Surgery for symptomatic infant-onset epileptic encephalopathy with and without infantile spasms

Abstract—Children undergoing surgery with infant-onset epilepsy were classified into those with medically refractory infantile spasms (IS), successfully treated IS, and no IS history, and the groups were compared for pre- and postsurgery clinical and Vineland Adaptive Behavior Scale (VABS) developmental quotients (DQ). Children without an IS history were older at surgery and had longer epilepsy durations than those with IS despite similar substrates, surgeries, and seizure frequencies. In all groups, better postsurgery VABS-DQ scores were associated with early surgical intervention indicating that infant-onset epilepsy patients with or without IS are at risk for seizure-induced encephalopathy.

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Childhood-onset epileptic encephalopathies, such as infantile spasms (IS), are disorders in which patients with uncontrolled seizures or frequent interictal EEG activity are at risk for cognitive and neurologic disabilities.1,2 Resective neurosurgery is a treatment option for patients with therapy-resistant IS and unilateral symptomatic substrates.3 However, it is unknown if seizure control and developmental outcomes from surgical treatment are the same for patients with IS and hypsarrhythmia at the time of surgery vs those whose IS were successfully treated but continued to have refractory non-IS partial seizures. Likewise, it is unclear if patients with IS show presurgical and postsurgical characteristics that distinguish them from other infant-onset epilepsy surgery patients who do not have IS. Therefore, this study was designed to test the hypothesis that infant-onset epilepsy surgery patients were at risk for epilepsy-induced encephalopathy, and early surgical intervention would be important to maximize cognitive development.

Methods. The cohort consisted of resective surgery patients operated at the University of California, Los Angeles (UCLA) Pediatric Epilepsy Surgery Program from 1986 to 2003 (n = 277). Details of the surgical protocol have been previously published.3 Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 22 issue to find the link for this article.

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At the initial clinical evaluation, patients were considered to have a positive IS history if they had seizures described as brief (few seconds) mostly bilateral spastic-like muscle contractions involving the neck, trunk, or extremities that occurred in clusters, scalp EEG reports confirmed hypsarrhythmia or one of the modified hypsarrhythmia variants,3 and the events had been medically treated with ACTH, B6, nitrazepam, or vigabatrin.

Patient groups. Based on medical history, patients were classified into the following groups:

Active IS. Children who had hypsarrhythmia or modified hypsarrhythmia at the time of presurgery EEG/video telemetry despite medical therapy, and were referred for resective surgery because they were having active therapy-resistant IS.

Treated IS. Patients who had IS history (seizure description and prior EEG), and had been successfully treated by medical therapy prior to presurgery EEG/video telemetry (no hypsarrhythmia or modified hypsarrhythmia at evaluation). They were referred for surgery because of therapy resistant partial or secondarily generalized seizures.

No history of IS. This group included resective surgery patients with infant-onset epilepsy who never had a history of IS.

Clinical variables. Information abstracted from the medical records included:

Presurgery. Age at seizure onset, age at EEG/video telemetry, age at surgery, temporal or extratemporal epilepsy syndrome, side resected, and gender. Age at seizure onset was defined as the first clinical seizure, which may or may not be IS. The etiology of the seizures was classified into those with, hemimegalencephaly (HME), cortical dysplasia, tuberous sclerosis, infantile/ischemia, Rasmussen encephalitis, Sturge-Weber disease, limbic lesions (hippocampal sclerosis, temporal lobe low grade tumors, and dual pathalogy), infection, or other.4 Surgical procedures were classified into hemispherectomy, multilobar (two lobes or more), lobar (e.g., temporal, frontal), or focal (smaller than lobar) resections.5

Presurgery EEG/video telemetry. Digital EEG/video records were retrospectively reassessed for interictal and ictal EEG abnormalities by board certified clinical neurophysiologists (R.J., S.K., and J.Y.W.). In addition to hypsarrhythmia or modified hypsarhythmia, the entire EEG record was evaluated for the presence of repeated independent interictal ipsilateral and contralateral epileptiform spikes, paroxysmal fast activity (PFA), and background frequency slowing (from those expected for age). The number of EEG-confirmed clinical ictal events per 24-hour period, and the percentage of ictal events that localized to the side of surgery were calculated.

