Risk Factors for Seizure Worsening After Epilepsy Surgery in Children and Adults: A Population-Based Register Study

Johan Bjellvi, MD [*‡]
Anna Edelvik Tranberg, MD, PhD [*‡]
Bertil Rydenhag, MD, PhD [*§]
Kristina Malmgren, MD, PhD [*‡]

*Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ‡Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden; §Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden

Parts of these data have been presented at the following congresses: as an abstract and platform presentation at the 12th European Congress on Epileptology (ILAE) in Prague, Czech Republic, on September 11-15, 2016; and as an abstract and poster presentation at the 13th European Congress on Epileptology (ILAE) in Vienna, Austria, on August 26-30, 2018.

Correspondence:
Johan Bjellvi, MD,
Department of Clinical Neuroscience,
Institute of Neuroscience and Physiology,
Sahlgrenska Academy,
University of Gothenburg,
Blå stråket 7,
413 45 Göteborg, Sweden.
Email: johan.bjellvi@vgregion.se

Received, March 20, 2019.
Accepted, September 2, 2019.
Published Online, December 3, 2019.

BACKGROUND: Increased seizure frequency and new-onset tonic-clonic seizures (TCS) have been reported after epilepsy surgery.

OBJECTIVE: To analyze potential risk factors for these outcomes in a large cohort.

METHODS: We studied prospectively collected data in the Swedish National Epilepsy Surgery Register on increased seizure frequency and new-onset TCS after epilepsy surgery 1990-2015.

RESULTS: Two-year seizure outcome was available for 1407 procedures, and data on seizure types for 1372. Increased seizure frequency at follow-up compared to baseline occurred in 56 cases (4.0%) and new-onset TCS in 53 (3.9%; 6.6% of the patients without preoperative TCS). Increased frequency was more common in reoperations compared to first surgeries (7.9% vs 3.1%; $P = .001$) and so too for new-onset TCS (6.7% vs 3.2%; $P = .017$). For first surgeries, binary logistic regression was used to analyze predictors for each outcome. In univariable analysis, significant predictors for increased seizure frequency were lower age of onset, lower age at surgery, shorter epilepsy duration, preoperative neurological deficit, intellectual disability, high preoperative seizure frequency, and extratemporal procedures. For new-onset TCS, significant predictors were preoperative deficit, intellectual disability, and nonresective procedures. In multivariable analysis, independent predictors for increased seizure frequency were lower age at surgery (odds ratio (OR) 0.70 per increasing 10-yr interval, 95% CI 0.53-0.93), type of surgery (OR 0.42 for temporal lobe resections compared to other procedures, 95% CI 0.19-0.92), and for new-onset TCS preoperative neurological deficit (OR 2.57, 95% CI 1.32-5.01).

CONCLUSION: Seizure worsening is rare but should be discussed when counseling patients. The identified risk factors may assist informed decision-making before surgery.

KEY WORDS: Epilepsy surgery, Seizure outcome, Adverse effects, Register study, Multicenter study

Neurosurgery 87:704–711, 2020 DOI:10.1093/neuros/nyz488 www.neurosurgery-online.com

Epilepsy surgery aims to treat seizures in patients with drug-resistant epilepsy. For a proportion of those who have surgery, seizures recur after the procedure. Several studies use the terms seizure recurrence and surgical failure synonymously,[1-4] but the definition of failure ultimately depends on the patient's expectations.[5] Because of the pronounced negative effects of refractory seizures, patients may regard a reduction in seizure frequency as worthwhile, even if they do not become seizure free.[6] In contrast, an increase in seizure frequency or the occurrence of more severe seizure types would constitute an obvious failure for most patients and caregivers. Therefore, unexpected seizure worsening is an important part of preoperative counseling.

ABBREVIATIONS: AED, antiepileptic drug; **CI,** confidence interval; **OR,** odds ratio; **SNESUR,** Swedish National Epilepsy Surgery Register; **TCS,** tonic-clonic seizures

Supplemental digital content is available for this article at www.neurosurgery-online.com.

To our knowledge, only 1 study addresses risk factors for seizure worsening after epilepsy surgery. In this single-center cohort, the authors found that extratemporal resections and lower preoperative seizure frequency were associated with increased postoperative seizure frequency, whereas cases with new-onset tonic-clonic seizures (TCS) were too few to explore risk factors.[7]

The aim of the present study was to estimate the risk for seizure worsening after epilepsy surgery (defined as an increase in monthly seizure frequency or the new-onset occurrence of TCS) in a large series and to explore risk factors for these events.

