

Developmental outcome of epilepsy surgery in tuberous sclerosis complex

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ABSTRACT – In Tuberous sclerosis complex (TSC), neurological dysfunction, usually in association with epilepsy, is responsible for the greatest degree of disease-related disability. Epilepsy surgery is increasingly recognized as a therapeutic option given the often medication-resistant nature of the disease. Seven subjects with medically refractory epilepsy associated with TSC, who underwent surgery at a tertiary care epilepsy center and in whom both preoperative and postoperative neuropsychological data were available, were examined. The Vineland Adaptive Behavior Scales, and in one case, the WISC-III were utilized. Postoperatively, the composite standard scores declined in six of the seven subjects, although for the most part this decline was quite modest (8 points or less in 5/6 subjects). The mean overall developmental/intellectual quotients were comparable across assessments (preoperative $M = 55$, $SD = 20.3$; postoperative $M = 49$ $SD = 16.6$). Good outcomes appeared to be related to seizure relief. Age estimates of developmental level indicated developmental progress in the majority of subjects in the current sample, and may yield greater clinical information for individuals with developmental delay than do standard scores.

Key words: tuberous sclerosis complex, neuropsychology, epilepsy surgery, development, cognition

Tuberous sclerosis complex (TSC) is an inherited, multisystem disorder with genetic mutations localized to either chromosome 9 or 16. Two-thirds of cases are thought to be due to a spontaneous genetic mutation. Neurological phenomena include cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, dyslaminated cortex, and white matter abnormalities. TSC is also associated with high rates of epilepsy in those who present for medical attention (Bebin *et al.* 1993). Mental retardation (Joinson *et al.* 2003), autism (Hunt and Shepherd 1993), and other behavioral abnormalities, including inattention

and hyperactivity (Asato and Hardan 2004), are common to the disorder, and are associated with lifelong reduction in quality of life and significant financial burden for afflicted individuals and their caregivers (Ferguson *et al.* 2002).

Antiepileptic medication is the treatment of choice for individuals with seizure disorders. However, in TSC, epilepsy is in many cases refractory to medication, owing to the diffuse nature of the disease. As such, polytherapy is often required, which in itself presents risks for cognitive and behavioral impairment. Surgical intervention is becoming increasingly com-

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mon for the treatment of epilepsy in TSC. Despite the aggressive nature of the disease, surgery can be an effective option. In a recent review of 12 studies dating to 1991 (Romanelli *et al.* 2004), more than 50% of the subjects in each series experienced greater than 50% reduction in seizure frequency. High rates of seizure freedom were also noted in many of the series reviewed (Bebin *et al.* 1993, Koh *et al.* 2000, Sinclair *et al.* 2003, Vigliano *et al.* 2002). Epileptic activity confined to a single cortical region with convergent clinical and imaging data and lack of developmental delay, have been identified as factors associated with good surgical outcome when the outcome measure is seizure-freedom (Jarrar *et al.* 2004, Romanelli *et al.* 2001). In individuals without developmental delay, positive postoperative outcomes may be maintained on a long term basis (Jarrar *et al.* 2004). In the series by Jarrar *et al.*, none of the individuals with excellent long-term outcome had developmental delay at the time of surgery. In contrast, all individuals with developmental delay at the time of surgery showed poorer outcome, reflected in either initial postoperative seizures or recurrence of seizures following a period of seizure control.

Seizure relief/control is the goal of surgery in TSC. Promoting neurodevelopment is a secondary aim, although the contribution of epilepsy surgery to neurodevelopment is not clear. The general trend points toward improvement in cognition and behavior in at least certain subgroups of patients, especially those who become seizure-free (Guerreiro *et al.* 1998, Karenfort *et al.* 2002, Koh *et al.* 2000, Romanelli *et al.* 2001, Vigliano *et al.* 2002). However, some reports mention only preoperative or postoperative assessments, not both (Avellino *et al.* 1997, Bebin *et al.* 1993, Conzen and Opiel 1990, Jarrar *et al.* 2004). Additionally, the omission of standardized assessment or equivalent measures in those that do undergo assessment preoperatively and postoperatively complicate available findings.

