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Hemispherotomy Revised: A complication overview and a systematic review meta-analysis

Maria D. Karagianni [a,*], Alexandros G. Brotis [a], Anastasia Tasiou [a], Daniel Delev [b,c,d], Marec von Lehe [e], Olaf E.M.G. Schijns [f,g,h], Konstantinos N. Fountas [a,i]

[a] Department of Neurosurgery, General University Hospital of Larissa, Mezourlo, Larissa, 41110, Greece
[b] Department of Neurosurgery, Faculty of Medicine, RWTH Aachen University, Aachen, Germany
[c] Neurosurgical Artificial Intelligence Laboratory Aachen (NAILA), RWTH Aachen University Hospital, Aachen, Germany
[d] Center for Integrated Oncology, Universities Aachen, Bonn, Cologne, Duesseldorf (CIO ABCD), Germany
[e] Department of Neurosurgery, Brandenburg Medical School, University Hospital Ruppin Brandenburg, Fehrbelliner Str. 38, Neuruppin, Germany
[f] Department of Neurosurgery, Maastricht University Medical Center, Maatricht, the Netherlands
[g] Academic Center for Epileptology, Maastricht, Kempenhaeghe, the Netherlands
[h] School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands
[i] Faculty of Medicine, University of Thessaly, Biopolis, Larissa, 41110, Greece

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ABSTRACT

Introduction: Hemispherectomy/hemispherotomy has been employed in the management of catastrophic epilepsy. However, initial reports on the associated mortality and morbidity raised several concerns regarding the technique's safety. Their actual, current incidence needs to be systematically examined to redefine hemispherotomy's exact role.

Research question: Our current study examined their incidence and evaluated the association of the various hemispherotomy surgical techniques with the reported complications.

Material & methods: A PRISMA-compliant systematic review and meta-analysis was performed. We searched PubMed, Scopus, and Web of Science until December 2022. Fixed- and random-effects models were employed. Egger's regression test was used for estimating the publication bias, while subgroup analysis was utilized for defining the role of the different hemispherotomy techniques.

Results: We retrieved a total of 37 studies. The overall procedure mortality was 5%, with a reported mortality of 7% for hemispherectomy and 3% for hemispherotomy. The reported mortality has decreased over the last 30 years from 32% to 2%. Among the observed post-operative complications aseptic meningitis and/or fever occurred in 33%. Hydrocephalus requiring a shunt insertion occurred in 16%. Hematoma evacuation was necessary in 8%, while subgaleal effusion in another 8%. Infections occurred in 11%. A novel post-operative cranial nerve deficit occurred in 11%, while blood transfusion was necessary in 28% of the cases.

Discussion and conclusion: Our current analysis demonstrated that the evolution from hemispherectomy to hemispherotomy along with neuroanesthesia advances, had a tremendous impact on the associated mortality and morbidity. Hemispherotomy constitutes a safe surgical procedure in the management of catastrophic epilepsies.

1. Introduction

Drug-resistant epilepsy (DRE) constitutes a challenging clinicopathological entity with serious socio-economic consequences. The adjectives "intractable" and "catastrophic" accurately highlight the prognosis of certain types of epilepsy. Catastrophic epilepsy is usually caused by a wide spectrum of pathological entities such as hemimegalencephaly, Rasmussen's encephalitis, Sturge-Weber syndrome, diffuse unilateral cortical dysplasia, and perinatal (middle) cerebral artery infarcts of various etiologies, which manifest with severe functional disability. Despite the best medical treatment, these patients end up hemiplegic, frequently dysphasic or aphasic (if the dominant hemisphere is affected), hemianopic, while suffering from DRE and epileptic encephalopathy.

Several surgical interventions, with a varying invasiveness, offer an

* Corresponding author. Department of Neurosurgery Larissa University Hospital, 13 Profiti Ilia St, Larissa, Thessaly, 41335, Greece.
E-mail address: maria.karagianni.1994@gmail.com (M.D. Karagianni).

