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The impact of a history of status epilepticus for epilepsy surgery outcome

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ABSTRACT

Objective: Patients with focal drug resistant epilepsy are excellent candidates for epilepsy surgery. Status epilepticus (SE) and seizure clusters (SC), described in a subset of patients, have both been associated with extended epileptogenic cerebral networks within one or both hemispheres. In this retrospective study, we were interested to determine if a history of SE or SC is associated with a worse surgical outcome.
Methods: Data of 244 patients operated between 2000 to 2018 were reviewed, with a follow-up of at least 2 years. Patients with a previous history of SE or SC were compared to operated patients without these conditions (control group, CG).
Results: We identified 27 (11%) and 38 (15.5%) patients with history of SE or SC, respectively. No difference in post-operative outcome was found for SE and SC patients. Compared to the control group, patients with a history of SE were diagnosed and operated significantly at earlier age($p = 0.01$), and after a shorter duration of the disease ($p = 0.027$), but with a similar age of onset.
Significance: A history of SE or SC was not associated with a worse post-operative prognosis. Earlier referral of SE patients for surgery suggests a heightened awareness regarding serious complications of recurrent SE by the referring neurologist or neuropediatrician. While the danger of SE is evident, policies to underline the impact for SC or very frequent seizures might be an efficient approach to accelerate patient referral also for this patient group.

1. Introduction

Epilepsy is a common disease affecting 0.5 to 1% of the general population, with a cumulative incidence of 3% (Fiest et al., 2017). The pharmacological armamentarium, developed during the last few decades has improved seizure control, complications (Ryvlin et al., 2011) and quality of life for patients (Birbeck et al., 2002); however, in 30–40% of the cases, seizures are not controlled by medications (Kwan and Brodie, 2000). These patients may be good candidates for epilepsy surgery (Engel et al., 2012). Several studies identified factors related to surgical failure or success, reviewed recently (West et al., 2015); however, no indication of the influence of a history of status epilepticus (SE) or seizure clusters (SC) has been provided.

SE is a life-threatening neurological condition defined as an epileptic activity lasting longer than 5 min for generalized seizures and 10 min for focal seizures, and/or repetitive seizures without regaining baseline conditions in between (Trinka et al., 2015). SE may provoke neurotoxicity, recruitment of remote brain structures and irreversible brain injury with high morbidity and mortality rates (Neligan and Shorvon, 2011). Hence, it can be postulated that patients experiencing SE might have a worse prognosis following surgical epilepsy treatment.

The definition of seizure clustering (SC) is less uniform, but usually implies ≥ 2 seizures within 12–24 h (Haut, 2015). It is reported in up to 30% of patients suffering epilepsy and seems to occur more frequently in patients with focal seizures (Buelow et al., 2016; Chiang et al., 2020; Jafarpour et al., 2019). SC is found to be associated with younger age at onset, pharmacoresistance, cortical dysplasia and CNS infections (Chen et al., 2017). Since SC may represent a continuum with SE given that it is often not clear from witness reports, if the patient regains a normal neurological status between events, we decided to evaluate in addition the impact of SC on surgery outcome.

To our knowledge, no previous study aimed at determining whether SE or SC have a predictive role on the surgical outcome of epilepsy in terms of seizure control. We hypothesized that a history of SE or SC is

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related to worse surgical outcomes, as it is the case with bilateralized seizures (Baud et al., 2015; Spencer et al., 2005).

2. Methodology

2.1. Patients

We consulted our registry on operated patients and identified all patients with pre-operative spontaneously reported SE or SC. All patients who underwent epilepsy surgery from 1.1.2000 to 1.6.2018 at Geneva University Hospitals (HUG) were assessed for inclusion, according to the following inclusion criteria: i) patients referred for pre-surgical evaluation with pharmacoresistant epilepsy; ii) patients with $\geq$ 3 days of EEG-recording; iii) unifocal epilepsy; iv) minimum 2 years follow-up. Exclusion criteria were: i) generalized or multifocal epilepsy, ii) genetic or immunologic epilepsy etiology.

We used as definition of SE a history of or objectively confirmed seizures of $\geq$ 5 min duration (or intermittent seizures lacking return to baseline conditions in between). SC were defined as have $\geq$ 2 seizures occurring within 24 h, but with patients regaining consciousness in-between and not explained by anti-seizure medication (ASM) withdrawal or other provoking factors for increased seizure occurrence. Seizures' patterns were reported in the patients' seizure diary. SE and SC were mutually exclusive, in case of occurrence of both, SE was retained.