The current report describes developmental outcome in seven individuals with TSC who underwent surgical intervention for the treatment of medically refractory epilepsy. All individuals received psychometric assessment using the same methods, pre- and post-operatively.

Methods

Seven patients who underwent surgery for removal of epileptogenic tissue associated with TSC between August 1999 and October 2003 were included (four females and three males) in this study. The age at surgery varied from two years, five months to twenty-one years.

In six of the seven subjects, the Vineland Adaptive Behavior Scales Interview Edition Expanded Form [Sparrow *et al.* Circle Pines: American Guidance Services I, 1984 [Sparrow *et al.* 1984]] was administered to caregivers. The Vineland Adaptive Behavior Scales is a structured, car-

egiver interview widely used in studies of functional capacities in children with epilepsy, particularly those with developmental delay (Berg *et al.* 2004, Jonas *et al.* 2004, Koh *et al.* 2004). The measure provides information on communicative, daily living, socialization, and motor skills. Additionally, an overall composite score is determined. All standard scores are provided on a common metric with a mean of 100 and a standard deviation of 15. The measure also allows for derivation of age equivalents. In one subject, a short form of the Wechsler Intelligence Scale for Children – Third Edition (Wechsler 1991) was administered.

The study was approved by the New York University Medical Center Institutional Review Board. Informed consent was obtained from all subject caregivers.

Results

Table 1 contains information on gender, neuroimaging, preoperative seizure semiology and frequency, preoperative EEG findings, surgical procedure, age at surgery, and postoperative seizure frequency. Intracranial monitoring was used in all subjects prior to surgery to aid in seizure localization, as surface EEG in many cases detected multiple seizure foci. Developmental outcomes are provided in table 2, including the Vineland Adaptive Behavior Scales Composite Standard Score (VABC SS) or IQ score and corresponding age equivalents, and Vineland Adaptive Behavior Scales Domain Standard Scores, consisting of the Communication Domain, Daily Living Skills Domain, Socialization Domain, and in some cases the Motor Skills Domain. The age at preoperative and postoperative assessment is also provided.

In six of the seven subjects (all but subject 4), composite standard scores declined, although for the most part this decline was quite modest (8 points or less in 5/6 subjects: subjects 2, 3, 5, 6, 7) and mean overall developmental/intellectual quotients were comparable across assessments (preoperative $M = 55$, $SD = 20.3$; postoperative $M = 49$ $SD = 16.6$). In examining individual Vineland Domain scores in the six subjects in which it was used, surgery appeared to exert a beneficial effect on the abilities measured under the Socialization scale for one subject, as the standard score increased considerably in this individual.

Age equivalents increased in all subjects, though the degree of increase varied across subjects (range 1-19 months). In four of the subjects, the increase in developmental age level was approximately one third of that which would occur if developmental progresses were normal (subjects 1, 2, 5, and 6). In another subject (subject 7), developmental gain was minimal (one month over a 14 month span). In two other subjects, developmental gains appeared to occur at a normal rate (subjects 3, 4). Seizure-freedom appeared to play a role in developmental

Table 1. Gender, neuroimaging findings, and seizure and surgical characteristics.