METHODS

Patients and Data Collection

The Swedish National Epilepsy Surgery Register (SNESUR) provides prospectively collected, population-based data on all adults and children operated on in Sweden since 1990, including extensive preoperative data, surgical data including complications, and postoperative follow-up. All 6 operating centers in Sweden report to the database at specific time points using a predetermined protocol. The validity of the data is regularly checked as described previously.[8]

Patient characteristics including results of preoperative investigations are reported to the database. Seizure types and average monthly seizure frequency the last year preceding surgery are reported at the time of the work-up based on information from the patient or caregivers. Complications are assessed at surgery and 3 mo postoperatively. Major complications are defined as unexpected surgical or neurological adverse events with persisting symptoms after 3 mo.[8]

Two years postoperatively, each surgical team reports seizure types and average monthly seizure frequency for the last year before follow-up, based on a new report from the patient or caregivers. For patients with continuing seizures or seizure relapse postoperatively, the mean monthly seizure frequency in the last year of follow-up is also categorized as follows: ≥75%, 50%-74%, or 0%-49% reduction in seizure frequency or increased seizure frequency.

The study was conducted in accordance with the STROBE statement. The regional board of medical ethics approved the study and considered follow-up after epilepsy surgery as a quality control measure not necessitating individual consent.

We analyzed data for epilepsy surgery procedures performed during January 1990 through December 2015.

Outcomes and Variables

First, we considered increased seizure frequency, defined in SNESUR as an increase in average monthly seizure frequency the last year before follow-up compared to baseline, independent of seizure types, and number of seizure days. In a post hoc analysis, we computed the number of patients with >100% increase in average monthly seizure frequency the last year before follow-up compared to the year preceding surgery.

Second, we considered TCS, defined as focal to bilateral TCS or, in generalized symptomatic epilepsy, generalized TCS. New-onset TCS are defined as TCS reported last year before follow-up 2 yr after surgery, but not the year before surgery.

Major histopathology diagnoses were categorized as hippocampal sclerosis, malformation of cortical development, low-grade tumor, vascular abnormality, gliosis, or other. Intellectual disability was categorized as none (IQ > 70), mild (IQ 50-70), or severe (IQ < 50).

Preoperative seizure frequency was analyzed both as a continuous variable and dichotomized as ≥30 seizures/mo vs <30 seizures/mo at baseline.[7,9]

Statistical Analysis

Descriptive statistics were used to report increased seizure frequency and new-onset TCS according to potential predictors. Significance tests were 2-tailed and conducted at the 5% significance level. For comparison between 2 groups, Fisher's exact test was used for dichotomous variables and Mantel–Haenszel's chi-squared test for ordered categorical variables.

Univariable binary logistic regression was used to determine the influence of each predictor variable on each of the 2 outcome variables. In the regression analyses, only first surgeries were included to avoid dependent observations for several surgeries in a single patient.

The following variables were tested: age at surgery, age at epilepsy onset, epilepsy duration, sex, preoperative neurological deficit, intellectual disability, preoperative seizure frequency (analyzed as a continuous variable and dichotomized as defined above), type of surgery, complications related to surgery, and histopathology. *P* values and odds ratios (OR) with corresponding 95% CI were calculated. Variables reaching a 2-tailed *P* value of <.10 were entered into a stepwise multivariable binary logistic regression model, in which *P* values <.05 were considered significant. The present work was an exploratory study to identify possible risk factors for worsening. No correction for multiple comparisons was used, as this would increase the risk for type 2 error.

IBM SPSS 24 was used for all statistical analyses.

RESULTS

During 1990 to 2015, 1587 epilepsy surgery procedures were performed in 1365 patients. Of these procedures, 917 (57.8%) were temporal lobe resections (TLR), 437 (27.5%) were extratemporal, including multilobar and hamartoma procedures, 75 (4.7%) were hemispheric surgeries, and 158 (10.0%) were nonresective procedures, including callosotomies and subpial transections. A total of 293 of 1587 procedures (18.5%) were reoperations. A total of 834 (52.6%) surgeries were performed in males. Mean age at surgery was 26 yr (range 2 mo-75 yr), mean age for the first seizure 11 yr (range 0-58), and mean epilepsy duration 14 yr (range 0-61).

Two-year data were available for 1407 procedures (88.7%). Reasons for lack of follow-up were epilepsy-related death (N = 10), nonepilepsy-related death (N = 5), reoperation within 2 yr (N = 95), and other specified reasons or unknown (N = 70). There were no significant differences in the proportion with follow-up related to sex, intellectual disability, preoperative neurological deficit, type of surgery, or complications at surgery. Seizure types were reported before surgery for 1574 procedures (99.2%), 2 yr after surgery for 1382 procedures (87.1%), and before and after surgery for 1372 procedures (86.5%).

Increased Seizure Frequency

At the 2-yr follow-up, increased seizure frequency last year before follow-up compared to last year before surgery occurred in 56 out of 1407 procedures (4.0%). Of the patients who were not completely seizure free since surgery (with or without aura), 56 out of 819 (6.8%) had increased frequency (Table 1).

