New-onset temporal lobe epilepsy in children

Lesion on MRI predicts poor seizure outcome

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Abstract—Objective: To determine factors predictive of long-term seizure outcome in children with new-onset temporal lobe epilepsy (TLE). Methods: A community-based cohort of 77 children with new-onset TLE, including 14 with possible TLE, were followed prospectively with formal review 7 and 14 years following seizure onset. Diagnoses were re-evaluated at each review, and changed when new clinical, EEG, or imaging data were compelling. Results: Sixty-four patients sustained the diagnosis of TLE over time; two were lost to follow-up. Age at follow-up was 12 to 29 years (median 20 years). Median follow-up was 13.7 years, 95% being followed for greater than 10 years. Nineteen patients were seizure free (SF) and off treatment, having not had seizures for 5 to 15 years. Duration of active TLE in the SF group was 1 to 8 years, the children being treated with 0 to 3 antiepileptic drugs (AEDs). Forty-three patients were not seizure free (NSF) and had ongoing seizures or had undergone epilepsy surgery. These children were treated with 1 to 10 AEDs. Fifteen NSF patients experienced 22 nonterminal seizure remissions of 1 to 7 years duration. Seventeen children had a significant antecedent to TLE. Lesions were identified on neuroimaging in 28 and included hippocampal sclerosis (HS) in 10, tumor in 8, and dysplasia in 7. All children with lesions on MRI were NSF (p < 0.001). Focal slowing on EEG was also associated with persistent seizures (p = 0.05), although this was correlated with a lesion on MRI. Infantile onset of epilepsy, family history of seizures, initial seizure frequency, antecedents, and early seizure remissions were not predictive of seizure outcome. Conclusion: Seizures spontaneously remit in approximately one third of children with new-onset TLE. A lesion on MRI predicts intractable seizures in TLE and the potential need for epilepsy surgery.

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Temporal lobe epilepsy (TLE) in adults frequently begins in childhood; 70 to 80% of patients are refractory to medication. Epilepsy surgery is considered in suitable candidates, with superior results when compared with continued medical treatment. Studies of adults with TLE have shown a long delay from seizure onset to presentation for epilepsy surgery. Recognition of features present at seizure onset that might differentiate children with a benign course from children whose seizures will be intractable may improve treatment.

There is little published on the natural history of TLE in children since the comprehensive Oxford study of long-term outcomes. This study has limited relevance today as 1) it preceded modern neuroimaging; 2) its descriptions of etiologic factors were limited to birth injury, trauma, and CNS infection; and 3) only a small number had surgery yielding definitive pathology. Advances in antiepileptic drug (AED) and surgical treatment further remove this study from modern practice. More recent outcome studies of TLE in children have been based in tertiary centers, had small patient numbers, or were not focused specifically on TLE.

With the aim of better understanding the natural history of TLE in childhood, a community-based cohort of children with recent-onset and well-characterized TLE was followed from the early 1990s, primarily to identify features at presentation that might predict long-term outcome. Here we report seizure outcome 15 years from study commencement.

Methods. Ascertainment and initial assessment. During 1991 to 1993, 318 children with suspected, recent-onset partial seizures of temporal lobe origin were ascertained from a variety of sources in the state of Victoria, Australia. Criteria for enrollment in the cohort were a history of two or more unprovoked partial seizures
of temporal lobe origin, with onset of seizures before age 15 years, between 1989 and 1992, and while resident in the state of Victoria. EEG and imaging corroboration of the clinical diagnosis were not necessary. A total of 241 children were confidently excluded because they either had generalized or extratemporal seizures, nonepileptic events, or temporal lobe seizures outside the onset criteria. Fourteen children were diagnosed as having possible TLE, having insufficient information to confidently diagnose or exclude TLE at enrollment; they included children with definite partial epilepsy but uncertainty about seizure localization, infants with stereotyped episodes suggestive of temporal lobe seizures but lacking supportive EEG and imaging data thought necessary to substantiate a diagnosis of TLE at this age, and children with generalized convulsive seizures and a history of a preceding aura but no independent complex partial seizures. Sixty-three children were reclassified as TLE at enrollment as having definite TLE, their clinical and investigation findings being previously reported. Information obtained at enrollment in the 77 children with TLE and possible TLE included demographic data, descriptions of seizure semiology, seizure frequency, presence or absence of significant antecedents, history of febrile convulsions, family history of seizures, AEDs prescribed, initial response to AEDs, developmental and cognitive status, behavioral and psychosocial profiles, and initial imaging findings. MRI was performed in 65 children, and CT in 10; no imaging was performed in two children with possible TLE. Video-EEG monitoring (VEM) was performed in children with frequent or predictable seizures. All 77 children were followed prospectively with maintenance of seizure and AED diaries. Patients were managed by their treating neurologist or pediatrician.

