Danish experience with paediatric epilepsy surgery

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ABSTRACT

INTRODUCTION: Epilepsy surgery is increasingly used to treat children with medically intractable epilepsy. This study investigates the aetiology and seizure outcome in Danish children operated between 1996 and 2010.

METHODS: Retrospectively collected data on structural magnetic resonance imaging (MRI) diagnoses, surgical procedures and seizure outcomes classified according to the Engel Classification were used. Changes over time grouped as 1996-2000, 2001-2005 and 2006-2010 were analysed.

RESULTS: A total of 95 children underwent epilepsy surgery. Sixty-three operations were performed in Denmark and 50 abroad. In all, 14 children needed reoperation. The median follow-up period was four years. At the latest follow-up, Engel class I (indicating no disabling seizures) was found in 67% of the patients. Cortical dysplasia, mesial temporal sclerosis and tumour were the most common MRI findings. The percentage of tumours operated decreased over time, and frontal lobe resections increased. In the 2006-2010 period, resections with normal MRI were performed, resulting in a less favourable Engel outcome. Persistent, unexpected complications were seen in three of 113 operations.

CONCLUSIONS: The majority of children who undergo epilepsy surgery have a good, worthwhile seizure outcome. The seizure outcome for Danish children corresponds to that of other epilepsy surgery centres. The clinical criteria for selection of patients changed over time.

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At the age of 15 years, approximately 1.3% of Danish children have been diagnosed with epilepsy, and the incidence has been estimated to 360 per year [1]. Some 25-30% of these children will develop medically intractable epilepsy (MIE) which leads to a debilitating life for the child and a burden for the families [2]. Chronic epilepsy can delay cognitive development [3], and early surgery may yield a better seizure outcome [4]. In the past two decades, these findings have triggered an increased activity in the field of paediatric epilepsy surgery. The Commission on Neurosurgery of the International League Against Epilepsy (ILAE) initiated the Paediatric Epilepsy Surgery Subcommission to formulate international guidelines for referral of paediatric patients to specialised epilepsy centres in 2006 [5]. The latest studies report seizure-free outcome after epilepsy surgery in approximately two thirds of the children [6, 7]. Surgical complications have decreased significantly over time [8], and epilepsy surgery should be considered at an early stage in patients with MIE. In 1991, the Danish Health and Medicines Authority restricted epilepsy surgery to resections of the temporal lobe and recommended a cautious attitude towards epilepsy surgery, especially in children. As a consequence of that policy, children in need of extratemporal operations were referred to epilepsy surgery centres abroad (Gothenburg, Sweden; Bielefeld and Vogtareuth, Germany; Cleveland and Rochester, USA; and Paris, France) at the expense of the Danish Health Authorities. These restrictions were lifted in 2004; and extratemporal resections as well as intracranial investigations could from then on be performed in Denmark except for hemispherectomy and callosotomy where referral to Gothenburg in Sweden remains necessary.

In this study, we evaluate the aetiology and seizure outcome for all Danish children who had epilepsy surgery performed between 1996 and 2010, and we analyse the changes over time in five-year periods.

METHODS

This retrospective study comprised 95 Danish children (50 boys, 45 girls) with MIE who had epilepsy surgery performed in the 1996-2010 period. Patients who were younger than 19 years at the time of surgery were included. The inclusion criteria were incapacitating epileptic seizures (≥ 4 seizures/month with impaired consciousness) in patients who had been treated with a minimum of three anti-epileptic drugs (AED) and who had tried a minimum of two AEDs simultaneously. Data were collected by reviewing the patients' medical records.

Data on structural magnetic resonance imaging (MRI) diagnoses were registered at first surgery, and data on seizure outcome were collected from the latest surgery follow-up consultation. In the analysis of surgical procedures, data from the patients' latest surgery were used. All 113 operations were included in the investigation of surgical complications.

The patients were referred from all Danish regions and were followed either at Rigshospitalet (33 children) or at Epilepsy Hospital Filadelfia (62 children). The same

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TABLE 1

Post-operative outcome after last surgery was classified according to the Engel classification[a]. The values are n (%).

