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Evolution of pediatric epilepsy surgery program over 2000–2017: Improvement of care?

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ABSTRACT

Purpose: We assessed trends in spectrum of candidates, diagnostic algorithm, therapeutic approach and outcome of a pediatric epilepsy surgery program between 2000 and 2017.
Methods: All pediatric patients who underwent curative epilepsy surgery in Motol Epilepsy Center during selected period (n = 233) were included in the study and divided into two groups according to time of the surgery (developing program 2000–2010: n = 86, established program 2011–2017: n = 147). Differences in presurgical, surgical and outcome variables between the groups were statistically analyzed.
Results: A total of 264 resections or hemispheric disconnections were performed (including 31 reoperations). In the later epoch median age of candidates decreased. Median duration of disease shortened in patients with temporal lobe epilepsy. Number of patients with non-localizing MRI findings (subtle or multiple lesions) rose, as well as those with epileptogenic zone adjacent to eloquent cortex. There was a trend towards one-step procedures guided

Abbreviations: MCD, malformation of cortical development; FCD, focal cortical dysplasia; TSC, tuberous sclerosis complex; FBTCS, focal to bilateral tonic-clonic seizure; ILAE, International League Against Epilepsy; fMRI, functional magnetic resonance imaging; DTI, ictal SPECT, ictal single photon emission tomography; FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography (PET); MRS, magnetic resonance spectroscopy; IOM, intraoperative monitoring; ECoG, electrocorticography; SEEG, stereoelectroencephalography; DQ, developmental quotient; IOM, intraoperative monitoring (intraoperative monitoring of motor functions and awake craniotomy).

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by multimodal neuroimaging and intraoperative electrophysiology; long-term invasive EEG was performed in fewer patients. Subdural electrodes for long-term invasive monitoring were almost completely replaced by stereo-EEG. The number of focal resections and hemispherotomies rose over time. Surgeries were more often regarded complete. Histopathological findings of resected tissue documented developing spectrum of candidates. 82.0% of all children were seizure-free two years after surgery; major complications occurred in 4.6% procedures; both groups did not significantly differ in these parameters.
Conclusion: In the established pediatric epilepsy surgery program, our patients underwent epilepsy surgery at younger age and suffered from more complex structural pathology. Outcomes and including complication rate remained stable.

1. Introduction

Epilepsy surgery is proven to be an effective treatment option in patients with intractable focal epilepsy, both adults and in children.[1,2] Although the core principle - elimination of seizures by removing the epileptogenic zone - remains unchanged, epileptologists and neurosurgeons face some specific challenges in pediatric patients, i.e. greater proportion of patients with malformations of cortical development (MCD),[3] frequent localization of epileptogenic zone outside the temporal lobe,[4] generalized electroencephalographic (EEG) patterns and non-conclusive seizure semiology.[5,6] In addition, the risk of psychomotor delay and irreversible loss of cognitive potential due to poor seizure control and frequent polytherapy represent a specific concern in children with epilepsy.[7,8]

In the last decades we have seen substantial technical advances, both in surgical techniques and pre-surgical diagnostic work-up.[9] These have made epilepsy surgery feasible also in patients with challenging epilepsy syndromes and complex structural pathologies.[10–12] However, it has not yet been clearly established how these advances have affected epilepsy surgery outcomes and rate of complications. Patients with increasingly complex underlying pathologies previously deemed inoperable, have become epilepsy surgery candidates. Therefore, it is complicated to evaluate the effectiveness of pediatric epilepsy surgery in such a diverse patient cohort.

In our study we aimed first to detect changes in the spectrum of epilepsy surgery candidates between the two periods of the pediatric epilepsy surgery program (developing vs. established); in their clinical, neuroimaging and electrophysiological variables, underlying pathologies and surgical approaches. Secondly we analyzed changes in epilepsy surgery outcomes in terms of freedom from seizures and antiepileptic drugs, cognitive functions and complication rates.

2. Methods

2.1. Patients

We included all pediatric patients (≤19 years) who underwent pre-surgical evaluation and subsequently resective epilepsy surgery or hemispherotomy in Motol Epilepsy Center between January 1st, 2000 (beginning of our epilepsy surgery program) and December 31st, 2017 (cut-off point). Patients who underwent invasive monitoring without subsequent resection and palliative procedures such as vagus nerve stimulation were excluded.

2.2. Study design

This is a retrospective study of a pediatric epilepsy surgery program between 2000 and 2017. Patients who fulfilled criteria were divided in two groups according to the time of (the last) surgery. The division is reflecting the development of pediatric epilepsy surgery program in our center (developing program 2000–2010: n = 86, established program 2011–2017: n = 147), more specifically: a) number of performed procedures stabilized after 2010 on 20–27 surgeries per year, b) long-term invasive EEG exploration using stereo-EEG (SEEG) was introduced in our center at the same time. Data on presurgical, surgical and outcome variables were obtained from epilepsy surgery database of our center. For evaluation of epilepsy surgery results we included only patients with follow-up two years or more and thus compared children operated on between 2000 and 2010 with patients undergoing surgery in the period 2010–2015 (n = 111).

