3 patients had a pathological mutation in TSC1 (11%), and 1 patient had results of NMI (4%).

Relationship of Group to Genetic Mutation: Results are shown in Table 2. Fisher’s exact test showed statistical significance in the percentage of patients with TSC1 versus TSC2 mutations between these two groups (p = 0.0067).
**Treatment with Vigabatrin (Table 2)**

Group 1: Of the 14 patients who were diagnosed with focal seizure prior to spasm onset, the majority (13 patients) received VGB treatment. The specific dosage or titration of VBG administered was often not documented in the patients’ records. 7 of the 13 patients had an effective response with a reported near complete or complete cessation of spasms after initiation or up titration of VGB dose (54%). 5 of the 13 patients had an ineffective response with a reported continuation of spasms even after VGB dose up titration (38%). 1 of the 13 patients’ responses to VGB was not specifically reported and therefore, could not be classified as either an effective or ineffective response (8%). 9 of the 13 patients were concurrently receiving AED treatment for focal seizure at the time of VGB initiation. AEDs included VPA, PHB, LEV, PHT, CBZ, RFM, and PBT. Overall, of the 14 patients who were diagnosed with focal seizure prior to spasm onset, 8 patients became spasm-free with medical treatment (57%). Of the 2 patients who achieved spasm freedom without VGB (VGB not trialed as treatment), 1 had an effective response to ZNS and LEV while the other patient had an effective response to ACTH. Of the 6 patients with an effective response to VGB, 2 achieved focal seizure control with their AED regimen (33%) and 4 developed refractory epilepsy (67%). All of the 4 patients who had an ineffective response to VGB developed refractory epilepsy (100%). Of the 3 patients with an unclear response to VGB, 1 patient was lost to follow-up (33%) and 2 patients developed refractory epilepsy (67%). The 1 patient, who did not receive VGB treatment, had an ineffective response to the combination of ZNS and OXC, but an effective response to ZNS and LEV.

Group 2: Of the 36 patients diagnosed with spasms prior to focal seizure onset, the majority (23 patients) received VGB treatment. 18 of the 23 patients had an effective response with a reported near complete or complete cessation of spasms after initiation or up titration of VGB dose (78%). The specific dosage or titration of VBG administered was often not documented in the patients’ records. 4 of the 23 patients had an ineffective response with a reported continuation of spasms even after VGB dose up titration (17%). 1 of the 23 patients’ responses to VGB was not specifically reported and therefore, could not be classified as either an effective or ineffective response (4%). 13 of the 23 patients who received VGB treatment were not concurrently treated with other AEDs at the time.
of VGB therapy initiation. 4 of the 18 patients who had an effective response to VGB for IS had previously failed other therapies (including CZB, TBG, OXCZ, ACTH, PHB, LEV, LTG) for IS. 1 of the 23 patients who received VGB treatment had an ineffective response to LEV at the time of VGB initiation. There was no specific report of concurrent AED treatment for 9 of the 23 patients who received VGB treatment. Of 4 patients who had an ineffective response to VGB, 1 patient had an effective response to the combination therapy of CBZ and the ketogenic diet; 1 patient also failed treatment with ACTH, LEV, and CCZM; 1 patient failed treatment with the combination VGB and TPM therapy; 1 patient had no report of effective or ineffective therapy. Of the 13 patients who did not receive VGB therapy, 6 patients had no report of either successful or failed treatments, 5 received ACTH treatment (3 patients had an effective response and 2 patients had an unclear response); 1 patient failed PBT treatment then had an effective response to the combination of MPB and CZM and ACTH; 1 patient had an ineffective response to the combination treatment of PHT and MBP without report of any other successful or failed treatments. Overall, of the 36 patients diagnosed with spasms prior to focal seizure onset, 23 patients became spasm-free with medical treatment (64%). Of the 18 patients who had an effective response to VGB, 12 patients achieved focal seizure control with their AED regimen (67%) and 6 patients developed refractory epilepsy (33%). Of the 4 patients who had an ineffective response to VGB, 1 patient achieved focal seizure control with their AED regimen (25%) and 3 patients developed refractory epilepsy (75%). The 1 patient who had an unclear response to VGB achieved seizure control with her AED regimen.

