Research Article

Intelligence Quotient Outcome Following Epilepsy Surgery in Pediatric Age – A Systematic Review and Meta-Analysis

Alferes AR[1]*, Oliveiros B[2,3] and Pereira C[1,4]

[1]Faculty of Medicine, University of Coimbra, Portugal
[2]Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine, University of Coimbra, FMUC, Portugal
[3]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, FMUC, Portugal
[4]Department of Neuropediatrics, Centro Hospitalar e Universitário de Coimbra, Member of the ERN EpiCARE, Coimbra

*Corresponding authors: Alferes AR, Faculty of Medicine, University of Coimbra, Portugal

Abstract

There is a deep-rooted correlation between refractory epilepsy in pediatric age and intelligence development. However, little is known about whether surgical procedures used in pediatric epilepsy treatment can affect Intelligence Quotient (IQ) or not. Factors that might influence postoperative IQ are also a matter of study in several articles. To tackle these issues, a systematic review with meta-analysis was conducted with the terms "epilepsy", "epileptic", "surgery", "surgical", "Wechsler Scale" and "intelligence tests" in PubMed, the Cochrane Library, EMBASE and Clinical Trials.gov. A descriptive data synthesis was carried out to address each of the objectives and then a meta-analysis using a random effects model was conducted. A meta-regression was performed to ascertain possible factors that could influence postoperative IQ. The meta-analysis of the studies included found a mean difference between postoperative and preoperative full-scale IQ values of 1.014 standardized points (p < 0.001). Among all the articles regarding curative surgeries, only three reported an overall significant improvement in IQ after surgery. Regarding palliative procedures, both studies with anterior corpus callosotomy reported a significant improvement in full-scale IQ values two years after surgery. The meta-regression performed did not find any predictors of change in full-scale IQ.

Keywords: Epilepsy; Surgery; Intelligence Quotient; Pediatric Age

Abbreviations

AED: Antiepileptic Drug; CC: Corpus Callosotomy; DQ: Development quotient; FSIQ: Full-scale intelligence quotient; ILAE: International League Against Epilepsy; IQ: Intelligence Quotient; NOS: Newcastle-Ottawa Scale; PIQ: Performance Intelligence Quotient; RCT: Randomized Control Trial; RE: Refractory Epilepsy; VCI: Verbal Comprehension Index; VIQ: Verbal Intelligence Quotient; WAIS: Wechsler Adult Intelligence Scale; WASI: Wechsler Abbreviated Scale of Intelligence; WIS: Wechsler Intelligence Scales; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Pre-School Primary Scale of Intelligence.

Introduction

Rationale

Epilepsy is one of the most frequent chronic neurologic conditions in pediatric age and is the most common childhood brain disorder in the United States [1]. According to the latest estimates, epilepsy affects 4% of children from developed countries and 8% from underdeveloped countries. The incidence varies with age. The highest values reported occur in the first year of age, with 1 to 2 cases per 1000 children. On the other hand, the prevalence increases with age, with 4 to 6 cases per 1000 children at the age of 10 [2-40].

Although there are several treatment options for epilepsy, in some cases, seizures may not respond to medication. According to the International League Against Epilepsy (ILAE), patients who fail to achieve sustained freedom from seizures, despite adequate trials of two antiepileptic drugs –either as monotherapy or in combination – are considered to have a condition called Refractory Epilepsy (RE) [5]. In these cases, epilepsy surgery may be an option for freedom from seizures (curative procedures) or to reduce their severity (palliative procedures). Examples of curative procedures include lesionectomy/lesion resection, lobectomy/lobe resection and corticectomy, whereas disconnection procedures such as Corpus Callosotomy (CC) are palliative procedures. Hemispherectomy, hemispherotomy and multiple subpial transections can be curative or palliative [6-8].

There is a well-established correlation between RE in pediatric age and intelligence development.

Nevertheless, whether the previously mentioned surgical procedures can affect Intelligence Quotient (IQ) or not is still a matter of investigation. A recent meta-analysis about callosotomy which included both children and adults at the time of surgery [9] showed no significant change on IQ from pre- to post-surgery. However, it was found that this palliative surgery had a negative effect in the performance IQ values of patients with average values before surgery. On the other hand, there was no significant modification in the performance IQ values of the patients with below-average performance IQ before surgery. In a recent study [10], it was found that five children who underwent hemispherectomy showed improvement in cognitive abilities across all subsets of the Wechsler Intelligence Scale for Children (WISC). Another study about hemispherectomy with nine children tested with the same intelligence test reported that all but one patient kept the same

intellectual levels [11]. A number of studies about lobe resection surgery report significant IQ improvements [12,13] while others report no significant modifications [14,15]. One way of measuring intelligence levels is by determining the IQ using intelligence tests. Nowadays, the Wechsler Intelligence Scales (WIS) are considered the gold standard tests for intelligence assessment [16-18].

The WIS include the Wechsler Pre-School Primary Scale of Intelligence (WPPSI), the WISC, the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Abbreviated Scale of Intelligence (WASI). The WPPSI is used for ages ranging from 2 years and 6 months to 7 years and 7 months. The WISC is used for ages ranging from 6 years to 16 years and 11 months. The WAIS is used for ages ranging from 16 years to 90 years and 11 months. The WASI can be used for the same ages as the WISC and the WAIS. All of these tests have been revised and updated over the years to incorporate advances in the intelligence field as well as to better reflect the abilities of test-takers from different cultural environments. For example, the original WISC, the WISC-Revised (WISC-R) and the WISC-Third Edition (WISC-III) provided a verbal IQ (VIQ) and a Performance IQ (PIQ) score. The WISC-Fourth Edition (WISC-IV) and the WISC-Fifth Edition (WISC-V) no longer provide these quotients. The WISC-III introduced four new index scores to represent more narrow domains of cognition, one of them being the Verbal Comprehension Index (VCI), which was designed to provide an overall measure of verbal acquired knowledge and verbal reasoning. All versions provide a Full-Scale Intelligence Quotient (FSIQ), with an average mean score of 100, which measures the individual overall level of general cognitive and intellectual functioning.