2.3. Data collection

Motol Epilepsy Center is a tertiary center for patients with drug-resistant epilepsy. Department of Pediatric Neurology, 2nd Faculty of Medicine Charles University and Motol University Hospital manages the majority of children from Czech Republic and Slovakia plus individual cases from other European countries (e.g. Slovenia, Ukraine). All patients undergo standardized diagnostic protocol including MRI with specialized epilepsy protocol, neuropsychological examination and long-term video/EEG. Other examinations (PET, SPECT, fMRI, DTI, MRS, Wada test) are performed if information obtained via standardized protocol is not sufficient to delineate extent of the epileptogenic zone or to localize eloquent cortex. Results of all examinations are discussed in multidisciplinary meetings. Although the team grew gradually, the core members - PK (neurologist), MT (neurosurgeon), MK (neuroradiologist) and JZ (pathologist) participated in all procedures since the beginning of the program. Details on presurgical examinations, surgery and outcome of patients undergoing epilepsy surgery are recorded in our epilepsy surgery database. Follow-up data were obtained during planned in- and outpatient visits one and two years after the surgery. Majority of patients undergo a short hospitalization with 24 h video/EEG monitoring, control MRI and neuropsychological examination.

Since the study is observational in nature and no experimental procedures were performed, the approval of Motol University Hospital ethical committee was not required. Informed consent with the pre-surgical evaluation and epilepsy surgery was obtained prior to all procedures from patients or their legal representatives.

2.3.1. *Presurgical data collection*

We collected data on patients' history (gender, family history of epilepsy, potential risk factors: febrile seizures, head trauma, encephalitis etc.), the course of epilepsy (age at seizure onset, suspected localization of epileptogenic zone, seizure types, status epilepticus), neurological findings, details of neuropsychological assessment, including DQ or IQ, and results of pre-surgical neuroimaging and electrophysiological examinations. Patients were classified in six groups according to presumed localization of the epileptogenic zone judged from presurgical electro-clinical data and data from long-term invasive EEG monitoring (extratemporal, mesial temporal, neocortical temporal, multilobar, hemispheric, midline – hypothalamic hamartoma). Findings of MRI were classified as it follows: gross lesion (e.g. tumor, obvious localized FCD type II, hippocampal sclerosis), subtle lesion – discrete abnormalities with a limited localizing value detected only by an expert neuroradiologist (typically FCD type I or other findings possible to use for SEEG study planning but insufficient to perform one-step resection), multifocal – multiple lesions with no localizing value without complex evaluation (typically TSC), non-lesional – normal finding on brain. Long-term invasive EEG monitoring was indicated if 1) MRI showed no or subtle lesion with unclear borders, 2) structural abnormity was adjacent to eloquent areas, 3) findings of non-invasive examinations were discordant.

2.3.2. *Pre- and postsurgical neuropsychological work-up*

Neuropsychological examination was performed before the (first) surgery and at one year follow-up after the last procedure using (according to patients' age and cognitive level) Wechsler adult intelligence scale III, Wechsler intelligence scale for children III, Stanley–Bailey score or developmental quotient assessment. Patients were stratified in six groups according to IQ/DQ – above average (≥110 IQ points), average (90–109 IQ points), below average (70–89 IQ points), mild mental retardation (50–69 IQ points), moderate mental retardation (35–49 IQ points) and severe mental retardation (<35 IQ points). Preoperative testing was not feasible in 12 patients (due to severe clinical status in one patient and language barrier in eleven others) and postoperative in 34 patients (health insurance of patients from abroad did not cover another neuropsychological examination) and in 19 patients who did not have one year follow-up. Three patients were lost to follow-up. Postoperative change in cognitive abilities was regarded relevant if the difference in postoperative and preoperative IQ/DQ was 10 points or more.[13]

2.3.3. *Epilepsy surgery-related data collection*

Epilepsy surgery-related information comprised the age and epilepsy duration at surgery, type of procedure, long-term invasive EEG and/or intraoperative ECoG, including type of electrodes used, side and extent of surgery (focal, unilobar, multilobar, hemispheric), histopathological findings and number and type of complications. All findings of cortical malformations were re-classified according to the current International League Against Epilepsy (ILAE) classification scheme.[14] Completeness of the resection was judged by comparison of preoperative and postoperative MRI (performed in all patients within 24 h from the surgery) and available intracranial EEG study at the time of surgery. In patients who did not have clear finding on preoperative MRI the judgment was based only on intracranial EEG study data.[15]

