Incidence and prevalence of major epilepsy-associated brain lesions

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A B S T R A C T

Epilepsy surgery is an effective treatment option for drug-resistant focal epilepsy patients with associated structural brain lesions. However, little epidemiological data are available regarding the number of patients with these lesions. We reviewed data regarding (1) the prevalence and incidence of epilepsy; (2) the proportion of epilepsy patients with focal epilepsy, drug-resistant epilepsy, and drug-resistant focal epilepsies; and (3) the number of epilepsy presurgical evaluations and surgical resections. We also assessed the relative proportion of brain lesions using post-surgical histopathological findings from 541 surgical patients from the Cleveland Clinic and 9,523 patients from a European multi-center cohort. Data were combined to generate surgical candidate incidence and prevalence estimates and the first lesion-specific estimates for hippocampal sclerosis (HS), low-grade epilepsy-associated brain tumors (LEAT), malformations of cortical development (MCD), glial scars, vascular malformations, and encephalitis.

The most frequently diagnosed brain lesions were HS (incidence = 2.32 ± 0.26 in 100,000, prevalence = 19.40 ± 2.16 in 100,000) for adults and MCD (incidence = 1.15 ± 0.34 in 100,000, prevalence = 6.52 ± 1.89 in 100,000) for children. Our estimates can guide patient advocacy groups, clinicians, researchers, policymakers in education, development of health care strategy, resource allocation, and reimbursement schedules.

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Introduction

It has been estimated that approximately a third of people with epilepsy can be classified as drug-resistant and that this proportion could be higher for people with focal epilepsies [1]. Surgery is especially effective for drug-resistant focal epilepsy patients that have associated structural brain lesions such as hippocampal sclerosis (HS), low-grade developmental and epilepsy-associated brain tumors (LEAT), and malformations of cortical development (MCD) such as focal cortical dysplasia (FCD) [2,3].

Although the prevalence and incidence of epilepsy have been well-established by multiple epidemiological studies in both adults and children, no population-based studies on the frequency of epilepsy-associated brain lesions in the general population have ever been performed. As such, epidemiological estimates for the incidence and prevalence of these lesions in the pediatric and adult general population remain unknown. However, the proportions of epilepsy-associated brain lesions surgically resected from drug-resistant epilepsy patients—including HS, FCD, and LEAT—have been established through histopathological studies [2,4].

In order to improve diagnostic and surgical treatment settings, the frequency of surgically treatable epilepsy and epilepsy-associated brain lesions in the general population must be better understood. Such data are required to optimize resource allocation...
for health care services, including the training of specialists, the
types of hospital and support services provided, and the imple-
mentation of public health programs. Herein, we combined epi-
demiological data from the literature with histopathological
findings from surgical patients from the Cleveland Clinic and a
European multicenter cohort to generate incidence and prevalence
estimates of resective surgical candidates. We also provide the first
lesion-specific estimates for hippocampal sclerosis (HS), low-grade
epilepsy-associated brain tumors (LEAT), malformations of cortical
development (MCD), glial scars, vascular malformations, and
encephalitis for both adults and children in the general population
based on data from the last decades.

Methods

Approach to estimate surgical burden and brain lesion prevalence and
incidence

In order to estimate the prevalence and incidence of surgically
resectable epilepsy among adults and children, our overall
approach was to make use of existing and related epidemiological
data to calculate estimates. We first performed a systematic review
to identify studies with data related to the frequency of epilepsy,
drug-resistant focal epilepsy, and epilepsy surgery. Then, we pro-
gressively combined available epidemiological data points into
all possible sequences starting from the overall prevalence or inci-
dence of epilepsy and ending at the prevalence or incidence of epi-
lepsy surgery candidates (see Fig. 2). For example, we estimated
the prevalence of surgical candidates by combining the prevalence
of epilepsy with the rate of focal epilepsy among epilepsies, the
rate of drug-resistant epilepsy among focal epilepsies, and the rate
of epilepsy surgery among patients with drug-resistant focal epi-
lepsy. The estimated prevalence or incidence of surgical candidates
was then combined with histopathological classification results
from patients who underwent resective epilepsy surgery to calcu-
late the individual prevalence and incidence of common types of
epilepsy-associated brain lesions.

Study identification by systematic review

In order to identify studies with data related to the frequency of
epilepsy surgery, we conducted a systematic literature review of
the literature using the PubMed database on May 2020 according
to the Preferred Reporting Items for Systematic Reviews and
Meta-Analyses (PRISMA) guidelines [5].

Study identification of epilepsy subtypes for both adults and children

Using multiple search queries (Table 1), we identified studies
with epidemiological data associated with epilepsy surgery includ-
ing (1) the prevalence and incidence of epilepsy; (2) the proportion
of epilepsy patients with focal epilepsy, drug-resistant epilepsy,
and drug-resistant focal epilepsies; (3) rates of presurgical evalu-
ation and subsequent selection for surgery in epilepsy patients; and
(4) published reports specifying the frequency of various epilepsy-
associated brain lesions in surgically-resected brain tissue (Table 1).
The search was limited to studies published between January 1, 2000 and May 28, 2020. For articles involving drug-
resistant epilepsy, we only considered those which adhered to
the definition of drug-resistant epilepsy given by the International
League Against Epilepsy [6]. Two independent reviewers manually
screened the resulting articles at the title, abstract, and full text
level to eliminate reports that met our exclusion criteria (Fig. 1).
We extracted data from full text articles that met inclusion criteria

| Table 1 |

| Epidemiological Estimate | PubMed Search Query |
|--------------------------|---------------------|
| Prevalence of epilepsy    | Epilepsy AND Prevalence AND Epidemiological OR Meta-Analysis |
| Prevalence of epilepsy subtypes | Epilepsy AND Focal OR Drug Resistant OR Intractable OR Refractory AND Prevalence |
| Focal epilepsy studies   | Epilepsy AND Focal AND Cohort OR Frequency OR Population AND Retrospective(y) OR Prospective(y) |
| Drug-resistant epilepsy studies | Epilepsy AND Drug Resistant OR Intractable OR Refractory AND Cohort OR Frequency OR Population AND Retrospective(y) OR Prospective(y) OR (a)etiology |
| Epilepsy surgery and surgical evaluation studies | Epilepsy AND Surgery AND Evaluation(s) AND Prevalence OR Cohort(s) OR Candidacy AND Focal OR Drug Resistant OR Intractable OR Refractory |

and cross-referenced the included studies to identify additional
studies that met our selection criteria (Table 1; Appendix S1).