Objectives

Understanding whether IQ changes after epilepsy surgery in pediatric age is of great importance since children may require additional parental support or even special education in school. Therefore, this meta-analysis has three objectives. The main goal is to evaluate whether surgery for pediatric epilepsy treatment influences post-surgery IQ values or not. The secondary objectives are to ascertain whether these results differ between curative and palliative surgical procedures and which factors have prognostic value for post-operative IQ.

Methods

Protocol and registration

The PRISMA guidelines were followed for this study methodology. A protocol was registered in PROSPERO on the second of December of 2020, with the code number [CRD42020216548] and can be accessed at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=216548. More information regarding this protocol can be seen in Supplementary Information I.

Eligibility criteria

The included studies had to meet the following inclusion criteria: 1) observational and experimental studies with more than 10 participants; 2) children (at most 18 years of age), with epilepsy, submitted to a surgical procedure for epilepsy treatment; 3) follow-up after surgery equal to or longer than one year for each participant. If the follow-up continued after the patient reached 18 years of age,

that patient would still be included if the surgery had been performed in pediatric age; 4) a pre- and post-operative measurement of IQ with the WIS; 5) studies in English, French, Spanish or Portuguese published since 2000.

Studies that met the following criteria were excluded: 1) less than 10 participants; 2) adults (over 18 years of age) at the time of surgery; 3) children with follow-up of less than one year; 4) no reference to the type of epilepsy surgical procedure; 5) other intelligence tests; 6) no reference to the pre- and post-operative IQ values; 7) studies not in English, French, Spanish or Portuguese; 8) reviews or meta-analysis; 9) incomplete studies; 10) data present in a different format (IQ values only available in the form of intervals or graphics without any reference to the mean or median IQ values of the sample).

Information sources and search strategy

The following electronic databases were searched, until the ninth of March of 2021, for relevant literature: PubMed, the Cochrane Library, EMBASE and ClinicalTrials.gov. Only finished studies published in English, French, Spanish, Portuguese and that met the inclusion criteria were used.

Only articles published since 2000 were used. The keywords used for this search included: "epilepsy", "epileptic", "surgery", "surgical", "Wechsler Scale" and "intelligence tests". Search terms were combined with operators, such as "AND" and "OR". In PubMed, the filters "human" species, "English, French, Spanish, Portuguese" language and "child: birth - 18 years" age were used. In PubMed, the Cochrane Library and EMBASE, the "year of publication" filter was used to rule out studies published before 2000. In the Cochrane Library and EMBASE the truncations "child*", "infan*" and "adolesce*" were used to cover root words that have multiple endings. In the Cochrane Library, only clinical trials were selected. In ClinicalTrials.gov, the filters "completed", "terminated" and "child (birth - 17)" were applied. A detailed search strategy for PubMed is shown in Supplementary Information II.

Study selection

The review author (ARA) and one collaborator (Dr. HD) independently screened titles and abstracts retrieved using the search strategy, as well as those from additional sources, to identify studies that would potentially meet the inclusion criteria stipulated. Duplicates were eliminated. Full texts of these potentially eligible studies were retrieved and both ARA and the co-advisor (BO PhD) independently applied eligibility criteria to select the appropriate articles.

Data collection process and data items

ARA and BO PhD independently extracted relevant data regarding study participants' characteristics, interventions and outcomes, according to the previously stated inclusion criteria. Any uncertainties were resolved by discussion with the advisor (CP MD) until consensus was reached. Five study authors (Dr. Anne Vagner Jakobsen PhD, Dr. Christoffer Ehrstedt PhD, Dr. Martin M. Tisdall MD, Dr. Barry Sinclair MD and Dr. Shuli Liang PhD) were contacted to obtain and confirm data regarding their studies.

Data regarding the variables "gender", "age at epilepsy onset", "duration of epilepsy", "age at surgery", "seizure type", "epilepsy

type", "etiology", "affected hemisphere", "epilepsy surgery type", "follow-up time", "Engel classification", "Wechsler Intelligence Scale", "pre-surgery IQ" and "post-surgery IQ" was extracted and summarized in a dataset. Since one of the aims of this study was to evaluate the effect of epilepsy surgery on IQ by analyzing preoperative *versus* post-operative IQ values and since these values must have been measured with the WIS, there was no necessity for a comparator/control. However, base values were considered as the comparator for the post-operative values.

Risk of bias assessment

The study quality was assessed by ARA and BO PhD with the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. Study heterogeneity was, firstly, analyzed by observing the funnel plot and then confirmed with the I2 test and Cochran's Q test of heterogeneity. The publication bias was investigated with the Egger's test and the Begg and Mazumdar test after observing the forest and funnel plots.

Summary measures

The measure of effect was the standardized difference between mean post-operative FSIQ values and mean preoperative FSIQ values (d) reported by individual studies. Since the included studies have reported standard deviations measured in both time points and not the standard deviations from the mean differences between time points, these were estimated according to the procedure reported by Wolfgang Viechtbauer, from the Maastricht University, in his lecture of 2019-02-07, assuming that the correlation between measures of both time points was constant and equal to the correlation measured between studies mean time points (r = 0.985).

Synthesis of results

A descriptive data synthesis was performed to address each of the objectives, focusing on the population characteristics, type of intervention and different outcomes. Then, a meta-analysis using a random effects model with the eight eligible articles was conducted because of the limited number of studies and because there was a high level of heterogeneity between them.