Classification	1996-2000	2001-2005	2006-2010[b]	Total
Engel I	10 (71.4)	22 (73.3)	29 (61.7)	61 (67)
Engel II	1 (7.1)	1 (3.3)	4 (8.5)	6 (6.5)
Engel III	3 (21.4)	5 (16.7)	8 (17)	16 (17.6)
Engel IV	-	2 (6.7)	6 (12.8)	8 (8.8)
Total	14	30	47	91

a) I: free of disabling seizures; II: rare disabling seizures ("almost seizure-free"); III: worthwhile improvement; IV: no worthwhile improvement.
b) Excluded are 4 patients who were regarded as unclassifiable.

TABLE 2

Diagnosis based on structural MRI scan before first surgery and the number of patients with outcome Engel I after last surgery. The values are n (%).

Diagnosis	1996-2000	2001-2005	2006-2010	Total	Engel I[a]
Cortical dysplasia	3 (21.4)	6 (17.7)	14 (29.8)	23 (24.2)	14 (60.9)
MTS	1 (7.1)	4 (11.8)	12 (25.5)	17 (17.9)	16 (94.1)
Tumour/DNET	3 (21.4)	6 (17.6)	4 (8.5)	13 (13.7)	7 (53.8)
Infarction	-	6 (17.7)	3 (6.4)	9 (9.5)	5 (55.6)
Uncertain MRI findings	2 (14.3)	2 (5.9)	3 (6.4)	7 (7.4)	5 (71.4)
Hypoplasia or atrophy	1 (7.1)	2 (5.9)	-	3 (3.2)	-
Hemimegaencephaly	1 (7.1)	3 (8.8)	-	4 (4.2)	3 (75)
Rasmussen syndrome	-	3 (8.8)	2 (4.3)	5 (5.3)	2 (40)
Sturge-Weber	1 (7.1)	1 (2.9)	-	2 (2.1)	1 (50)
AV-malformation	-	-	2 (4.3)	2 (2.1)	1 (50)
Haemorrhagia	-	-	1 (2.1)	1 (1.1)	1 (100)
Normal	-	-	4 (8.5)	4 (4.2)	1 (25)
Other[b]	2 (14.3)	1 (2.9)	2 (4.3)	5 (5.3)	5 (100)
Total	14	34	47	95	61

AV = arteriovenous; DNET = dysembryoplastic neuroepithelial tumour; MRI = magnetic resonance imaging; MTS = mesial temporal sclerosis.
a) % of Engel I is calculated for each diagnosis separately.
b) Include sequelae from earlier surgery, cysts, schizencephaly or sequelae from encephalitis

TABLE 3

Site of operation and Engel I classification after last surgery. The values are n (%).

Site	1996-2000	2001-2005	2006-2010	Total	Engel I[a]
Temporal lobe	6 (42.9)	14 (46.7)	22 (43.1)	42 (44.2)	32 (76.2)
Frontal lobe	–	2 (6.7)	14 (27.5)	16 (16.8)	8 (50.0)
Hemisphere	2 (14.3)	7 (23.3)	7 (13.7)	16 (16.8)	12 (75)
Multilobular	4 (28.6)	6 (20.0)	1 (2.0)	11 (11.6)	5 (45.5)
Corpus callosum	–	–	4 (7.8)	4 (4.2)	–
Parietal lobe	1 (7.1)	1 (3.3)	1 (2.0)	3 (3.2)	2 (66.7)
Occipital lobe	1 (7.1)	–	1 (2.0)	2 (2.1)	2 (100)
Cerebellum	–	–	1 (2.0)	1 (1.1)	–
Total	14	30	51	95	61

a) % of Engel I is calculated for each site of operation separately.

paediatric neurologist, Peter Uldall, followed all patients during the evaluation programme for epilepsy surgery. The programme included video electroencephalogram (EEG) monitoring, MRI and neuropsychological evaluation (data not included). Preoperatively, the patients were scanned at Hvidovre Hospital in a 1.5-Tesla Siemens Vision Scanner using a dedicated MRI epilepsy protocol. A few patients were scanned in a three-Tesla Siemens Trio Scanner. A subset of children also had interictal and/or ictal single photon emission computer tomography and positron emission tomography (41 and 22 patients, respectively). Furthermore, 15 patients were evaluated with intracranial EEG.