Study selection and generation of epilepsy-related epidemiological
data points

We stratified studies based on the type of reported epidemi-
ological data points, whether the studies were meta-analyses or
cohort studies, and the reported age groups (0–17 years of age
for children, 18 years of age or older for adults). For reports regard-
ing the presurgical evaluation of patients for epilepsy surgery, we
considered the fraction of patients which were selected for surgery
after a multi-disciplinary pre-surgical evaluation and not just the
fraction of evaluated patients who ultimately underwent surgery. If
one or more meta-analyses for an epidemiological data point
was available, only the largest and most recent meta-analysis
was considered. For epilepsy-related epidemiological data points
with no available meta-analyses and more than one independent
report that met our study criteria, a weighted mean was calculated
using the R package “meta” [7]. Weighted means were calculated
using a random effects model to account for variation between
studies. For epidemiological data points with only a single report
that met our study criteria, only the singular reported data point
was considered. We also conducted sensitivity analysis by examin-
ing the effect of (1) no stratification based on age, (2) more permis-
sive article inclusion criteria and (3) using a fixed effects model
to calculate weighted averages.

Collection of surgical evaluation and surgery rate data from the
Cleveland Clinic Epilepsy Center (2018–2019)

In addition to published data [2], we acquired data from the CCF
ECOR database regarding the number of patients who under-
went pre-surgical evaluation, the proportion of these patients
selected for surgery, and the number of patients who ultimately
underwent surgical treatment during the years 2018 and 2019 as
data were only available for this time period (Table 1). The data
from the CCF ECOR was considered when calculating a weighted
mean for the proportion of patients considered surgical candidates
after presurgical evaluation.

Collection of histopathological outcomes data from the Cleveland
Clinic Epilepsy Center (2010–2018)

In addition to published data [2], we acquired data from the CCF
ECOR database regarding 541 patients with surgically treated epi-
lepsy who underwent surgery during the period from 2010 to 2018.
in our center. Data were only available for this time period. We combined this data with previously published data from the European Epilepsy Brain Bank consortium (EEBB) to then calculate both annual period prevalence and incidence estimates for the most common surgically treatable epilepsy-associated brain lesions by combining surgical candidate estimates with post-surgical histopathological findings (Table 4). Histopathological review of resected brain tissue was performed and interpreted by board-certified clinical neuropathologists at the Cleveland Clinic Foundation in all patients and a detailed re-review by one of the co-authors (IB). Before surgery, all patients underwent an extensive evaluation that was followed by a discussion at a

Fig. 1. Flow diagram of the comprehensive literature review. n = number of studies. Exclusion criteria are included for both the initial title and abstract screen, as well as the full-text review.

Fig. 2. Estimation of annual period prevalence and incidence in the general population of candidates for epilepsy surgery based on reported epidemiological estimates. Each box represents a literature-reported estimate or calculated pooled estimate (see Methods for details and Table 2 for specific values used for calculations). Surgical candidate prevalence and incidence estimates were calculated by sequentially combining these pooled estimates. For example, to generate prevalence estimate one for adults, the estimated prevalence was calculated by combining the annual period prevalence of epilepsy with the rate of focal epilepsy among epilepsies, the rate of drug-resistant epilepsy among focal epilepsies, and the rate of epilepsy surgery among patients with drug-resistant focal epilepsy.
multidisciplinary patient management conference where a surgical strategy was developed. The Outcomes Registry is approved by the Institutional Review Board of the Cleveland Clinic. Written informed consent for the use of histopathological data was obtained from patients or their representative.

Histopathological diagnosis was based on light microscopic inspection of formalin-fixed paraffin-embedded tissue blocks stained with hematoxylin and eosin or additional histochemical and immunohistological stainings when indicated [8]. Hippocampal sclerosis was defined histopathologically by segmental neuronal cell loss in anatomical sectors of the cornu ammonis of the hippocampus, as specified in the consensus classification of the ILAE [9]. Brain tumors were classified according to the WHO classification of tumors of the central nervous system [10,11]. Focal cortical dysplasia was defined according to the consensus classification system of the ILAE [12]. Vascular malformations included cavernoma and meningeal angiomatosis, excluding ischemic or hemorrhagic stroke. Glial scars included traumatic brain injury and perinatal infarcts, excluding postsurgical scarring. Encephalitis included Rasmussen, limbic, or any other focal infection, excluding any inflammatory response to intracerebral neurophysiology recordings.

Results

Collection of epidemiological data points related to resective epilepsy surgery

Our PubMed literature review identified a total of 2352 unique articles (see Methods, Fig. 1). An initial title and abstract screen yielded 210 full-text articles for further consideration. Of these 210 abstracts, 35 articles met all criteria for final inclusion in our analysis (see Methods). We also considered five additional studies which were identified through cross-referring articles which met our inclusion criteria, for a total of 40 articles included in our analysis (Fig. 1).

Collection of data points for adults and children

Of the 40 articles, nine only reported prevalence estimates or rates related to pediatric epilepsy, 28 were only related to adult epilepsy, and three provided separate estimates for both.

Collection of data points for epilepsies

Our literature review identified epidemiological data associated with epilepsy surgery, such as the annual prevalence or incidence of epilepsy, the prevalence or rate of focal or drug-resistant epilepsy, and rates of pre-surgical evaluation and epilepsy surgery (Table 2). There were ten instances where multiple sources were available for a single data point. Since the overarching goal of this study was to identify data points for incidence and prevalence calculations, we calculated weighted averages for these data points from the overlapping sources (see Methods).

Estimating the prevalence and incidence of resective epilepsy surgery candidates by combining literature-derived data points

Evidence-based estimates for the incidence and prevalence of surgically treatable epilepsy in the general population have yet to be established. In order to estimate the annual period prevalence and incidence of resective epilepsy surgery candidates in both the adult and pediatric general population, we combined data points from reported epidemiological data and calculated literature-derived weighted averages (Table 2). We made use of different combinations of these data points to derive multiple estimates for both prevalence and incidence (Fig. 2). Four surgical candidate prevalence and incidence estimates were derived for adults from different combinations and two were derived for children. For adults, based on an estimated annual period prevalence of active epilepsy of 543 in 100,000 and an incidence of epilepsy of 64.81 in 100,000 adults, we estimated an average annual period prevalence of 44.63 ± 5.63 and an average incidence of 5.33 ± 0.59 surgical candidates in 100,000 adults. Based on these estimates, 8.2% of adults with epilepsy would qualify as surgical candidates. For children, based on an estimated annual period prevalence of active epilepsy of 480 in 100,000 and an incidence of epilepsy of 85.29 in 100,000 children, we estimated an average annual period prevalence of 16.36 ± 9.29 and an average incidence of 2.90 ± 0.85 surgical candidates in 100,000 children. Based on these estimates, 3.4% of children with epilepsy would qualify as surgical candidates. Performing the same analysis without age-based study stratification or age-based study exclusion resulted in estimates similar to those calculated for adults (Fig. S1 and Table S1).