The RStudio, version 1.3.1093, (*2009-2020 RStudio, PCB) of the R software, version 4.0.3, (2020-10-10) was used for handling data and conducting meta-analysis. The level of significance (α) considered was 0.05 (5%).

Additional analysis

A meta-regression was conducted given possible factors or covariables that could influence the outcomes reported in the individual studies and, as such, have an impact in the estimated global effect and variability of IQ. These covariables included: gender (% of males), age of epilepsy onset, duration of epilepsy, age at surgery, etiology (% of dysplasias, % of mesial temporal sclerosis and % of tumors), type of surgery (% of curative surgery), Engel classification (% at grade I) and affected hemisphere (% left hemisphere). The measure of effect was the regression coefficients. Statistical significance was considered by a type I error of 0.05 (5%).

Results

Study selection and characteristics

A total of 383 articles were identified using the search strategy previously mentioned. Three additional records were identified *via* other sources. Then, 53 duplicates were removed. Of the remaining 333 articles, 246 were excluded after screening their titles and abstracts, since they did not meet the inclusion criteria. Eighty-seven studies were read in full to assess eligibility. Seventy-four full-text articles were then excluded since they met one or more of the exclusion criteria. The reasons for each exclusion are summarized
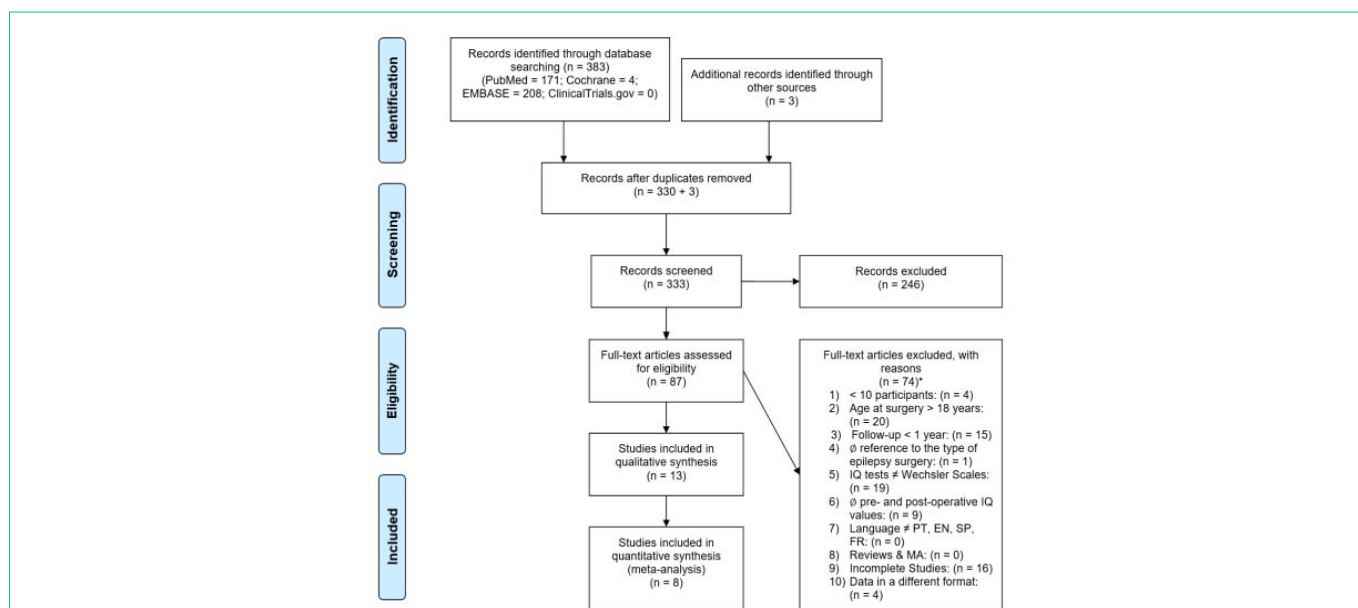
Figure 1: Flow of information diagram for study selection.
*Three studies met exclusion criteria 2) and 5); two studies met exclusion criteria 1) and 3); two studies met exclusion criteria 3) and 5); one study met exclusion criteria 3) and 6); one study met exclusion criteria 5) and 6); one study met exclusion criteria 2) and 6); one study met exclusion criteria 5) and 10); one study met exclusion criteria 2) and 3) and one study met exclusion criteria 3), 4) and 6). **Abbreviations:** EN: English; FR: French; IQ: Intelligence Quotient; MA: Meta-Analysis; PT: Portuguese; SP: Spanish.

Table 1: Characteristics of the included studies.

