Use of Anterior Temporal Lobectomy for Epilepsy in a Community-Based Population

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Objective: To assess the hypothesis that use of anterior temporal lobectomy (ATL) for temporal epilepsy has diminished over time.


Setting: The Rochester Epidemiology Project based in Olmsted County, Minnesota.

Participants: Residents of Olmsted County.

Main Outcome Measures: Poisson regression was used to evaluate changes in ATL use over time by sex.

Results: Over a 17-year period, from 1993 to 2009, 847 ATLs were performed with the primary indication of epilepsy (average, 50 procedures/year). Of these, 26 occurred among Olmsted County residents. The use rates declined significantly between 1993 and 2000 (8 years) and 2001 and 2009 (9 years) according to Poisson regression analysis, from 1.9 to 0.7 per 100,000 person-years (P=.01). The rate of ATL use among Olmsted County residents was 1.2 (95% CI, 0.9 to 2.4) per 100,000 person-years of follow-up over this 17-year period. The sex-specific rates were 1.6 (95% CI, 0.9 to 2.4) and 0.7 (95% CI, 0.2 to 1.3) per 100,000 person-years for females and males, respectively.

Conclusions: In this community-based cohort, the rate of ATL use was 1.2 per 100,000 person-years of follow-up. Use of this procedure has declined over time; the reasons for this are unknown but do not include referral pattern changes.

or more effective medical treatment, representing an opportunity for further investigation.

METHODS

This protocol was approved by the Mayo Clinic Rochester institutional review board. Cases were identified by searching the database of the neurosurgical department at the Mayo Clinic in Rochester, Minnesota, for epilepsy or medically intractable seizures as the primary indication and temporal lobectomy as the primary procedure. To ensure complete case accrual, we also undertook a second search of the Mayo Clinic medical database using all patients with TLE admitted for ATL (International Classification of Diseases, Ninth Revision, Clinical Modification codes 345.41 and 345.51; primary procedure code, 01.53). These records were then reviewed to ensure proper inclusion. All patients undergoing ATL for seizure control of TLE between 1993 and 2010 were included. Temporal lobe epilepsy was confirmed by a neurologist specialized in the treatment of seizures; all patients had appropriate semiology and video electroencephalogram confirmation of this diagnosis.

ROCHESTER EPIDEMIOLOGY PROJECT

Epidemiologic research in OC is possible because of the country’s isolation from other major cities and the comprehensive medical records linkage system of the REP, which includes the records of visits to all providers of medical care to residents of OC.10 All neurosurgical care to local residents is delivered by the Mayo Clinic because there are no facilities where such care is available locally.1,10 According to the US census data, the population of OC was 106,479 in 1990, increased to 124,277 in 2000, and increased further in 2010 to 144,248.10,11 Olmsted County residency was defined as residence within OC for at least 1 year prior to the patient’s ATL.

GENETIC EPIDEMIOLOGY OF SEIZURE DISORDERS IN ROCHESTER STUDY

The Genetic Epidemiology of Seizure Disorders in Rochester Study (GESDR) database, used in this study to assess incidence of both focal epilepsy and febrile seizures in patients with epilepsy, is a population-based investigation of familial risks of epilepsy using REP resources. The GESDR has been previously described.12 Briefly, the GESDR comprised all residents of Rochester born in 1920 or later who had incidence of either epilepsy (2 or more unprovoked seizures) or an isolated unprovoked seizure from 1935 through 1994.13 Information on each patient’s history of febrile seizures was obtained through a comprehensive review of all information in the medical record.

OVID MEDLINE PUBLICATION SEARCH

Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1948 to Present (Ovid Technologies, Inc) were used to search mesh terms epilepsy, temporal lobe with surgery. Then these publications were binned by year from 1980 to 2010 to demonstrate the overall publications related to ATL.

STATISTICAL ANALYSES

We computed use rates for ATL using as the numerator surgeries among OC residents and as the denominator the OC population size as determined by census data with linear interpolation for the intercensal years according to published methods.10,11 Statistical analysis was performed with JMP version 8.0 (SAS Institute Inc) for analysis of variance and Kruskal-Wallis trend tests; further specialty programming with SAS was used to perform Poisson regression analysis. Linear regression of trends was performed in GraphPad Prism (GraphPad Software Inc).