#	Gender	MRI findings	Preoperative seizures (frequency)	Intracranial/surface VEEG seizure focus	Surgery	Age at surgery	Postop seizures and frequency
1	M	Large tubers in left temporal lobe and right posterior quadrant, other smaller tubers	Simple partial seizures of the right extremities (2-3 daily) Complex partial seizures (2-3 daily) Absence seizures	Right posterior/occipital Left temporal	Right parieto-occipital and left anterior temporal tuber resection	2 yrs 5 months	None in 6 months
2	F	Multiple subcortical tubers, edema surrounding several lesions in the high convexity of the anterior frontal lobe	Decreased responsiveness, right hand twitching (2-5 daily)	Left parasagittal	Left frontopolar, mesial premotor tuber resections, resection of two tubers posterior to the motor strip	3 yrs 9 months	1 in 8 months
3	F	Consistent with a left frontotemporal structural abnormality	Staring spells (1 every 2 weeks) Generalized seizures (12 per month)	Left frontal	Left frontal resection	~10 yrs	None
4	M	Enhancing mass in right frontal region	Bilateral stiffening (2-3 daily)	Frontal, not lateralized	Partial resection of the right anterior frontal and anterior mid temporal lobe	21 yrs 10 months	3 seizures (in one day) over 15 months
5	F	Multiple cortical lesions	Partial seizures with right eye and head deviation (20-30 daily)	Right temporal and parietal	Resection of (2) right anterior frontal tubers, resection of the anterior-most 3 cm of right temporal lobe, and further right frontal and temporal resection	2 yrs 5 months	Right sided clonic activity (2-4 daily)
6	M	Consistent with tuberous sclerosis	Left eye blinking, unresponsiveness, loss of tone (10-20 daily)	Right posterior frontal	Right temporal tuber resection	3 yrs 7 months	Absence, gagging, emesis (1-2 daily)
7	F	Numerous lesions, the most prominent in the right motor strip	Empty stare, bilateral upper and lower extremity jerking (4-6 daily)	Multifocal, earliest onset midtemporal	Right frontal and temporal resection	4 yrs 2 months	Unresponsiveness, head deviation, at times with clonic activity (multiple daily)

Table 2. Preoperative and postoperative developmental findings.

#	Preop age	Preop VABS AE/SS*	Postop age	Postop VABS AE/SS	Preop Comm*	Postop Comm	Preop DLS*	Postop DLS	Preop Soc*	Postop Soc	Preop Motor*	Postop Motor
1	2 yrs 4 mo	1 yr 9 mo SS 73	7 yrs 1 mo	3 yrs 4 mo SS 50	74	61	84	40	85	63	83	
2	3 yrs 7 mo	1 yr 3 mo SS 50	4 yrs 5 mo	1 yr 6 mo SS 48	55	52	57	52	55	52	52	53
3	~9 yrs	N/A IQ 87	~11 yrs	N/A IQ 84								
4	21 yrs 2 mo	4 yrs 8 mo SS 25	23 yrs 1 mo	6 yrs 3 mo SS 35	25	23	40	51	19	41		
5	2 yrs 4 mo	3 mo SS 48	4 yrs 1 mo	10 mo SS 41	54	47	56	41	51	53	49	35
6	2 yrs 11 mo	1 yr 3 mo SS 59	4 yrs 7 mos	1 yr 10 mo SS 51	66	56	62	58	62	56	68	53
7	4 yrs 3 mo	1 yr 0 mo SS 43	5 yrs 5 mo	1 yr 1 mo SS 36	47	42	47	34	54	49	39	30

*VABS = Vineland Adaptive Behavior Scales Adaptive Behavior Composite (AE) Age Equivalent/(SS) Standard Score, Comm = Communication, DLS = Daily Living Skills, Soc = Socialization, Motor = Motor Skills.

outcome, as with the two subjects who progressed the most, one was seizure-free postoperatively (subject 3) and one had only a cluster of three seizures in one day over a 15 month period (subject 4); with the two other subjects in this group who had developmental increases of one third the normal rate, one subject was seizure-free (subject 1) and the other had experienced only one seizure in the eight, postoperative months (subject 2). In the three subjects with continued seizures, one had minimal developmental improvement (subject 7) and two demonstrated developmental increases of one third of the normal rate (subjects 5, 6).

Discussion

The present report describes developmental outcome in seven subjects who underwent surgery for relief of seizures associated with TSC. As indicated by increases in developmental age equivalents (*i.e.* mental age), all subjects in the present study exhibited some developmental gain. Progression in development of adaptive skills was judged to be normal in two subjects, whereas four showed gains of one third that of the published normative sample, and one subject demonstrated negligible gain.