Postsurgery. This information included seizure control and antiepilepsy drug (AED) use as previously described.6 Seizure frequency was scored as class 1, no seizures; class 2, one seizure per month; class 3, two to four seizures per month; class 4, 5 to 30 seizures per month; and class 5, >30 seizures per month.7 Post-surgery AED recorded the number of medications taken by the patient at the time of presurgery evaluation and at 6 months, 1 year, 2 years, and 5 years postsurgery.8

Pre- and postsurgery development assessment. Levels of developmental attainment were assessed using the Adaptive Behav-
Table Age (in years) at presentation by infantile spasm (IS) group (mean ± SD)

<table>
<thead>
<tr>
<th>Age variable</th>
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<th>Treated IS</th>
<th>No history of IS</th>
<th>p Value</th>
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<td>Age at seizure onset</td>
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<td>0.2 ± 0.3</td>
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<td>Age at surgery</td>
<td>1.2 ± 1.0†</td>
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<td>Seizure onset to telemetry</td>
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<td>2.6 ± 3.3†</td>
<td>4.1 ± 4.0†</td>
<td>p &lt; 0.0001</td>
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<tr>
<td>Seizure onset to surgery</td>
<td>1.1 ± 0.9†</td>
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<td>Telemetry to surgery</td>
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<td>0.4 ± 0.7</td>
<td>0.5 ± 0.6</td>
<td>p = 0.31</td>
</tr>
</tbody>
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* Indicates significant post-hoc analysis (p < 0.01) for one group vs two groups.
† All groups were different.

p Value = analysis of variance.

Results. In the UCLA pediatric resective surgery cohort, age at seizure onset was 1 year or less in 55.2% (153/277) of patients. Of patients with a history of IS (n = 85), the age at seizure onset was 1 year or less in all cases except 1, and the remaining spasm case was 14 months of age at seizure onset. In those patients whose seizures began by age 1 year, 54.9% (84/155) had a history of IS.

IS groups. Using 14 months as the upper limit for age at seizure onset, 39 children were classified into the active IS group (25.3%), 46 children with treated IS (29.9%), and 69 with no history of IS (44.8%). Thus, medical therapy successfully controlled hypsarrhythmia and spasms in 54% (46/85) of our patients with IS before surgery. There were eight (5%) patients with infant-onset seizures who eventually had surgery for limbic epilepsy. All were in the no history of IS group, and their etiologies were hippocampal sclerosis (HS; n = 2), temporal lesions without HS (tumors, dysplasia; n = 4), and dual pathology (HS and lesion; n = 2).

Presurgery clinical variables by IS group. Children with a history of IS (active IS and treated IS) had a younger age at seizure onset vs those without spasms (no history of IS; table, analysis of variance [ANOVA]; p < 0.0001; see * for post-hoc results). In addition, the ages at EEG/video telemetry and surgery were younger for the active IS group compared with treated IS, and treated IS cases were younger than patients with no history of IS (table 1, see †). Despite the difference for age at seizure onset, children with active IS had the shortest intervals from seizure onset to EEG/video telemetry and seizure onset to surgery (epilepsy duration), the treated IS group were intermediate, and the patients with no history of IS had the longest intervals (table 1, see †). The interval from EEG/video telemetry to surgery averaged (± SD) 4 ± 7 months (median 3 months), and was not different between IS patient groups (p = 0.31). Exclusion of the eight limbic epilepsy cases from the no history of IS group did not alter the statistical results.

Other presurgical clinical variables were not different between IS patient groups (see table E-1 on the Neurology Web site at www.neurology.org). Gender and side resected were not different between active IS, treated IS, and no history of IS groups (p > 0.28). The most common pathology was malformation of cortical development (cortical dysplasia, HME, tuberous sclerosis; 68.8%), followed by infarct/ischemia (12.3%), and there were no differences between IS patient groups (p = 0.42). The most frequent surgery was hemispherectomy (51.9%) followed by lobar resection (16.9%), and the type of surgical procedure was not different between IS patient groups (p = 0.40).