RESULTS

MAYO CLINIC ATL USE

Over a 17-year period, from 1993 to 2009, 847 ATLs were performed with the primary indication of medically intractable epilepsy. Fifty procedures were performed on average per year. Of these, 26 were performed on OC residents. One patient declined research use of his or her medical records and was therefore excluded. Table 1 re-

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Cases</th>
<th>% of Total Cases</th>
<th>95% CI</th>
<th>OC Cases</th>
<th>% of Total Cases</th>
<th>95% CI</th>
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<td>63</td>
<td>7</td>
<td>6-9</td>
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<td>8</td>
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<tr>
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<td>80</td>
<td>9</td>
<td>8-12</td>
<td>6</td>
<td>23</td>
<td>11-42</td>
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<tr>
<td>1995</td>
<td>86</td>
<td>10</td>
<td>8-12</td>
<td>3</td>
<td>12</td>
<td>4-29</td>
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<tr>
<td>1996</td>
<td>76</td>
<td>9</td>
<td>7-11</td>
<td>2</td>
<td>8</td>
<td>2-24</td>
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<tr>
<td>1997</td>
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<td>8</td>
<td>6-10</td>
<td>3</td>
<td>12</td>
<td>4-29</td>
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<tr>
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<td>35</td>
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<td>4</td>
<td>1-19</td>
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<tr>
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<td>4</td>
<td>3-6</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>2009</td>
<td>28</td>
<td>3</td>
<td>2-5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 847 100 26 100

Abbreviation: OC, Olmsted County, Minnesota.
ports the number of cases per year, percentage of total cases per year, and the 95% CIs for both the total cases performed and OC cases. The first 5 years (1993-1997) had significantly more cases than later years (Figure 1). Linear regression analysis demonstrated a negative slope of −0.37 (95% CI, −0.47 to −0.25; \( P < .001 \)). Overall, there is a reduction in cases over the study period.

**POPULATION-BASED ANALYSIS**

To determine whether this change resulted from changes in referral patterns or a reduction in ATL use over time, we analyzed population-based ATL use. Because of small numbers, we divided the data into 2 periods: 1993 to 2000 (8 years) and 2001 to 2009 (9 years). The use rates declined significantly between these 2 periods according to Poisson regression analysis, from 1.9 to 0.7 per 100 000 person-years (\( P = .01 \)) (Figure 2). The population-based use rate of ATL in OC was 1.2 (95% CI, 0.9 to 2.4) per 100 000 person-years of follow-up over the 17-year period. Use rates were higher in females than males (1.6; 95% CI, 0.9 to 2.4 vs 0.7; 95% CI 0.2 to 1.3 per 100 000 person-years; \( P = .03 \)).

**TLE AND SURGERY PUBLICATIONS**

Publication trends should reflect contemporary practice activity and may give insight into use of a procedure. Certainly publication trends would not increase the incidence of ATL; however, they likely reflect the procedure’s increased use. Our Ovid MEDLINE search revealed 2327 publications pertaining to mesh terms temporal lobe epilepsy and surgery. From 1980 to 2010, 2099 articles were published. Figure 3 demonstrates the trend in publications over this period. There was a significant increase in publications starting after 1988 (\( P < .001 \), linear regression analysis).
therefore, this study was undertaken to provide evidence
and further investigation is warranted as to the cause of this.
are potential candidates for surgical
12-16 Therefore, it is possible that a reduction in
of focal epilepsy of unknown cause among Rochester residents in the same REP population.12
Figure 3. Number of publications per year of anterior temporal lobectomy and epilepsy. From 1980 to 2010, 2099 of 2327 publications pertaining to mesh terms temporal lobe epilepsy and surgery occurred via search of Ovid MEDLINE. This figure demonstrates the trend in publications over this period. There is a significant increase in publications starting after 1988 (P < .001). The line demonstrates the linear regression of this trend, which has a slope significantly greater than zero (mean [SD] slope = 4.082 [0.3196]; r² = 0.849; P < .001). Overall, there is a substantial increase in publications over the study period.