We also combined literature-derived weighted means (Table 2) to estimate an average prevalence of focal drug-resistant epilepsy among adults of 145.58 in 100,000 and a prevalence of drug-resistant epilepsy among children of 105.6 in 100,000. In order to estimate the proportion of patients with drug-resistant epilepsy which would qualify as candidates for resective epilepsy surgery, we took the proportion between these estimates and the surgical candidate average prevalence estimates (Fig. 2). From this, we estimate that 30.6% of adults with focal drug-resistant epilepsy and 15.5% of children with drug-resistant epilepsy would qualify as candidates for epilepsy surgery.

Due to high heterogeneity between the studies included in the pooled estimates (Figs. S2-S11), we made use of a fixed effects model when calculating our estimates. Regardless, sensitivity analysis with a random effects model did not significantly alter the calculated estimates (Table S2). Additionally, to further evaluate potential study selection bias due to our exclusion criteria (Fig. 1), we performed an additional sensitivity analysis with less strict article inclusion criteria. For this analysis, we did not exclude (i) studies based on hospital administrative databases and (ii) studies that reported on drug-resistant epilepsy but did not meet or specify the standard definition of drug-resistant epilepsy according to the International League Against Epilepsy (N = 14, Table S1). Including these additional 14 data points resulted in incidence and prevalence estimates similar to our main analysis (Table S2).

Estimating the prevalence and incidence of surgically resectable epilepsy-associated brain lesions

To date, no study has reported on the population frequency of common focal epilepsy-associated lesions such as hippocampal sclerosis and MCD. We first generated weighted average proportions for each major epilepsy-associated brain lesion by combining data from the CCF ECOR database regarding 541 patients who underwent surgical resection between 2010 and 2018 (408 adults and 133 children) and published data from an independent multicenter European series of 9,523 patients (6,900 adults and 2,623 children) from the European Epilepsy Brain Bank consortium (EEBB) who underwent surgical resection between 1990 and 2014 (2) (Table 3). We then calculated both annual period prevalence and incidence estimates for the most common surgically treatable epilepsy-associated brain lesions by combining the adult and pediatric surgical candidate estimates with post-surgical histopathological findings from adults and children (Table 4). Using the combined histopathological findings data, hippocampal sclerosis was the most common surgically treatable brain lesion among adults and MCDs were the most common surgically
Table 2
Studies included and calculated pooled epidemiological estimates.