2.2. Statistical analysis

Patients without SE and SC were considered as control group (CG) and compared to SE and SC patients. We performed chi-square tests to binary variables, and independent t-tests for group comparisons, after verification of normal distribution. A p-value of < 0.05 was considered significant. With respect to the surgical outcome, we adopted a shortened version of the Engel or ILAE classification (Durnford et al., 2011): we identified all patients who were free of seizures with alteration of consciousness for at least 2 years following the intervention. All other patients were considered as having persistent seizure activity (Engel 2–4, ILAE 2–6) and compared to the seizure free group. Given that young children suffer from different syndromes and have an immature cerebral development, possibly interfering with the propensity to develop to SC or SE, we also compared SE and SC occurrence in patients with onset at $<$ 3 years vs $>$ =3 years of age.

3. Results

3.1. Overall cohort

A total of 244 patients (116 females, 47%, mean age: 39.5 ± 16.3 years) were eligible for further analysis. Mean age at the diagnosis of epilepsy was 11.8 years (± 10.8), at operation 26.3 years (± 14.9), resulting in a mean duration of 14.6 years (± 12.4) of disease before operation. Right versus left epilepsy focus were equally distributed ($p = 0.4$). Temporal lobe epilepsy (TLE) concerned 175 patients (72%; for details see Table 1).

Regarding the post-operative seizure control, Engel class 1 was achieved in 200 patients (82%), while 16 (6.5%) patients had a $>$ 80% decrease of seizures, 17 patients (7%) between 50–80% decrease and 11 (4.5%) remained without notable change in seizure frequency. Post-operative seizure freedom was achieved more frequently in TLE than in extratemporal epilepsy (ETLE) (147/169 (87%) versus 53/75 (70%); $p = 0.004$).

3.2. Status epilepticus (SE)

A total of 27 patients (11%, N = 10 females) had a history of SE. The mean age at epilepsy diagnosis was 9.2 (± 12.3) years. Mean age at surgery was 19.7 (± 14.2) years and mean time-to-surgery was 10.6 years (SD ± 9.2); these time lapses were significantly shorter in the SE group than in the CG (Table 1).

Table 1
Clinical information of the 3 patient groups and comparisons.

	Control group (no SE/no SC; N = 179)	SE (N = 27)	SE vs control group	SC (N = 38)	SC vs control group
Mean age at diagnosis (years)	12.6 (±10.9)	9.2 (± 16.9)	p = 0.18	9.6 (± 8.6)	p = 0.072
Mean age at surgery (years)	27.6 (± 14.6)	19.7 (± 14.2)	p = 0.01	24.7 (± 15.8)	p = 0.30
Time to surgery (years)	15.2 (± 13.1)	10.6 (± 9.2)	P = 0.027	14.9 (± 11.1)	P = 0.86
Sex (M/F)	97/82	17/10	p = 0.39	14/24	p = 0.052
Left vs right epilepsy (L/R)	92/87	17/10	p = 0.26	20/18	p = 0.89
Focus localization (TLE/ETLE)	128/51	15/12	p = 0.14	26/12	p = 0.86
Surgical outcome (Engel class 1/ Class 2-4)	147/32	24/3	p = 0.38	29/9	p = 0.41

SE: Status epilepticus, SC: seizure clusters, TLE: temporal lobe epilepsy, ETLE: extratemporal lobe epilepsy, L: left, R: right

3.3. Seizure cluster (SC)

Thirty-eight patients were known for SC (15.5%; 24 females) with a mean age at diagnosis of 9.6 (± 8.6), mean age at surgery was 24.7 (± 15.8), and a mean disease duration of epilepsy of 14.9 years (± 11.1). Regarding surgical outcome or other clinical data, no major difference emerged (Table 1).

3.4. Localization and etiologies

The underlying focus localization and etiologies did not differ between the 3 groups, including or excluding the mixed category "other causes" (Table 2). This category comprised 3 patients with post-traumatic epilepsy, 3 with post-infectious epilepsy, 1 with Rasmussen's encephalitis and 1 with epilepsy symptomatic of an arachnoid cystic lesion. Given that congenital developmental malformations are the earliest insults and maybe more likely to cause remote pathological changes, we compared this etiology against the rest. While surgical outcome was worse in patients with developmental malformations (45/65 (69%) patients seizure free; $p = 0.003$), there were no differences in occurrence of SE or SC among patients with developmental malformations compared to those without.

Table 2
Etiologies of epilepsy in the different groups.

Etiologies of Epilepsy	SE	SC	No SE/ no cluster
Congenital malformation	10 (37.5%)	13 (34%)	42 (23%)
Hippocampal sclerosis	10 (37.5%)	15 (39%)	79 (44%)
Tumor	2 (7%)	7 (18%)	37 (21%)
Vascular	2 (7%)	2 (6%)	17 (10%)
Other causes	3 (11%)	1 (3%)	4 (2%)
	n = 27	*n* = 38	*n* = 179

SE: Status epilepticus, SC: seizure clusters
Other causes include: undetermined, immunologic, cystic, post-traumatic, tuberous sclerosis, genetic and post-infectious epilepsies.