Of the 56 procedures that were followed by increased seizure frequency, 17 were TLR, 14 frontal lobe resections,

TABLE 1. Seizures 2 yr after Surgery, Procedures With 2-yr Follow-up by First Surgeries and Reoperations (N = 1407)

Seizures 2 yr after surgery	First surgeries N = 1141 N (%)	Reoperations N = 266 N (%)	All procedures N = 1407 N (%)
Completely seizure free since surgery	456 (40.0)	62 (23.3)	518 (36.8)
Only aura since surgery	56 (4.9)	14 (5.3)	70 (5.0)
A few seizures since surgery then seizure free	84 (7.4)	14 (5.3)	98 (7.0)
Atypical seizures during AED tapering	12 (1.1)	2 (0.8)	14 (1.0)
≥75% seizure reduction	201 (17.6)	44 (16.5)	245 (17.4)
50% to 74% seizure reduction	120 (10.5)	30 (11.3)	150 (10.7)
0% to 49% seizure reduction	177 (15.5)	79 (29.7)	256 (18.2)
Increased seizure frequency	35 (3.1)	21 (7.9)	56 (4.0)

AED = antiepileptic drug.

TABLE 2. Increased Seizure Frequency and New-Onset TCS per Type of Surgery, First Procedures, and Reoperations With 2-Yr Follow-up (N = 1407)

Type of surgery	N	Increased seizure frequency N (%)			New-onset TCS* N (%)		
		First surgeries	Reoperations	All procedures	First surgeries	Reoperations	All procedures
Resective procedures	1274	30 (2.9)	14 (4.9)	44 (3.5)	29 (2.8)	14 (6.2)	43 (3.4)
TLR	823	11 (1.6)	6 (4.7)	17 (2.1)	18 (2.6)	10 (8.2)	28 (3.5)
Extratemporal resections	383	16 (5.4)	7 (8.0)	23 (6.0)	10 (3.4)	3 (3.6)	13 (3.5)
Hemispheric surgeries	68	3 (6.5)	1 (4.5)	4 (5.9)	1 (2.2)	1 (4.8)	2 (3.0)
Nonresective procedures	133	5 (4.8)	7 (25.0)	12 (9.0)	7 (7.1)	3 (11.5)	10 (8.1)
Total	1407	35 (3.1)	21 (7.9)	56 (4.0)	36 (3.2)	17 (6.7)	53 (3.9)

*Data on pre- and postoperative seizure types were not available for 35 procedures.

10 callosotomies, 4 multilobar resections, 4 hemispheric surgeries, 3 hamartoma procedures, 2 subpial transections, 1 parietal lobe, and 1 occipital lobe resection. Increased seizure frequency was less common in TLR (2.1%) compared to extratemporal resections (6.0%), hemispheric surgery (5.9%), and nonresective procedures (9.0%; $P < .001$), and less common in resective (3.5%) compared to nonresective procedures (9.0%; $P = .005$; Table 2). None of the patients were off antiepileptic drugs (AEDs) at follow-up.

Increased seizure frequency was more common after reoperations (21 out of 266, 7.9%) compared to first surgeries (35 out of 1141, 3.1%; $P = .001$). In reoperations, increased frequency was more common in nonresective (7 out of 28, 25%) compared to resective procedures (14 out of 238, 5.9%; $P = .003$; Table 2).

In the binary logistic regression analysis, only first surgeries were considered (N = 1141). In univariable analysis, the following variables were significant at the $P < .05$ level: lower age of onset, lower age at surgery, shorter epilepsy duration, preoperative neurological deficit, intellectual disability, high preoperative seizure frequency (≥30/mo), and nontemporal procedures (Figure 1 and **Table, Supplemental Digital Content 1**). No additional variables reached the $P < .10$ level predetermined for inclusion in multivariable analysis. In a stepwise multivariable logistic regression model, lower age at surgery and type of surgery were independent predictors, with OR 0.70 per 10-yr increase in age (95% CI 0.53-0.93; $P = .013$) and OR 0.42 (95% CI 0.19-0.92; $P = .030$) for TLR compared to other procedures, respectively. For illustration, Table 3 shows the proportion of first surgeries followed by increased seizure frequency in different age groups.

In a post hoc subgroup analysis, we divided first surgeries into TLR and other procedures (**Table, Supplemental Digital Content 2**). In binary logistic regression analysis, the correlation between age at surgery and increased seizure frequency was statistically significant for procedures other than TLR (OR 0.61 per 10-yr interval of age, 95% CI 0.41-0.92; $P = .017$), but not for TLR (OR 0.83, 95% CI 0.55-1.26; $P = .39$).