Year	Author	Study Design	Study Size	Gender	Age of Epilepsy Onset; Mean (SD)	Duration of Epilepsy; Mean (SD)	Age at Surgery; Mean (SD)	Epilepsy/ Seizure Type	Etiology	Hemi- sphere	Epilepsy Surgery Type	Follow-up time; Mean (SD) (Range)	Engel Class.	WIS	Pre-surgery IQ; Mean (SD)	Post-surgery IQ; Mean (SD)
2020	Jakobsen AV et al. [22]	Retros-pective	n=43	(M)=23 (F)=20	4.4 (2.9)	NA	11.1 (3.3)	FE	Dys: 14 MTS: 13 Other: 15 #n = 42	(L)=25 (R)=18	Resection T: 28 EXT: 15	2 [1.9 - 2.4]	I=28 II-IV=12 #n = 40	WISC-III	FSIQ=64.5 (21.2) #n=28	FSIQ=70.0 (23.1) #n = 28
2019	Skirrow C et al. [23]	Case Control	Surgery n=39 Control n=13	Surgery (M)=21 (F)=18 Control (M)=7 (F)=6	Surgery 6.3 (4.3) Control 3.9 (3.7)	Surgery 7.4 (4.5) Control* 6.8 (3.5)	Surgery 13.5 (3.2) Control* 10.7 (3.3)	FE	Surgery Dys: 11 MTS: 3 Tumor: 19 Other: 6 Control Dys: 1 MTS: 1 Tumor: 3 Other: 8	Surgery (L)=23 (R)=16 Control (L)=9 (R)=2 (NL)=2	Focal Resection T: 17 P: 7 FR: 9 ML: 6	Surgery 7.2 [1.6 – 15.7] Control 5.9 (2.1)*	Surgery I=28 II-IV=11 Control I=2 II-IV=11	WPPSI-II WPPSI-R WISC-III WISC-IV WAIS-III WAIS-IV WASI	Surgery FSIQ=86.6 (18.1) Control* FSIQ=87.8 (14.3)	Surgery FSIQ=91.3 (18.0) Control* FSIQ=85.6 (17.1)
2018	Ehrstedt C et al. [24]	Retros-pective	n=11	NA	7.7 (5.1)	NA	13.2 (3.5)	FSZ GSZ	Tumor: 11	(L)=3 (R)=6 NA=2	Resection T: 9 EXT: 2	[>2]	I=9 II-IV=2	WISC-IV WAIS-IV (Swedish Versions)	FSIQ=84.1 (21.3)	FSIQ=95.2 (14.8)
2017	Faramand AM et al. [25]	Retros-pective Cohort	n=121	NA	NA	4.2 (2.2 - 8)**	9.3 (6 - 14)**	FSZ	Tumor: 121	(L)=52 (R)=40 #n=92	Lesionectomy	[1]	I=74 II-IV=18 #n = 92	WISC	FSIQ=81 (71-95)** #n=90	FSIQ=86 (71-100)** #n=41
2015	Shurtleff HA et al. [26]	Retros-pective Cohort	n=15	NA	NA	1.3 (1.4)	4.9 (1.7)	FSZ	Dys: 2 Gliosis: 1 MTS: 2 Tumor: 10	(L)=9 (R)=6	Lesionectomy FR: 3 T: 2 ATL: 4 STL: 3 Superior and middle frontal gyrus: 2 Inferior frontal gyrus: 1	3.4 (1.9) [1.5 - 6.9]	I=14 II=1	WPPSI-III WPPSI-R WISC-III WISC-IV WASI	FSIQ=100 (13.1) VIQ=103 (18.3) PIQ=99 (12.4) #n=11	FSIQ=106 (17.7) VIQ=109 (17.2) PIQ=103 (15.1) #n=12
2015	Lee YJ et al. [27]	Retros-pective Cohort	n=20	(M)=12 (F)=8	7.3 (2.9)	6.6 (3.2)	12.8 (3.2)	NA	Dys: 2 MTS: 12 Tumor: 4 Other: 2	(L)=8 (R)=12	ATL+AH	3.6 (2.0) [2.5 - 4.8]	I=14 II=6	WPPSI WISC WAIS (Korean Versions)	FSIQ=78.5 (25.0)	FSIQ=81.5 (25.1)
2014	Liang S et al. [28]	Pros-pective Cohort	Surgery n=23 Control n=37	Surgery (M)=16 (F)=7 Control (M)=22 (F)=15	Surgery 5.1 (1.7) Control 5.4 (1.9)	Surgery 4.4 (2.1) Control* 4.3 (2.2)	Surgery 9.5 (2.2) Control* 9.7 (2.4)	FSZ GSZ	NA	NA	Anterior CC	[2]	Surgery I=3 II-IV=20 #n=23 Control I=2 II-IV=32 #n=34	WISC (Chinese Revision)	Surgery FSIQ=56.1 VIQ=57.0 PIQ=56.2 #n=23 Control* FSIQ=55.3 VIQ=55.4 PIQ=56.8 #n=37	Surgery FSIQ=61.2 VIQ=60.3 PIQ=63.6 #n=23 Control* FSIQ=51.8 VIQ=52.3 PIQ=52.7 #n=34
2013	Lee YJ et al. [29]	Retros-pective	n=76	(M)=54 (F)=22	2.2 (2.9)	5.4 (3.1)	7.6 (3.7)	FSZ GSZ	Dys: 33 EM: 17 Other: 12 NA: 14	NA	Lobar resection Single lobar: 13 ML: 16 HSPO: 10 CC: 37	[2]	I=24 II=6 III=4 IV=5 #n=39	WISC WAIS (Korean Versions)	FSIQ=40.4 (14.9) #n=42	FSIQ=46.1 (19.0) #n=27
2012	Liang S et al. [30]	Retros-pective	n=206	(M)=112 (F)=94	NA	7.7	11.3 (2.4)	FSZ GSZ FE	Dys: 111 EM/Gliosis: 36 MTS: 38 TS: 4 Tumor: 10 Other: 7	NA	EZR: 107 ATL: 60 SAH: 11 Combined Anterior CC: 28	[2]	I = 149 II = 32 III-IV = 25	WISC (Chinese Version)	FSIQ=78.0	FSIQ=84.9
2011	Skirrow C et al. [13]	Retros-pective	Surgery n=42 Control n=11	Surgery (M)=21 (F)=21 Control (M)=4 (F)=7	Surgery 4.0 (4.0) Control 3.7 (3.2)	NA	13.3 (3.1)	FSZ	Surgery MTS: 26 Tumor: 16 Control MTS: 5 NA: 6	Surgery (L)=25 (R)=17 Control (L)=7 (R)=5	Resection T: 42	[≥5]	Surgery I=36 II-IV=6 Control I=4 II-IV=7	WISC-R WISC-III WAIS-R WAIS-III	Surgery FSIQ=82.5 (19.8) Control* FSIQ=77.1 (18.3)	Surgery FSIQ=88.5 (20.3) Control* FSIQ=78.5 (16.5)