4. Discussion

To the best of our knowledge, this is the first study examining a relationship between SE or SC and surgical outcome. We initially postulated that a SE or SC history was predictive for a worse outcome in patients undergoing epilepsy surgery, as a surrogate of larger and more distributed epileptic network. However, our results did not confirm our initial hypothesis. Surgery in patients with SC was previously reported to be related to better outcome, but only in those with TLE (Asadi-Pooya et al., 2016). However, in our cohort, TLE was associated with a higher rate of post-operative seizure control, but this was not different for SC or SE patients.

While the overall duration of epilepsy was slightly shorter in our population compared to other large single-center studies including all ages (14.6 vs around 18–20 years) (Jobst and Cascino, 2015), patients with SE, but not SC, had a significantly shorter time to surgery. This observation suggests that a history of SE motivates the referring physician to send patients earlier for surgery. These subjects underwent evaluation 4–5 years earlier than those lacking a SE history, corresponding to an approximately 30% shorter disease duration. An earlier onset does not explain this finding (since SE patients were not younger at diagnosis compared to SC or CG). This reflects the fact that SE is considered a severe complication of epilepsy requiring swift referral to a specialized epilepsy center. Alternatively, medical care by specialized epilepsy centers may be more attentive to patients presenting with SE.

Our observation also gives support for initiatives to accelerate referral of patients with chronic epilepsy to level 3 or 4 epilepsy centers, by pointing out the danger of chronic epilepsy. Assertive education on sudden unexpected death in epilepsy (SUDEP) (Ryvlin et al., 2013), could be another viable road to underline the hazards of persisting seizures, prompting treating neurologists to refer patients earlier. It is of note that in almost all patients, SE or SC pattern, as identified in the patient's history were also observed during hospital-based monitoring, suggesting that SE or SC are not related to ASM withdrawal but to pre-existing seizure pattern.

In line with previous evidence (Téllez-Zenteno et al., 2010), patients with congenital malformations, similar to patients with ETLE, had worse post-operative outcome, but this was unrelated of the presence of SE or SC.

Regarding a potential localizing information of SE or SC, our results did not confirm observations of a particular relationship between those seizure pattern and site of onset. Previous retrospective data reported that more than half of the patients with frontal lobe epilepsy had a history of SE or SC (Jobst et al., 2000), suggestive of a localizing information, while SC was found to be significantly associated with both frontal and temporal seizure onset (Ferastraoaru et al., 2016) or just frontal onset (Haut, 2015). In a non-surgical population, SC was rather associated with ETLE (Haut et al., 2005). Interestingly, in a previous study, SC was significantly associated with a history of convulsive SE, which suggests that both SC and SE can be considered as part of the same spectrum (Mitchell, 2002). Seizures arising in clusters do not differ in their localization from isolated seizures in (Kim et al., 2014), therefore careful evaluation of seizure semiology is necessary for both types of presentation. Our results support this notion and could not find arguments in favor for a predominance of particular onset site in SE-SC patients.

Overall, SE and SC appeared to be relatively frequent in the population of patients with chronic epilepsy. In our cohort, 27% of our patients undergoing epilepsy surgery had a history of SE or SC, which taken together seems larger than in unselected epilepsy types or idiopathic generalized epilepsy (Bosak et al., 2019; Langenbruch et al., 2021; Sillanpää and Shinnar, 2002). Conversely, in studies focusing on SE, 30% (Leitinger et al., 2019) to 60% (Bergin et al., 2019; Novy et al., 2010) report pre-existing epilepsy.

Limitations of our study include its retrospective nature, which raises the possibility that some cases of SE or SC may be missed due to underreporting. However, the combined proportion of SE and SC seems roughly comparable to other assessments suggesting a reasonable external validity. Another limitation is the inclusion of SC for which there is no established definition. Our definition may be too generic, but it is the most frequently adopted definition by patients and referring physicians. If our definition of SC is too permissive, differences between CG and SC patients could have been masked. Future studies on the impact of SC are mandatory, once a consensual definition is approved.

To conclude, history of SE and SC do not seem to carry a worse prognosis for surgical outcome in epilepsy patients. They are not related to a particular focus localization, but a history of SE prompts earlier referral for evaluation and consequently, a shorter duration of epilepsy. The urgency of presurgical evaluation seems more easily recognized in patients experiencing SE compared to those with isolated seizures. Prospective studies could shed additional light on the prognostic value of SE or SC in this clinical context. Looking into the role of SE as part of the patient history might confirm an indirect positive effect, namely a more aggressive and effective therapy at an earlier stage of the disease.

Ethical approval 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.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

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Statements

The study was approved by the Research Ethic Committee of the Republic and Canton of Geneva [project number 2020–02214].

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