Doubled Seizure Frequency

In addition to any increase in seizure frequency, we calculated the number of patients with at least doubled average monthly seizure frequency in the second postoperative year. This was seen in 39 out of 1404 (2.8%) of the patients. Similar to increased seizure frequency, this outcome was significantly more common in reoperations (14 out of 264, 5.3%) compared to first surgeries

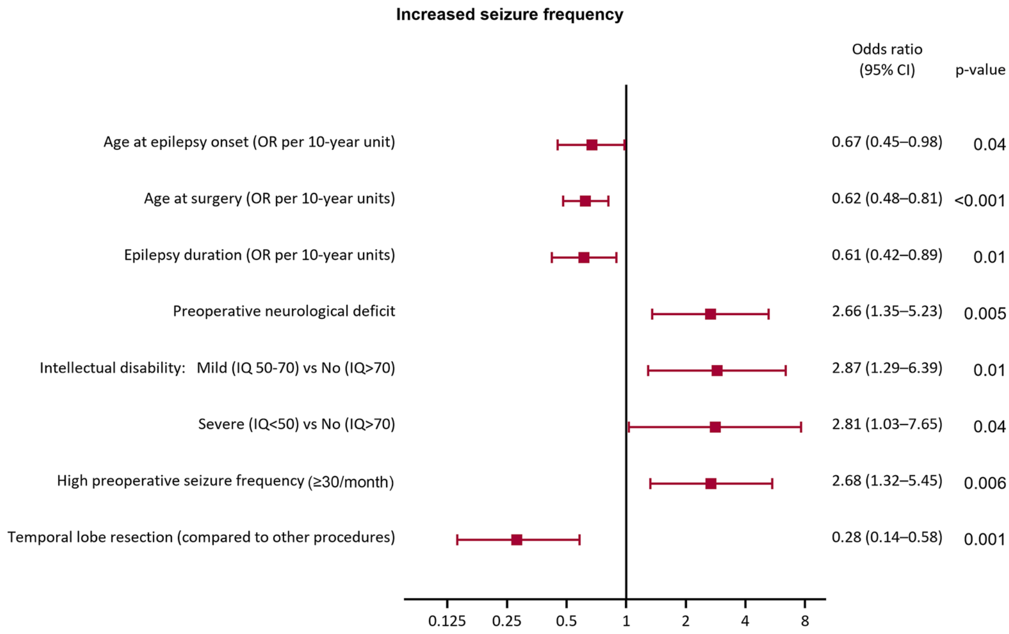

FIGURE 1. *Univariable logistic regression analysis for increased seizure frequency 2 yr after epilepsy surgery; first surgeries (N = 1141). Variables with P < .10 are shown in the figure. CI = confidence interval.*

TABLE 3. Increased Seizure Frequency and New-Onset TCS per Age Group: First Surgeries (N = 1141)

	Increased seizure frequency		New-onset TCS*	
Age (yr)	N	N (Percent within age group) with increased seizure frequency	N	N (Percent within age group) with new-onset TCS
Under 3	41	4 (9.8)	41	1 (2.4)
3 to 11	210	12 (5.7)	205	7 (3.4)
12 to 17	143	6 (4.2)	143	8 (5.6)
18 to 34	392	10 (2.6)	383	9 (2.3)
35 and over	355	3 (0.8)	348	11 (3.2)
Total	1141	35 (3.1)	1120	36 (3.2)

*Data on pre- and postoperative seizure types were not available for 21 first surgeries.

(25 out of 1140, 2.2%; $P = .011$). Furthermore, it was more common in nonresective (9 out of 130, 6.9%) compared to resective procedures (30 out of 1274, 2.4%; $P = .007$).

For binary logistic regression analysis, first surgeries were considered (N = 1140). Lower age at surgery, shorter epilepsy duration, preoperative neurological deficit, intellectual disability, high preoperative seizure frequency, and extratemporal procedures were significant predictors for doubled seizure frequency in univariable analysis. In stepwise multivariable analysis, lower age at surgery was the only independent predictor for doubled seizure frequency (OR 0.64 per increasing 10-yr interval, 95% CI 0.47-0.87).

New-Onset Tonic-Clonic Seizures

Of the 1372 cases with available data on seizure types before and after surgery, TCS occurred preoperatively in 564 (41.1%) and 2 yr postoperatively in 275 (20.0%). New-onset TCS occurred in 53 cases (3.9% of the whole cohort; 6.6% of the patients without preoperative TCS), whereas 342 (24.9%) had TCS before but not after surgery (Figure 2). Of the followed-up patients without seizure freedom since surgery (with or without aura), 53 out of 787 (6.7%) had new-onset TCS.

The cases with new-onset TCS comprised 28 TLR, 9 callosotomies, 7 frontal lobe resections, 2 hemispheric surgeries, 2 multilobar, 2 parietal lobe, 2 occipital lobe resections, and 1 stereotactic lesion. New-onset TCS were more common after nonresective (10 out of 124, 8.1%) than after resective or hemispheric procedures (43 out of 1248, 3.4%; $P = .023$; Table 2), and more common in reoperations (17 out of 252, 6.7%) than in first surgeries (36 out of 1120, 3.2%; $P = .017$; Figure 2). All patients had AEDs. A total of 9 of the 53 patients with new-onset TCS (16.7%) also had increased seizure frequency.