FOCAL AND FEBRILE SEIZURES

Patients with focal seizures in which one can identify the seizure-onset zone are potential candidates for surgical therapy for epilepsy. Further, some studies have suggested that occurrence of febrile seizures (either complex or simple) is a risk factor for the development of TLE, although this relationship has not been definitively established.13-16 Therefore, it is possible that a reduction in use of ATL may be caused by a reduction either in the incidence of focal epilepsy or a risk factor leading to focal epilepsy, such as febrile seizures. To evaluate this possibility, we used the GESDR data to assess the incidence of focal epilepsy of unknown cause and the prevalence of a history of antecedent febrile seizures in individuals with incidence of focal epilepsy of unknown cause among Rochester residents in the same REP population.12

Figure 4 A demonstrates a progressive decrease over time in the cumulative incidence of focal epilepsy of unknown cause among Rochester residents. Further, among individuals with incidence of focal epilepsy of unknown cause, the proportion who had a history of febrile seizures in Rochester was lower in the final decade studied in GESDR (1985-1994) than in the preceding 3 decades. In each of the 3 earlier decades, 10% or more of cases had febrile seizures (15.4% overall, from 1955-1984), whereas in the final decade relative to our data, there was a reduction to 4.9% (P = .08).

COMMENT

To our knowledge, this is the first study to assess the population-based use rate of ATL for TLE. It is clear that ATL has proliferated over the past 30 years in both procedures performed and publications.17 At our institution, we have noted a significant reduction in ATL use for TLE, and therefore, this study was undertaken to provide evidence for this observation. Several explanations for the decreased use of ATL are possible. First, the referral base for the procedure may be reduced because of more widespread use of the procedure at more centers. Second, it is possible that the source of these surgical cases, ie, focal epilepsy, is reducing or that medical intervention has decreased associated risk factors such as febrile seizures. Third, with improved imaging, perhaps cases previously diagnosed as mesial temporal lobe epilepsy may have been more recently diagnosed as extratemporal epilepsy. Fourth, the higher rate of use in the earlier years of our study may have resulted in part from a lead time bias due to the increased identification of mesial temporal sclerosis (MTS) with the introduction of magnetic resonance imaging in the late 1980s to early 1990s. Finally, the introduction of improved antiepileptic medications may have reduced the need for surgery. Regardless, it is clear from our data that despite the procedure’s popularity and efficacy, the use rate of ATL for TLE has declined and further investigation is warranted as to the cause of this.

Temporal lobectomy as a surgical procedure has been performed throughout the 20th century and is a main-
Table 2. New Anticonvulsant Medications Approved for Use in the United States From 1993 to 2009

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Year of FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigabatrin</td>
<td>1990</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1992</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1993</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1995</td>
</tr>
<tr>
<td>Tiagabine hydrochloride</td>
<td>1996</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1999</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>2000</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2000</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>2004</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, Food and Drug Administration.

FDA, Food and Drug Administration.

Fosphenytoin sodium is not included because it is not administered orally and it was previously available as phenytoin.

stay in modern epilepsy surgery. However, proliferation of this procedure away from specialized centers may have occurred because of the procedure’s popularization in the early 1980s, potentially reducing use at a single institution. To address this question, we used REP resources to assess changes in use within the stable referral population of OC residents. The rate of use of ATL among OC residents declined significantly over the 17-year period of this study, from 1.9 to 0.7 per 100,000 person-years. Although confidence in this finding is reduced somewhat because of the small number of OC residents with ATL and resulting wide confidence intervals, the distribution of the OC cases appears to be proportional to the total number of cases in the same periods. Patients in OC do not or rarely seek medical care outside of the county; therefore, all neurosurgical care is delivered to these patients at the Mayo Clinic. Therefore, given this information, we believe that the reduced use rate is highly unlikely to be due to changes in referral patterns, i.e., patients seeking care at a facility other than that which is immediately available.

One possible explanation for the reduction in use is a reduction in either the incidence of focal epilepsy or febrile seizures, a potential risk factor for medically intractable TLE. We are unable to confirm with certainty that the incidence of focal epilepsy has declined with time in OC; however, there does appear to be a trend in reduction of the incidence of focal epilepsy of unknown cause among Rochester residents (i.e., a subset of OC). Perhaps this could be due to reduction in an inciting incident such as febrile seizures. Falconer proposed the hypothesis that: MTS is the most common single lesion to be found post mortem in the brains of chronic epileptics who die a natural death. Evidence shows that it usually arises in infancy, often as a result of a prolonged febrile convulsion.

