Developmental outcome of epilepsy surgery in tuberous sclerosis complex

Charles M. Zaroff, Chris Morrison, Nina Ferraris, Howard L. Weiner, Daniel K. Miles, Orrin Devinsky
Clinical Neuropsychology, NYU Comprehensive Epilepsy Center, New York, USA
Received February 21, 2005; Accepted July 25, 2005

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, dysplaminated 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-
In six of the seven subjects, the Vineland Adaptive Behavior Scale yield 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 1, 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.

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

**Table 2. Preoperative and postoperative developmental findings.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 yrs 4 mo</td>
<td>1 yr 9 mo SS 73</td>
<td>7 yrs 1 mo</td>
<td>SS 50</td>
<td>74</td>
<td>61</td>
<td>84</td>
<td>40</td>
<td>85</td>
<td>63</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 yrs 7 mo</td>
<td>1 yr 3 mo SS 50</td>
<td>4 yrs 5 mo</td>
<td>SS 48</td>
<td>55</td>
<td>52</td>
<td>57</td>
<td>52</td>
<td>55</td>
<td>52</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>~9 yrs</td>
<td>N/A IQ 87</td>
<td>~11 yrs N/A</td>
<td>IQ 84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21 yrs 2 mo</td>
<td>4 yrs 8 mo SS 25</td>
<td>23 yrs 1 mo</td>
<td>SS 35</td>
<td>25</td>
<td>23</td>
<td>40</td>
<td>51</td>
<td>19</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 yrs 4 mo</td>
<td>3 mo SS 48</td>
<td>4 yrs 1 mo</td>
<td>SS 41</td>
<td>54</td>
<td>47</td>
<td>56</td>
<td>41</td>
<td>51</td>
<td>53</td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>2 yrs 11 mo</td>
<td>1 yr 3 mo SS 59</td>
<td>4 yrs 7 mo</td>
<td>SS 51</td>
<td>66</td>
<td>56</td>
<td>62</td>
<td>58</td>
<td>62</td>
<td>56</td>
<td>68</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>4 yrs 3 mo</td>
<td>1 yr 0 mo SS 43</td>
<td>5 yrs 5 mo</td>
<td>SS 36</td>
<td>47</td>
<td>42</td>
<td>47</td>
<td>34</td>
<td>54</td>
<td>49</td>
<td>39</td>
<td>30</td>
</tr>
</tbody>
</table>

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 subsec-

References


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. □