In the binary logistic regression analysis, only first surgeries (N = 1120) were considered. In univariable analysis, the following variables were significant at the $P < .05$ significance level: preoperative neurological deficit, intellectual disability, and

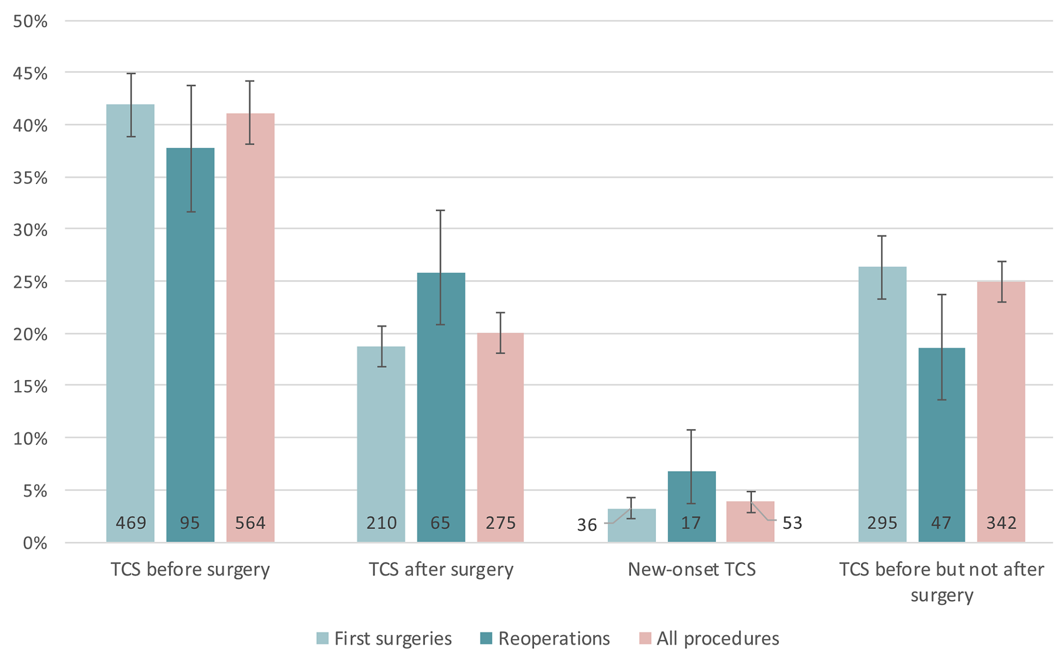

FIGURE 2. *TCS the year before surgery and the year before 2-yr follow-up. First surgeries (N = 1120) and reoperations (N = 252); proportions with 95% CI.*

nonresective procedures (compared to resective procedures and hemispheric surgeries). In addition to these, high preoperative seizure frequency (≥30/mo) and complications related to surgery reached the $P < .10$ level for inclusion in multivariable analysis (Figure 3 and **Table, Supplemental Digital Content 1**). In the stepwise multiple binary regression model, only preoperative neurological deficit retained significance (OR 2.57, 95% CI 1.32-5.01; $P = .006$). The proportion of patients with new-onset TCS in categorical age groups is shown in Table 3.

DISCUSSION

In this population-based cohort, increased seizure frequency 2 yr postoperatively occurred in 4.0% of the procedures, and new-onset TCS in 3.9%. We propose that the complete national coverage of SNESUR, including the entire range of epilepsy surgery procedures, facilitates generalization in a clinical setting. Follow-up data prospectively collected at predetermined time points minimizes the risk for reporting bias. The large size of the cohort made it possible to explore risk factors for both increased seizure frequency and new-onset TCS.

Outcomes

The rate of increased seizure frequency, 6.8% of patients not completely seizure free (with or without aura) since surgery, is comparable to the single-center study from Cleveland, where 9.8% of the patients with seizure recurrence had at least doubled seizure frequency at follow-up.[7] The proportion of cases with new-onset TCS, 3.8% of the procedures, corresponds to 6.7% of the cases without complete seizure freedom. This is higher than in the Cleveland study, where 1.4% of patients with seizure recurrence had new-onset TCS.[7] Of note, the Cleveland cohort comprised only unilobar resections. Our series also included nonresective procedures, which were associated with an increased risk for new-onset TCS.

It is important to note differences in classifications of seizure outcome. The Engel[5] classification of 1987 contained no exact definition of worsening (class IV C). As mentioned, SNESUR defined in 1990 increased seizure frequency as increase in the average number of seizures per month during the year preceding surgery or follow-up. In the 2001 ILAE proposal, worsening (class 6) is defined as a >100% increase in the baseline number of seizure days per year.[10] Although this reduces the likelihood of registering minor variability as worsening, it is less suitable for patients with very high preoperative seizure frequency. In particular, many children with drug-resistant epilepsy have daily seizures,[11] which gives rise to a ceiling effect in which increased frequency can occur without increase in the number of seizure days.