Year	Author	Study type	Study Size	Gender	Age at onset	Duration	Age at surgery	Seizure type	Etiology	Hemisphere	Surgery	Follow-up	Engel	WIS	Surgery IQ	Control IQ
2011	Datta AN et al. [31]	Retrospective	n=57	(M)=29 (F)=28	0.1 – 16	0.5 (0.3)	11.7 (3.9)	NA	Dys: 7 MTS: 11 Tumor: 19 TS: 5 Vascular: 2 Other: 3 NA: 10	(L)=29 (R)=27 CC=1	Resection AT: 30 FR: 11 P: 7 O: 3 ML: 9 CC:1	[≥1]	I=38 II=10 III=4 IV=5	WPPSI WISC WAIS	FSIQ=89.0 VIQ=89.5 PIQ=89.6	FSIQ=89.0 VIQ=89.9 PIQ=91.0
2009	Lee YJ et al. [32]	Retrospective	n=19	(M)=11 (F)=8	8.3 (3.1)	6.4 (4.0)	14.6 (2.8)	FSZ	Dys: 9 Tumor: 5 MTS: 11 DP: 6	NA	ATL+AH: 14 ATL without AH: 2 Subtotal temporal lobectomy: 3	2.1 [1.2 – 3.5]	I=12 II=5 III=2 IV=0	Age-appropriate WIS (Korean Version)	FSIQ=78.1 (25.0) VIQ=81.7 (24.7) PIQ=78.1 (23.2)	FSIQ=78.0 (25.5) VIQ=80.1 (25.2) PIQ=78.9 (26.3)
2005	Korkman M et al. [33]	Prospective	n=38	(M)=21 (F)=17	NA	NA	11.6 (4.2)	NA	GC: 19 Tumor: 9 MTS: 5 TS: 1 Other: 4	(L)=19 (R)=19	Resection T: 23 EXT: 3 ML: 5 HSPE/ HSPO: 7	2 [1.8 – 2.4]	I=29 II=3 III=3 IV=3	WPPIS-R WISC-R WISC-III WAIS-R	VIQ=79.3 (20.6) PIQ=81.3 (20.8)	VIQ=80.7 (21.9) PIQ=82.8 (26.0)

The unit of time is year. Study Size represents the number of children that underwent epilepsy surgery in each study. Follow-up time was defined as the time from epilepsy surgery to the post-operative neuropsychological evaluation with the Wechsler Intelligence Scale. Surgery refers to the Surgery Group and Control refers to the Control Group. #Represents the number of participants whose data was available. *Baseline values used for Control Groups. **Median (IQR) values.

Abbreviations: AH: Amygdalohippocampectomy; AT: Anterior Temporal; ATL: Anterior Temporal Lobectomy; CC: Corpus Callosotomy; DP: Dual Pathology; Dys: Dysplasia; EM: Encephalomalacia; EXT: Extratemporal; EZR: Epileptogenic Zone Resection (including lesion resection); F: Female; FE: Focal Epilepsy; FR: Frontal; FSIQ: Full-Scale Intelligence Quotient; FSZ: Focal Seizures; GC: Gliotic Change; GSZ: Generalized Seizures; HSPE: Hemispherectomy; HSPO: Hemispherotomy; L: Left; M: Male; ML: Multilobar; MTS: Mesial Temporal Sclerosis; NA: Not Available; NL: Non-Localizing; O: Occipital; P: Parietal; PIQ: Performance Intelligence Quotient; R: Right; SAH: Selective Amygdalohippocampectomy; SLT: Selective Temporal Lobectomy; T: Temporal; TS: Tuberous Sclerosis; VIQ: Verbal Intelligence Quotient; WAIS: Wechsler Adult Intelligence Scale; WASI: Wechsler Abbreviated Scale of Intelligence; WIS: Wechsler Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WPPIS: Wechsler Preschool and Primary Scale of Intelligence.

in Figure 1. In the end, thirteen publications were included in the qualitative synthesis and eight in the meta-analysis. This process of selection is summarized in a flow of information diagram presented in Figure 1.

None of the included studies are Randomized Control Trials (RCTs). Twelve studies are cohorts (ten retrospective and two prospective) and one is a case-control study. For each of these studies, data was extracted regarding study size (number of patients that underwent epilepsy surgery), participant characteristics (gender, age at epilepsy onset, duration of epilepsy, age at surgery,

seizure type, etiology, affected hemisphere, Engel Classification, WIS used and pre-surgery IQ), interventions (type of epilepsy surgery), outcomes (post-surgery IQ) as well as the follow-up period (defined as the time from epilepsy surgery to post-surgery neuropsychological evaluation with the WIS). An overview of the extracted data for each study is shown in Table 1.

Risk of bias assessment

None of the included articles were considered of poor quality. Overall, no selection bias was identified. The quality assessment for each cohort and case-control study is reported in Table 2 and Table 3, respectively.

By observing the funnel plot (Supplementary Information III), the studies included in the meta-analysis appeared to have a high level of heterogeneity which was later confirmed by the I2 and Cochran's Q test of heterogeneity (I2 = 85.52%; Q(7) = 43.70 (p < 0.001)). We may assume that there is no publication bias as the effect size is not correlated with its variance (Begg-Mazumdar test: Kendal tau = 0.143; p = 0.720) and is independent from study precision (Egger regression: b= -0.034; p = 0.868).

Results of individual studies

Overall effect of epilepsy surgery on post-operative IQ values:

Table 2: Quality assessment for cohort studies with the Newcastle-Ottawa Scale.