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Abbreviations list

DRE	Drug-resistant epilepsy
Q1	Question 1
Q2	Question 2
Q3	Question 3
Q4	Question 4
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
RCTs	Randomized Controlled Trials
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
USA:	United States of America
UK:	United Kingdom
AH	Anatomical Hemispherectomy
HT	Hemispherotomy
FH	Functional Hemispherectomy
IVH	Interhemispheric Vertical Hemispherotomy
NR	Not Reported
PIH	Peri-insular lateral hemispherotomy
VPH	Vertical parasagittal hemispherotomy
HDC	Hemidecortication
TKFH	Transsylvian keyhole functional hemispherectomy
NT	Not tested

alternative to the best available medical treatment. Hemispherectomy, with resection of various parts of the affected hemisphere, and hemispherotomy, aiming to disconnect the dysfunctional and epileptogenic hemisphere from the healthy one, constitute such surgical methodologies. The surgical procedure of hemispherectomy was initially described by Walter Dandy for managing extensive gliomas (Jusue-Torres et al., 2021). Since then, hemispherectomy has been successfully adopted for treating DRE.

The frequency and severity of complications, associated with the initial surgical procedures, as well as its associated mortality, stigmatized hemispherectomy. In 1983, functional hemispherectomy was described, a technique preserving the frontal and occipital lobes, while removing varying amounts of temporal lobe tissue. A few years later, Schramm et al., introduced the transsylvian, keyhole hemispherotomy (Schramm et al., 2001). Likewise, Villemure et al., and Delalande et al., described disconnection techniques, the peri-insular and the vertical parasagittal hemispherotomy variants, respectively (Villemure and Daniel, 2006; Delalande et al., 2007). Notably, the extent of cortical resection with hemispherotomy techniques is significantly less than with anatomical or functional hemispherectomy.

A thorough study of the literature shows inconsistency in the frequency of the reported complications causing, along with its technical complexity, underutilization of the procedure. The primary aim of our current study was to estimate the pooled incidence of the complications associated with hemispherotomy (Q1), including mortality (Q2). Secondarily, we aimed to identify variations in the reported complication frequency according to the adopted surgical technique (Q3), and to record the temporal trends in the incidence of complications (Q4).

2. Methodology

2.1. Search strategy

We designed the search methods, eligibility criteria, and data extraction process prospectively. The search strategy is displayed in Table 1.

The utilized definition of the associated complications is summarized in Table 2.

We did not intend to address the adequacy or completeness of resection/disconnection in our current study. Our meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) (Moher et al., 2009; Page et al., 2021).

Table 2
Definitions for hemispherotomy-associated complications used in our current study.

Complication (s)	Definition
Mortality	Frequency of deaths
Hydrocephalus	Postoperative hydrocephalus requiring ventriculoperitoneal shunt
Infection	Meningitis, ventriculitis, wound infection, osteomyelitis, empyema
Hemosiderosis	Deposition of hemosiderin on arachnoid membranes
Aseptic meningitis	Fever or cerebrospinal fluid biochemical abnormalities
Intracerebral hemorrhage	Parenchymal hemorrhage
Extra-axial fluid collections	Epidural or subdural hematoma or hygroma requiring surgical evacuation
Anemia	Severe blood loss requiring blood transfusion
Pyramidal/Sensory Tract	Hemiparesis, monoparesis, hemisensory deficit
Cranial nerve deficits	Diplopia, paresis of frontal branch of facial nerve
Visual field defects	Hemianopsia, quadranopsia
Subgaleal fluid collection	Subgaleal fluid accumulation requiring surgical intervention
Cyst formation	Dural adhesions and cysts requiring re-intervention
Language disorders	Aphasia, dysphasia, mutism
Cognitive deficits	Memory, naming
Psychiatric	Depression, confusion, euphoria, psychosis, mania, anxiety
Medical complications	Deep vein thrombosis, pulmonary embolism, myocardial infarction, urinary tract infection, acute kidney or lung disorders, respiratory distress or failure
Other	Dysphagia, jaw pain, epileptic status

Table 1
Description of our literature search strategy to identify complications associated with hemispherectomy/hemispherotomy.

Frame	Keywords	Search	Inclusion criteria	Exclusion Criteria	Sources
Patients	#1. "Intractable epilepsy" OR "catastrophic epilepsy" OR "drug-resistant epilepsy" OR "medically refractory epilepsy"	#1 AND #2 AND #3	Randomized controlled trials, observational and case series Published in peer-reviewed journals English language	Studies not reporting on hemispherectomy or hemispherotomy or functional hemispherotomy Irrelevant title, abstract and full text Studies with inadequate description of the surgical technique Studies without extractable quantitative data on complications and the associated surgical technique Non-English Study design other than case series or randomized controlled trials or cohort studies, including editorials, reviews (included systematic reviews), letters to the Editor, meta-analyses, original studies, experimental non-human studies	Databases (PubMed, Scopus, and Web of Science) Reference list of the gathered records
Intervention	#2. "hemispherectomy" OR "hemispherotomy"				
Comparator	Not specified				
Outcome	#3. "complications"				
Time	Search period: From 1964 to 2022 Last search: May 2022				