Furthermore, an increase in seizure frequency by, for instance, 50% may be considered as significant by some individuals. What constitutes clinically significant seizure worsening from the patient's perspective has indeed not been investigated, and future studies defining minimum important change for worsening are

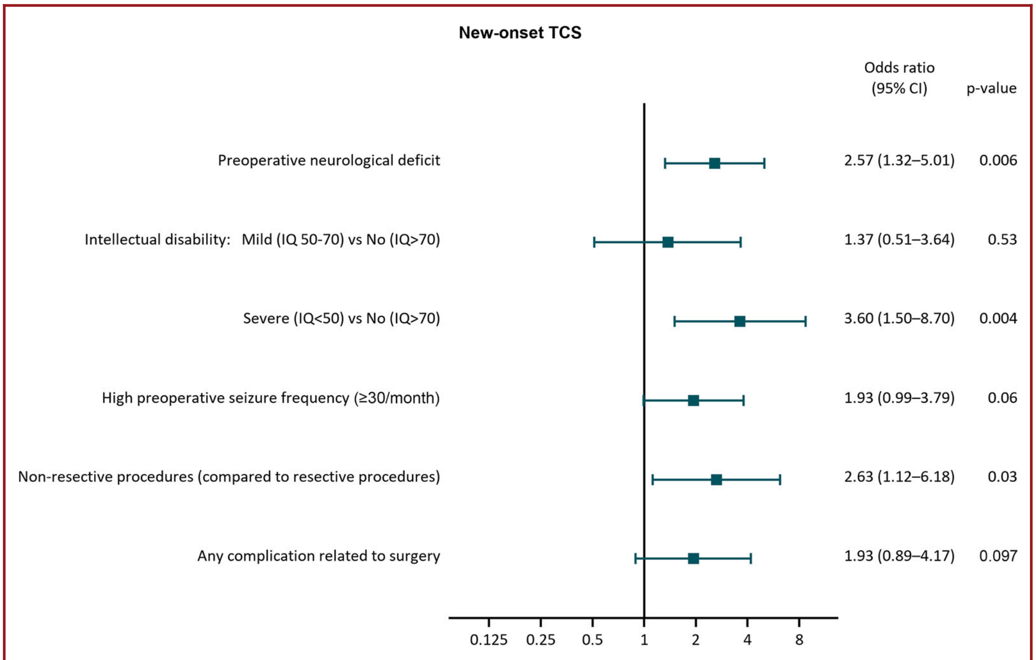

FIGURE 3. *Univariable logistic regression analysis for new-onset TCS 2 yr after epilepsy surgery; first surgeries ($N = 1120$). Variables with $P < .10$ are shown in the figure.*

warranted.[12] In our cohort, 4.0% of the patients had any increase in seizure frequency and 2.8% had a >100% increase, which indicates that a small minority have this unwanted outcome regardless of the chosen cut-off. Similar risk factors were identified for both outcomes.

Risk Factors

Seizure patterns after epilepsy surgery may change from a number of mechanisms, which can vary between types of surgery. In one study, an increased proportion of seizures evolving to bilateral TCS was found in patients with reduced seizure frequency after TLR.[13] More severe focal seizures were noted in a number of patients with reduced TCS after callosotomy.[14] In our series, reoperations carried a higher risk for increased seizure frequency and new-onset TCS. Considering first surgeries, increased seizure frequency was associated with preoperative neurological deficit, intellectual disability, extratemporal location, and high preoperative seizure frequency. New-onset TCS were associated with preoperative deficit, intellectual disability, and nonresective procedures. We hypothesize that these risk factors are markers for more complex epileptogenic networks, which are disrupted by the surgical procedure.

Several authors have linked extended epileptogenic networks to poorer outcome after epilepsy surgery.[15-18] Surgical procedures can alter network connectivity,[19] and these changes may facilitate seizure propagation in some cases. Because the numbers of cases in each group were small, the statistical analysis in our study has to be interpreted with caution, especially concerning risk factors and estimated odds ratios. However, intellectual disability, neurological deficit, and extratemporal procedures have previously been reported as risk factors for seizure recurrence after surgery,[20,21] and extratemporal resections for increased seizure frequency.[7] Similar mechanisms may be at play in these situations. In the Cleveland study, patients with <30 seizures/mo had a higher risk for increased seizure frequency. The authors hypothesized that this was due to a reporting factor or due to a ceiling effect in the propensity for seizure generation in some epileptogenic networks. We report the opposite association, which we believe is explained by the high proportion of extratemporal and nonresective procedures in our cohort.

Furthermore, we found that increased seizure frequency was associated with lower age at surgery. In a post hoc subgroup analysis, this was significant only for procedures other than TLR. Several studies have found a high proportion of malformations of cortical development in young patients with extratemporal epilepsies.[22-25] It is possible that lower age is a marker for more complex pathology in these patients. However, we could not explore the relationship between age and histopathology further in our study because of the small number of cases. More research is needed to elucidate this hypothesis.