	Selection	Comparability	Outcome	Total (in 9*)
Jakobsen AV, 2020[22]	***	**	*	6*
Ehrstedt C, 2018[24]	***	*	**	6*
Faramand AM, 2017[25]	***	**	*	6*
Shurleff HA, 2015[26]	***	**	**	7*
Lee YJ, 2015[27]	***	**	**	7*
Liang S, 2014[28]	***	**	**	7*
Lee YJ, 2013[29]	***	**	*	6*
Liang S, 2012[30]	**	*	**	5*
Skirrow C, 2011[13]	****	**	**	8*
Datta AN, 2011[31]	***	*	**	6*
Lee YJ, 2009[32]	***	**	**	7*
Korkman M, 2005[33]	***	**	**	7*

Table 3: Quality assessment for case-control studies with the Newcastle-Ottawa Scale.

	Selection	Comparability	Outcome	Total (in 9*)
Skirrow C, 2019[23]	***	**	**	7*

Overall, none of the publications included reported a significant decline in IQ values after surgery, regardless of the surgical procedure. However, since different follow-up periods were reported among these studies, three subgroups were made for a more accurate analysis: a short follow-up group (one year), a medium follow-up group (two years) and a long follow-up group (three or more years).

Three studies [25,29,31] reported that the effect of surgery was not significant in post-operative IQ after one year of follow-up. Two studies [32,33] with a two-year follow-up period reported no significant post-operative IQ changes. On the other hand, three studies [22,28,29] reported an overall significant improvement.

Table 4: Overall effect of epilepsy surgery in post-operative IQ values.

	Short follow-up	Medium follow-up	Long follow-up
Jakobsen AV, 2020[22]	-----	Significant improvement	-----
Skirrow C, 2019[23]	-----	-----	Improvement
Ehrstedt C, 2018[24]	-----	-----	Significant improvement
Faramand AM, 2017[25]	No significant effect	-----	-----
Shurleff HA, 2015[26]	-----	-----	No significant effect
Lee YJ, 2015[27]	-----	-----	No significant effect
Liang S, 2014[28]	-----	Significant improvement	-----
Lee YJ, 2013[29]	No significant effect	Significant improvement	-----
Liang S, 2012[30]		Improvement	-----
Skirrow C, 2011[13]	-----	-----	Significant improvement
Datta AN, 2011[31]	No significant effect	-----	-----
Lee YJ, 200932	-----	No significant effect	-----
Korkman M, 2005[33]	-----	No significant effect	-----

Table 5: Effect of curative *vs* palliative surgical procedures in post-operative IQ values.

	Curative Surgery	Curative Surgery	Hemispherectomy/ Hemispherotomy
Jakobsen AV, 2020[22]	Significant improvement	-----	-----
Skirrow C, 2019[23]	Improvement	-----	-----
Ehrstedt C, 2018[24]	Significant improvement	-----	-----
Faramand AM, 2017[25]	No significant effect	-----	-----
Shurleff HA, 2015[26]	No significant effect	-----	-----
Lee YJ, 2015[27]	No significant effect	-----	-----
Liang S, 2014[28]	-----	Significant improvement	-----
Lee YJ, 2013[29]	Not analyzed	Not analyzed	Not analyzed
Liang S, 2012[30]	Improvement	Significant improvement	-----
Skirrow C, 2011[13]	Significant improvement	-----	-----
Datta AN, 2011[31]	No significant effect	-----	-----
Lee YJ, 2009[32]	No significant effect	-----	-----
Korkman M, 2005[33]	No significant effect	-----	Decline

Finally, in the long follow-up group, two studies [26,27] reported that the effect of surgery was not significant in the post-surgical IQ values whereas two studies [13,24] reported a significant improvement and one study [23] reported a modest improvement. These results are shown in Table 4.

At an individual level, in Jakobsen AV, 22 35% of the sample had their FSIQ improved more than 10 points, 56% were unchanged and 9% underwent a decrease of more than 10 points. In Faramand AM,25 61% had a median gain of eight points in FSIQ, 2.5% had no change and 36.5% had a median decline of six points. Skirrow C, 201923 reported a gain in FSIQ of at least 10 points in 39% of the surgery patients.

Effect of curative *vs* palliative surgical procedures in post-

operative IQ values: In eleven studies, a curative surgical procedure (lesionectomy, lobectomy, selective amygdalohippocampectomy) was used for epilepsy treatment, whereas two studies [28,30] reported IQ changes after palliative interventions (CC). Hemispherectomy/ hemispherotomy was reported in one study [33]. In one study with 76 Lennox-Gastaut syndrome patients, [29] the surgical approaches included lobar resections, hemispherotomies and CCs. However, changes in IQ outcome regarding each type of surgery were not analyzed.

Considering all the studies with curative surgeries, only three [13,22,24] reported an overall significant improvement in IQ after surgery. Two of them [13,24] were also the ones with a longer follow-up period. Two studies [23,30] also reported an increase in IQ values.

Both studies with CC [28,30] reported a significant improvement in IQ values two years after surgery.

In one of these studies, [30] CC was used combined with a curative procedure in 28 patients whereas the remaining 178 patients underwent a curative procedure (169 had a normal IQ and nine had a low IQ before surgery). It was found that the participants with preoperative low IQ (FSIQ = 60.2) who underwent CC significantly improved their IQs (a +9.6 change; p < 0.05) when compared with those with normal (FSIQ = 81.8) or low (FSIQ = 62.1) preoperative IQs that did not undergo CC (a +6.4 and +7.4 change respectively). In the other study, [28] it was found that the surgery group (with 23 participants) had a +5.1 change in FSIQ after CC (p < 0.01) whereas the medicine group (with 37 participants) had a -3.6 change. It was also reported that both VIQ and PIQ significantly improved in the surgical group (+3.3 and +7.1 change; p < 0.01). On the other hand, the medicine group VIQ and PIQ values declined in the same follow-up time (-3.1 and -4.0 change respectively).