For complication assessment we used definition and classification proposed by Rydenhag and Silander.[16] Complication was defined as unwanted, unexpected and uncommon event after a diagnostic or therapeutic procedure which manifested immediately or up until three months following the surgery. We primarily considered surgical complications for statistical analyses (e.g. severe brain edema, inflammation, ischemia, hydrocephalus, bleeding or unplanned extension of the resection). Internal and anaesthesiological complications (electrolyte imbalance, deep vein thrombosis) were considered in case they affected neurological function and/or led to prolonged hospitalization. Adverse events related to intracranial EEG studies were evaluated separately. According to their severity, we distinguished major a minor complications. Major complications were considered those that were directly life-threatening, causing significant neurological deficit and/or affected activities of daily living (ADL) and lasted longer than three weeks. Minor complications were considered those that resolved within three weeks and/or were not associated with significant neurological deficit and/or did not lead to limitation in ADL. Expected postoperative neurological deficits (i.e. homonymous hemianopia or worsening of hemiparesis after hemispherotomy) were reported separately and were not regarded as complications.

2.3.4. *Outcome data collection*

Seizure outcome was classified according to modified Engel's scheme[17]: (I) completely seizure-free, auras only or only early postoperative seizures; (II) ≥90% seizure reduction; (III) ≥50% seizure reduction; and (IV) < 50% seizure reduction two years following surgery (2 years follow-up) and medication status and seizure outcome to January 1, 2018 (final follow-up). According to postoperative medication policy patients were divided in three groups – antiepileptic drug (AED)-free, with reduced therapy and without change in AEDs compared prior surgery. Therapy reduction was defined as a decrease in number of AEDs used. Postoperative tapering of AEDs in seizure-free patients was most frequently started one year after epilepsy surgery. No universal protocol on AED withdrawal was used. Particular approach in each patient was tailored according to the complex knowledge of the case and modified by patient's and caregiver's preference.

2.4. *Statistical analysis*

We performed univariate statistical tests for each observed variable in the study. In case of nominal variables, we created contingency tables where columns are the time periods 2000–2011 and 2011 and more. The rows are the possible values of each variable, that can be binary (present/not-present) or generally nominal with more states such as epileptic syndrome etc. The contingency tables we tested using Fisher's exact tests optimized for the dimensions of the table. In case of 2 × 2 tables and statistically significant result, we also calculated the odds ration with its confidence interval (CI) at 95% level. The continuous variables such as age at surgery, IQ points or duration of epilepsy, we tested using non-parametric rank-sum test. The tested classes for continuous variables were the time periods. In case of a statistical significance, we calculate median difference within the classes and its 95% confidence interval using Hodges–Lehman estimator. p values< 0.05 were considered statistically significant. For survivor analysis we used Kaplan–Meier non parametric estimator, where the failure time is represented by the duration of seizure freedom of the patient after the last surgery. Subjects in the survivor analysis are censored when they are seizure free at their last follow-up. We used the cox proportional hazard model for censored data, where the period is used as predictor variable and similarly to the survivor analysis the censoring variable is the seizure freedom at final follow-up.

For the calculations software MatLab version 2017b and its statistical computing toolbox was used.

3. Results

Between 2000 and 2017 264 curative surgeries (including 31 reoperations) were performed in 233 patients. The number of performed surgeries was rising with some fluctuations until 2010, and then it stabilized on 20–27 surgeries per year.

Table 1 – Changes in patients' clinical characteristics in our cohort.

variable	overall	2000–2010	2011–2017	p-value
median age at first seizure [years]	3,5	3,88	3,08	0,39
duration of epilepsy at surgery [years]	4,7	5,34	4,34	0,07
sex [%]				0,35
female	51,07	54,84	48,57	
male	48,93	45,16	51,43	
family history of epilepsy [%]				1
no	84,98	84,95	85	
yes	15,02	15,05	15	
prenatal risks [%]				0,84
no	87,98	87,1	88,57	
yes	12,02	12,9	11,43	
febrile seizures [%]				**0,005**
no	92,27	86,02	96,43	
yes	7,73	13,98	3,57	
trauma [%]				0,44
no	97	95,7	97,86	
yes	3	4,3	2,14	
Inflammation [%]				0,53
no	95,17	94,62	96,43	
yes	4,29	5,38	3,57	
Preoperative IQ/DQ [%]				0,769
≥110 points	7,24	7,23	7,25	
90–109 points	27,15	31,33	24,64	
70–89 points	38,01	34,94	39,86	
50–69 points	19,46	19,28	19,57	
35–49 points	5,43	6,02	5,07	
<35 points	2,71	1,20	3,62	
Epileptogenic zone localization [%]				0,44
extratemporal	45,06	46,24	44,29	
mesial temporal	30,9	31,18	30,71	
temporal other than mesial	11,59	15,05	9,29	
hemispherical	9,87	6,45	12,14	
other	2,15	1,08	2,86	
multilobar	0,43	0	0,71	
seizure frequency [%]				**0,003**
daily	65,67	63,44	67,14	
weekly	14,59	7,53	19,29	
monthly	7,3	8,6	6,43	
less than monthly	12,45	20,43	7,14	