Limitations

The lack of controls precludes causal inference between surgical procedures and seizure worsening, especially in the individual patient. The course of drug-resistant epilepsy is complex, and for a number of patients, increasing seizure frequency may be due to continuing progression of the seizure disorder.[5,7] As SNESUR reports an average monthly seizure frequency over a year, we minimize the influence of short-term fluctuations in seizure frequency, but slow progression cannot be ruled out. In some patients, postoperative seizure worsening can be ascribed to precipitating factors. In 1 study, new-onset TCS after TLR were associated with a reduction in AED therapy.[26] In the present study, however, no patients were off medication at the time of follow-up.

We acknowledge that the given figures may somewhat underestimate the risk for seizure worsening. It is conceivable that for a proportion of the 95 cases with reoperation before follow-up, seizure worsening may have prompted the decision to perform another surgery. Early reoperations should not greatly influence the relevant risk factors for seizure worsening, because there were no significant differences between cases with or without follow-up. There are also limitations inherent to the study design. Because this is a register study, the analyses were limited to the prospectively collected variables in SNESUR.

In the group of patients with new-onset TCS as here defined, we cannot rule out that some patients were free from TCS the year before surgery but had TCS earlier during the course of their epilepsy. For instance, some patients who are free from TCS with AEDs but continue to have drug-resistant focal unaware seizures may have had TCS before starting treatment. These data are not in SNESUR, but we presume that also in these patients, the occurrence of postoperative TCS would constitute an unwanted outcome.

We further acknowledge that we could not address some types of seizure worsening that are not covered in the SNESUR. These include status epilepticus,[7] persistent seizures with loss of aura, potentially implying a higher risk for injuries,[27] and changed diurnal seizure patterns, which may lead to more unpredictable or disturbing seizures.[5] Because of incomplete data on the frequency of TCS before and after surgery, we could not define a group with worsening of TCS after surgery.[7]

Finally, seizure data in SNESUR are dependent on subjective reports from the patients and caregivers. This methodological issue we share with most treatment studies for epilepsy but should be kept in mind when interpreting the data, as underreporting of seizures is known to be common, also for TCS.[28]

CONCLUSION

Increased seizure frequency and new-onset TCS are rare after epilepsy surgery, especially considering the much higher rate of substantial reduction of seizures, including freedom from TCS in many patients who have TCS preoperatively. Although we cannot establish a causal relationship between surgery and seizure worsening, patients who consider epilepsy surgery and their caregivers should be counseled adequately about the relevant risks. The identified risk factors can assist in decision-making before surgery.

Disclosures

This study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (grants ALFGBG-517901 and ALFGBG-723151), and from the Margarethahemmet foundation. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Bjellvi has received fees as a scientific advisor for the Swedish Medical Products Agency, the National Board of Health and Welfare, and the Swedish Agency for Health Technology Assessment and Assessment of Social Services, and has participated in clinical trials without personal compensation for Bial, Eisai, and Sage Therapeutics, outside the submitted work. Dr Malmgren has received fees as a scientific advisor for the Swedish Agency for Health Technology Assessment and Assessment of Social Services, outside the submitted work.