| Study | PMID | Study Type | Adults | Events | Total | Proportion [CI] | Children | Events | Total | Proportion [CI] |
|-------|------|------------|--------|--------|-------|----------------|----------|--------|-------|----------------|
| **Annual period prevalence of active epilepsy** | | | | | | | | | | |
| Fiest et al., [15] | 27986877 | Meta-Analysis | 22 studies | 543/100,000 | | | 22 studies | 480/100,000 | |
| **Cumulative incidence of epilepsy** | | | | | | | | | | |
| Fiest et al., [15] | 27986877 | Meta-Analysis | 3 studies | 64.81/100,000 | | | 5 studies | 85.29/100,000 | |
| **Proportion of epilepsy patients with DRE** | | | | | | | | | | |
| Aaberg et al., [27] | 29789444 | Cohort | - | - | - | 178 | 600 | 0.3 | |
| Berg et al., [60] | 16685695 | Cohort | - | - | - | 142 | 613 | 0.23 | |
| Boonluksiri et al., 2015 | | | 26819940 | Cohort | - | - | - | 129 | 308 | 0.42 | |
| Gandy et al., [43] | 23201610 | Cohort | 61 | 130 | 0.47 | - | - | - | |
| Geerts et al., [48] | 22417003 | Cohort | - | - | - | 50 | 413 | 0.12 | |
| Giussani et al., [33] | 26731716 | Cohort | 83 | 584 | 0.14 | 24 | 100 | 0.24 | |
| Hui et al., [57] | 17628339 | Cohort | 103 | 260 | 0.4 | - | - | - | |
| Kong et al., [38] | 24910376 | Cohort | 120 | 557 | 0.22 | - | - | - | |
| Nickels et al., [44] | 22989286 | Cohort | - | - | - | 134 | 467 | 0.29 | |
| Picot et al., [56] | 18363709 | Cohort | 81 | 360 | 0.22 | - | - | - | |
| Ramos-Liziana et al., [54] | 19328019 | Cohort | - | - | - | 30 | 343 | 0.09 | |
| Silis et al., [62] | 15857428 | Cohort | 230 | 400 | 0.57 | - | - | - | |
| Tellez-Zenteno et al., [39] | 24828683 | Cohort | 82 | 250 | 0.33 | - | - | - | |
| Pooled Estimate | | | 7 studies | 0.32 | | | 7 studies | 0.22 | |
| **Proportion of epilepsy patients with FE** | | | | | | | | | | |
| Bosak et al., 2019 | 31077939 | Cohort | 458 | 653 | 0.7 | - | - | - | |
| Chen et al., [28] | 28475999 | Cohort | 2911 | 4116 | 0.71 | - | - | - | |
| El-Tallawy et al., [45] | 27257380 | Cohort | 113 | 198 | 0.57 | - | - | - | |
| Fang et al., [66] | 22753012 | Cohort | 408 | 736 | 0.55 | - | - | - | |
| Garcia-Martin et al., [47] | 22749918 | Cohort | 389 | 515 | 0.76 | - | - | - | |
| Guekht et al., [30] | 21035312 | Cohort | 1430 | 1753 | 0.82 | - | - | - | |
| Guekht et al., [51] | 28142100 | Cohort | 818 | 1351 | 0.61 | - | - | - | |
| Hamer et al., [58] | 17201718 | Cohort | 77 | 101 | 0.76 | - | - | - | |
| Hunter et al., [46] | 22836331 | Cohort | 208 | 291 | 0.71 | - | - | - | |
| Nguyen et al., [42] | 23419568 | Cohort | 843 | 1051 | 0.8 | - | - | - | |
| Oun et al., [67] | 12536056 | Cohort | 294 | 396 | 0.74 | - | - | - | |
| Picot et al., [56] | 18363709 | Cohort | 229 | 360 | 0.64 | - | - | - | |
| Silis et al., [62] | 15857428 | Cohort | 270 | 400 | 0.68 | - | - | - | |
| Subramaniam et al., 2020 | 32094071 | Cohort | 116 | 211 | 0.55 | - | - | - | |
| Tellez-Zenteno et al., [39] | 24828683 | Cohort | 142 | 250 | 0.57 | - | - | - | |
| Pooled Estimate | | | 16 studies | 0.69 | | | 16 studies | 0.69 | |
| **Proportion of FE patients with DRE** | | | | | | | | | | |
| Garcia et al., 2014 | 25616468 | Cohort | 248 | 515 | 0.48 | - | - | - | |
| Gilisoli et al., [49] | 22368022 | Cohort | 453 | 1155 | 0.39 | - | - | - | |
| Tellez-Zenteno et al., [39] | 24828683 | Cohort | 52 | 142 | 0.37 | - | - | - | |
| Pooled Estimate | | | 3 studies | 0.42 | | | 3 studies | 0.42 | |
| **Proportion of DRE patients with FE** | | | | | | | | | | |
| Alexandre et al., [52] | 20132292 | Cohort | 782 | 933 | 0.84 | - | - | - | |
| Choi et al., [32] | 27205407 | Cohort | 282 | 403 | 0.7 | - | - | - | |
| Conte et al., [26] | 30308426 | Cohort | 512 | 640 | 0.8 | - | - | - | |
| Gandy et al., [43] | 23201610 | Cohort | 56 | 61 | 0.92 | - | - | - | |
| Kong et al., [38] | 24910376 | Cohort | 66 | 120 | 0.55 | - | - | - | |
| Picot et al., [56] | 18363709 | Cohort | 61 | 81 | 0.75 | - | - | - | |
| Pooled Estimate | | | 6 studies | 0.77 | | | 6 studies | 0.77 | |
| **Proportion of patients with DRE who underwent surgery** | | | | | | | | | | |
| Berg et al., [53] | 19638447 | Cohort | - | - | - | 11 | 132 | 0.08 | |
| Lim et al., [41] | 24192043 | Cohort | - | - | - | 53 | 463 | 0.11 | |
| Pooled Estimate | | | 2 studies | 0.11 | | | 2 studies | 0.11 | |
| **Proportion of patients with focal DRE who underwent surgery** | | | | | | | | | | |
| Fois et al., 2016 | 25935890 | Cohort | 204 | 612 | 0.33 | - | - | - | |
| **Proportion of patients with DRE who underwent presurgical evaluation** | | | | | | | | | | |
| Berg et al., [53] | 19638447 | Cohort | - | - | - | 54 | 132 | 0.41 | |
| Lim et al., [41] | 24192043 | Cohort | - | - | - | 160 | 463 | 0.35 | |
| Pooled Estimate | | | 2 studies | 0.37 | | | 2 studies | 0.37 | |
| **Proportion of patients with focal DRE who underwent presurgical evaluation** | | | | | | | | | | |
| Dugan et al., [29] | 28378422 | Cohort | 200 | 407 | 0.49 | - | - | - | |

(continued on next page)
treatable brain lesions among pediatric patients. Among the MCDs, FCD II was the most prevalent. To evaluate discrepancies between surgical databases, we also calculated additional prevalence and incidence estimates using the two different brain lesion proportions reported by the more recently collected CCF ECOR database (2010–2018) and older EEBB data (1990–2014) (Table S3). The estimates calculated from the older EEBB data alone were similar to those calculated from the combined data (Table 4). However, we observe that, unlike the combined estimates, malformations of cortical development were the most frequent surgically treatable brain lesions observed in the more recent CCF ECOR (2010–2018) for both adults and children (adult population prevalence: 15.58 ± 1.24, pediatric population prevalence: 9.15 ± 3.51).

Discussion

We estimated both the prevalence and incidence of surgical candidates and the most common surgically amenable epilepsy-associated brain lesions among adults and children in the general population by combining data from the literature with findings from the Cleveland Clinic and a European multicenter cohort. For surgical candidates, we estimate an annual incidence of 2.90 ± 0.85 in 100,000 children and 5.33 ± 0.59 in 100,000 adults as well as an annual period prevalence of 16.36 ± 9.29 in 100,000 children and 44.63 ± 5.63 in 100,000 adults (Fig. 2). From these, we estimate that 30.66% of adults with focal drug-resistant epilepsy and 15.5% of children with drug-resistant epilepsy would qualify as candidates for surgical resection (see Results). Furthermore, we provide the first epidemiological estimates for the most common surgically-treatable epilepsy-associated brain lesions ever reported in the literature for both the adult and pediatric populations (Table 4).

Previous studies estimating the frequency of all individuals with surgically treatable epilepsy have relied on survey-based approaches and clinician estimation to determine the proportion of epilepsy cases amenable to surgical treatment [13,14]. The results of these studies have varied greatly: from 3% surgical can-

| Study | PMID | Study Type | Adults | Events | Total | Proportion \([CI]\) | Children | Events | Total | Proportion \([CI]\) |
|-------|------|------------|--------|--------|-------|----------------|----------|--------|-------|----------------|
| Fois et al., 2016 | 25935890 | Cohort | 306 | 612 | 0.5 | - | - | - |
| Roberts et al., [37] | 25107882 | Cohort | 42 | 107 | 0.39 | - | - | - |
| Pooled Estimate | 3 studies | | | | 0.48 \([0.43; 0.52]\) | - | - | - |

Table 2 (continued)

Proportion of patients who underwent surgery after presurgical evaluation

Berg et al., [64] | 14636351 | Cohort | 368 | 522 | 0.7 | - | - | - |
Cleveland Clinic, 2018–2019 | n/a | Cohort | 225 | 388 | 0.58 | 217 | 271 | 0.8 |
Cloppenberg et al., [22] | 30577071 | Cohort | 1357 | 1916 | 0.71 | 751 | 1300 | 0.58 |
Conte et al., [36] | 30384267 | Cohort | 109 | 249 | 0.44 | - | - | - |
Dugan et al., [29] | 28378422 | Cohort | 200 | 200 | 0.56 | - | - | - |
Fois et al., 2016 | 25935890 | Cohort | 204 | 306 | 0.67 | - | - | - |
Haque et al., [35] | 26092414 | Cohort | - | - | - | 51 | 131 | 0.39 |
Lim et al., [41] | 24192043 | Cohort | - | - | - | 53 | 160 | 0.33 |
Picot et al., [31] | 27955433 | Cohort | 119 | 289 | 0.41 | - | - | - |
Pooled Estimate | 7 studies | | | | 0.59 \([0.49; 0.68]\) | - | - | - |

CI = confidence intervals; DRE = drug-resistant epilepsy; FE = focal epilepsy.