All patients were examined at six weeks and at six, 12, 18, and 24 months post-surgery. Additional follow-up consultations were carried out if needed. The follow-up period therefore ranged 1-15 years. Five children had surgery in 2010 and therefore some have not completed the standard two-year follow-up programme before cut-off for this study in February 2012. Four patients were excluded from the general analysis on seizure outcome as they had undergone a palliative operation (callosotomy) where a seizure-free outcome is not expected. During the follow-up period, AED treatment was reduced on an individual basis without strict guidelines (data not included). Seizure outcome was classified according to the Engel classification I, II, III and IV [9]. Post-operative complications were divided into three categories; persistent unexpected complications (hemiplegia, severe behavioural changes), temporary complications (hemiplegia, paresis, aseptic meningitis) and minor complications (e.g. quadrant hemianopsia, temporary adverse behavioural changes and depressive episodes).

Trial registration: The Danish Data Protection Agency approved the project with record number: 2013-41-2459.

RESULTS

Fourteen patients had epilepsy surgery in 1996-2000, 34 patients in 2001-2005 and 47 in 2006-2010. The median age at epilepsy onset was three years with an age span from two months to 18 years at the time of surgery (median 12 years). The median time from onset of epilepsy to first surgery was five years. Time from inclusion in the epilepsy surgery programme to surgery was 1.1 years. In total, 113 operations were performed on 95 patients, ten patients had two operations and four had three operations. There were 63 operations in Denmark and 50 operations abroad. The number of patients who had surgery performed increased over time (**Table 1**). The percentage of patients who underwent operation in Denmark increased from 36% (five out of 14) to 77% (36 out of 47) from the first to the last period. The median follow-up time was four years.

Post-operative outcome

In all, 67% of all patients in the study were classified as

Engel I indicating no disabling seizures at the latest follow-up, including seven re-operated children (Table 1). For 24% of the patients, the post-operative outcome was classified as Engel II or III indicating rare disabling seizures or a worthwhile improvement, whereas less than 10% had Engel IV, i.e. no worthwhile improvement. Fewer children were classified as Engel I in the last time period (2006-2010) than in the two previous periods.

Structural magnetic resonance imaging diagnoses

The three most frequent MRI diagnoses were cortical dysplasia (24.2%), mesial temporal sclerosis (MTS; 17.9%) and tumour/dysembryoplastic neuroepithelial tumour (DNET; 13.7%). Changes over time were seen with an increasing percentage of patients with cortical dysplasia and MTS and a decreasing number of patients with tumours (**Table 2**). Patients in Engel class I were unequally distributed according to the MRI diagnoses. MTS had the best result for Engel class I (94%) and reoperated children were included in the analysis. Among children with normal MRI, only 25% were classified as Engel I. **Figure 1** illustrates the MRI findings in a child with hemimegaencephaly and a child with MTS.

Site of resection and type of surgery

Temporal lobe resection was the most common type of resection (44.2%), followed by frontal lobe resection (16.8%), hemispheric resection (16.8%) and multilobular resection (11.6%) (**Table 3**). The percentage of frontal lobe resections increased over time, whereas multilobular resections decreased. Focal resections, standard temporal resection with amygdalohippocampectomy and functional hemispherectomies were the three dominating surgical procedures throughout the time intervals. The largest proportion of patients with Engel class I was seen in the cases in which the surgical procedure standard temporal resection with amygdalohemicampectomy (AHE) was performed. None of the patients operated with corpus callosotomy became seizure-free, but three patients had a worthwhile seizure reduction, especially with respect to the devastating drop attacks.

Complications

Persistent unexpected complications were found in three out of 113 operations. One patient developed hemiplegia after a focal temporal resection of a tumour, and two patients experienced severe worsening of attention deficit disorder after one frontal resection and one standard temporal resection with AHE. Ten operations had temporary complications and eight operations had minor complications.

Regions

Most patients were referred from the Region of Southern Denmark (23 patients), followed by the Capital Region (20 patients) and the Central Denmark Region (19 patients). Two patients were from the Faroe Islands and one from Greenland. One patient had moved abroad at cut-off for this study. When considering the number of operated patients per 10,000 inhabitants in each region, most patients were from Region Zealand (0.22 per 10,000), followed by Region of Southern Denmark and Region of North Denmark (0.19 per 10,000 each). The Capital Region had the lowest number with 0.11 per 10,000 inhabitants.