2.2. Information sources

Two authors (MK and AB) independently identified studies through an electronic search of three databases: PubMed, Scopus, and Web of Science. We performed no registry or multi-database search. Likewise, we did not search the gray literature or the "health data" on Google. We used the following MeSH terms, including synonyms, in all potential fields: "intractable epilepsy", "catastrophic epilepsy", "drug-resistant epilepsy", "medically refractory epilepsy", "hemispherectomy", "hemispherotomy", and "complications", in any possible combination (Table 1). The search period extended from 1964 until December 2022. The last search in all databases took place on the 8th of December 2022. No search filters were used. Finally, the references of the eligible studies were searched for any further relevant citations. Duplicates were manually removed.

2.3. Eligibility criteria

We focused on RCTs reporting on complications associated with hemispherectomy or hemispherotomy and published in peer-reviewed journals. In their absence, we looked for observational or case-series studies. The review process was limited to English literature.

2.4. Study selection

After duplicate removal, two authors (AB and MK) independently assessed the retrieved articles for their title and abstract relevance. Initially, we discarded articles with irrelevant content, non-English studies, editorials, reviews and meta-analyses, underpowered studies (<10 patients), and studies focusing on a single complication. When relevant, their full texts were evaluated, and we excluded studies with an inadequate description of the surgical technique or without extractable data. If more than one technique was studied, we included studies reporting numerical data on complications for each technique, separately. Any disagreement between the two reviewers was resolved through a discussion with the senior author (KF). The remaining studies formed the basis of our systematic review and meta-analysis. The study selection process is outlined in Fig. 1.

2.5. Data collection

Each study was identified by the name of the first author and the year of publication. The following data were collected: 1) the study's hosting country, 2) the study type, 3) the size of the patient sample and its demographic characteristics, 4) the type of the surgical procedure, and 5) the rate of complications.

2.6. Quality appraisal in individual studies and overall evidence

Two authors (AB and MK) performed the quality appraisal of the collected articles independently based on the type of the study. Case series, observational studies, and RCTs were considered "Low", "Moderate", or "High" quality studies, respectively. The quality of evidence was assessed on each question, according to the GRADE working group, as "High", "Moderate", "Low", or "Very Low" (overview of the grade approach, 2023). In the case of disagreement, the authors reached a consensus after consulting the senior author (KF).

2.7. Data synthesis and statistical analysis

Fixed- and random-effects model meta-analysis was conducted to assess the proportion estimate for each outcome individually, while the