Follow-up assessments. Formal review was performed during 1997 to 1999 in 75/77 (97%) and during 2004 in 72/77 (94%). Two patients were lost to follow-up shortly after enrollment and contributed no follow-up information. One was a 15-month-old infant with partial seizures and prior Haemophilus influenzae meningitis in whom CT brain was normal but MRI was not performed. The other was a 5-month-old infant with temporal lobe seizures confirmed on VEM in whom MRI was normal. Two children with a seizure onset in adolescence were reviewed in 1997, at ages 17 and 18 years, but were unable to be contacted in 2004. A third child did not participate in formal review but underwent epilepsy surgery, from which perioperative information and 2 years of postoperative follow-up data were available. These latter three children each contributed 8 years follow-up to the analysis. All reviews in 1997 to 1999 were in person. Reviews in 2004 were conducted in person in 58 patients and via telephone in 14, as many patients were now young adults living independently, some interstate. Data on seizure frequency, seizure semiology, AEDs, new family history, education, vocation, and behavior were obtained at both reviews. Neuropsychological testing was repeated following wider recognition and acceptance of infantile forms of TLE,16–20 we re-classified three infants with clinical features of TLE but no corroborative EEG or imaging findings to the TLE group; we had previously included only the one infant with VEM confirmation of temporal lobe seizures. The remaining nine possible TLE cases were ultimately excluded. New diagnoses in six included idiopathic partial epilepsy in two, extratemporal epilepsy in two, and generalized epilepsies in two. There were insufficient data to make a definite diagnosis in two cases, with a suggestion that their episodes were nonepileptic. A child being followed with episodic rage following herpes simplex encephalitis did not develop typical complex partial seizures. Thus, 64 children were ultimately diagnosed with new-onset TLE and 62 (97%) had long-term follow-up. The classification of patients at enrollment and subsequent reviews is summarized in figure 1. These 62 patients are the basis of the subsequent analysis. Temporal lobe seizures were ultimately recorded on VEM in 31/62 (50%) children. MRI was ultimately performed in 58/62 (94%) patients, 51 having repeat MRI at 1.5 T using a high-resolution epilepsy protocol; CT imaging only was performed in three children and no imaging was performed in one infant with a short duration of TLE and subsequent seizure remission.

Classification of patients. Diagnoses in the TLE and possible TLE groups were re-evaluated at each review by a panel consisting of two pediatric epileptologists and one adult epileptologist. The panel was not blinded to previous reviews. A change in diagnosis was made where subsequent clinical, EEG, or imaging data were considered sufficient, such as the finding of an epileptogenic lesion on MRI or recording of events with VEM. However, the enrollment principle that corroborative EEG or imaging data were not mandatory to diagnose TLE was maintained. Seizure outcome. Seizure frequency during the course of TLE was categorized as daily, weekly, monthly, quarterly, and yearly for each calendar year of follow-up. Seizure outcome at the most recent follow-up was categorized according to the presence or absence of seizures and medication status. A seizure free (SF) group was defined as those patients having no seizures and being off AEDs for a minimum of 2 years. A not seizure free (NSF) group was defined as those patients with persistent seizures, regardless of AEDs, seizure frequency, progression to epilepsy surgery, or postoperative seizure outcome. Time to intractability was defined as time to efficacy failure of two or more AEDs;17 seizure frequency was not used in our definition of intractability. Clinical features and investigation findings present at enrollment were assessed with respect to long-term seizure outcome. Categorical data were analyzed using χ2. Kaplan-Meier survival curves were used to test the equality of the survival distributions for different factors.
Figure 1. Classification of the 318 children ascertained with possible new-onset partial seizures of temporal lobe origin. In the original description of the cohort there were 63 children in whom a confident diagnosis of temporal lobe epilepsy (TLE) was made and 14 children in whom the diagnosis was possible. At the 2004 review, two of these children were lost to follow-up, definite diagnoses of TLE were made in five with possible TLE, and TLE was excluded in four of the original 63 with TLE. This left the 62 children with new-onset TLE and long-term follow-up who are the basis of this report.

Over the course of follow-up and repeat MRI, two children with previously normal imaging had abnormalities subsequently identified. A child with infrequent partial seizures and severe global delay preceded by encephalitis in early infancy, not imaged with MRI at enrollment, was found to have bilateral HS on scans at age 3 and 11 years. A child with VBM-confirmed independent bilateral temporal seizures and severe global delay was believed to have a normal MRI when enrolled as an infant; he was later found to have heterotopic gray matter and prominent signal abnormality in the temporal lobe white matter bilaterally, suggesting cortical dysplasia, not appreciated on earlier scans due to incomplete myelination.