Relationship of Group to VGB Response: Results are shown in Table 3. Comparison between Groups 1 and 2, excluding the 2 patients whose response to VGB was not documented, revealed that 58% of patients in Group 1 had an effective response to VGB, while 82% of patients in Group 2 had an effective response to VGB (p = 0.22). Fisher’s exact test did not show statistical significance between these two groups.

**Neurocognitive Data (Table 3)**

Group 1: Of the 14 patients who were diagnosed with focal seizure prior to spasm onset, 9 patients had formal neurocognitive testing performed. These tests included:
Wechsler Intelligence Scale for Children (WISC), Stanford-Binet, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Bayley Mental Scales. The median IQ of these patients was 53 (range, 40 – 75). 6 patients were classified as having moderate ID (67%), 1 patient as having mild ID (11%), 2 patients as having borderline ID (22%). None of the patients classified as having normal IQ. Of the 5 patients who did not have formal neurocognitive testing, 3 patients were noted to have developmental delays by parents and providers (60%), 1 patient was noted to have severe ID (qualitative, not quantitative) (20%), and 1 patient was noted to have met age-appropriate milestones (patient is 1 year old) (20%). Overall, 13 patients had some level of cognitive impairment (93%) and 1 patient was developing consistent with cognitively normal milestones (7%). Of the 14 total patients in Group 1, 3 patients received a diagnosis of autism spectrum disorder (22%). 2 of the patients with autism spectrum disorder received formal neurocognitive testing and classified as having moderate ID (14%). 1 of the patients with autism spectrum disorder did not have formal neurocognitive testing, but was qualitatively reported to have severe ID (33%).

Group 2: Of the 36 patients diagnosed with spasms prior to focal seizure onset, 21 patients had formal neurocognitive testing performed. These tests included: Wechsler Intelligence Scale for Children (WISC), Stanford-Binet, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Bayley Mental Scales. The median IQ of these patients was 55 (range 40 – 111). 8 patients were classified as having moderate ID (38%), 6 patients as having mild ID (29%), 3 patients as having borderline ID (14%), and 4 patients were classified as having normal IQ (19%). Of the 15 patients who did not have formal neurocognitive testing, 8 patients were reported to have cognitive impairment (the extent of the patients’ impairment was not detailed) (53%), 2 patients were reported to have normal cognition (13%), 1 patient was reported to have developmental delay as he had not met age-appropriate milestones (patient age 3) (7%), and 4 patients were reported to have met age-appropriate milestones (patient age range 2 - 3) (27%). Overall, 26 patients had some level of cognitive impairment (72%) and 10 patients were described as cognitively normal or meeting appropriate developmental milestones (28%). Of the 36 total patients in Group 1, 5 patients received a diagnosis of autism spectrum disorder (14%). 4 of the patients with autism spectrum disorder received formal neurocognitive
testing (11%). 2 of the patients classified as having moderate ID and 2 of the patients classified as having mild ID. The 1 patient who did not have formal neurocognitive testing was reported to have met age-appropriate developmental milestones (patient age 2).

Relationship of Group to Neurocognitive Outcomes: Results are shown in Figure 6 and Table 4. Fisher’s exact test did not show statistical significance in comparison of the percent of patients with cognitive impairment versus normal cognition/development in Group 1 and Group 2 (p = 0.15). Mann-Whitney U test analysis did not find statistical difference in IQ between Group 1 and Group 2 (p = 0.36). Fisher’s exact test did not show statistical significance in comparison of the percent of patients with autism between Group 1 and Group 2 (p = 1).

Epilepsy Outcome (Table 4)

Group 1: Of the 14 patients who were diagnosed with focal seizure prior to spasm onset, 1 patient was lost to follow-up and 11 patients continued to have epilepsy refractory to AED medication (85%). Of the 6 patients who underwent epilepsy surgery, 5 patients continued to have refractory epilepsy after surgery and 1 patient achieved seizure control after epilepsy surgery. Thus, 2 patients achieved seizure control via AEDs and/or epilepsy surgery (15%).

Group 2: Of the 36 patients diagnosed with spasms prior to focal seizure onset, 2 patients were lost to follow-up and 12 patients continued to have epilepsy refractory to AED medication (35%). 21 patients achieved seizure control with medication treatment (62%). Of the 7 patients who underwent epilepsy surgery, 2 patients achieved seizure control after epilepsy surgery and 5 patients continued to have refractory epilepsy after surgery. Thus, 23 patients achieved seizure control via AEDs and/or epilepsy surgery (68%).