Retrospective EEG analyses from inpatient digital telemetry records were conducted on 38% (n = 59) of patients. To determine if patients who had EEG evaluations were representative of the entire cohort, we compared presurgery variables in those cases with and without EEG analysis and found no differences (p > 0.21). Patients with active IS, compared with treated IS and no history of IS groups, showed increased independent contralateral interictal spikes, ipsilateral and contralateral PFA, and contralateral background slowing (table E-2; p = 0.029 or less for each univariable comparison). In addition, if each spasm was counted as a separate seizure, the number of ictal behavioral/EEG events per 24-hour period was increased in patients with active IS vs the other two IS groups (p = 0.0052). However, if each cluster of spasms was counted as single seizure events, there were no differences in seizure frequencies between the IS patient groups (p = 0.94).

Postsurgery seizure and AED use. All patients had uncontrolled epilepsy prior to surgery, and the seizure scores were not different by IS patient group (p = 0.455). Postsurgery information was available on 138 (90%) patients with an average (± SD) follow-up of 3.5 ± 1.8 years. There were no differences in presurgery clinical variables in the 10% of patients without follow-up compared with those with postsurgery seizure information (p > 0.35). After surgery, 70.6% of patients were seizure free at 6 months, 69.3% at 1 year, 62.0% at 2 years, and 46.9% at 5 years. In the active IS patient group, if there were persistent seizures immediately after surgery their EEG showed resolution of hypsarrhythmia in all patients (n = 10). Numerically, more patients in the treated IS group were seizure free at 0.5, 1, and 2 years after surgery compared with the other IS groups, but the differences were not significant (table E-3; χ²; p > 0.20). Age at surgery (p = 0.49), epilepsy duration (p = 0.43), pathology (p = 0.56), type of surgical resection (p = 0.34), and presurgery scalp EEG abnormalities (p > 0.16) were not associated with seizure control at the last follow-up evaluation. For patients with persistent seizures after surgery, 45.3% had seizure scores of 4 or 5 indicating they had more than one seizure per week, and there were no differences between IS patient groups (p = 0.85).
Prior to surgery all but two patients (1.3%) were taking AEDs. The mean (± SD) number of AEDs per patient was 2.5 ± 1.0, and AEDs per patient did not differ by IS patient group (p = 0.16). After surgery, 8.0% of patients in this cohort were no longer taking AEDs at 6 months, 18.7% at 1 year, 38.5% at 2 years, and 47.0% at 5 years. AED use did not differ by IS patient group at 0.5 (p = 0.96), 1 (p = 0.72), 2 (p = 0.49), and 5 (p = 0.66) years after surgery.

Morbidity and mortality. Overall, 29 (19%) of patients had short- or long-term postoperative problems ranging from serious (n = 10), moderate (n = 14), to minor (n = 5). There are six known deaths in this cohort. Two deaths (one active IS; one no history of IS) occurred intraoperatively from excessive blood loss or metabolic acidosis.9 In addition, four deaths occurred many months to years after surgery. One died from head injury and intracranial bleeding after a fall (active IS), another from status epilepticus (active IS), the third from pneumonia (no history of IS), and the last from progression of their leukodystrophy (active IS). Other serious complications included three emergent reoperations for acute postsurgery epidural/subdural hematomas (two active IS; one treated IS), and a case of an unexpected posterior cerebral artery infarction (treated IS).

Of the moderate complications, the most frequent was reoperation to extend the surgical resection for recurrent seizures (n = 12; 5 active IS, 3 treated IS, and 4 no history of IS), followed by one patient with a chronic subdural hygroma treated with a subdural shunt (treated IS), and one patient requiring cranioplasty for a skull defect (treated IS). Of the 12 reoperations for recurrent seizures, control after the final procedure was achieved in 33% (1/5 active IS, 1/3 treated IS, and 2/4 no history of IS). Minor complications consisted of postoperative cranial infections, all successfully treated with antibiotics (two active IS, two no history of IS), and one patient had a transient 3rd nerve palsy (active IS). In this series, patients with active IS had a higher incidence of morbidity and mortality (36%) compared with treated IS (15%) and no history of IS patient groups (12%; p = 0.01). Shunts, which were not considered an operative complication, were necessary in 38 (24.7%) patients, and there were no differences between active IS (31%), treated IS (20%), and no history of IS (25%) patient groups (p = 0.56).