DISCUSSION

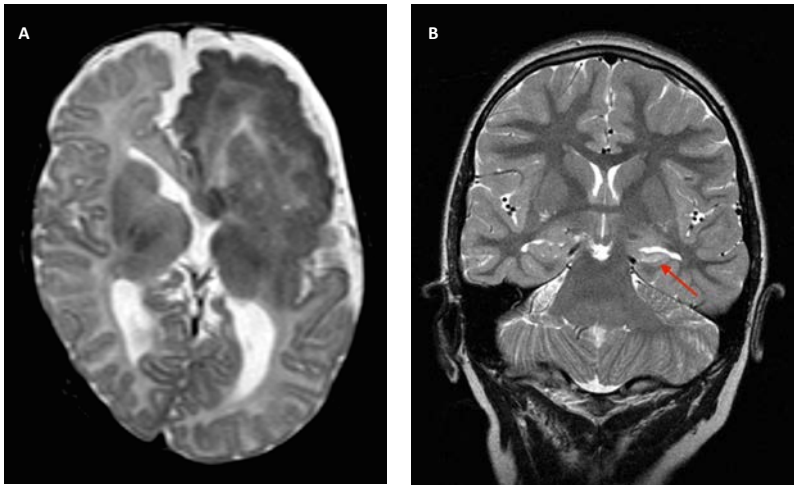
In childhood epilepsy surgery, the purpose is to render the patient seizure-free by removing the epileptogenic zone or by interrupting the neuronal network without creating new deficits. Additional improvements of developmental, psychosocial and behavioural impairment are hoped for.

In this study of 113 surgical procedures performed in Denmark and abroad in children with MIE, we found that seizure freedom or a significant reduction of seizure frequency was the result for the vast majority of operated patients. Engel class I was found in 67% and rare disabling seizures or worthwhile improvement in an additional 24% at a median follow-up of four years.

The present study consists of a nation-wide population of children, and all children were evaluated and followed in the same epilepsy surgery programme. A detailed multidisciplinary assessment by an epilepsy surgery team to localise the epileptogenic zone is critical before a decision about surgery can be made. Based on

FIGURE 1

A. The structural magnetic resonance imaging of a ten-week-old child with hemimegaencephaly (axial T2 weighted, 1.5 Tesla). **B.** The structural magnetic resonance imaging of a nine-year-old child with mesial temporal sclerosis (paracoronal T2 weighted, 1.5 Tesla).



the accumulated current experience, the ILAE has therefore recently proposed recommendations for diagnostic test utilisation [10]. In the majority of our patients, a non-invasive pre-surgical workup was sufficient. Nevertheless, in recent years a small subset of patients included in the evaluation programme for epilepsy surgery had no lesion on MRI. This highlights the importance of the developments in advanced MRI, functional imaging and intracranial EEG to define the epileptogenic zone; and these developments open possibilities for patients not previously considered for epilepsy surgery [11]. As found in other studies, Engel class I was less frequently found in those of our patients who had a normal MRI. Most patients with MTS were Engel class I, and this favourable result may be due to that reoperated patients were included in the analysis.

Our data are in agreement with previous publications about seizure outcomes of paediatric epilepsy surgery. In the study by Hallbook et al [12], approximately 50% of the children became seizure-free after surgery, and another 13% experienced a considerable reduction in the number of seizures. This favourable seizure outcome remained throughout a long-term follow-up period of 5-21 years, a time period somewhat longer than our study (1-15 years). The follow-up period is important because it has been shown that the number of seizure-free patients may decline with time [13].

With regard to surgical procedures and site of operation, several studies highlight that focal resections of the temporal lobe have the most favourable seizure outcome [6, 14]. These procedures also dominated in our study and may have contributed to the good overall seizure outcome of 67% of the children being classified as Engel I. In patients with extratemporal epilepsy, the presence of a visible MRI-detected lesion and tumourous aetiology has been reported by Hanáková et al to be associated with significantly better seizure outcome as compared with no demonstrated lesion [15]. Extratemporal epilepsy surgery was also studied by McIntosh [16] who found a probability of freedom from disabling seizures of 14.7% with a follow-up of five years, whereas the number in the study by Hanáková et al reached 37.5% at five years post-operatively. However, a more favourable result for extratemporal surgery has recently been presented by Englot et al [17]. In their systematic review and meta-analysis including 1,259 patients, the percentage of seizure-free patients after extratemporal surgery was 56%. This result is in accordance with our study, where Engel I was found in 45% of multilobular resections, in 50% of frontal resections and in 67% of parietal resections. The seizure outcome for the hemispherectomies was also in accordance with that reported in other studies. These patients' preoperative pareses were, in general, unchanged post-operatively.