REFERENCES

1. Harroud A, Bouthillier A, Weil AG, Nguyen DK. Temporal lobe epilepsy surgery failures: a review. *Epilepsy Res Treat*. 2012;2012:201651.
2. Surges R, Elger CE. Reoperation after failed resective epilepsy surgery. *Seizure*. 2013;22(7):493-501.
3. Englot DJ, Han SJ, Rolston JD, et al. Epilepsy surgery failure in children: a quantitative and qualitative analysis. *J Neurosurg Pediatr*. 2014;14(4):386-395.
4. Barba C, Rheims S, Minotti L, et al. Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. *Brain*. 2016;139(Pt 2):444-451.
5. Engel J, Jr. Outcome with respect to epileptic seizures. In: Engel J, Jr., ed. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1987:553-571.
6. Ozanne A, Graneheim UH, Ekstedt G, Malmgren K. Patients' expectations and experiences of epilepsy surgery – a population-based long-term qualitative study. *Epilepsia*. 2016;57(4):605-611.
7. Sarkis RA, Jehi L, Bingaman W, Najm IM. Seizure worsening and its predictors after epilepsy surgery. *Epilepsia*. 2012;53(10):1731-1738.
8. Bjellvi J, Flink R, Rydenhag B, Malmgren K. Complications of epilepsy surgery in Sweden 1996–2010: a prospective, population-based study. *J Neurosurg*. 2015;122(3):519-525.
9. Edelvik A, Rydenhag B, Olsson I, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology*. 2013;81(14):1244-1251.
10. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*. 2001;42(2):282-286.
11. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for drug-resistant epilepsy in children. *N Engl J Med*. 2017;377(17):1639-1647.
12. Wiebe S, Matijevic S, Eliasziw M, Derry PA. Clinically important change in quality of life in epilepsy. *J Neurol Neurosurg Psychiatry*. 2002;73(2):116-120.
13. Henry TR, Drury I, Schuh LA, Ross DA. Increased secondary generalization of partial seizures after temporal lobectomy. *Neurology*. 2000;55(12):1812-1817.
14. Spencer SS, Spencer DD, Glaser GH, Williamson PD, Mattson RH. More intense focal seizure types after callosal section: the role of inhibition. *Ann Neurol*. 1984;16(6):686-693.
15. Bartolomei F, Lagarde S, Wendling F, et al. Defining epileptogenic networks: contribution of SEEG and signal analysis. *Epilepsia*. 2017;58(7):1131-1147.
16. Bonilha L, Jensen JH, Baker N, et al. The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy. *Neurology*. 2015;84(18):1846-1853.
17. Lagarde S, Roehri N, Lambert I, et al. Interictal stereotactic-EEG functional connectivity in refractory focal epilepsies. *Brain*. 2018;141(10):2966-2980.
18. Spencer DD, Gerrard JL, Zaveri HP. The roles of surgery and technology in understanding focal epilepsy and its comorbidities. *Lancet Neurol*. 2018;17(4):373-382.
19. Taylor PN, Sinha N, Wang Y, et al. The impact of epilepsy surgery on the structural connectome and its relation to outcome. *Neuroimage Clin*. 2018;18:202-214.
20. Bell GS, de Tisi J, Gonzalez-Fraile JC, et al. Factors affecting seizure outcome after epilepsy surgery: an observational series. *J Neurol Neurosurg Psychiatry*. 2017;88(11):933-940.

21. Clusmann H, Kral T, Fackeldey E, et al. Lesional mesial temporal lobe epilepsy and limited resections: prognostic factors and outcome. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1589-1596.
22. Nordborg C, Eriksson S, Rydenhag B, Uvebrant P, Malmgren K. Microdysgenesis in surgical specimens from patients with epilepsy: occurrence and clinical correlations. *J Neurol Neurosurg Psychiatry*. 1999;67(4):521-524.
23. Dorward IG, Titus JB, Limbrick DD, Johnston JM, Bertrand ME, Smyth MD. Extratemporal, nonlesional epilepsy in children: postsurgical clinical and neurocognitive outcomes. *J Neurosurg Pediatr*. 2011;7(2):179-188.
24. Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. *J Neurosurg Pediatr*. 2013;12(2):126-133.
25. Ramantani G, Kadish NE, Mayer H, et al. Frontal lobe epilepsy surgery in childhood and adolescence: predictors of long-term seizure freedom, overall cognitive and adaptive functioning. *Neurosurgery*. 2018;83(1):93-103.
26. Blume WT, Girvin JP. Altered seizure patterns after temporal lobectomy. *Epilepsia*. 1997;38(11):1183-1187.
27. Binder DK, Garcia PA, Elangovan GK, Barbaro NM. Characteristics of auras in patients undergoing temporal lobectomy. *J Neurosurg*. 2009;111(6):1283-1289.
28. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol*. 2007;64(11):1595-1599.

Acknowledgments

The authors thank Mattias Molin and Nils-Gunnar Pehrsson for assistance with statistical analysis, the steering committee of the SNESUR, and the Swedish epilepsy surgery teams (in Gothenburg, Linköping, Lund, Stockholm, Umeå, and Uppsala).

***Supplemental digital content** is available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content 1. Table. Univariable logistic regression analysis of predictors for increased seizure frequency and new-onset tonic-clonic seizures (TCS).

Supplemental Digital Content 2. Table. Post hoc subgroup analysis of correlation between age at surgery and increased seizure frequency in TLR and in other procedures.

COMMENT

The present study is a prospective cohort study analyzing the Swedish National Epilepsy Surgery Register for factors associated with increased seizure frequency and new onset tonic-clonic seizures (TCS) after epilepsy surgery performed between 1990-2015. The authors take advantage of this unusually large registry (over 1400 procedures with follow-up) to find that increased seizure frequency and new onset TCS after epilepsy surgery were both rare but not insignificant, occurring in approximately 4% of cases. After adjusting for other variables, they found that younger age and extra-temporal resections were associated with greater odds of increased seizure frequency and preoperative neurologic deficit was associated with greater odds of new onset TCS after surgery. The findings are not surprising given that the identified risk factors have frequently been associated with lower likelihood of seizure freedom. However, the rarity of worsening seizures and new onset TCS (at least in reported literature) and their higher than expected rates in this study make this a worthwhile report. While the factors are not modifiable they are important for informed decision-making.

Brett E. Youngerman
Guy M. McKhann
New York, New York