In one study, [33] the IQ outcome of the hemispherectomy group (seven patients) was compared with the post-surgical IQ of the temporal lobe resection group (23 participants) and the extra temporal/multilobar resection group (8 participants) after two years of follow-up. A significant between groups effect of type of surgery was found (p < 0.001), where the hemispherectomy group had a significant lower VIQ and PIQ than the other groups (p < 0.01). Both VIQ and PIQ changed from a mean of 60.9 to 55.1 and from 61.4 to 51.3, respectively, after two years of follow-up. These conclusions can be seen in Table 5.

## Factors with prognostic value for post-operative IQ

Lee YJ, 2015 [27] and Korkman M [33] analyzed the possible relation between gender and FSIQ change but no correlation was reported.

Age of epilepsy onset did not significantly influence post-operative FSIQ in two studies (Skirrow C, 2011 [13] and Faramand AM [25]). Lee YJ, 2015 [27] found that later onset of epilepsy was a good predictor of post-operative FSIQ (p = 0.046) and children with declines over five negative points in FSIQ and VIQ were of early age at onset. Skirrow C, 2019 [23] also reported a similar significant correlation (p=0.001), although later age at epilepsy onset did not correlate with FSIQ change (p=0.88).

Shorter duration of epilepsy was associated with higher gains in

Table 6: Meta-regression coefficients using each of the listed variables as moderators.

Variable	Coefficient b (p value)
Gender (% Males)	-2.3811 (0.5917)
Age of Epilepsy Onset	-0.1983 (0.1103)
Duration of Epilepsy	0.0969 (0.5747)
Age at Surgery	0.0269 (0.7606)
% Dysplasias	-0.0442 (0.9814)
% MTS	-0.4621 (0.7335)
% Tumor	0.9573 (0.4192)
Type of Surgery (% Just curative surgery)	-0.2203 (0.8410)
Engel Classification (% Engel Class. = I)	0.9692 (0.6576)
Affected Hemisphere (% Left hemisphere)	1.4831 (0.9577)
Follow-up Duration (years)	0.0897 (0.5167)
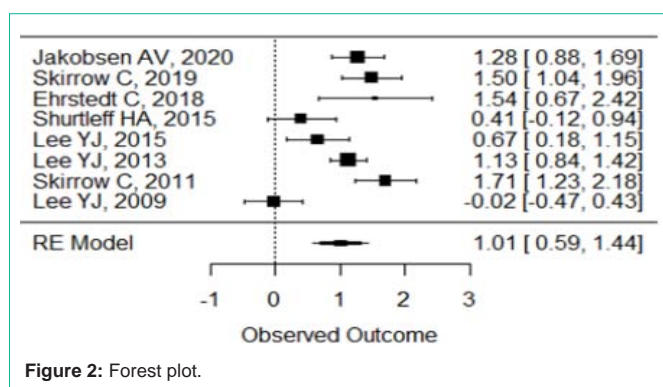
Figure 2: Forest plot.

FSIQ in three studies (+13 points in Shurleff HA; [26] ≥+5 points in Lee YJ, 2015 [27] and +9.5 points *vs* +0.9 points in Lee YJ, 2013 [29]) when compared with longer durations. However, these differences were only statistically significant in the Lee studies [27,29]. Lee YJ, 201527 also reported that shorter epilepsy duration was a good predictor of PIQ after surgery (a gain over five points). In three different studies (Jakobsen AV; [22] Faramand AM [25] and Skirrow C, 2011[13]) no correlation between post-operative FSIQ and duration of epilepsy was found. In Skirrow C, 2019,[23] it was reported that post-operative FSIQ was inversely correlated with a longer duration of epilepsy but there was no correlation with FSIQ change between pre- and post-surgery.

Age at surgery was not correlated with FSIQ change in four studies (Skirrow C, 2019; [23] Faramand AM; [25] Lee YJ, 2015 [27] and Liang S, 2014 [28]). Liang S, 201230 mentioned that early age of surgery might prevent long-term impairment of intelligence and Korkman M33 reported that children who underwent interventions at younger ages had poorer IQ outcome.

Regarding Engel classification, four studies (Jakobsen AV; [22] Lee YJ, 2015; [27] Lee YJ 2013 [29] and Liang S, 2012 [30]) reported that Engel classification I was a good predictor of post-operative FSIQ since seizure-free patients had significantly higher FSIQ gains when compared with the non-seizure-free. On the other hand, Skirrow C, 2019; [23] Liang S, 2014; [28] Skirrow C, 2011 [13] and Korkman M [33] found no significant association between post-operative seizure status and FSIQ change.

When it comes to the affected hemisphere, the four studies that studied a possible association between intervened hemisphere and FSIQ change [22,23,26,27] found no significant association. On the other hand, Jakobsen AV [22] reported that VCI statistically improved in right-handed children with left hemisphere surgery and that all children with left-sided temporal surgery maintained or improved their VCI values. Skirrow C, 2011 [13] found VIQ improvements only in the left hemisphere surgery group. Korkman M [33] reported that the left hemisphere group tended to have poorer VIQ outcome although not statistically significant. This could be due to the fact that there were more left hemispherectomy patients in this study and this surgery is usually performed in patients with lower base IQ values.

Skirrow C, 2019 [23] and Lee YJ, 2015 [27] reported no correlation between etiology and FSIQ change.

Skirrow C, 2019 [23] mentioned that longer duration of follow-up was associated with greater IQ improvement.

Four studies (Jakobsen AV; [22] Lee YJ, 2015; [27] Lee YJ 2013 [29] and Skirrow C, 2011 [13]) reported that Antiepileptic Drugs (AED) reduction after surgery was a good predictor of post-operative FSIQ. Furthermore, Skirrow C, 2011 [13] mentioned that maintaining AED, mainly topiramate, was a bad predictor for FSIQ outcome. However, Skirrow C, 2019 [23] found no correlation between AED cessation and IQ change.