Table 3

Proportion of major epilepsy-associated brain lesions among adults and children undergoing epilepsy surgery.

| Lesion type | CCF ECOR 2010–2018 (%) | EEBB 1990–2014 (%) | Weighted Average Proportion (%) \([95\% CI]\) |
|-------------|------------------------|---------------------|-----------------------------------------------|
| Adults | | | |
| Hippocampal Sclerosis | 106 (25.98%) | 3,070 (44.49%) | 43.46% \([42.33; 44.60]\) |
| MCD | 131 (32.11%) | 856 (12.41%) | 13.51% \([12.74; 14.31]\) |
| FCD I | 6 (1.47%) | 101 (1.46%) | 1.46% \([1.21; 1.77]\) |
| FCD II | 55 (13.48%) | 412 (5.97%) | 6.39% \([5.85; 6.97]\) |
| FCD (NOS) | 3 (0.74%) | 118 (1.71%) | 1.66% \([1.39; 1.98]\) |
| Other MCD | 67 (16.42%) | 225 (3.26%) | 4% \([3.57; 4.47]\) |
| LEAT | 35 (8.58%) | 1,530 (22.17%) | 21.41% \([20.49; 22.37]\) |
| Glial scar | 36 (8.82%) | 311 (4.51%) | 4.75% \([4.28; 5.26]\) |
| Vascular malformation | 17 (4.17%) | 497 (7.20%) | 7.03% \([6.47; 7.64]\) |
| Encephalitis | 5 (1.23%) | 59 (0.86%) | 0.88% \([0.69; 1.12]\) |
| Children | | | |
| Hippocampal Sclerosis | 15 (11.28%) | 394 (15.02%) | 14.84% \([13.56; 16.22]\) |
| MCD | 66 (49.62%) | 1032 (39.34%) | 39.84% \([38.03; 41.68]\) |
| FCD I | 2 (1.50%) | 167 (6.37%) | 6.13% \([5.31; 7.09]\) |
| FCD II | 41 (30.83%) | 447 (17.04%) | 17.71% \([16.33; 19.18]\) |
| FCD (NOS) | 1 (0.75%) | 88 (3.35%) | 3.23% \([2.63; 3.96]\) |
| Other MCD | 22 (16.54%) | 333 (12.70%) | 12.88% \([11.68; 14.18]\) |
| LEAT | 19 (14.29%) | 714 (27.22%) | 26.6% \([24.98; 28.28]\) |
| Glial scar | 14 (10.53%) | 153 (5.83%) | 6.06% \([5.23; 7.01]\) |
| Vascular malformation | 2 (1.50%) | 84 (3.20%) | 3.12% \([2.53; 3.84]\) |
| Encephalitis | 5 (3.76%) | 86 (3.28%) | 3.3% \([2.7; 4.04]\) |

CCF ECOR = Cleveland Clinic Epilepsy Center Outcomes Registry database, EEBB = European Epilepsy Brain Bank, MCD = Malformation of cortical development, FCD I = Focal cortical dysplasia type I, FCDII = Focal cortical dysplasia type II, FCD (NOS) = Focal cortical dysplasia (not otherwise specified), LEAT = Low-grade developmental and epilepsy-associated brain tumors.
The average of these (Fig. 2). We also performed multiple sensitivity analyses to evaluate study selection bias and heterogeneity.

Furthermore, our approach accounts for some of the publication bias and it is difficult to account for varying underlying population structures. For example, our comprehensive literature review revealed that reports from low-income countries are scarce (Supplementary Appendix S1). As such, most studies included in our analysis either originate from high-income countries (Supplementary Appendix S1) or provide data more easily applied to high-income countries [15]. Accordingly, our surgical candidate and associated brain lesion incidence and prevalence estimates are similarly more easily applied to higher-income countries. However, previous studies have reported that the overall prevalence and incidence of epilepsy is higher in low-middle income countries than in higher-income countries [15,16] and that these low-resource areas are also those with the largest treatment gap, including epilepsy surgery [17]. Therefore, our reported estimates may potentially be applied to low-middle income countries as conservative lower bound estimates, with the caveat that the true incidence and prevalence of surgically-remediable brain lesions such as hippocampal sclerosis and focal cortical dysplasia (Table 4). Since our estimates are based on post-surgical histopathological outcomes from resective surgery, we do not provide estimates for other lesional epilepsy-associated pathologies which were not operated on until more recently (e.g., polymicrogyria) or are primarily treated through newer surgical methods such as neuromodulation techniques and laser ablation therapies and therefore only have neuroradiological findings and no histopathological diagnoses (e.g., periventricular nodular heterotopia, deeper brain lesions). However, our study includes incidence and prevalence estimates for the most frequently occurring and commonly resected types of surgically treatable epilepsy-associated brain lesions, based on cohorts from time periods prior to the use of newer surgical methods [2].

