Pre- and postoperative cognitive function and predictors of cognitive outcome in a Danish pediatric epilepsy surgery cohort

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Introduction: The recurrent seizures of pediatric medically intractable epilepsy (MIE) are known to impair brain development and can lead to a loss in cognitive functioning. Surgery is increasingly being used to treat children suffering from MIE. The ultimate goals of resective epilepsy surgery are to achieve freedom from seizures and discontinue antiepileptic drug (AED) treatment, thereby stabilizing or improving developmental capacities. The aims of this study were to investigate the pre- and postoperative cognitive function in a 20-year pediatric epilepsy surgery cohort and to identify predictive determinants of postoperative cognitive development.

Method: 135 Danish, Greenlandic and Faroese children ≤ 18 years and with varying MIE syndromes underwent various forms of resective epilepsy surgery between January 1996 and December 2016. 111 children were included in this study. 90 children were single-operated, 16 were multi-operated and 5 underwent callosotomy. Each subset was examined separately. All underwent preoperative cognitive evaluation and were reevaluated at 1-year and/or 2-year follow-up. The Bayley Scales of Infant and Toddler Development or the Mullen Scale of Early Learning was used in patients up to age 70 months and in patients with severe and profound mental retardation. Older patients were evaluated using Wechsler Intelligence Tests. Latest post-operative IQ scores were compared to preoperative IQ scores.

Results:

Table 1: Patient characteristics

	Single-operated patients	Multi-operated patients	Callosotomy-operated patients
Total, n	90	16	5
Boys, n (%)	48 (53.3)	9 (56.3)	3 (60.0)
Number with multiple surgeries, n (%)	NA	2 surgeries: 12 (75.0%) 3 surgeries: 4 (25.0%)	2 surgeries: 1 (20.0%)
Median age at epilepsy onset, years (IQR)	3.79 (1.31; 7.08)	2.79 (0.19; 7.92)	0.64 (0.27; 1.49)
Median age at surgery, years (IQR)	11.72 (8.15; 14.01)	1. surgery: 11.83 (3.04; 14.73) 2. surgery: 12.89 (5.12; 16.51) 3. surgery: 9.58 (6.13; 15.42)	10.75 (3.10; 14.48)
Median time from onset to surgery, years (IQR)	5.41 (3.14; 9.62)	1. surgery: 3.91 (2.49; 9.59) 2. surgery: 6.85 (4.57; 10.99) 3. surgery: 8.09 (2.94; 14.46)	10.24 (2.59; 13.68)
Histological diagnosis, n (%)			
- MTS	23 (25.6)	0 (0.0)	0 (0.0)
- Tumor, AV-malformation, hamartom	16 (17.8)	2 (12.5)	0 (0.0)
- Cortical dysplasia grade 1, grade 2, unspecified	25 (27.8)	4 (25.0)	1 (20.0)
- Astrogliosis, DNET, Rasmussen syndrome, Sturge-Weber, normal, other, no sample	26 (28.9)	10 (62.5)	4 (80.0)
Type of operation, n (%)			
- Standard + AHE/Spencer	35 (38.9)	1. surgery: 0 (0.0) 2. surgery: 0 (0.0) 3. surgery: 0 (0.0)	0 (0.0)
- Focal resection	44 (48.9)	1. surgery: 12 (75.0) 2. surgery: 13 (81.3) 3. surgery: 3 (75.0)	0 (0.0)
- Focal resection + subpial transaction, callostomy, functional hemispherectomy, anatomical hemispherectomy	11 (12.2)	1. surgery: 4 (25.0) 2. surgery: 3 (18.8) 3. surgery: 1 (25.0)	5 (100.0)
Site of resection, n (%)			
- Temporal lobe	53 (58.9)	1. surgery: 9 (56.3) 2. surgery: 5 (31.3) 3. surgery: 0 (0.0)	0 (0.0)
- Frontal lobe, parietal lobe, occipital lobe	15 (16.6)	1. surgery: 3 (18.8) 2. surgery: 7 (43.8) 3. surgery: 1 (25.0)	0 (0.0)
- Cerebellum, hemisphere, mulilobar, corpus callosum	22 (24.4)	1. surgery: 4 (25.0) 2. surgery: 4 (25.0) 3. surgery: 3 (75.0)	5 (100.0)

Single-operated patients:

- **IQ:** A significant difference in pre- and postoperative IQ was found (*p-value*: 0.03) (Figure 1, Table 2). 53.3% showed increased IQ postoperatively, with an average increase of 12.9 points. 36.7% had decreased postoperative IQ, with an average decrease of 10.2 points. 10% remained unchanged in IQ score.
- **AEDs:** 93.0% received fewer AEDs postoperatively, with a significant postoperative reduction in the number of patients in treatment with >2 AEDs (*p-value*: <0.001) (Table 2).
- **Seizure rate:** 92.2% experienced a reduced seizure rate postoperatively. 67.8% became seizure-free (*p-value*: <0.001) (Table 2).
- **Predictive variables for IQ change:** Significant predictive variables for IQ change in univariate linear regression analyses included gender, age at surgery, histological diagnosis and site of resection. In a multivariate analysis, preoperative IQ was found to be a predictive factor of IQ change (Table 3).