Thus, there were 28 patients with lesions on MRI that would have been present at onset of TLE, being identified either at enrollment, on subsequent review of enrollment scans, or with subsequent MRI. The temporal lobe lesions were HS in 10 (bilateral in 2), tumor in 8, dysplasia in 7, and temporal lobe atrophy, gliosis, or cystic change in 3. Of the 17 children with significant antecedents to TLE, 16 had MRI performed and temporal lobe lesions were identified in 14, 10 having HS (p < 0.001).

Seizure outcome and treatment. At the most recent follow-up, 19 patients (31%) are seizure free and off treatment (SF group), with a median seizure-free duration of 10 years (range 5 to 15 years). Forty-three (69%) children either continue to have seizures on or off treatment, or have progressed to epilepsy surgery because of refractory seizures (NSF group). There were no patients with seizures controlled on AEDs at follow-up, other than some postoperative patients. The age at onset of seizures, periods of ongoing seizures and seizure remissions, age at epilepsy surgery, and age at the recent review are shown schematically in figure 2.

Clinical and investigation findings present at onset and early in the course of TLE are presented in the table, separated by SF and NSF status. A lesion on MRI was the only independent predictor of seizure outcome, all children with lesions having persistent seizures or undergoing epilepsy surgery for medically resistant seizures (p < 0.001). Temporal slowing on interictal EEG recordings at seizure onset was associated with seizure intractability, though this was associated with lesion status (p = 0.04). Although more children with significant antecedents had persistent seizures, this did not reach significance and it also correlated with lesion status (p < 0.001). Although not significant, the majority of the SF group had infrequent seizures at enrollment, with only four children having a seizure frequency greater than monthly at onset.

In the SF group, five children were never treated with AEDs. Of the 14 children treated, carbamazepine was the first drug in all cases. Only two treated children had no further seizures after commencement of AEDs. Seven treated children had a sustained reduction in seizure frequency and five had no change in seizure frequency until later eventual remission. Only four children in the SF group commenced a second AED and one child commenced a third AED, 5 months to 6 years (median 14 months) after seizure onset. In the NSF group, all but one child was treated with AEDs. The untreated child had persistent but infrequent simple partial seizures. The first drug was carbamazepine in 37, sodium valproate in 4, and phenobarbital in 1. One to 10 AEDs (average 3) were trialed over the
course of follow-up, the second AED being commenced between 1 month and 7 years from seizure onset.

Nine NSF children had not yet commenced a third AED or progressed on to other nonmedical therapies. For the remaining 35 children in the NSF group, time to intractability (as defined) ranged from 3 months to 15 years (median 3 years). All but four children progressing to a third AED had monthly or greater seizure frequency. One child in the SF group (figure 3, Case 11) would have met criteria for intractability 3 years following seizure onset; at follow-up she had been seizure free for 10 years and off treatment for 8 years. The time to intractability according to lesion status is illustrated in figure 3.

The duration of epilepsy in the SF group was 1 to 8 years (median 4). Follow-up without seizures in this SF group is 8 to 15 years (median 10). Only two children in the SF group had a period without seizures of greater than 1 year followed by a recurrence of seizures, prior to terminal remission. However, excluding seizure free periods following epilepsy surgery, 13 NSF children accounted for 22

Table Clinical and investigation findings present at seizure onset and early in the course of their epilepsy for the 62 children followed with new-onset temporal lobe epilepsy, separated according to long-term seizure outcome (median follow-up 13.7 years)

<table>
<thead>
<tr>
<th>Clinical and investigational data</th>
<th>Seizure free, n = 19</th>
<th>No seizure free, n = 43</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant onset of epilepsy*</td>
<td>5</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>Significant antecedent</td>
<td>3</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Febrile convulsions (all)</td>
<td>4</td>
<td>9</td>
<td>1.00</td>
</tr>
<tr>
<td>Prolonged febrile convulsions</td>
<td>2</td>
<td>5</td>
<td>0.09</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>3</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Seizure frequency per week at enrollment</td>
<td>5</td>
<td>20</td>
<td>0.1</td>
</tr>
<tr>
<td>EEG temporal slowing</td>
<td>5</td>
<td>23</td>
<td>0.05</td>
</tr>
<tr>
<td>EEG temporal epileptiform</td>
<td>8</td>
<td>24</td>
<td>0.3</td>
</tr>
<tr>
<td>EEG normal</td>
<td>8</td>
<td>9</td>
<td>0.10</td>
</tr>
<tr>
<td>MRI lesion†</td>
<td>0</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early seizure control on antiepileptic drugs‡</td>
<td>4</td>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Age < 2 years.
† MRI performed in only 58/62.
‡ Early seizure control defined as entering terminal remission or seizure-free period > 1 year within the first 2 years.