Fortunately, MTS is currently unlikely to be found post mortem but instead has been a common postoperative pathology after ATL after its proper identification by preoperative magnetic resonance imaging. Vaccination programs and preventive pediatric care may have impacted the number of events felt to be the precursor to MTS, such as complex and simple febrile convulsions. Although we cannot definitively link antecedent febrile seizure and diagnosis of MTS in our surgical cases, preventive care might have an impact on ATL use. As an example, there was a logarithmic reduction in measles cases in 1964 secondary to vaccination. Further, other viral and bacterial-related vaccination programs proliferated from the 1950s to current times. Therefore, primary prevention of infection-related fevers and associated febrile seizures or perhaps the secondary prevention of viral and now bacterial meningococcal disease may have produced a reduction in overall MTS cases seen during our study period. The introduction of these vaccination programs is concordant with our observed decrease in focal epilepsy associated with febrile seizures; however, again, it is still early to link this definitively to the decline in ATL use.

It is further possible that there was increased use at the outset of our study because of an event that brought more people to surgery in the early 1990s. An example of this is that in 1992 the initial reports regarding MTS and its magnetic resonance imaging signature of reduced volume and T2 signal changes were conducted by authors at the Mayo Clinic. This has led to an influx of cases for MTS in the early years of this study disproportionate to the referral rates for the Mayo Clinic in later years. Magnetic resonance imaging led to a similar reported increase in the incidence of acoustic neuromas in the early 1990s that was later revealed to be secondary to increased detection. Alternatively, proliferation of publications may have popularized this procedure and brought more patients to surgery during this period, as inferred by the number of publications (Figure 3). In either case, a lead time bias related to these possible sources of increased use cannot be ruled out. In conjunction with imaging improvement, it is further possible that patients previously diagnosed with MTS may have subsequently been diagnosed with extratemporal epilepsy because of improved imaging during the accrual period of this study. This could certainly account for a reduction in ATL use.

Finally, the availability of newer antiepileptic drugs may have led to better seizure control and a reduction in the use of ATL. Table 2 demonstrates the introduction of multiple medical therapies during the period of this study, which may have contributed to the decline in use of ATL. Even if these newer drugs did not increase the rates of seizure control in individuals with epilepsy, they may have provided more palatable adverse effect profiles and prevented primary surgery.

There are several limitations to this study. Overall, there are low numbers of index cases available to test our primary hypothesis, leading to wide confidence intervals. Although the sample size is small, the unique availability of the REP in our study allows estimation of the population-based use rates of ATL, which were previously unknown. The other limitations in this study are those that have been recognized previously with the REP, namely that the population is predominantly white and has unusually good access to medical care. Overall, these limitations do not appear to severely limit this study’s internal validity but may affect the generalizability to other settings. Finally, this study does provide compelling evidence to support an overall reduction in the use of ATL; it is not fully equipped to identify the cause of this re-
We report a reduction over time in the number of ATLs performed at our institution. Further, population-based use rates of the procedure have declined significantly, from 1.9 to 0.7 per 100,000 person-years. The reasons for this are unknown but may include a rapid use of available local cases, a reduction in the number of surgically treatable cases, or availability of improved antiepileptic drugs. However, referral pattern changes as a cause of reduced use are highly unlikely as shown in this unique population of patients within the REP. Overall, the population-based use rate of ATL in OC is 1.2 (95% CI, 0.9 to 2.4) per 100,000 person-years of follow-up over the 17-year period. Use rates were significantly higher in females than males.

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Conflict of Interest Disclosures: Dr Ottman serves on the scientific advisory board for and holds stock options in TriGeminal Solutions Inc; received funding for travel from the International League Against Epilepsy, the National Institutes of Health, Fallon Medica LLC, EDJ Associates Inc, and Tel Aviv University; has received speaker honoraria for nonindustry-sponsored lectures; serves as a consultant to Ortho-McNeil Jannsen Scientific Affairs LLC; received compensation from the Italian Ministry of Health; and received research support from the National Institutes of Health through grants R01 NS043472 (principal investigator), R01 NS036319 (principal investigator), R03 NS065346 (principal investigator), RC2 NS070344 (multiple principal investigators), R01 NS039422 (coinvestigator), R01 NS036630 (coinvestigator), R01 NS035398 (coinvestigator), and P20 HG005535 (coinvestigator). Dr Worrell is on the scientific advisory board for NeuroVista.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES