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Trends in epilepsy diagnosis and surgery in western China during 2009–2017

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ABSTRACT

Objective: Despite the strong evidence for the efficacy of surgery to treat temporal lobe epilepsy, the number of such surgeries has plateaued in western countries. This study examined trends in the number of epilepsy cases diagnosed, number of surgeries performed, and certain characteristics of surgery patients in western China between January 2009 and December 2017.

Methods: Data were obtained for a population-based sample from a healthcare information system, as well as for a patient population from West China Hospital. Age at epilepsy onset, age at surgery, duration of epilepsy, and type of epilepsy pathology based on surgical samples were analyzed.

Results: Data were obtained for 14,710 hospitalizations from the healthcare system and 17,302 hospitalizations from West China Hospital. The number of hospitalizations, but not the number of epilepsy surgeries, increased during the study period. Patients' age at epilepsy onset, age at surgery or epilepsy duration did not change significantly during the study period.

Significance: Our analysis suggests that in western China, as in western countries, the number of temporal epilepsy surgeries has plateaued. In contrast, disease-modifying factors have not changed over time in western China. Further studies are needed to explore what may contribute to these findings.

1. Introduction

Epilepsy surgery is effective against temporal lobe epilepsy (TLE), especially the drug-resistant form [1]. International guidelines about presurgical evaluation and epilepsy surgical therapy have improved [2], video electroencephalography monitoring [3,4] has become more widespread, and imaging techniques have advanced. Nevertheless, the number of resective TLE surgeries has plateaued over the past decade, based on data from the United States [5], Germany [6], and Australia [7]. It is unclear whether this trend applies also to China, where the cultural background, genetic background, the healthcare system and referral patterns can differ substantially from those in the West. We are unaware of reports on trends in the number of epilepsy cases and surgeries in China.

The health care system in China underwent a major reform in 2009 to expand coverage of essential health services. As a result, > 95% of the Chinese population became covered by one of three major social health insurance schemes: a rural cooperative medical scheme, urban employee basic medical insurance and urban resident basic medical insurance [8]. The present study aimed to examine how the numbers of epilepsy cases and of epilepsy surgeries have changed since the 2009 reform, particularly in comparison with western countries. It drew on hospitalization data from a healthcare information system of a large city in western China, as well as on data from West China Hospital, the largest hospital in western China.

2. Methods

2.1. Data sources

To examine the trends in epilepsy diagnosis, hospitalization data covering the period 2009–2017 were obtained from a healthcare system in a large city of western China. Hospitalization data were also obtained from West China Hospital during 2009–2017, which is the largest

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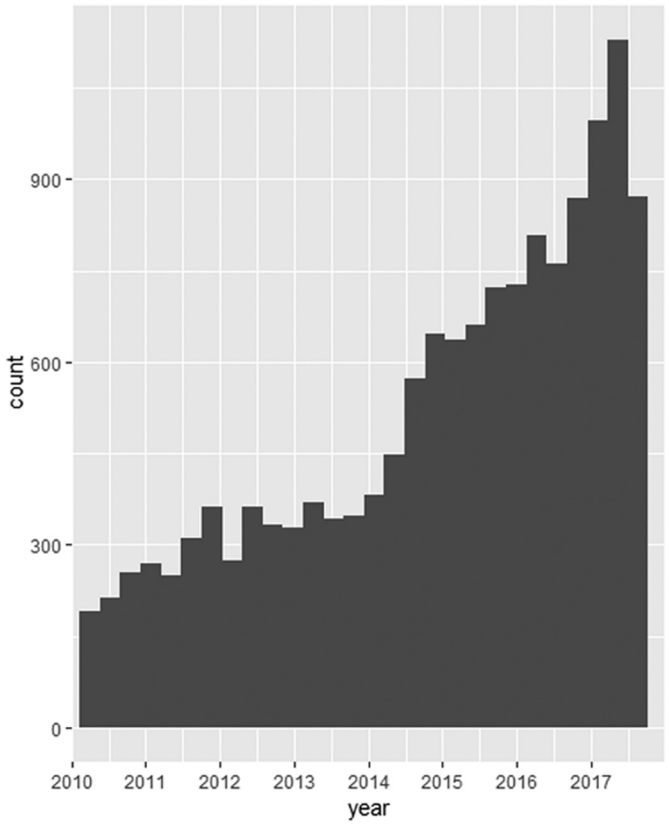


Fig. 1. Number of hospitalizations for epilepsy during the study period. Data refer to a population-based sample from a healthcare system.

hospital in western China and is located in Chengdu, the capital of Sichuan Province. The entire province has a population of 80.4 million based on 2010 census data (http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm). West China Hospital has 4300 beds and every year, 243,200 patients from various parts of western China are admitted and 161,200 surgeries are performed. This study was approved by the Biomedical Research Ethics Committee of West China Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR1800017687).

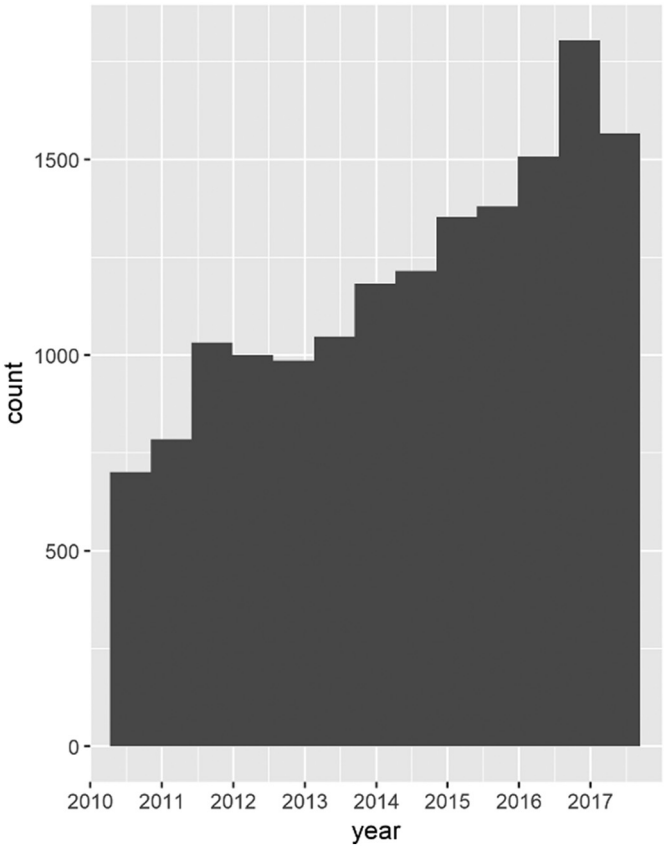


Fig. 3. Number of hospitalizations for epilepsy during the study period. Data refer to a sample from West China Hospital.

2.2. Search strategies and data extraction

Data on admission date, admitting hospital, gender and age were obtained from the healthcare information system on all patients during the study period who were diagnosed with “epilepsy”. For patients hospitalized multiple times, only data from the first hospitalization were collected. This database does not contain information on patients' epilepsy duration, epilepsy type or surgery. Hospitals were classified as grade 3 (higher volume) or non-grade 3 (lower volume), based on the grading system in China (https://www.hqms.org.cn/usp/roster/index.

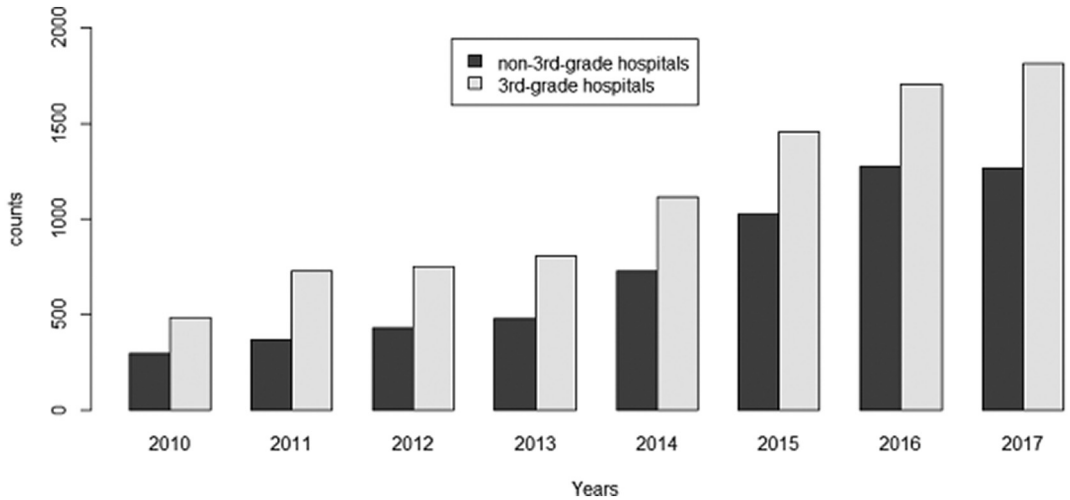


Fig. 2. Numbers of epilepsy hospitalizations at grade-3 (higher-volume) hospitals or non-grade-3 (lower-volume) hospitals in western China. Data refer to a population-based sample from a healthcare system.

Table 1
Number of epilepsy-related hospitalization from West China Hospital, number of surgical treatment of epilepsy, number of epilepsy surgery for each calendar year.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient[a]	*P* value
Epilepsy-related hospitalization[b]	629	1056	1720	1744	1836	2185	2421	2904	2807	0.156	< 0.001
Surgical treatment of epilepsy (01.59, 01.52, 01.53)	88	117	207	151	142	181	203	311	172	−0.064	0.004
Epilepsy surgery (excluding neoplastic lesion)[b]	24	25	117	86	64	78	63	89	80	0.0098	0.81
Population[c]	8185	8045	8050	8076	8107	8140	8204	8262	8302	0.003	0.03

[a] Slope coefficient according to negative binomial regression model.
[b] Data were from West China Hospital.
[c] Resident population (year-end)(10000 persons).

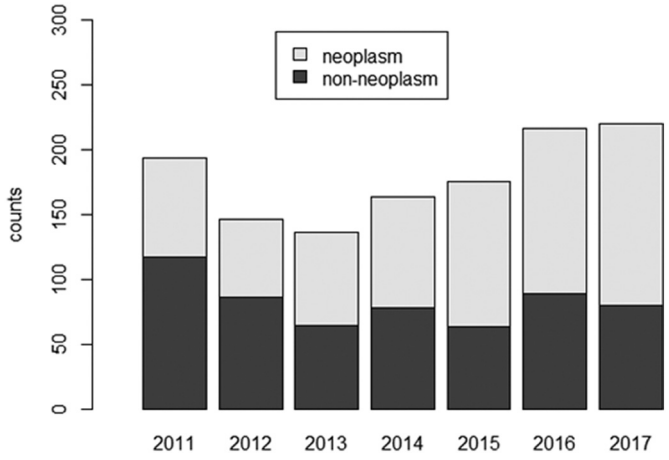


Fig. 4. Numbers of surgeries to treat epilepsy performed at West China Hospital during the study period. Results are shown separately for surgeries to treat neoplasm or non-neoplasm epilepsy.

jsp).

Data were also collected from the inpatient database at West China Hospital by initially searching using the keywords "epilepsy/seizure" as diagnosis. Adults and children who had been diagnosed with epilepsy/seizures and also undergone surgical treatment of epilepsy were identified by the presence of three ICD-9-CM procedure codes (01.52 for hemispherectomy, 01.53 for brain lobectomy, and 01.59 for other excision of the brain including amygdalohippocampectomy and partial brain lobectomy). For patients who underwent repeated surgeries, only data from the first surgery were extracted. For surgery patients, data were collected on patient identification number, age at epilepsy onset, gender, duration of epilepsy before surgery, age at surgery, ethnicity, as well as side and location of the resected lesion. Patients were classified as having intractable or controlled epilepsy based on their response to drug treatment according to guidelines of the international league against epilepsy (ILAE) [9]. Pathology findings from surgical samples were classified as hippocampal sclerosis (HS), vascular lesions, developmental abnormalities, neoplasm, inflammation, or "no finding". We differentiate the epilepsy surgery from the surgical treatment of epilepsy by removing those with neoplasms from the latter group.

2.3. Statistical analysis

Linear correlation between hospitalization counts and year was assessed using the Pearson correlation coefficient. Comparison of the different pathology types of epilepsy with regard to age at onset, age at surgery, and epilepsy duration were assessed using the Kruskal-Wallis test with *post hoc* comparison. We also used negative binomial regression to test for temporal trend. We regarded number of hospitalization/number of surgical treatment of epilepsy/number of epilepsy surgery as the outcome term and year as the predictor term. Offset term was included to correct the number of events for population size. Population, number of hospitalization, number of surgical treatment of epilepsy was set separately as offset term while regressing on number of hospitalization, number of surgical treatment of epilepsy and number of epilepsy surgery. Statistical significance was defined as a 2-sided $P < .05$. All analyses were conducted and graphs created using R (version 3.5.0) [10].

3. Results

3.1. Epilepsy diagnosis

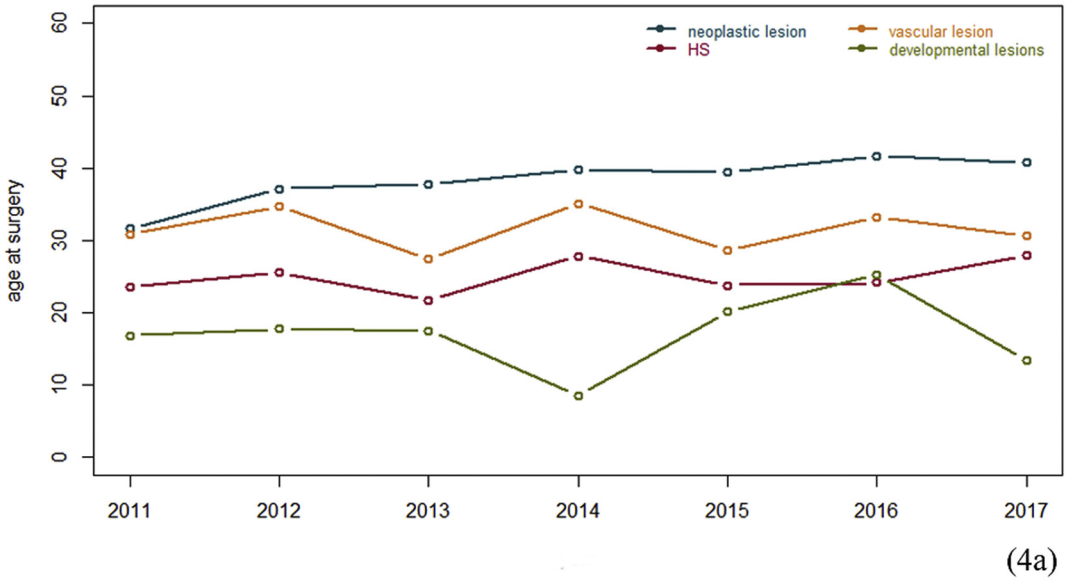
A total of 14,710 hospitalizations from January 2010 to December 2017, involving 8607 (58.51%) male patients and 6103 (41.49%) female patients, were extracted from the healthcare system. Among them, 12,355 were older than 14 yrs. and 2355 were younger than 14. Mean age at hospitalization was 45.73 yrs. (range, 1 day - 110 yrs.; SD, 25.0 yrs.).

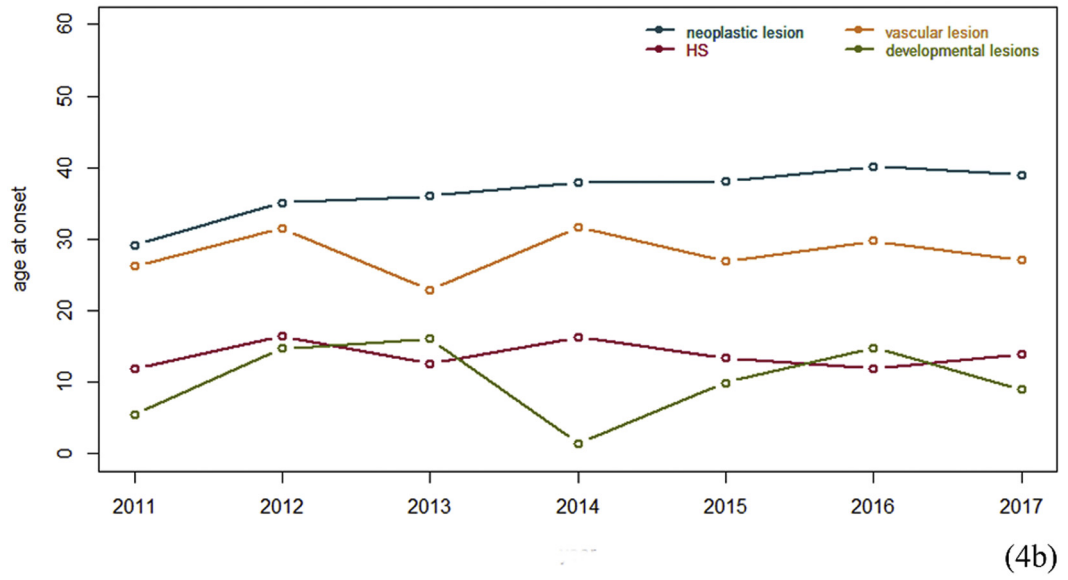
The number of hospitalizations per year increased significantly over time ($r = 0.97$, $P < .001$; Fig. 1; slope coefficient = 0.20, $P < .001$). The number of hospitalizations increased in both low- and high-volume hospitals, with a greater increase occurring in high-volume institutions in recent years (Fig. 2). Similar to this tendency, data from West China Hospital on a total of 17,302 hospitalizations (2009 to 2017) showed an increase in the number of patients diagnosed with epilepsy over the study period (Fig. 3). Results from negative binomial regression demonstrated a slope coefficient of 0.156 with *P* value < .001. In fact, the number diagnosed in 2017 (2807) was 2.66-fold higher than the number in 2010 (1056).

In contrast to the substantial increase in the number of hospitalizations, the number of surgical treatment of epilepsy decreased with statistical significance with a slope coefficient of −0.064 ($P = .004$) according to negative binomial regression setting number of hospitalization as offset term. After excluding those with neoplastic lesions, the number of epilepsy surgeries remain stable over time ($P = .81$ for slope coefficient). Table 1 presents the number of hospitalization, number of surgical treatment of epilepsy and number of epilepsy surgery (excluding those with neoplastic lesion) for each calendar year. Resident population for each year was extracted from official website (http://data.stats.gov.cn/easyquery.htm?cn=E0103). Fig. 4 showed surgery numbers to treat neoplasm or non-neoplasm epilepsy. Of the 17,302 patients at West China Hospital, 159 (0.9%) underwent gamma knife treatment; six, vagus nerve stimulation; and one, deep brain stimulation.

3.2. Pathology types

We identified 1350 epileptic patients (age range, 2 months to 91 yrs.) from West China Hospital who underwent surgical treatment of epilepsy and for whom pathology specimens were available. Nearly half of these patients (659, 48.8%) were diagnosed with TLE based on pathology findings. Among all the patients, 475 had drug-resistant epilepsy, and one quarter had intractable TLE (337/1350, 25.0%). Among those drug-resistant, 296 (62.32%) suffered childhood onset (< 18 yrs.) and 75 (15.79%) suffered seizure onset at ages younger than 6 yrs. However, most of the patients with drug-resistant epilepsy underwent