Figure 3. Kaplan-Meier survival curve showing the development of intractable temporal lobe epilepsy over time, with and without a temporal lobe lesion on MRI. Lesional cases (solid line), non lesional (dashed line). p < 0.0001; hazard ratio 5.1 (4.5 to 18.9). Intractability was defined as efficacy failure of two antiepileptic drugs.
periods of temporary seizure remission of 1 year or more. These temporary seizure remissions lasted 1 to 7 years (mode 1, median 2).

Twenty-one patients underwent epilepsy surgery, all having lesions. Duration of TLE prior to surgery was 0.3 to 14 years (median 6). The delay to surgery from onset of intractability, defined as the time of failure of a second AED, was 0 to 8 years (median 1). Surgery was temporal lobectomy in 14 and corticectomy or lesionectomy in 7. Histologically confirmed lesions were HS in 7, dysembryoplastic neuroepithelial tumor in 3, ganglioglioma in 2, astrocytoma in 2, cortical dysplasia in 6, and Rasmussen encephalitis in 1. Dual pathology was noted in one patient with left temporal lobe cortical dysplasia identified on MRI and confirmed on histopathology, and a hypothalamic hamartoma identified on subsequent MRI. Following surgery, nine children are seizure free, four have isolated auras only, and eight have seizures at a reduced frequency. Of the remaining seven lesional patients who have ongoing seizures, three are surgical candidates but four are not, due to bilateral temporal lobe lesions and independent bilateral seizure onsets.

Discussion. We found during a median follow-up of 13.7 years that TLE spontaneously remitted in approximately one third of children and persisted in two thirds, the only factor present at seizure onset which predicted persistent seizures being the presence of a temporal lobe lesion on MRI.

In the recent epilepsy literature there are several important outcome studies dealing with childhood epilepsies overall, but few studies of localization-related epilepsies in children, and TLE more specifically. In one outcome study 29 children with complex partial seizures (83% temporal) were recruited from pediatric neurologists in a tertiary referral center and followed for 14 years. At follow-up, 28% were medically responsive, with 20% obtaining seizure freedom, and 72% were medically refractory, with 45% progressing to surgery. Our study reports twice the number of patients, with ascertainment soon after seizure onset and at a community level, likely explaining the higher rate of seizure remission.

Young age at seizure onset, developmental delay, early risk factors, status epilepticus, frequent pre-treatment seizures, poor initial response to AEDs, structural brain abnormalities, and diffuse abnormality on interictal EEG are reported in various pediatric epilepsy studies, not specifically TLE, to be associated with poor seizure outcome. In our study, 5/13 children with seizure onset before age 2 years became seizure free, such that young age at onset was not an independent predictor of poor outcome in TLE. Four infants had a course typical of benign partial epilepsy of infancy, a syndrome that was not well established at study commencement such that three children were initially classified as having possible TLE. We did not find an association between significant antecedents and seizure outcome, though there was an association between significant antecedents and lesion on MRI, specifically prolonged febrile seizures and HS. There was a trend for less frequent seizures at onset in children who became seizure free, though the categorization of seizures in TLE by interseizure periods is made difficult by seizure variability and clustering. Focal slowing on interictal EEG was associated with persistent seizures, but not unexpectedly was associated with lesion status; it did not remain an independent predictive factor when lesion status was controlled. Focal temporal epileptiform activity on EEG was not predictive of seizure outcome.

Early response to treatment or a period of seizure freedom within the first 2 years was not predictive of long-term seizure freedom in our study. This finding is in contrast to previous reports where response to treatment with the first AED was highly predictive of outcome at 2 years in children with TLE. In addition, failure of initial AED treatment was predictive of poor seizure outcome in a study of 525 adults, with only 11% of patients refractory to the first drug becoming subsequently seizure free. These findings however do not necessarily imply that an initial good response to medication predicts long-term seizure remission, particularly as drug honeymoons are well recognized in TLE. It is reported in patients referred for epilepsy surgery that 26% had a prior seizure remission with a mean duration of 2 years, younger age being associated with a higher probability of temporary remission, suggesting an early benign course does not necessarily ensure a good long-term outcome. The early course that epilepsy takes during treatment may reflect the nature of the seizure disorder in some instances, and at best be an early marker of intractability, but it is neither a biologic determinant of prognosis nor a factor that can be considered at presentation in patients with TLE.