Our estimates of lesion incidence and prevalence are based on surgical outcomes from two independent cohorts from different time periods (CCF ECOR: 2010–2018; EEBB: 1990–2014), which reported different proportions for each lesion type (Table 3). Specifically, we observe a lower proportion of hippocampal sclerosis patients and a higher proportion of cortical malformations in the CCF ECOR data compared to the EEBB data (Table 3). Therefore, we provide additional brain lesion incidence and prevalence estimates calculated using the CCF ECOR and EEBB data separately (Table S3). The two datasets may represent different trends in clinical practice and the management of surgical candidates at the Cleveland Clinic Epilepsy Center or other US surgical centers compared to European surgical centers. However, the time period in which these data were collected could potentially also contribute to the observed discrepancy, as the landscape of epilepsy surgery

Table 4
Estimated annual period prevalence and incidence of epilepsy-associated brain lesions in adults and children in the general population.

| Lesion type                  | General population period prevalence in 100,000 | General population incidence in 100,000 |
|-----------------------------|-----------------------------------------------|----------------------------------------|
|                             | Est. 1, Est. 2, Est. 3, Est. 4, Average ± SD  | Est. 1, Est. 2, Est. 3, Est. 4, Average ± SD |
| Adults                      |                                               |                                        |
| Hippocampal Sclerosis       | 22.57 ± 19.37, 19.19 ± 16.47, 19.40 ± 2.16, 2.69 ± 2.30, 2.30 ± 1.97, 2.32 ± 0.26 |
| MCD                         | 7.02 ± 6.02, 5.96 ± 5.12, 6.03 ± 0.67, 0.84 ± 0.71, 0.71 ± 0.62, 0.72 ± 0.08 |
| FCD I                       | 0.76 ± 0.65, 0.64 ± 0.55, 0.65 ± 0.07, 0.09 ± 0.07, 0.07 ± 0.07, 0.08 ± 0.01 |
| FCD II                      | 3.32 ± 2.85, 2.82 ± 2.42, 2.85 ± 0.32, 0.39 ± 0.34, 0.34 ± 0.28, 0.34 ± 0.04 |
| FCD (NOS)                   | 0.86 ± 0.74, 0.73 ± 0.63, 0.74 ± 0.08, 0.09 ± 0.09, 0.09 ± 0.07, 0.09 ± 0.01 |
| Other MCD                   | 2.08 ± 1.78, 1.77 ± 1.52, 1.79 ± 0.20, 0.24 ± 0.21, 0.21 ± 0.19, 0.21 ± 0.02 |
| LEAT                        | 11.12 ± 9.54, 9.45 ± 8.11, 9.56 ± 1.07, 1.33 ± 1.14, 1.12 ± 0.97, 1.14 ± 0.13 |
| Glial scar                  | 2.47 ± 2.12, 2.10 ± 1.80, 2.12 ± 0.24, 0.30 ± 0.24, 0.24 ± 0.21, 0.25 ± 0.03 |
| Vascular malformation       | 3.65 ± 3.13, 3.10 ± 2.66, 3.14 ± 0.35, 0.43 ± 0.37, 0.37 ± 0.32, 0.37 ± 0.04 |
| Encephalitis                | 0.46 ± 0.39, 0.39 ± 0.33, 0.39 ± 0.05, 0.06 ± 0.04, 0.04 ± 0.04, 0.04 ± 0.01 |
| Children                    |                                               |                                        |
| Hippocampal Sclerosis       | 3.13 ± 1.72, 2.43 ± 0.71, 0.56 ± 0.31, 0.44 ± 0.13 |
| MCD                         | 8.41 ± 4.63, 6.52 ± 1.89, 1.49 ± 0.82, 1.15 ± 0.34 |
| FCD I                       | 1.29 ± 0.71, 1.00 ± 0.29, 0.24 ± 0.13, 0.18 ± 0.05 |
| FCD II                      | 3.74 ± 2.06, 2.90 ± 0.84, 0.65 ± 0.36, 0.51 ± 0.15 |
| FCD (NOS)                   | 0.68 ± 0.38, 0.53 ± 0.15, 0.13 ± 0.07, 0.1 ± 0.03 |
| Other MCD                   | 2.72 ± 1.50, 2.11 ± 0.61, 0.49 ± 0.27, 0.38 ± 0.11 |
| LEAT                        | 5.61 ± 3.09, 4.35 ± 1.26, 1.00 ± 0.55, 0.77 ± 0.23 |
| Glial scar                  | 1.28 ± 0.70, 0.99 ± 0.29, 0.22 ± 0.13, 0.17 ± 0.05 |
| Vascular malformation       | 0.66 ± 0.36, 0.51 ± 0.15, 0.11 ± 0.07, 0.09 ± 0.02 |
| Encephalitis                | 0.70 ± 0.38, 0.54 ± 0.16, 0.13 ± 0.07, 0.1 ± 0.03 |

Est.1,2,3,4 = Estimate 1,2,3,4; SD = Standard Deviation; MCD = Malformation of cortical development; FCD I = Focal cortical dysplasia type I; FCD II = Focal cortical dysplasia type II; FCD (NOS) = Focal cortical dysplasia (not otherwise specified); LEAT = Low-grade developmental and epilepsy-associated brain tumors.
has evolved and seen major changes over the past years. It has previously been reported that clinical practices in epilepsy surgery and the selection of candidates have evolved and seen major changes over the years [18,21–23]. Specifically, changing clinical trends describe an increasing proportion of surgical procedures performed for non-temporal lesions compared to temporal lobectomies in recent years [18,22,23]. The observed discrepancy between the combined data analysis and the estimates calculated from the more recent CCF ECOR data (a lower proportion of hippocampal sclerosis patients and a higher proportion of cortical malformations) is consistent with these recent reports on changing clinical trends.

Epilepsy surgery has been associated with a reduction in mortality for patients with drug-resistant epilepsy, regardless of whether seizures are completely abolished or their frequency is reduced [24,25]. Understanding both the frequency of drug-resistant epilepsy patients eligible for resective surgical treatment as well as the frequency of various underlying pathologies is needed to optimize the planning of healthcare services such as the training of specialists, support services provided, and implementation of public health programs. In the absence of wide-scale empirical population-based data, our estimates can help guide patient advocacy groups, clinicians, researchers, and policymakers in community education as well as the development of health care strategies, resource allocation, and reimbursement schedules.

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Ethical Statement
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Given the study's retrospective design, and the fact that only aggregate data and no personal data was utilized, the requirement for informed consent was waived.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2022.100527.

References
[1] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314–9.
[2] Blümcke I, Spreafico R, Hauke G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. N Engl J Med 2017;377(17):1648–56.
[3] Wibos S, Blume WT, Girvin JP, Elziawawi M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345(5):311–8.
[4] Jehi L, Vardh R, Chang K, Tassi L, Russo GL, Wonnell C, et al. Development and validation of nomograms to provide individualized predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. Lancet Neurol 2015;14(3):283–90.
[5] Page MJ, McKenzie JE, Bossuyt PM, Broutrn I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;371.
[6] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51 (6):969–77.
[7] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Mental Health 2019;22(4):153–60.
[8] Blümcke I, Aronica E, Miya J, Sarnat HB, Thom M, Roessler K, et al. International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2016;57(3):348–58.
[9] Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2013;54(7):1315–29.
[10] Blümcke I, Aronica E, Urbach H, Alexopoulos A, Gonzalez-Martinez JA. A neuropathology-based approach to epilepsy surgery in brain tumors and proposal for a new terminology use for long-term epilepsy-associated brain tumors. Acta Neuropathol 2014;128(1):39–54.
[11] Blümcke I. Chapter 33 - Epilepsy-associated brain tumors. In: Stefan H, Theodore WH, editors. Handbook of clinical neurology [Internet]. Elsevier; 2012 (cited 2019). p. 559–68. (Epilepsy; vol. 108). Available from: http://www.sciencedirect.com/science/article/pii/B9780444528995000150.
[12] Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters VH, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission1. Epilepsia 2011;52(1):158–74.
[13] Lhatoo S, Solomon J, McEvoy A, Kitchen N, Shorvon S, Sander J. A prospective study of the requirement for and the provision of epilepsy surgery in the United Kingdom. Epilepsia 2001;44(5):673–6.
[14] Vaughan KA, Lopez Ramos C, Buch VP, Mekary RA, Amundson JR, Shah M, et al. An estimation of global volume of medically treatable epilepsy based on a systematic review and meta-analysis of epilepsy. J Neurosurg 2019;139(4):1127–41.
[15] Fietz KM, Sauro KM, Wiebe S, Patten SB, Kwan C-S, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(1):296–303.
[16] Beghi E. Heusdorfer D. Prevalence of epilepsy—An unknown quantity. Epilepsia 2014;55(7):963–7.
[17] Broyer A-C, Dua T, Ma J, Szapera S, Birbeck G. Global disparities in the epilepsy treatment gap: A systematic review. Bull World Health Organ 2010;88(4):269–6.
[18] Kailborboom K, Malikbashroum AM, Zrlik A, Daif A, Schiltz NM, Labiner DM, et al. Epilepsy surgery in the United States: Analysis of data from the National Association of Epilepsy Centers. Epilepsy Res 2015;116:105–9.
[19] Kang JY, Wu C, Tracy J, Lorenzo M, Evans J, Nei M, et al. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. Epilepsia 2016;57(2):325–34.
[20] Wellner J, Voges J, Parpale Y. Lesion guided radiofrequency thermocoagulation (L-RFTC) for hypothalamic hamartomas, nodular heterotopias and cortical dysplasias: Review and perspective. Seizure 2016;21:206–10.
[21] Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. Epilepsy surgery trends in the United States, 1990-2008. Neurology 2012;78(16):1200–6.
[22] Cloppenborg T, May TW, Blümcke I, Fauser S, Grewe P, Hopf JL, et al. Differences in pediatric and adult epilepsy surgery: A comparison at one center from 1990 to 2014. Epilepsia 2016;57(2):233–45.
[23] Jehi L, Friedman D, Carlsson C, Cascino G, Dewar S, Elger C, et al. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. Epilepsia 2015;56 (10):1526–33.
[24] Sperling MR, Barlow S, Nei M, Asadi-Pooya AA. A reappraisal of mortality after epilepsy surgery. Neurology 2016;86(21):1938–44.
[25] Conte F, Legros B, Van Paeschen W, Avbereuk A, Muglia P, Depondt C. Long-term seizure outcomes in patients with drug-resistant epilepsy. Seizure 2018;52:74–8.
[26] Aaseberg KM, Bakken IJ, Lossius MI, Lund Søraas C, Tallur KK, Stoltenberg C, et al. Epilepsy surgery in the United States: Analysis of data from the National Association of Epilepsy Centers. Epilepsia 2015;66(1):87–92.
[27] Chen R, Choi H, Hirsch IJ, Katz A, Legge A, Wong RA, et al. Prevalence and risk factors of seizure clusters in adult patients with epilepsy. Epilepsy Res 2017;133:98–102.
[28] Dubeau L, Carlson C, Jetté N, Wiebe S, Kuzniecky R, et al. Derivation and initial validation of a surgical grading scale for the preliminary evaluation of adult patients with drug-resistant focal epilepsy. Epilepsia 2017;58 (5):792–800.
[29] Guehl A, Zharkibekova N, Shpak A, Hauser WA. Epilepsy and treatment gap in urban and rural areas of the Southern Kazakhstan in adults. Epilepsy Behav 2017;69:98–104.
[30] Picot MC, Jaussent A, Neeve D, Kahane P, Crespel A, Gelisse P, et al. Cost-effectiveness analysis of epilepsy surgery in a controlled cohort of adult
patients with intractable partial epilepsy: A 5-year follow-up study. Epilepsia 2016;57(10):1669–79.

Choi H, Hayat MJ, Zhang R, Hirsch LJ, Bazil CW, Mendiratta A, et al. Drug-resistant epilepsy in adults: Outcome trajectories after failure of two medications. Epilepsia 2016;57(7):1152–60.

Gussani G, Caneli V, Bianchi E, Franchi C, Nobili A, Erba G, et al. A population-based study of active and drug-resistant epilepsies in Northern Italy. Epilepsy Behav 2016;55:30–7.

Haque OJ, Mandrekar J, Wyatt K, Nickels KC, Wong-Kisiel L, Wetjen N, et al. Yield and predictors of epilepsy surgery candidacy in children admitted for surgical evaluation. Pediatr Neurol 2015;53(1):58–64.

Roberts JH, Hrazdil C, Wiebe S, Sauer K, Hanson A, Federico P, et al. Feasibility of using an online tool to assess appropriateness for an epilepsy surgery evaluation. Neurology 2014;83(10):913–9.

Kong ST, Ho CS, Ho PC, Lim S-H. Prevalence of drug resistant epilepsy in adults with epilepsy attending a neurology clinic of a tertiary referral hospital in Singapore. Epilepsy Res 2014;108(7):1253–62.

Téllez-Zenteno JF, Hernández-Ronquillo L, Buckley S, Zahagun R, Rizvi S. A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. Epilepsia 2014;55(6):829–34.

Lim ME, Bowen JM, Sneed OC, Elliott I, Donner E, Weiss SK, et al. Access to surgery for paediatric patients with medically refractory epilepsy: a systems analysis. Epilepsy Res 2013;107(3):286–96.