3.1. Patients' characteristics

Median age at first surgery decreased significantly between the two reported epochs (12.4 years in patients operated in 2000–2010 and 10.2 years in those operated in 2011–2017, $p = 0.02$, median difference −1.8, CI (−3.4;−0.4)). The decrease was more prominent in patients with temporal lobe epilepsy (median age 15.7 and 11.4 years, respectively, $p = 0.004$, median difference −3.2, CI (−5.5;−1.1)). Duration of epilepsy decreased in patients with temporal lobe epilepsy – median in the first group was 8.4 years, while in the second 3.3 years ($p = 0.004$, median difference −3.4 years with CI (−5.8;−1)). In all patients duration of epilepsy slightly shortened, not reaching the level of statistical significance (Table 1). Gender ratio, age at onset of epilepsy and family history of epilepsy did not significantly change (Table 1).

Incidence of febrile seizures was lower in later operated group ($p = 0.005$, odds ratio 0.2, CI (0.1; 0.7)), whereas other potential risk factors (family history of epilepsy, prenatal risks, trauma, inflammation) did not differ. Distribution of types of epilepsy (respective presumed localization of epileptogenic zone) among candidates was stable over time, with extratemporal unilobar epilepsy followed by mesial temporal epilepsy being the two most common. Spectrum of patients according their seizure frequency prior surgery changed significantly in favor of patients with daily (71.0% vs. 86.4%) and weekly (7.5% vs. 19.3%, both with $p = 0.003$) seizures. Occurrence of infantile spasms, focal to bilateral tonic-clonic seizures (FBTCS) and status epilepticus was equal in both groups. Spectrum of patients according to their cognitive abilities did not differ between both groups with majority of patients having IQ under average or higher (72.4% of all patients).

3.2. Diagnostic work-up

We observed an increase of patients with non-localizing finding on MRI. Number of patients with identified gross lesion on preoperative MRI was stable. Number of patients with subtle and multiple lesions increased under level of statistical significance in contrast to decrease of number of patients with normal finding on MRI (Table 2).

We noted significant changes in neuroimaging methods performed as a part of presurgical diagnostic work-up (Table 2). fMRI and DTI were increasingly used, in contrast to ictal SPECT) and MRS. Number of performed FDG-PET examinations was stable over years. Wada test was almost abandoned.

Long-term invasive EEG was less frequently utilized in more recently operated group (27.9% vs. 16.9%, $p = 0.05$). Types of electrodes used for invasive monitoring differed with SEEG being far more frequently used after 2011 (0% vs. 73.1%); in contrast to subdural strips and grids both in isolate use (59.3% vs. 3.7%) and in combination with intracerebral electrodes (40.7% vs. 22.2%, all with $p < 0.001$).

3.3. Surgical variables

We noticed a significant increase in number of tailored resections (32.7% vs. 48.1%) and hemispherotomies (7.7% vs. 11.3%), whereas lobar (43.3% vs. 29.4%) and multilobar resections (16.4% vs. 11.3%) have been less frequently used (all with $p = 0.03$). Although use of intraoperative ECoG was stable (77.3%), post-resection ECoG was performed less often (41.4% vs. 29.4%, odds ratio 0.6, $p = 0.05$). Continuous intraoperative motor function mapping became a routine procedure after 2010 (10.6% vs. 33.8%, odds ratio 4.3, $p < 0.001$) suggesting frequent resections in vicinity to eloquent cortical and subcortical structures. This correlates with an increased

Table 2 – Pre-surgical diagnostic tests 2000–2010 vs. 2011–2017.

variable	overall [%]	2000–2010 [%]	2011–2017 [%]	p-value	odds ratio	CI95
MRI				0,171		
gross lesion	76,29	75,27	76,98			
subtle lesion	10,78	9,68	11,51			
multiple lesions	7,33	5,38	8,63			
non-lesional	5,6	9,68	2,88			
FDG-PET				0,69		
performed	64,77	66,35	63,75			
not performed	35,23	33,65	36,25			
ictal SPECT				0,03	0,6	(0.3; 0.9)
performed	33,33	41,35	28,12			
not performed	66,67	58,65	71,88			
fMRI				0,02	1,9	(1.1; 3.1)
performed	41,67	32,69	47,5			
not performed	58,33	67,31	52,05			
DTI				<0.001	11,4	(6.1; 21.4)
performed	46,97	15,38	67,5			
not performed	53,03	84,62	32,5			
MRS				<0.001	0,1	(0.1; 0.2)
performed	32,58	61,54	13,75			
not performed	67,42	38,46	86,25			
WADA test				<0.001	0,1	(0.0; 0.3)
performed	10,23	21,15	3,12			
not performed	89,77	78,85	96,88			