Pre- and postsurgery developmental assessments. VABS interviews were conducted on 83 (53.9%) patients, before (n = 75) and after surgery (n = 63). Of these, 55 patients had both pre- and postsurgery assessments. To determine if patients who had VABS assessments were representative of the entire cohort, we compared presurgery variables in patients with and without interviews and found no differences (p > 0.08). The mean (± SD) follow-up interval was 1.8 ± 0.4 years for postsurgery VABS interviews and was not different between IS patient groups (p = 0.36).

Single factor statistical analyses found that higher postsurgery VABS ABC DQ scores were associated with: 1) treated IS patient group; 2) shorter epilepsy duration; 3) postsurgery seizure control; and 4) better presurgery VABS DQ scores. Prior to surgery, the average (± SD) VABS ABC DQ score was 39.2 ± 23 (range 6 to 122), and there were no differences between IS patient groups (figure A, p = 0.44). After surgery, the average (± SD) VABS DQ score was 41.2 ± 19 (range 5 to 114), and there were differences between IS patient groups (figure A, p = 0.0034) with treated IS greater than no history of IS cases. A slight majority of patients (53%) had increased postsurgical VABS ABC DQ scores compared with presurgery. There were significant differences between the IS patient groups in the degree of postsurgical improvement in developmental attainments. The treated IS group showed a greater increase in DQ scores compared with the active IS group (figure A right, p = 0.023).

Higher VABS DQ scores postsurgically correlated with shorter epilepsy duration for all IS patient groups in an analysis of covariance (ANCOVA; figure B). Patients with seizure control at last follow-up had higher DQ scores compared with those with persistent postsurgery seizures (figure C). In addition, increased VABS DQ scores postsurgically positively correlated with higher presurgery VABS DQ scores (r = +0.474; p = 0.0003; data not shown). Veland DQ scores after surgery did not correlate with pathologic etiology (p = 0.66), type of surgery (p = 0.15), gender (p = 0.70), side resected (p = 0.74), age at seizure onset (p = 0.07), and age at surgery (p = 0.32).

To determine which significant components from the single factor analyses contributed to postsurgery development, we performed a multiple regression statistical analysis with IS patient group, presurgery DQ score, postsurgery seizure control, and epilepsy duration as the independent variables and postsurgery VABS DQ scores as the dependent variable. Results showed that the following were associated with increased postsurgery Veland DQ scores in the multiple regression analyses; higher presurgery VABS DQ scores (p = 0.0012), IS patient group (p = 0.0014), postsurgery seizure control (p = 0.044), and shorter epilepsy duration (p = 0.049). In other words, all four clinical variables noted in the single factor statistical analyses contributed to postsurgery developmental attainment in infant-onset epilepsy surgery patients undergoing resective neurosurgery.

Discussion. In this cohort of infant-onset epilepsy surgery patients, we found that 55% of children with seizure onsets by 1 year had a history of IS. Active IS were the youngest, treated IS intermediate, and patients with no history of IS were the oldest at EEG/video telemetry and surgery (table 1). Patients with active IS, compared with the other two IS groups, had increased contralateral spikes and background frequency slowing, bilateral PFA (see table E-2), and greater short- and long-term morbidity and mortality. By comparison, patients with treated IS had numerically better seizure control 0.5 to 2 years after surgery, and significant improvements in postsurgery VABS DQ scores (figure A). Finally, increased VABS DQ scores postsurgically were associated with better presurgery developmental assessments, postsurgery seizure control (figure C), and shorter epilepsy duration (figure B) for all infant-onset epilepsy surgery patients.

It is important to recognize the potential limitations of our study when interpreting the results. For example, this is a retrospective analysis, although we did obtain VABS DQ scores pre- and postsurgery, and like most surgical studies there is no nonsurgical group of infants with unilateral symptomatic
substrates to compare with those undergoing surgery. Likewise, we cataloged patients based on their reported IS history, and whether the hypsarrhythmia was successfully treated prior to presurgery EEG/video telemetry. Reviewing previous scalp EEG reports performed at other centers, and determining if patients were treated for spasm-like clusters helped to confirm patient classification. However, it is possible that a few patients could have been misclassified because we often did not have access to the original EEG recordings, and did not clinically observe the spasm-like events before treatment. In addition, our results were based on patients with IS who underwent resective neurosurgery for unilateral symptomatic cortical abnormalities. Our finding may or may not be applicable to patients with IS that had cryptogenic causes or bilateral cortical and subcortical etiologies. Finally, we were only able to assess a portion of our patients for presurgery EEG and postsurgery developmental assessments. The group of patients with data showed similar presurgery characteristics with the entire cohort, and our sample sizes were large enough to find significant differences in VABS and EEG abnormalities between IS patient groups, supporting the notion that the sampled group was representative of the cohort.