Table 2: Pre- and postoperative median IQ, AED treatment >/≤ 2 AEDs and seizure-freedom for single-operated patients

	Preoperative	Postoperative	P-value
IQ, median (IQR)	66.0 (46.8; 90.0)	72.0 (42.8; 90.0)	0.03
AED, n (%)			
- ≤ 2 AEDs	59 (68.6)	79 (91.9)	<0.001
- > 2 AEDs	27 (31.4)	7 (8.1)	
Freedom from seizures, n (%)	0 (0.0)	61 (67.8)	<0.001

Figure 1: Median pre- and postoperative IQ for single-operated patients

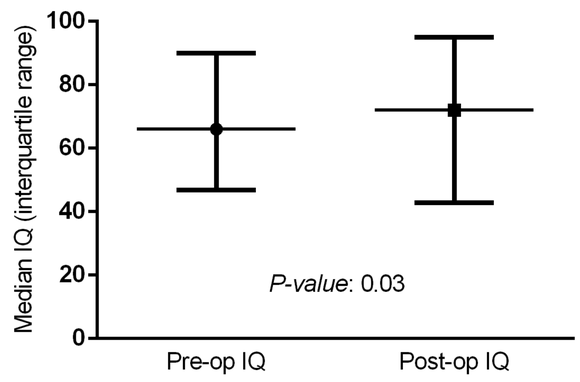

Table 3: Factors that influence **change in IQ** following surgery in single-operated patients.

Univariate analysis				
Predictive variable	Coefficient	*P-value*	CI 95%	
Gender, male	-6.08	0.04	-11.75	-0.41
Age at surgery	0.80	0.01	0.18	1.42
Histology				
- Dysplasia	-8.26	0.03	-15.88	-0.63
- Astrogliosis, DNET, Rasmussen, Sturge-Weber	-9.75	0.01	-17.42	-2.08
Operation site	-9.02	0.01	-16.03	-2.01
- Cerebellum, hemisphere, multilobar				
Multivariate analysis				
Predictive variable	Coefficient	*P-value*	CI 95%	
Preoperative IQ	-0.13	0.02	-24.50	-0.02

Multi-operated patients:

- **IQ:** Median pre- and postoperative IQ was 57.5 and 58.0, respectively. No significant difference in pre-and postoperative IQ was found.
- **AEDs:** The postoperative number of AEDs remained unchanged in 56.3% of patients. 31.3% received fewer AEDs and 12.5% received more AEDs. No significant postoperative reduction in the number of patients in treatment with >2 AEDs was found.
- **Seizure rate:** 81.3% of patients experienced a decrease in seizure rate postoperatively. 18.7% remained unchanged in seizure rate. Totally, 56.3% became seizure-free (*p-value*: 0.004).

Callosotomy-operated patients:

- **IQ:** Median pre- and postoperative IQ was 40.0. Postoperative IQ remained stable in three patients. One patient showed a ten-point improvement. One patient (the only one to undergo multiple surgeries) fell in IQ by 17 points.
- **AEDs:** Preoperatively, patients received between two and four AEDs. Two years after surgery, two patients had reduced AED treatment, two had increased AED treatment and one received the same number of AEDs.
- **Seizure rate:** All five patients experienced a fall in seizure rate one year after surgery. At latest follow-up, the seizure rate remained reduced in four patients but returned to pre-operation level in one patient.

Discussion & Conclusion:

Single-operated patients: After resective epilepsy surgery, single- operated patients received reduced AED treatment and experienced a decrease in seizure rate. IQ increased postoperatively. We conclude that surgery has a stabilizing effect on diminishing IQ and allows for IQ gains in the years following surgery.
Multi-operated patients: Patients requiring multiple surgeries (where primary surgery has been unsuccessful) did not experience a reduction in AED treatment. Surgery and continued AED treatment did, however, result in better seizure control. IQ did not fall postoperatively, as would be expected if surgery was not carried out. No IQ gains, however, were found. This patient group may take longer to show cognitive gains following surgery.
Callosotomy-operated patients: Callosotomy-operated patients undergo surgery for palliative reasons. Surgery resulted in better seizure control for the majority of patients but had no effect on AED treatment. IQ was low both before and after surgery. The nature and severity of MIE in this group is extreme and significant IQ gains cannot be expected following surgery.
Limitations:

- Longer follow-up periods are needed in order to assess the extent of the beneficial effects of surgery on cognitive ability.
- Due to ethical reasons, an appropriate comparison group is not possible.