proportion of resections in proximity to eloquent cortex among patients with extratemporal epilepsy ($p = 0.038$, odds ratio 0.4, CI (0.1; 0.9)). Histopathological findings revealed significant changes in etiology ($p = 0.007$) – a rise in number tuberous sclerosis complex (TSC) and hypothalamic hamartomas, benign tumors, and a decline in incidence of hippocampal sclerosis. Proportion of patients with MCD was steadily high (and rose in absolute numbers) (Fig. 1). Number of complete resections judged by postoperative MRI and intracranial EEG at the time of surgery increased (62.5% vs. 76.9%, $p = 0.03$). Reoperation rate did not significantly change over years (12.1% of all performed procedures). Complication rate (of resections and invasive monitoring) decreased, but not reaching the level of statistical significance - major complications in 4.8% vs. 4.4% of procedures, minor in 11.5% vs. 8.2% ($p = 0.64$). Occurrence of expected neurological deficit changed also non-significantly (20.2% vs.17.5%, $p = 0.63$). During years there was one perioperative death in a patient with post-infectious epilepsy due to herpes simplex virus encephalitis who developed malignant brain edema after uneventful surgery.

3.4. Outcome

Median follow-up in patients operated 2000–2010 was 11.0 years; while in those operated 2011–2015 4.9 years. 82% of our patients were seizure-free at two years after surgery (Fig. 2). Results in terms of seizure freedom did not differ significantly between both groups with 84.7% vs. 79.8% seizure-free patients ($p = 0.45$). In final follow-up 41.2% vs. 37.6%, patients were drug-free and in 15.3% vs. 21.1% the therapy was reduced ($p = 0.75$), Fig. 3. 24% of children reached better IQ/DQ score postoperatively, for further details see Fig. 4. Later operated patients tended to have greater increase in IQ/DQ; however the difference did not reach level of statistical significance. Further details on pre- and postoperative neuropsychological assessment are included in Table 3. Analysis of long-term outcomes revealed 64.5% patients, CI (58.4%–70.6%) remained seizure free at 5 years and 37.8%, CI (29.6%–45.90%) at 10 years after surgery (Fig. 5). There was no significant difference in long-term outcomes between both groups.

4. Discussion

We studied a cohort of pediatric patients operated on in Motol Epilepsy Center between 2000 and 2017, divided in two subgroups – 2000–2010 and 2011–2017, in order to analyze significant trends in our practice and in patients' outcomes. The spectrum of both surgical candidates and performed procedures changed over time. Focal resections and hemispherotomies have been increasingly indicated. Number of procedures regarded complete rose. Including younger patients and more challenging cases did not negatively affect epilepsy surgery outcome in terms of freedom from seizures and antiepileptic medication.

Similarly to Baud et al. we observed a decrease in median age of patients undergoing epilepsy surgery in the later period.[9] We consider this trend particularly important since the most severe epileptic encephalopathies manifest in early

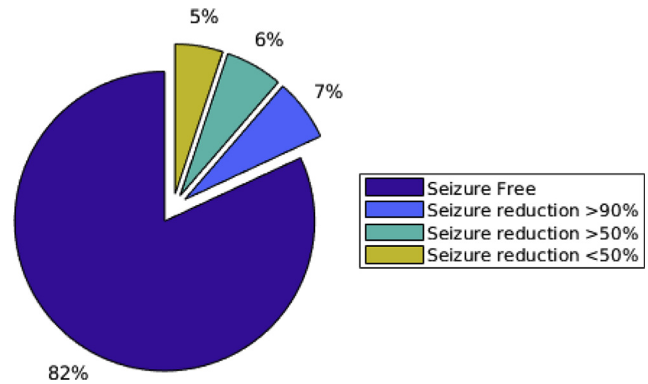

Fig. 2 – Seizure outcome 2 years after surgery.

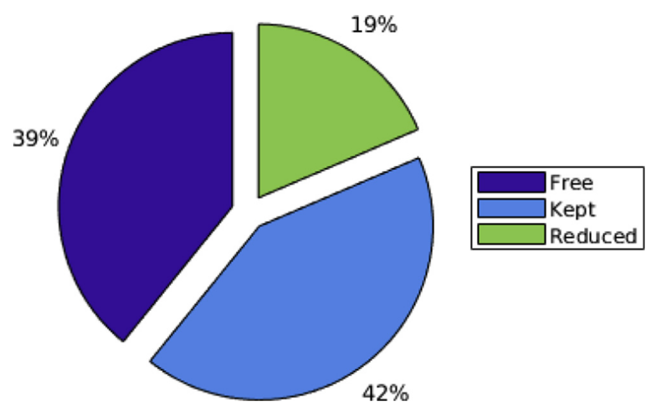

Fig. 3 – AED medication status to January 2018, AED free = AED discontinued.