This study found that better postsurgery seizure and developmental outcomes occurred in patients with IS that responded to medical therapy with resolution of hypsarrhythmia prior to surgery (treated IS group), which is a similar predictor of developmental outcomes for nonsurgical patients with IS. This finding suggests that lack of response to medical therapy may be an indirect indicator of more diffuse or bilateral brain pathology in a subgroup of children that present with IS.10

We also found that children without IS vs those with IS had comparable pathologic substrates, surgical procedures, presurgery EEG abnormalities including seizure frequency, and presurgery Vineland DQ scores. What differed between patients with IS and non-IS patients with infant-onset epilepsy was the longer interval from seizure onset to EEG/video telemetry and surgery. As an apparent consequence, non-IS surgery patients had worse postsurgery developmental levels vs patients with IS that re-

Figure. (A) Box plots showing pre- and postsurgery and the difference from pretosurgery for Vineland Adaptive Behavior Composite (ABC) developmental quotients (DQ), (B) scatter graph illustrating the decrease in Vineland DQ scores with longer epilepsy duration for all infantile spasms (IS) patient groups, and (C) box plot showing Vineland DQ scores by postsurgery seizure control. Numbers above or below the box plots indicate the mean (± SD). (A) Prior to surgery (left box), there were no differences in Vineland DQ scores in the active IS (n = 28), treated (Rx’d) IS, (n = 24), and no history of (H/O) IS groups (n = 23; ANOVA [analysis of covariance]; p = 0.44). After surgery, the IS patient groups (n = 25, 19, and 19) showed a difference in Vineland DQ scores (ANOVA; p = 0.0034) with treated patients showing increased scores compared with no history of IS cases (post-hoc; p = 0.0008). Post-presurgery Vineland DQ scores also showed differences between IS patient groups (n = 23, 20, and 12; ANOVA; p = 0.023). Post-hoc analysis found that treated IS group had increased DQ differences compared with active IS group (p = 0.0063). (B) By analysis of covariance (ANCOVA), longer epilepsy duration negatively correlated with lower Vineland DQ scores in all IS patient groups (p = 0.0043), and there was still a difference between IS patient groups (p = 0.0016) without an interaction between these variables (p = 0.622). R-values for the linear regression of each patient group are indicated in the figure. (C) Patients with postsurgery seizure control at last follow-up had increased Vineland DQ scores vs those with persistent seizures (t-test; p = 0.0016).
sponded to medical therapy and had earlier surgery. Put another way, in pediatric epilepsy surgery patients IS was associated with better postsurgery developmental outcomes because spasm patients were identified and referred at an earlier age and had shorter epilepsy durations and earlier surgical intervention than infant-onset epilepsy surgery patients without IS.

References

MRI in biopsy-negative dermatomyositis

E.H. Wong, MRCP; A.C.F. Hui, FRCP; J.F. Griffith, MRCP; S.M. Wong, MRCP; and C.C. Szeto, MD, Hong Kong, China

A 66-year-old man presented with proximal myopathy and a heliotrope skin rash, suggestive of dermatomyositis. Serum creatine kinase was over 40,000 IU/L. Muscle biopsy of the left vastus lateralis failed to show evidence of necrosis or inflammation. MRI demonstrated edema of the pelvic girdle muscles, but the left vastus lateralis was spared (figure).

T2-weighted MRI, especially short-tau inversion recovery sequence, is sensitive in detecting muscle edema in acute myositis.1,2 Serial changes in magnetic resonance signal intensity corresponds to disease activity.1 The cost of MRI limits its use, but it may help to confirm muscle inflammation in patients with nondiagnostic biopsy.2

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Figure. Axial T2-weighted fat-suppressed MRI of the proximal thighs. The high signal areas represent muscle and subcutaneous edema. The adductor longus (*) and vastus lateralis (**) muscles were spared. The focal disruption of the subcutaneous tissue laterally (arrow) overlying the vastus lateralis muscle corresponds to the track of the percutaneous muscle biopsy.
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