Children in the SF group did not enter terminal remission until a median of 4 years from seizure onset. Persistence with monotherapy in this group, despite the majority not entering immediate seizure remission, perhaps reflects the lower seizure frequency in this group, the greater tolerability of partial seizures in young children, and the community-based management by pediatricians in many cases. Although all but one of the 43 refractory patients were treated with an appropriate first-line AED, only 39 commenced a second AED and 35 a third AED. The likelihood that more aggressive management in these cases would change long-term outcome is marginal. In a study of children presenting for epilepsy surgery, 21 were found to have had limited medical management, but institution of appropriate medical treatment led to improvement in only two. Repeated trials of AEDs following efficacy failure only rarely leads to improved seizure control. Thus, the persistence of seizures over prolonged follow-up in our study, regardless of treatment, is likely a reflection of inherent intractability in those patients.

In our study we found the presence of a lesion on
MRI to be the only significant and independent predictor of seizure outcome in childhood-onset TLE. Structural brain abnormalities or symptomatic etiology are associated with poor prognosis for epilepsies in children, though a direct association in TLE is not reported. Previous studies have identified the association of a temporal lobe abnormality on MRI with poor seizure outcome, however once results of treatment were known, the MRI findings did not contribute additional predictive value and any significance was deemphasized. Some studies in adult epilepsy have not shown an association between lesion status and seizure outcome, perhaps due in part to the greater proportion of cerebrovascular lesions in older patients compared with the highly epileptogenic dysplasias and developmental tumors that typify symptomatic focal epilepsy in children. The current implications of lesion status predicting seizure outcome in children with TLE are obvious when one considers the availability of high quality MRI, the evidence for detrimental developmental effects of complex partial seizures in children, and the availability of epilepsy surgery at pediatric centers worldwide. Our findings also highlight the importance of reviewing old MRI scans, and potentially repeating MRI scans, to identify subtle lesions that may have been missed, particularly in children where EEG shows focal slowing. In this study, 13% of children were initially believed to have normal MRI, but abnormalities were subsequently detected on re-review of original scans or on repeat MRI.

Our study has limitations. The diagnosis of TLE was based predominately on seizure descriptions, VEM being obtained in only half the cohort. However, diagnosis based on expert neurologic opinion was employed in several cohort studies, possibly with greater rigor in our study given the narrow diagnostic window and personal review of all cases. We believe potential inclusion of patients based on seizure descriptions alone should be considered a relative strength of our study, as children with infrequent seizures or normal imaging or EEG are underrepresented in hospital-based studies and surgical series. The commitment to redefining the cohort over time and transparency of subsequently excluded cases further strengthens the integrity of the cohort. The cases excluded on follow-up would all be correctly diagnosed if they presented now with the same clinical, EEG, and MRI findings at onset, given the advances in imaging and clinical epileptology, particularly the recognition of a wider spectrum of idiopathic partial epilepsies in childhood. Furthermore, the detailed description provided of the diagnostic process provides insight into the difficulties associated with managing TLE in children, with change of diagnosis being a not infrequent outcome in clinical practice. In patients not undergoing VEM, there is the possibility that seizure onset might have been juxta-temporal, with propagation to the temporal lobe. However, we believe potential inclusion of patients with juxta-temporal epilepsy would impact minimally on the overall findings of the study, in contrast to the impact of potential inclusion of patients with nonepileptic conditions and idiopathic partial epilepsies, conditions that we are confident were excluded.

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References

Anterior choroidal artery aneurysm mimicking cavernous sinus syndrome

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A 54-year-old man developed sudden left-sided headache and diplopia. There was complete left ophthalmoplegia and decreased sensation in the ophthalmic and maxillary divisions of the trigeminal nerve. CT angiography showed an aneurysm in the supraclinoid portion of the left internal carotid artery (figure). An emergent clipping of the aneurysm was done, which confirmed that the aneurysm originated from the proximal part of the left anterior choroidal artery (ACho). The ophthalmoplegia and trigeminal sensory loss gradually resolved in 1 month.

Although ACho aneurysm can produce ophthalmoplegia,1 our patient showed that extremely elongated aneurysm may produce symptoms mimicking cavernous sinus syndrome.

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Figure. CT angiography shows an elongated, 10 × 5 mm, posteriorly, inferiorly, and medially directed aneurysm in supraclinoid portion of the internal carotid artery (left lateral view) which seems to have mechanically compressed cranial nerves through dura matter. ACA = anterior cerebral artery; MCA = middle cerebral artery; ICA = internal carotid artery.
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