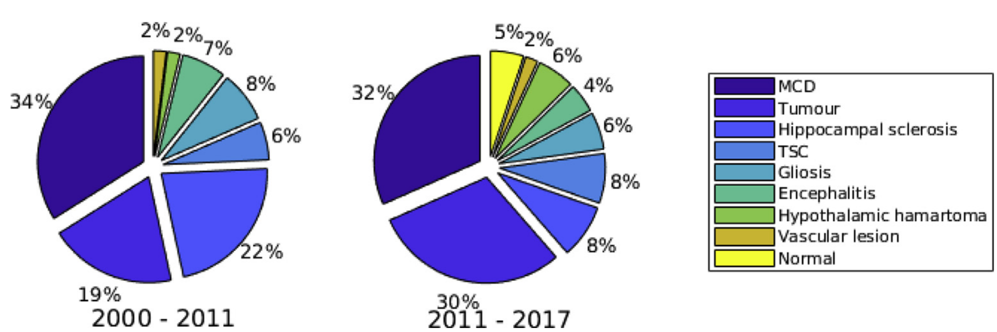

Fig. 1 – Evolution of etiological spectrum in our patients operated 2000–2010 vs. 2011–2017. MCD - Malformation of Cortical Development; TSC - Tuberous Sclerosis Complex.

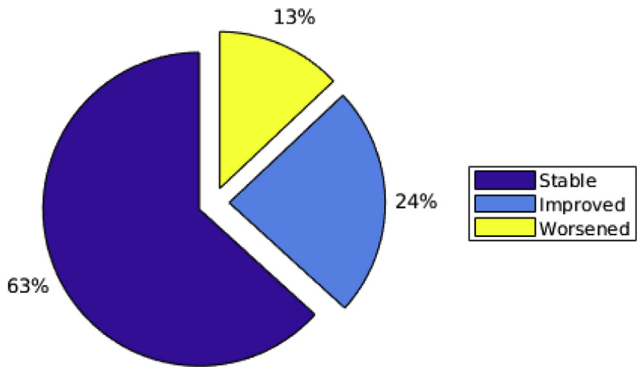

Fig. 4 – Cognitive outcome of patients one year after surgery. Change was defined as 10 IQ/DQ points or more.

childhood[11,18] and early intervention can prevent severe life-long cognitive deficits.[19,20] Moreover a correlation between early seizure onset and impaired cognitive development in infants has been described.[21] In contrast to previously mentioned study by Baud et al., duration of epilepsy significantly decrease only in a subgroup of patients with temporal lobe epilepsy. In the whole group, the decrease in duration of epilepsy was not significant. Similar study by Lamberink et al. showed significant decrease neither in age nor in duration of disease of patients.[22] These different observations might be explained by different design of the studies – Baud et al. compared patients operated on 1997–1998 with those operated on 2012–2013, whereas Lamberink focused on a continual period of time and therefore the difference cannot be as prominent. Nevertheless, our results suggest improving awareness of benefits of epilepsy surgery at least in group of patients with temporal lobe epilepsy among primary care physicians. Since it has been repeatedly reported patients with shorter duration of epilepsy have higher success rate in reaching seizure freedom[22–24] and more favorable cognitive outcome,[25] this trend can in future enhance positive effects of epilepsy surgery. Beyond reduction in seizure frequency, children with intractable epilepsy who underwent epilepsy surgery reached better scores with respect to behavior and quality of life.[2]

Recently, more patients with TSC, hypothalamic hamartoma and benign tumors have been included in the epilepsy surgery program, while representation patients with MCD was steadily high (equal or higher compared to other European centers),.[22,26] The number of patients with gross lesions was stable in our group. We introduced terms “subtle” and “multiple” lesions for patients where interpretation of MRI finding

Table 3 – Pre- and postsurgical neuropsychological characteristics of the groups 2000–2010 vs. 2011–2017.

	overall	2000–2010	2011–2017
Preoperative median IQ	80 (IQR = 28)	80 (IQR = 30)	79.5 (IQR = 26)
Postoperative median IQ	85 (IQ = 31)	79.5 (IQE = 33)	87 (IQR28.5)
Median IQ change	2 (IQR = 12)	2 (IQR = 13.5)	2 (IQR = 12)

IQR = interquartile range.

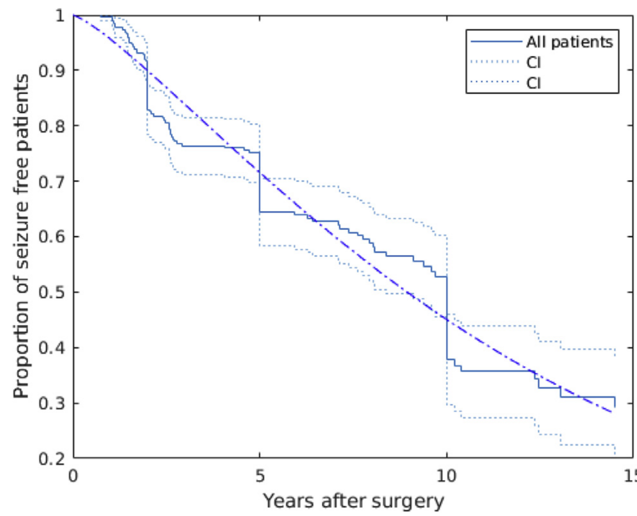

Fig. 5 – Empirical cumulative distribution of seizure recurrence over time expressed as proportion of seizure free patients.

and subsequent surgical intervention is frequently equally challenging as in non-lesional cases. Number of truly non-lesional patients decreased whereas number of patients with subtle and multiple lesions increased. Patients in those groups represent a minority compared to those with gross lesion, and therefore the difference did not reach level of statistical significance in whole group. Nevertheless, we suggest this result reflects rising experience and optimizing neuroimaging protocols designed specifically for potential epilepsy surgery candidates. A certain selection bias might be in place for children with negative findings on MRI, particularly because they may not be considered eligible for epilepsy surgery by their pediatric neurologist, and this may hamper their referring to a specialized center. However, given the fact that we treat all children with focal intractable epilepsy as potential epilepsy surgery candidates, we suggest improved neuroimaging provides more plausible explanation.[27,28] Baud et al. used traditional division on lesional and non-lesional MRI and reported a stable number of MRI negative cases in group of pediatric and adult patients from sixteen European centers (13.5%, vs. 11.8%, $p = 0.4$).[9]

We observed a decrease in number of long-term intracranial EEG studies. This trend apparently contrasts with increasing complexity of our candidates. Lamberink et al. reported an increased use of long-term intracranial monitoring – 1.8% vs. 11.8% of all procedures. This rate is approaching our current proportion of patients indicated for long-term intracranial EEG (16.8%). We therefore suggest these numbers suggest real proportion of pediatric patients indicated for long-term invasive monitoring in whom the epilepsy surgery cannot be safely and effectively performed unless this procedure is used. This proportion may vary between centers depending on availability of other diagnostic tools and experience with long-term invasive monitoring. In our center the decreased use of long-term intracranial EEG studies stems from an extensive experience of the team with the interpretation of intraoperative ECoG, greater availability of advanced multimodal neuroimaging in the neuronavigation as well as experience in intraoperative monitoring (IOM). The shift from subdural to intracerebral electrodes is related to a change of philosophy in long-term invasive monitoring that at least partly reflected previously mentioned change in underlying causes of epilepsy in our series: we encounter more patients with presumed epileptogenic lesions in deeper structures of the brain (e.g. insular and opercular cortex). There may be a certain bias since SEEG was introduced in 2011 in our center, nevertheless increased use of this procedure in our center cannot be explain solely by this.

Replacing earlier frequently performed multilobar resections with hemispherectomy reflects broader experience of the neurosurgical team with this type of procedure. Patients undergoing hemisherotomy have better chance of reaching seizure and drug freedom than those undergoing multilobar surgery.[29] Multilobar surgery was previously identified as an independent predictor of unfavorable outcome[22]; in addition, from our experience the complication rate is lower in hemispherotomy. Optimized use and greater experience with the interpretation of intra- and extraoperative invasive EEG as well as advance in neuroimaging resulted in a more limited extent of resections while preserving favorable outcome. We believe this trend may help decreasing complication rate and reaching better cognitive outcome in longer time horizon similarly as it was previously reported for declarative memory in patients after temporal lobe resectio.[30] Despite increasing number of patients with challenging etiology complication rate remain stable, relatively low and comparable to other European centers (although the terminology differs).[9,22,31]

As mentioned before, we suggest the complexity of our patients rose in general. Firstly we have proved a significant decrease of age of our patients and patients. In youngest patients interpretation of electro-clinical data and neuroimaging, as well as technical performance of surgery and subsequent perioperative care are challenging.[32] Secondly, number of hemispherotomies rose. We consider this procedure highly demanding on both neurosurgeon's experience and perioperative care. Thirdly, number of patients with TSC and hypothalamic hamartoma rose. Lastly, we noted an increase of resections in proximity of eloquent cortex in patients with extratemporal lobe epilepsy.

Considering increase of patients with resection in proximity of eloquent cortex and complex procedures such as hemispherotomy, a stable complication rate is a success. Short-term results of our program (seizure freedom in 82.0% patients, see section 3.4, Fig. 2) are comparable or superior to postoperative seizure freedom reported by Spencer et al. (58–78%in temporal lobectomies 59–70% in neocortical resections, 43–79% in hemipherotomies).[33] This is especially important if we consider the high proportion of patients with MCD (32.3%) and rising incidence of patients with TSC or hypothalamic hamartoma in whom the reported seizure freedom is generally lower.[10,34] Stable number of seizure free patients is somewhat contrasting with an increase in number of complete resections. It is important to bear in mind completeness of the resection was judged by postoperative MRI and intracranial EEG study assessment at the time of surgery.[15] In many patients removing whole structural pathology would not be sufficient to yield favorable outcome because of widespread epileptic network. There was no significant change in number of patients being drug-free at final follow-up (38.6%). Taking into account the fact patients operated in 2000–2010 had minimally 7 years of follow-up compared to 2–6 years in later operated group we expect the final rate of drug-free patients would rise in a few years. To summarize, overall seizure freedom remained high and complication rate low despite increasing complexity of patients and including patients in whom would be epilepsy surgery not feasible in past.