Relationship of Group to Epilepsy Outcome: Results are shown in Table 4. Excluding the 3 patients who were lost to follow-up, comparison of Group 1 and Group 2 showed that 77% of patients in Group 1 and 32% of patients in Group 2 developed epilepsy refractory to all interventions attempted. Conversely, 23% of patients in Group 1 and 68% of patients in Group 2 achieved seizure control with implemented interventions.
Fisher’s exact test showed statistical significance between rates of epilepsy refractory in these two groups (p = 0.0089).

Discussion

The association between TSC and spasms, particularly infantile spasms, is well described in the literature. However, the population of TSC patients who present with focal seizure onset prior to spasms has not yet been studied. Although focal seizure and spasms are not an uncommon occurrence on the TSC population, we were unable to include many patients from the MGH TSC database due to lack of documentation specifying seizure and/or spasm onset. Thus, the significance of the results of our study were limited by sample size. The predominance of TSC2 mutation among our patients and incidence of spasms in the Herscot Center for TSC population (34%) is consistent with other studies (Chu-Shore et al., 2010; Fukushima et al., 2001; O’Callaghan et al., 2004; Au et al., 2007; Hsieh et al., 2013).

Regarding event onset, we found a statistically significant difference in age of spasm onset between groups. In patients who presented with focal seizure prior to the development of spasms (Group 1), initial seizure onset was at about 3.5 months and the average age of time between seizure development and spasm development is 7.5 months. Spasm onset in this population occurred at 11 months. For patients who presented with spasm prior to the development of focal seizure (Group 2), initial spasm onset was at about 5 months and the average age of time between spasm and seizure development is about 5.5 months. Focal seizure onset in this population occurred at about 11.5 months. Infantile spasms are classically described as occurring between 3 – 8 months (Pellock et al., 2010). Thus, these results indicate that patients who present with focal seizure first tend to develop spasms at the later end of the described spectrum whereas patients who develop spasms first tend to develop spasms at the earlier end of the described spectrum.

Vigabatrin is currently the first-line therapy for treatment of IS due TSC to its efficacy in this population (Pellock et al., 2010; Elterman et al., 2010; Camposano, 2008; Willmore, 2008; Parisi, 2007; Thiele, 2004; Hancock and Osborne, 1999). We found that
58% of patients in Group 1 became spasm-free with VGB treatment whereas 82% of patients in Group 2 became spasm-free with VGB treatment. Thus, clinically meaningful difference in VGB response was observed, although it did not reach statistical significance. The treatment response to VGB in Group 1 is lower than that reported in the literature (Camposano, 2008; Parisi, 2007; Hancock and Osborne, 1999; Pellock et al., 2010; Elterman et al., 2010). Despite the later onset of spasms in Group 1, the VGB response rate in this group was higher when compared with the VGB response rate of TSC patients with ES reported by Hsieh et al. (Hsieh et al., 2013). Of the 14 patients in Group 1, 7 patients (50%) had spasm onset after 1 year of age. 3 of these 7 patients became spasm-free with VGB treatment (43%), which is consistent with the results reported by Hsieh et al. (Hsieh et al., 2013). The high response rate in Group 2 is consistent with previously published reports of VGB treatment of infantile spasms due to TSC (Camposano, 2008; Hancock and Osborne, 1999; Pellock et al., 2010; Elterman et al., 2010). Although VGB dosage was not documented in all patient charts, multiple patients in both groups achieved spasm control with titration up to 150-200 mg/kg/day. This is consistent with the results of a randomized control trial investigating spasm response to low versus high-dose VGB (Elterman et al., 2010). Thus, we recommend titration to this dose as needed to optimize efficacy (Thiele, 2004).