Nguyen DK, Mhacouf MT, Nguyen DB, Lasonde M. Prevalence of nonlesional focal epilepsy in an adult epilepsy clinic. Can J Neurol Sci 2013;40(2):198–202.

Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. Rates of DSM-IV mood, anxiety disorders, and suicidality in Australian adult epilepsy outpatients: a comparison of well-controlled versus refractory epilepsy. Epilepsy Behav 2013;26(1):29–35.

Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County, MN. Epilepsia 2012;53(12):2164–71.

El-Tallawy HN, Farghaly WMA, Shehata GA, Abdel-Hakeem NM, Mckay TA, et al. Prevalence of active epilepsy in rural Tanzania: a large community-based survey in an adult population. Seizure 2012;21(5):391–8.

Hunter E, Rogathi J, Chigudu S, Jusabani A, Jackson M, McNally R, et al. Prevalence of active epilepsy in the South of Spain. Epilepsy Res 2012;102(1-2):100–7.

Geerts A, Brouwer O, Stronkq H, van Donkelaar C, Peters B, Peeters E, et al. Onset of intractability and its course over time: the Dutch study of epilepsy in childhood. Epilepsia 2012;53(4):741–51.

Gilioni L, Vignoli A, Visani E, Casazza M, Canafoglia L, Chiesa V, et al. Focal epilepsies in adult patients attending two epilepsy centers: classification of drug-resistance, assessment of risk factors, and usefulness of “new” antiepileptic drugs. Epilepsia 2012;53(4):733–40.

Guechter A, Hauser WA, Milchakova L, Churilin Y, Shpak A, Gusev E. The epidemiology of epilepsy in the Russian Federation. Epilepsia 2010;92(2-3):209–18.

Alexandre V, Capovilla G, Fattore C, Franco V, Gambardella A, Guerrini R, et al. Characteristics of a large population of patients with refractory epilepsy attending tertiary referral centers in Italy. Epilepsia 2010;51(5):921–5.

Berg AT, Mathern GW, Bronen RA, Fulbright RK, DiMario F, Testa FM, et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. Brain 2009;132(10):2785–97.

Ramos-Lizana J, Aguilera-López P, Aguirre-Rodríguez J, Casetta I, Granieri E, Monetti VC, et al. Early prediction of refractory epilepsy in childhood. Seizure 2009;18(4):412–6.

Picot M-C, Baldy-Moulinitie M, Daurès J-P, Djouls P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsies in adults: a population-based study in a Western European country. Epilepsia 2008;49(7):1230–8.

Hui ACF, Wong A, Wong HC, Man BL, Au-Yeung KM, Wong KS. Refractory epilepsy in a Chinese population. Clin Neurol Neurosurg 2007;109(8):672–5.

Hamer HM, Spottele A, Leunke C, Reijer J, Strzelczak A, et al. Direct and indirect costs of refractory epilepsy in a tertiary epilepsy center in Germany. Epilepsia 2006;47(12):1665–72.

Berg AT, Vickrey BG, Testa FM, Levy SR, Shimmar D, Miano F, et al. How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 2006;60(1):73–8.

Sills GJ, Mohanna R, Butler E, McCrindle S, Collier L, Wilson EA, et al. Lack of association between the C3435T polymorphism in the human multidrug resistance (MDR1) gene and sensitivity to antiepileptic drug treatment. Epilepsia 2005;46(5):643–7.

Berg AT, Vickrey BG, Langfitt JT, Sperling MR, Walczak TS, Shimmar D, et al. The multicenter study of epilepsy surgery: recruitment and selection for surgery. Epilepsia 2003;44(11):1475–33.

Fong CCY, Mak W, Cheng TS, Chan KH, Fong JKY, Ho SL. A prevalence study of epilepsy in Hong Kong. Hong Kong Med J 2003;9(4):252–7.

Oun A, Haidere S, Magi M. Prevalence of adult epilepsy in Estonia. Epilepsia 2003;52(3):233–42.

Further reading

Burneo JG, Shariar SZ, Liu K, Leonard S, Saposnik G, Garg AX. Disparities in surgery among patients with intractable epilepsy in a universal health system. Neurology 2016;86(1):72–8.

Saygi S, Erol I, Alehan F. Early clinical predictors of intractable epilepsy in childhood. Turk J Med Sci 2014;44(3):490–5.

de Zélicourt M, de Toffol B, Vespignani H, Laurendeau C, Lévy-Bachelot L, Dauzais C, et al. Management of focal epilepsy in adults treated with polytherapy in France: the direct cost of drug resistance (ESPERA study). Seizure 2014;23(5):349–56.

Hellwig S, Mamalis P, Feige B, Schulze-Bonhage A, van Elst LT. Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery. Epilepsy Behav 2012;23(3):272–9.

Malik MA, Hamid MH, Ahmed TM, Ali Q. Predictors of intractable childhood epilepsy. J Coll Physicians Surg Pak 2008;18(3):158–62.

Gururaj A, Shritha L, Hertecant J, Eapen V. Clinical predictors of intractable childhood epilepsy. J Psychosom Res 2006;61(3):343–7.

Oksoua M, Webster BL, Zhang X, Shevell MI. Factors predictive of outcome in childhood epilepsy. J Child Neurol 2005;20(11):898–904.

Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. Neurology 2005;64(6):973–5.

Kwong KL, Sung WT, Wong SN, So KT. Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol 2003;29(1):46–52.

Chavala S, Aneja S, Kashyap R, Mallika V. Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol 2002;27(3):186–91.

Ohtsuka Y, Yoshinaga H, Kobayashi K, Murakami N, Yamatogi Y, Oka E, et al. Predictors and underlying causes of medically intractable localization-related epilepsy in childhood. Pediatr Neurol 2001;24(3):209–13.

Casetta I, Granieri E, Monetti VC, Gilli G, Tole MR, Paolino E, et al. Early predictors of intractability in childhood epilepsy: a community-based case-control study in Coppoaro, Italy. Acta Neurol Scand 1999;99(6):329–33.

Ko T-S, Holmes GL. EEG and clinical predictors of medically intractable epilepsy. Clin Neurophysiol 1999;110(7):1245–51.

Eriksson R, Koirikkio M. Prevalence, classification, and severity of epilepsy and epileptic syndromes in children. Epilepsia 1997;38(12):1275–82.

Semah F, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? J.A. López-Rivera, V. Smuk, C. Leu et al. Epilepsy & Behavior Reports 18 (2022) 100527