Age equivalents represent absolute gains, while standard scores indicate developmental progress in comparison to a normal control group. The data indicate no negative effect of surgery on developmental progression, with some suggestion of postoperative developmental gains. While composite standard scores declined in six of the seven subjects, in the six subjects evaluated, approximately one to two years postoperatively, composite scores were highly similar and in none did the mean score decline

more than 8 points. While merely maintenance of current development or a slowed rate of development in comparison to peers might represent an undesirable outcome in individuals without developmental delay undergoing surgery for seizure relief, the current sample requires judgment based on different criteria. Of the seven subjects in the current sample, five were developmentally delayed (*i.e.* developmental/intellectual quotients < 70), and only one was judged to be developmentally normal (*i.e.* developmental/intellectual quotient > 80). In an early childhood study of development in TSC (Humphrey *et al.* 2004), the gap between afflicted individuals and the normative sample widened over time. Any intervention that will limit this development lag is crucial, particularly since 50% of subjects with TSC present with cognitive impairment, and in the majority with such impairment, it is of the more severe variety (Joinson *et al.* 2003). Thus, by demonstrating comparable *standard scores* pre- and postoperatively and increases in age equivalents, the present study corroborates the improved postoperative developmental outcome noted in prior reports in at least some subjects (Karenfort *et al.* 2002, Koh *et al.* 2000, Romanelli *et al.* 2001, Vigliano *et al.* 2002), but does so more definitively, by using standardized psychometric assessment. In prior studies, positive developmental outcomes were defined by continued development (Vigliano *et al.* 2002), in some cases where preoperative development had stagnated (Karenfort *et al.* 2002), by age appropriate behaviors (*e.g.* employment, marriage) (Guerreiro *et al.* 1998), or based on parent reports (Koh *et al.* 2000).

Postoperative seizure control appeared to play a role in developmental outcome. The two subjects making the

biggest developmental gains postoperatively were seizure-free at the time of evaluation and two others with good seizure control had made some developmental progress. In contrast, those with refractory seizures exhibited either no or minimal progress. This issue warrants closer inspection as treatment-related, improved development outcome in TSC (incidentally observed in some surgical series) has only been documented with psychometric data in individuals treated with Vigabatrin (Jambaque *et al.* 2000). Additionally, preoperative developmental level may be even more important in tuberous sclerosis in determining postoperative developmental outcome than in other surgical series, where there is less likely to be such high rates of developmental delay.

The small size of the current sample and the lack of a disease control group impact the degree to which the current results can be generalized to the TSC population at large. However, it is difficult to find comparable control groups given the heterogeneity of the disease itself. Additionally, the present results show outcome mostly one to two years postoperatively. The subject who exhibited the greatest decline over time compared to age-related peers was assessed at a considerably longer postoperative latency (> 4 years) than the other six subjects. Thus, continued monitoring of developmental outcome is needed. Additionally, measures other than adaptive level and intellectual status need to be considered and may provide further information on the possible benefits of surgery as a treatment option. For example, autism is found in TSC at considerably greater frequencies than in the general population. In examining postoperative data in the five subjects in whom development assessment was conducted using the Vineland no more than two years postoperatively, a very modest benefit was actually observed in the subsection of the measure containing items pertinent to social skills, range of interests, and coping skills, although the broader change in a single individual may be responsible for such results. Nonetheless, these data might suggest that socialization skills benefit from surgery. Preoperative and postoperative standardized symptom/syndrome specific scales are needed to assess behaviors of concern such as autism, hyperactivity, and more generalized psychopathology, in addition to considering such areas as quality of life and specific cognitive skills. This is particularly relevant given the devastation to development attributed to autism. Autism in TSC has been associated with temporal lobe electrographic and structural abnormalities in some reports (Bolton 2004). Temporal lobe surgery for seizure relief in TSC may provide considerable insight into the nature of this disorder and how it can be treated, as there is almost no information concerning the impact of brain surgery on autistic symptoms.

Surgery may also shed further light on the relative contributions of neurological and genetic aspects of TSC. When genetic aspects are controlled, considerable variability in clinical manifestations of the disease still occurs (Hum-

phrey *et al.* 2004), which impacts developmental outcome. Greater number of tubers (Goodman *et al.* 1997) and specific epilepsy variables, including age at onset and seizure type (Hunt 1993, O'Callaghan *et al.* 2004), contribute to developmental outcome. Genetic factors also contribute to developmental outcome (Dabora *et al.* 2001) and surgery can aid in further isolating the roles that these two differing but complementary factors play in outcome. □

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