With respect to neurocognitive outcomes, we did not find statistically significant difference in level of cognitive impairment between Group 1 and Group 2. However, patients in Group 1 tended to have more a more severe clinical profile: lower rates of normal IQ/cognition (7 vs 28%) and higher rates of more severe intellectual disability. This difference in cognitive profile could be confounded by the less effective response to VGB in Group 1 as persistence of spasms is associated with greater intellectual disability and poorer behavioral outcomes (O’Callaghan, 2004). Interestingly, the same pattern of cognitive profile difference between groups was also observed among patients with a diagnosis of autism. The patients with autism in Group 1 tended to have a more severe cognitive profile (moderate to severe intellectual disability), whereas the patients with autism in Group 2 tended to have a less impaired cognitive profile (mild to moderate disability). However, the sample size of this sub-population is too small to draw generalizable conclusions.
The most significant and clinically meaningful finding observed between Group 1 and Group 2 was the differences in rates of refractory epilepsy. Patients in Group 1 developed significantly higher rates of refractory epilepsy (77% vs 32%) than in Group 2. Thus, the risk of TSC patients with focal seizures preceding spasms developing refractory epilepsy is 2.4 times greater than that of TSC patients who develop spasms before focal seizures (RR = 2.4). The majority of patients in Group 1 developed epilepsy refractory to AEDs alone (85%). Epilepsy control was attempted with surgery in about half of these patients, but the majority (83%) continued to have refractory epilepsy even after surgery. Thus, the epilepsy in this group was highly refractory to all attempted interventions.

Whereas in Group 2, a minority of patients developed epilepsy refractory to AEDs alone (35%). About half of these patients eventually underwent epilepsy surgery to achieve seizure control, but the majority continued to have uncontrolled seizures after surgery (71%). The rate of epilepsy surgery success in both of these groups is lower than reported rates of surgery success in patients with TSC (Jansen et al., 2007). Thus, our observations suggest that epilepsy surgery may be a less beneficial treatment option for patients with refractory epilepsy in either group. Overall, the significantly increased rate of refractory epilepsy in TSC patients with focal seizure preceding spasms has important implications for prognostication as well as early and aggressive treatment to minimize the adverse consequences of uncontrolled seizures in this vulnerable population.

**Conclusions**

In summary, the sub-population of TSC patients who have focal seizure onset preceding spasm onset have a more severe clinical profile and poorer prognosis with respect to vigabatrin treatment response, cognitive profile, and development of refractory epilepsy compared with TSC patients who present with spasm preceding focal seizure onset. They tend to have a less effective response to VGB treatment of spasms (58 vs 82%). These patients tend to have lower rates of normal IQ/cognition (7 vs 28%) and higher rates of intellectual disability (93 vs 72%) with a trend of more severe level of intellectual disability. These patients also develop significantly higher rates of refractory
epilepsy (77% vs 32%) and thus, have 2.4 times the risk of developing refractory epilepsy (RR = 2.4).

**Conflicts of Interest**

Rebecca MacRae has no conflicts of interest. Dr. Thiele serves as a consultant for GW Pharma, Zogenix Pharmaceuticals, Upsher Smith Pharmaceuticals, and Aquestive Pharmaceuticals.

**Acknowledgements**

This study was supported by the Carol and James Herscot Center for Tuberous Sclerosis Complex.
References


Tables and Figures

Figure 1: Distribution of age at spasm onset of 14 patients in Group 1.
Figure 2: Distribution of age at seizure onset of 14 patients in Group 1.

![Group 2 Age of Spasm Onset](image)

Figure 3: Distribution of age at spasm onset of 28 patients in Group 2.

![Group 2 Age of Seizure Onset](image)

Figure 4: Distribution of age at seizure onset of 11 patients in Group 2.
Figure 5: Distribution of age of spasm onset in Group 1 and Group 2.

Group 2: minimum = 1 mo, 25% = 3 mo, median = 4 mo, 75% = 6 mo, maximum = 15 mo.

Group 1: minimum = 3 mo, 25% = 4.5 mo, median = 11 mo, 75% = 16.75 mo, maximum = 36 mo.

p = 0.014
Figure 6: Distribution of IQ in Group 1 and Group 2.

Group 2: minimum = 40, 25% = 51, median = 55, 75% = 72, maximum = 111.
Group 1: minimum = 40, 25% = 49, median = 53, 75% = 60, maximum = 78.
p = 0.36
Relationship of Group to Genetic Mutation

<table>
<thead>
<tr>
<th>Genes</th>
<th>Group 1 (percent of patients)</th>
<th>Group 2 (percent of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1*</td>
<td>25% (2/8)</td>
<td>11% (3/27)</td>
</tr>
<tr>
<td>TSC2*</td>
<td>75% (6/8)</td>
<td>85% (23/27)</td>
</tr>
<tr>
<td>NMI</td>
<td>0% (0/0)</td>
<td>4% (1/27)</td>
</tr>
</tbody>
</table>

Table 1: Percentage of patients with known disease modifying mutation. * denotes statistically significant comparison.