Synthesis of results

By observing the forest plot (Figure 2), the meta-analysis of the eight included studies found a mean difference between post-operative and preoperative FSIQ values of 1.014 standardized points (p <0.001; 95%CI: 0.589 to 1.437).

Additional analysis

The meta-regression conducted, considering each one of the moderators described in Table 6, did not find any predictors of FSIQ change, which indicates that, with the available studies, the effect of surgery is independent of gender, age of epilepsy onset, duration of epilepsy, age at surgery, etiology (at least from dysplasias, MTS and tumors since only these were analyzed), type of surgery (curative *vs* palliative surgery), Engel classification, affected hemisphere and follow-up duration (p > 0.05 for all).

Discussion

Summary of evidence

The first conclusion to be drawn is that none of the publications included reported a significant decline in IQ values after surgery, regardless of the surgical procedure. Moreover, the meta-analysis of the eight included studies found a mean difference between post-operative and preoperative FSIQ values of +1.014 standardized points, which is clinically significant because it corresponds to an FSIQ improvement higher than one standard deviation. This is of great importance since parents concerned with possible adverse effects of epilepsy surgery on their children's intelligence [31] can be reassured that this is not expected to happen. Furthermore, children with RE who were not in a special education program before surgery are unlikely to require one for intellectual disability after surgery [34,35].

Another major finding of this work is that palliative procedures

– mainly CC – which are used in epileptic syndromes associated with RE, such as the Lennox-Gastaut Syndrome, have a positive effect on IQ in the studies analyzed. In one of these studies, (Liang S, 2014 [28]), FSIQ, VIQ and PIQ significantly improved in the surgical group when compared with the medicine group (whose three quotients declined in the same follow-up time). These results are in contrast to the findings of a meta-analysis about CC with both children and adult patients [9].

It should be noted that only studies from 1969 to 2011 with a patient's age at surgery of at least 10 years met the inclusion criteria for that meta-analysis. This means that studies such as Liang S, 2014 [28] were not included.

Furthermore, both partial and complete CC were included in that meta-analysis, while in both of Liang's studies the surgical procedure used was an anterior CC. Although the type of CC (partial *vs* complete) was not statistically correlated with any of the IQ changes, two studies [36,37] reported positive correlations between callosal morphology and intelligence measures, mainly in posterior callosal sections. This means that posterior regions of the corpus callosum might be important in explaining the anatomical substrates of intelligence. Selective removal of these regions could have a more negative impact on IQ change when compared with selective anterior CC. Therefore, further investigation in this area is required to draw more robust conclusions.

On the other hand, after analyzing possible predictors of post-operative IQ improvement such as gender, age of epilepsy onset, duration of epilepsy, age at surgery, etiology, Engel Classification, affected hemisphere and follow-up duration, this meta-analysis did not find any statistically significant differences. Since RE is associated with neurocognitive impairment, it was expected that a shorter duration of epilepsy and a post-operative seizure-free status would have a significant impact on IQ. A study about unknown onset epilepsy (previously referred to as cryptogenic localization epilepsy) [38] also reported no significant IQ differences (addressed with the WISC-R) regarding epilepsy duration and seizure frequency. A longer follow-up duration was expected to positively correlate with post-operative IQ improvement since several studies with shorter follow-up duration did not find any intellectual gains [13]. This was one of the reasons why only studies with at least one year of follow-up were included in this work.

Finally, the meta-regression coefficient of the variable "type of surgery" should be interpreted with caution because almost all of the included studies used curative procedures and most of them did not significantly influence IQ at an individual study level. Hemispherectomy and hemispherotomy were not part of this variable since they can be both curative and palliative. Because of the limited number of articles regarding these procedures, no solid conclusions could be drawn on how they might impact post-operative IQ.

Limitations

This study had several limitations. Firstly, no RCTs met the inclusion criteria. Because of this, only cohorts and one case-control study were included. Furthermore, most of these studies had a retrospective design, which has the disadvantage of having to rely on accurate recordkeeping and, as a result, limited the available data for further analysis. Secondly, the limited number of studies reporting IQ outcome after palliative surgeries in pediatric age significantly restricted the possibility of drawing solid conclusions regarding how these procedures might affect intelligence in children with RE. Thirdly, since only studies with IQ assessment with WISs were included and since these scales are not available for children with less than three years, this age group was not the focus of study in the articles included. Moreover, in some papers, children with severe cognitive impairment were excluded since they were not able to complete the WIS questionnaires.

This is one of the reasons why there were so few articles regarding hemispherectomy/hemispherotomy, since these procedures are usually performed in children whose condition is related to intellectual disability. One way of studying the two previous groups would be to include articles where the post-operative Developmental Quotient (DQ) was compared with the preoperative DQ. This quotient can be addressed with development scales, such as the Bayley Scales and the Griffiths Scales of Development [39,40]. Another way would be to include articles where DQ was considered equivalent to IQ, since this would reduce heterogeneity. However, this would create a bias because developmental tests do not measure the same functions as IQ tests. Although some authors state that DQ and later IQ are highly correlated, [41,42] DQ tests should not be considered as alternative assessments to measure IQ. Finally, although some studies report pre- and post-operative VIQ and PIQ values, the available data was not enough to conduct a meta-analysis regarding theses parameters.

Conclusion

In spite of all the limitations of this meta-analysis and the high level of heterogeneity between studies, epilepsy surgery in pediatric age seems to have an overall positive impact on IQ. Pediatric neurologists an parents of children with refractory epilepsy can be reassured that significant post-operative intellectual declines are not expected. It is not expected that a special education program for intellectual disability after surgery will be required. Anterior corpus callosotomy also appears to have a positive effect on IQ, although whether this improvement differs from the one obtained with curative procedures could not be accurately inferred with the available studies. No good predictors of post-operative IQ were found. Further research in these fields is required to draw more solid conclusions.

Acknowledgement

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