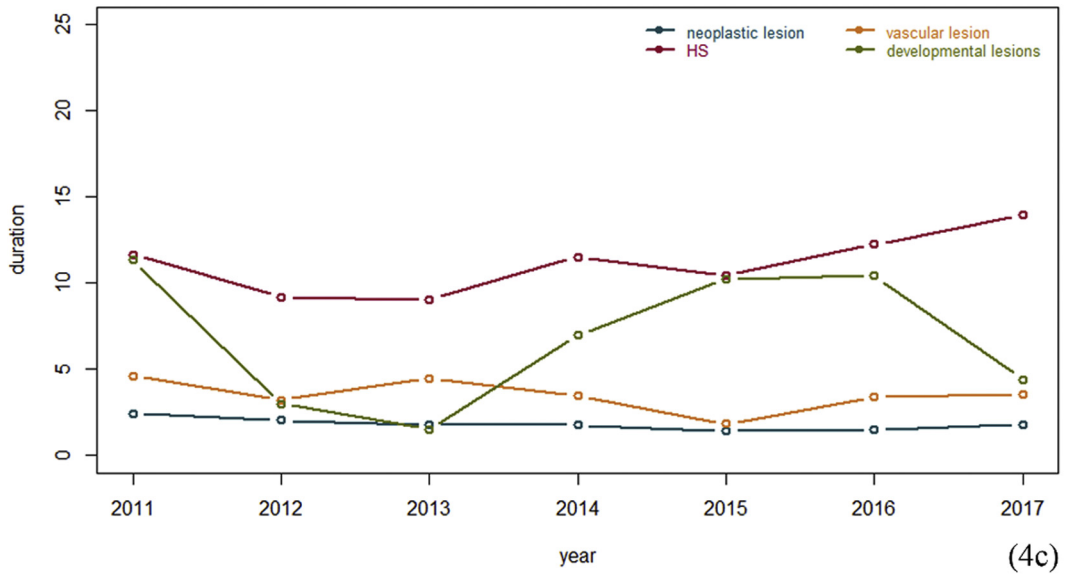


Fig. 5. Annual statistics on (a) patient age at surgery, (b) age at epilepsy onset, and (c) epilepsy duration during the study period. Data refer to a surgical patient sample from West China Hospital.

surgery as adults (368, 77.47%). Over half of all 1350 surgeries (690, 51.1%) involved resection of the left side. Age at onset was similar between patients in whom resection occurred on the left or right sides ($P = .27$).

Histopathology identified HS in 146 of the 1350 patients (10.8%); neoplasms, 724 (53.6%); vascular lesions, 227 (16.8%); developmental lesions, 35 (2.6%); gliosis, 57 (4.2%); inflammatory lesions, 43 (3.2%); focal encephalomalacia, 65 (4.8%); and "no finding", 53 (3.9%). Of those non-intractable, most of them (619/875, 70.74%) were neoplasms. Of the 337 patients with intractable TLE, neither the total number of surgeries nor the number of HS cases increased over time. The most frequent type of intractable TLE was HS, which accounted for 44.32% of cases.

At surgery, patients with HS lesions (24.70 ± 9.23 yrs.) were significantly younger than those with vascular lesions (31.68 ± 13.91 yrs., $P < .001$) or neoplasms (38.40 ± 16.87 yrs., $P < .001$), but significantly older than those with developmental lesions (19.22 ± 10.77 yrs., $P < .001$, *post hoc* tests). Epilepsy duration was significantly longer for patients with HS (11.07 ± 7.92 yrs.) than for those with vascular lesions (3.70 ± 5.92 yrs.; $P < .05$), neoplasms (1.77 ± 4.15 yrs.; $P < .05$) or developmental lesions (8.73 ± 7.45 yrs., $P > .05$). Patients with HS were similarly young at onset as those with developmental lesions (13.62 ± 9.23 *vs.* 10.55 ± 8.39, $P > .05$), and significantly younger at onset than those with vascular lesions (27.97 ± 14.26, $P < .05$) or neoplasms (36.62 ± 17.74, $P < .05$). Just over three-quarters of patients with HS (112, 76.7%) experienced their first seizure in childhood. Nevertheless, age at surgery, duration of epilepsy, and age at onset did not significantly vary during the study period (Fig. 5a-c).