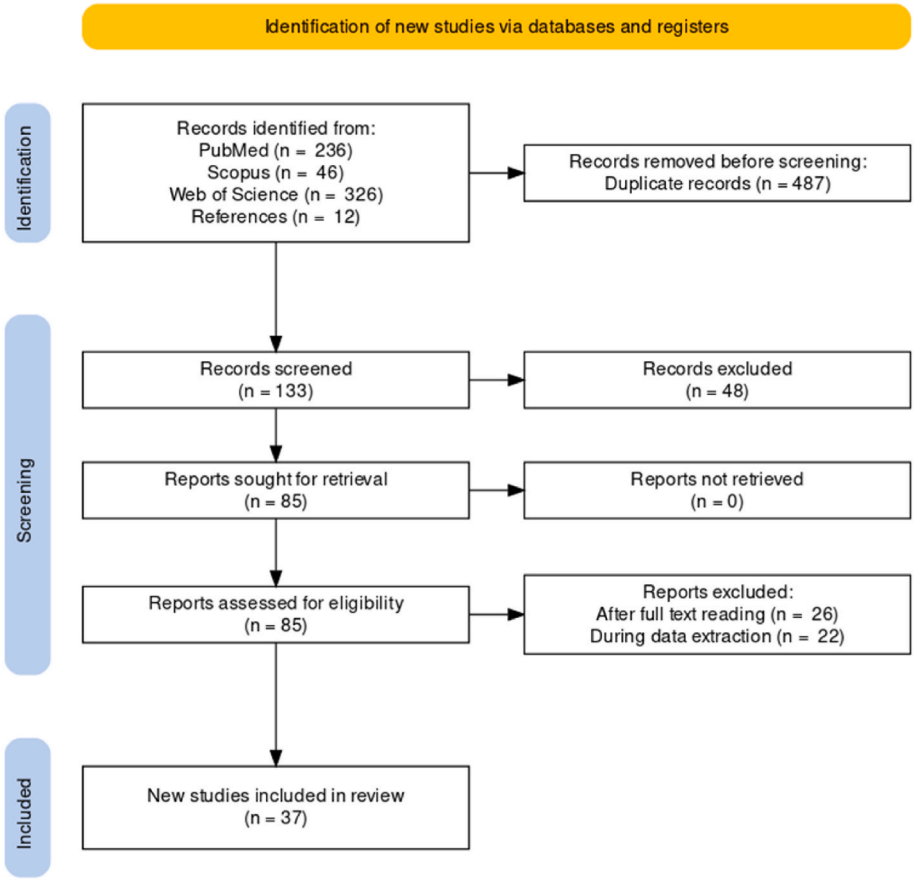

Fig. 1. Our current study's flowchart depicting that out of a total of 284 articles, 37 articles fulfilled our eligibility criteria and formed the basis of our meta-analysis.

I^2 statistic measured the inter-study heterogeneity. A value of I^2 less than 25% was regarded as low heterogeneity, 25%–75% as moderate, and greater than 75% as severe. The results were visualized in forest plots. We estimated the risk for publication bias using Egger's regression test. Subgroup analysis was used to identify differences between the utilized techniques. In cases with extreme statistical heterogeneity, we re-run the analysis after omitting the study with the greater contribution to the inter-study heterogeneity based on Baujat plots. To respond to Q3 and Q4, we stratified our results according to the implemented surgical technique, and the time of publication, using subgroup analysis. We used the statistical environment R for all statistical analyses (R a Language and Environment, 2010). Significance was set at $p<0.05$, and for complications associated with zero events, we used a continuity correction equal to 0.5.

3. Results

3.1. Literature search

Our search identified 133 studies. After screening for the title and abstract relevance, 48 articles were excluded. Twenty-six articles were discarded after reading the complete text, while twenty-two records had no extractable data. The remaining 37 records (between 1970 and 2021) formed the basis of our study (Fig. 1).

3.2. Eligible studies

Most studies were carried out in North America (17 studies – 14 in the USA and three in Canada), in Europe (11 studies – four in Italy, three in the UK, and one in Austria, France, Germany, and Switzerland, respectively), followed by Asia (seven studies – three in Japan, two in India, and one in China and Korea, respectively), and South America (two studies – both in Brazil). Twenty-eight and eight studies reported on pediatric and mixed populations, respectively, while only one involved solely adults. Unfortunately, this does not allow any meaningful comparison between pediatric and adult populations regarding mortality or complication incidence. The study sample ranged from 11 to 196 participants (mean 48 participants). Anatomical hemispherectomy was used in 16 studies (357 patients), functional hemispherectomy in 10 (194 patients), hemidecortication in six studies (140 patients), and hemispherotomy in 19 (517 patients). It has to be emphasized that the difference between functional hemispherectomy and hemispherotomy is in the amount of the resected cortical tissue, with minimal amount in the hemispherotomy techniques (Rangel-Castilla et al., 2012; Lopez et al., 2021a; Cook et al., 2004a). Unfortunately, many authors keep using interchangeably these terms, which perpetuates the existing confusion. The follow-up ranged from 1 month to 9 years. Most studies (34) included patients with mixed underlying pathologies. In contrast, there were only three studies with a single underlying pathology: Rasmussen encephalitis, hemimegalencephaly, and Sturge-Weber syndrome, respectively. Unfortunately, it was not possible to stratify our findings based on the underlying pathology. The basic characteristics of all eligible studies are summarized in Table 3.

3.3. Quality of evidence

Altogether, there were 30 studies of low-quality evidence (case series and surveys) and seven of moderate quality (cohort studies) in the absence of high-quality studies (RCTs). The overall quality of evidence for each complication was graded as "very low" in all instances, except for that of fever and aseptic meningitis, which was "low" (Table 4).

3.3.1. Morbidity (Q1)

The reported complications could be grouped into surgical (requiring either surgical or medical management), neurological, and neurocognitive ones, mostly for practical reasons. Superficial cerebral hemosiderosis, intra-operative blood loss, development of hydrocephalus, hematoma formation, fever, and post-operative infection represent the most common surgical complications. The most consistently reported ones are depicted in Table 5, and visualized in Supplementary Figs. 1–8 (Supplementary Material).