Relationship of Group to Vigabatrin Response Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1 (percent of patients)</th>
<th>Group 2 (percent of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VBG (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal Seizure Control</td>
<td>33% (2/6)</td>
<td>67% (12/18)</td>
</tr>
<tr>
<td>Refractory Epilepsy</td>
<td>67% (4/6)</td>
<td>33% (6/18)</td>
</tr>
<tr>
<td>VBG (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal Seizure Control</td>
<td>0% (0/0)</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Refractory Epilepsy</td>
<td>100% (4/4)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>VBG (+/-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal Seizure Control</td>
<td>0% (0/0)</td>
<td>100% (1/1)</td>
</tr>
<tr>
<td>Refractory Epilepsy</td>
<td>100% (3/3)</td>
<td>0% (0/0)</td>
</tr>
<tr>
<td>Spasm-Free with any medication (VGB, ACTH, other AEDs)</td>
<td>57% (8/14)</td>
<td>64% (23/36)</td>
</tr>
<tr>
<td>Refractory Epilepsy</td>
<td>75% (6/8)</td>
<td>30% (7/23)</td>
</tr>
</tbody>
</table>

Table 2: Percent of patients with known Vigabatrin response.
### Relationship of Group to Neurocognitive Outcome

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Median IQ = 53 (percent of patients)</th>
<th>Group 2: Median IQ = 55 (percent of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate ID</td>
<td>67% (6/9)</td>
<td>38% (8/21)</td>
</tr>
<tr>
<td>Mild ID</td>
<td>11% (1/9)</td>
<td>29% (6/21)</td>
</tr>
<tr>
<td>Borderline ID</td>
<td>22% (2/9)</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>Normal IQ (quantitative)</td>
<td>0% (0/0)</td>
<td>19% (4/21)</td>
</tr>
<tr>
<td>Developmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay/Cognitive Impairment (qualitative)</td>
<td>80% (4/5)</td>
<td>60% (9/15)</td>
</tr>
<tr>
<td>Normal Development/Cognition (qualitative)</td>
<td>20% (1/5)</td>
<td>40% (6/15)</td>
</tr>
<tr>
<td>Overall Total with Cognitive Impairment (quantitative and qualitative)</td>
<td>93% (13/14)</td>
<td>72% (26/36)</td>
</tr>
<tr>
<td>Overall Total with Normal Cognition/Development (quantitative and qualitative)</td>
<td>7% (1/14)</td>
<td>28% (10/36)</td>
</tr>
<tr>
<td>Autism</td>
<td>22% (3/14)</td>
<td>11% (4/36)</td>
</tr>
</tbody>
</table>

Table 3: Percentages of patients with known cognitive status. Per DSM-V classifications of intellectual disability, score classifications were defined as: borderline for IQ 70 – 79, mild for IQ 55 – 70, and moderate for IQ 40 – 54, severe for IQ 25 – 39, and profound for IQ less than 25 (American Psychiatric Association, 2013).
### Relationship of Group to Epilepsy Outcome

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (percent of patients)</th>
<th>Group 2 (percent of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory to AEDs (excluding other interventions)* (p = 0.0019)</td>
<td>85% (11/13)</td>
<td>38% (13/34)</td>
</tr>
<tr>
<td>Seizure control after epilepsy surgery</td>
<td>9% (1/11)</td>
<td>15% (2/13)</td>
</tr>
<tr>
<td>Refractory Epilepsy Total (AEDs, VNS, epilepsy surgery)* (p = 0.0055)</td>
<td>77% (10/13)</td>
<td>32% (11/34)</td>
</tr>
<tr>
<td>Seizure Control Total (AEDs, VNS, epilepsy surgery)* (p = 0.0089)</td>
<td>23% (3/13)</td>
<td>68% (23/34)</td>
</tr>
<tr>
<td>Refractory Epilepsy with prior spasm control (VGB or other medication)</td>
<td>60% (6/10)</td>
<td>64% (7/11)</td>
</tr>
</tbody>
</table>

Table 4: Percentage of patients with known epilepsy outcomes. 1 patient in Group 1 was lost to follow-up. 2 patients in Group 2 were lost to follow-up. * denotes statistically significant comparison.