4. Discussion

This retrospective study in western China, based on data from a population-based sample and a large inpatient population, provides the first data on trends in the numbers of epilepsy diagnoses and surgeries between 2009 and 2017 in this region of the country. Our data indicate a dramatic increase in the diagnosis of epilepsy, similar to results in the United States [5], but a plateau in the number of epilepsy surgeries. Similarly, a much slower rise in surgeries than in diagnoses for epilepsy has been reported for Germany [4].

Our analysis allows us to exclude several potential explanations for the lack of an increase in epilepsy surgeries. Our results do not appear to support an increasing number of referrals to low-volume hospitals, since we observed a steeper rise in hospitalizations to high-volume hospitals, in contrast to data from the US [5]. Our results also do not support a non-surgical treatments such as vagus nerve stimulation or deep brain stimulation, since few of the patients in our databases underwent these procedures. However, we cannot exclude the potential influence of the emergence of next-generation antiepileptic drugs (*e.g.*, levetiracetam). We speculate that the increase in the number of surgeries to treat neoplasms may reflect, in part, advances in imaging techniques that facilitate its diagnosis. However, imaging advances do not appear to have contributed to an increase in HS detection, which may mean that HS incidence has stabilized. Last but not least, our data, which is similar to the western countries, suggested that the plateau of epilepsy surgeries was not related to different cultural backgrounds, genetic backgrounds, various healthcare systems and also referral patterns.

Changes in epilepsy-modifying factors may help explain our results, as suggested by a three-center study in Germany [6]. However, in contrast to that study, we did not observe an increase in age at surgery or epilepsy duration over the study period [6]. The authors in that study reported an increase in patient age at surgery, which they interpreted to suggest a decrease in the number of HS patients. Our data, in contrast, suggest relatively constant incidence of HS. One contributor to this discrepancy may be the different study periods, which was 2009–2017 in our case and 1988–2008 in the German case. Further studies are needed to explore in greater depth the factors that influence the numbers of epilepsy diagnoses and surgeries.

Our results suggest that during the study period, neoplasm was the dominant pathology type of epilepsy in western China, followed by HS and vascular lesions. These three pathology types accounted for > 80% of all surgery cases. HS was the most frequent pathology among patients with drug-resistant TLE. Our study demonstrated only one-third of patients to be drug-resistant among all undergoing surgical treatment of epilepsy. It has to be noted that in our study, patients were classified whether intractable or not based on their response to drug treatment. And most patients with brain tumor had only been prescribed a kind of antiepileptic drug for only a very short period before surgery, which could be indicated by the short median duration of epilepsy (0.167 yrs.). Thus, these patients were not categorized as intractable due to inadequate dosage and insufficient length of time. The very short epilepsy duration might be accounted for by neurosurgeons' positive attittudes to refer patients for consideration of surgery.

The present work, covering the period 2009–2017, provides the first detailed insights into trends in epilepsy diagnosis and surgery for western China, and it provides the first data for any part of China for the years since 2011, which was the cut-off for all previous studies that we identified in the literature. Our analysis suggests that, despite the differences in health care systems and referral patterns between China and the West, the number of epilepsy surgery is not rising in line with the number of epilepsy diagnoses in either part of the world – even though the efficacy of TLE surgery is strongly supported and the necessary technology is well established and increasingly accessible. Future work should perform similar, up-to-date analyses of other regions of China to examine whether our findings from the western part of the country can be generalized. In addition, studies should investigate whether the new generation of antiepileptic drugs is affecting the numbers of epilepsy surgeries.

Ethical publication 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.

Declaration of Competing Interest

No undisclosed groups or persons had a primary role in the study and/or in manuscript preparation. All co-authors were substantially involved in the study and/or the preparation of the manuscript, they saw and approved the submitted version of the paper, and they accept responsibility for its content. None of the authors has any conflict of interest to disclose.

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