Stable postsurgical neuropsychological performance in majority of our candidates demonstrates epilepsy surgery does not have a negative impact on cognition in pediatric patients. The regression curve equation showed an increase in postsurgical IQ reaching 9.1 points. In another study we reported that postsurgical IQ/DQ was strongly correlated to presurgical IQ/DQ and the postoperative cognitive gain was more prominent in children with lower IQ/DQ.[35] Moreover, the nonsignificant trend to greater cognitive gain in later operated patients may suggest positive impact of early surgical intervention in selected group of patients. We expect this results may further improve since according to previously published results full cognitive gain is acquired in longer time horizon (at least 6 years after epilepsy surgery in pediatric temporal lobe epilepsy series).[25,36] Our results generally correlate with a review by Schooneveld and Braun, who observed an improved neuropsychological outcome in 19–29% of children undergoing epilepsy surgery, a deterioration in 10–11% and stable cognitive performance in 61–70%. The authors defined an improvement in cognitive development as an increase in IQ/MDI/DQ of at least 5–15 points or moving towards a better cognitive outcome category. In the subgroup of children undergoing hemispherotomy the cognitive gains were most prominent.[13] Moosa and Willie report stable cognitive outcome in 70% of pediatric epilepsy surgery candidates, improvement in cognition in 10–15% and decline in 10–15% cases. Postoperative cognitive gain (respective decline) is determined by functional capacity of epileptogenic zone and extent of reversible dysfunction of other areas caused by epileptogenic activity. The greatest risk of cognitive decline is in patients in whom the epileptogenic zone harbors significant cognitive function while negative influence on other brain areas is minimal.[37] This concept may explain postoperative cognitive decline in patients after otherwise successful epilepsy surgery (seizure-free and drug-free). In patients with ongoing seizures postoperative deterioration may be contributed rather to failure to stop epileptic encephalopathy than to surgery itself.

Proportion of patients being completely seizure free since the surgery at 5 and 10 years - 65%, respectively 38% fall within the range of published long-term outcomes (21%–91% at 5 and 41%–81% at 10 years).[38] However it is not possible to compare data from various studies since they differ both in methodology and studied populations (age, histopathology, proportion of patients with TLE, etc.). Some patients who experience seizure recurrence after epilepsy surgery may regain seizure control after introduction a new antiepileptic drug or due to running down phenomenon. A remote seizure control after initial failure of epilepsy surgery was observed in 8% (17/211) of patients with focal cortical dysplasia.[39] In our group this was the case in 4 patients (2% of patients with at least 2 years follow-up). Data on long-term outcome in purely pediatric population are sparse. In a study by Edelvik et al. 50% of operated children (n = 88) with mean follow-up 7.6 years were seizure-free, while 44% had sustained seizure freedom since surgery.[40]

This study has several limitations. Due to single center design we cannot exclude possible selection bias. We are aware not all neuroimaging methods were available at the beginning of the program; however one of aims of the study was to depict the evolution of the clinical praxis as it is. The limited number of patients in individual subgroups makes it impossible to statistically analyze some specific trends, such as changes in individual complication types. Concerning the outcomes analyses, the two year follow-up period is relatively short and thus the number of seizure-free patients might decrease over time. On the other hand we expect the increase in the number of drug-free patients, especially in the later operated group. Due to the timing of neuropsychological assessment (one year after the surgery), the postsurgical cognitive gain is probably underestimated. To better understand postoperative dynamics of cognitive development we plan to establish a long-term systematic follow-up with neuropsychological examination 2, 5 and 10 years after epilepsy surgery. More detailed prospective studies are needed to elucidate the possible effects of epilepsy surgery on postoperative cognitive performance. However, since some of our findings correspond to previously published studies on pediatric epilepsy surgery groups, we suggest they reflect general trends in evolution of pediatric epilepsy surgery in Europe.[9,22,26]

5. Conclusion

Epilepsy surgery is a safe and effective therapeutic option in children with focal intractable epilepsy. Due to technical advance in last decades the spectrum of possible epilepsy surgery candidates broadened. Both complication rate and short term results of epilepsy surgery remain stable despite rising rate challenging cases (young patients, patients with epileptogenic zone adjacent to eloquent cortex, TSC, hypothalamic hamartomas, patients indicated to hemispherotomy, etc.). While well correlating with findings from other centers we suggest these findings reflect not only increasing experience of our pediatric epilepsy surgery program, but also the technical advance and general increase of expertise in the field. In such situation an early referral of children with intractable epilepsy to a tertiary center bears a paramount importance as it has been repeatedly reported patients with shorter duration of epilepsy reach better outcomes in terms of seizure freedom and cognitive gains.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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