The operations were performed in several countries, with an increasing number of patients operated in Denmark in the later years, reflecting increased experience of the Danish epilepsy surgery team and a change of recommendations by the Danish health authorities. The benefit of being operated in familiar settings is obvious – avoiding long flight travel for a child with daily seizures and maintaining continuity with the clinicians. The reduced number of children with Engel class I in the latest period should be seen in connection with this period's first operations on children with a normal MRI and the increased number of children with frontal lobe epilepsy, which is well known to have a worse prognosis.

Three major unexpected complications occurred, and this is consistent with the complication rate reported in other studies [8, 18]. The complications associated with epilepsy surgery have decreased substantially over time. They are seen as an infrequent, but unavoidable consequence of epilepsy surgery [19]. There has been a historical reluctance to operate in very young patients, though experience is accumulating that persistent early seizures are detrimental, and recent reports, including one by Kumar et al [20], have reported that even in children under one year of age, epilepsy surgery is, in many cases, a good treatment option.

In addition to seizure outcome, it is important to investigate pre- and post-operative cognitive function in relation to epilepsy surgery, and an article regarding this topic will be published separately.

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LITERATURE

1. Christensen J, Vestergaard M, Pedersen MG et al. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res 2007;76:60-5.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314-9.
3. Bjornaes H, Stabell K, Henriksen O et al. The effects of refractory epilepsy on intellectual functioning in children and adults. A longitudinal study. Seizure 2001;10:250-9.
4. Bourgeois M, Di Rocco F, Roujeau T et al. [Epilepsy and focal lesions in children. Surgical management]. Neurochirurgie 2008;54:362-5.
5. Cross JH, Jayakar P, Nordli D et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47:952-9.
6. Zupanc ML, Rubio EJ, Werner RR et al. Epilepsy surgery outcomes: quality of life and seizure control. Pediatr Neurol 2010;42:12-20.
7. Teutonico F, Mai R, Veggiotti P et al. Epilepsy surgery in children: evaluation of seizure outcome and predictive elements. Epilepsia 2013; 54(suppl 7):70-6.
8. Hader WJ, Tellez-Zenteno J, Metcalfe A et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. Epilepsia 2013;54:840-7.
9. Engel Jr. J, Van Ness P, Rasmussen TB. Outcome with respect to epileptic seizures. New York: Raven Press, 1993:609-21.
10. Jayakar P, Gaillard WD, Tripathi M et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014;55: 507-18.

11. So EL, Lee RW. Epilepsy surgery in MRI-negative epilepsies. Curr Opin Neurol 2014;27:206-12.
12. Hallbook T, Tideman P, Rosen I et al. Epilepsy surgery in children with drug-resistant epilepsy, a long-term follow-up. Acta Neurol Scand 2013;128:414-21.
13. Najm I, Jehi L, Palmini A et al. Temporal patterns and mechanisms of epilepsy surgery failure. Epilepsia 2013;54:772-82.
14. Englot DJ, Chang EF. Rates and predictors of seizure freedom in resective epilepsy surgery: an update. Neurosurg Rev 2014;37:389-404.
15. Hanakova P, Brazdil M, Novak Z et al. Long-term outcome and predictors of resective surgery prognosis in patients with refractory extratemporal epilepsy. Seizure 2014;23:266-73.
16. McIntosh AM, Averill CA, Kalnins RM et al. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. Epilepsia 2012;53:970-8.
17. Englot DJ, Breshears JD, Sun PP et al. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. J Neurosurg Pediatr 2013;12:126-33.
18. Schulze-Bonhage A, Zentner J. The preoperative evaluation and surgical treatment of epilepsy. Dtsch Arztebl Int 2014;111:313-9.
19. Tebo CC, Evins AI, Christos PJ et al. Evolution of cranial epilepsy surgery complication rates: a 32-year systematic review and meta-analysis. J Neurosurg 2014;120:1415-27.
20. Kumar RM, Koh S, Knupp K et al. Surgery for infants with catastrophic epilepsy: an analysis of complications and efficacy. Childs Nerv Syst 2015;31:1479-91.