Among the medically managed complications, aseptic meningitis and fever were the most common, with an estimated frequency of 33% (95% CI: 0.24 - 0.46). In most cases, this complication followed an indolent course. Infections, mostly amenable to intravenous antibiotics, occurred with a frequency of 11% (95% CI: 0.8-0.16). Blood transfusion was required in 28% (95% CI: 0.18-0.43) of the cases. Among the neurological complications, novel post-operative cranial nerve deficits were reported in 11% (95% CI: 0.05-0.23). The occurrence of new motor deficits or worsening of pre-existing hemiparesis was reported in 17/37 studies. Likewise, procedure-associated visual changes were found in 8/37 studies. Our analysis demonstrated post-operative neurocognitive changes, such as altered behavior, cognitive and memory alterations, or intellectual deterioration, in 12/37 studies (Table 6).

Ventriculoperitoneal shunt insertion for hydrocephalus was the most frequent complication requiring surgical intervention, occurring in 16% (95% CI: 0.12-0.22). Intracerebral hemorrhages, extra-axial collections, and subgaleal effusions requiring surgical evacuation occurred in 9% (95% CI: 0.04-0.22), 8% (95% CI: 0.05-0.13), and 8% (95% CI: 0.03-0.39), respectively.

3.3.2. Mortality (Q2)

Based on 24 studies with 1060 patients, the overall mortality was 5% (95% CI: 0.03-0.08) (Fig. 2).

After omitting the study by Winston et al. (1992), due to its significant contribution to the inter-study heterogeneity, the mortality remained at the level of 5% (95% CI: 0.03-0.06). Anatomical hemispherectomy and hemispherotomy were associated with the highest (7%; 95% CI: 0.04-0.15) and the lowest (3%; 95% CI: 0.02-0.06) mortality, respectively. It is worth mentioning that the hemispherectomy/hemispherotomy mortality significantly dropped from 32% (95% CI: 0.21-0.48) in the 1970s to 2% (95% CI: 0.01-0.05) in the 2020s.

3.4. The role of surgical technique (Q3)

The subgroup analysis according to the type of surgery showed that the shunt insertion for hydrocephalus ($p = 0.026$) and the incidence of aseptic meningitis/fever ($p = 0.003$) differed among various techniques. The highest and lowest incidence of post-operative hydrocephalus occurred after anatomical hemispherectomy (AH) (26%, 95% CI: 0.17-0.39) and hemispherotomy (HT) (13%, 95% CI: 0.09-0.18), respectively. Similarly, the highest and lowest rates of aseptic meningitis and fever occurred after AH (51%, 95% CI: 0.37-0.71) and HT (19%, 95% CI: 0.21-0.29), respectively. The remaining complications were unaffected by the surgical technique employed. Despite the considerable variation in the mortality rate among the various surgical techniques, these differences did not reach the level of statistical significance ($p = 0.522$).

3.5. Temporal trends (Q4)

The incidence of intracranial hemorrhage ($p = 0.006$), subgaleal effusions ($p = 0.043$), and cranial nerve deficits ($p = 0.01$) significantly decreased over time (Fig. 3).

The incidence of intracranial hemorrhage was higher with AH (33%; 95% CI: 0.07-0.99), while it was infrequent in HT (6%, 95% CI: 0.02-0.13). However, the results regarding the subgaleal effusions and cranial nerve deficits were based on a limited number of studies. Therefore, the estimated incidence rates were not robust.

Table 3
General characteristics of included studies.

Author	Study design	Number of patients	Country (State/City)	Enrolment period	Population	Pathology	Type of surgery	Follow-up
Wilson et al. (1970) (Wilson, 1970)	Case series	50	UK (Swansea)	1949-1964	Mixed	Variable	NR	NR
Winston et al. (1992) (Winston et al., 1992)	Case series	11	USA (Massachu-setts)	1972-1988	Pediatric	Variable	Hemispherectomy	5.5 years (range 4.5–14 years)
Davies et al. (1993) (Davies et al., 1993)	Case series	17	USA (Minnesota)	1950-1971	NR	Variable	Hemispherectomy	28 years (range 19–38 years)
Peacock et al. (1996) (Peacock et al., 1996)	Case series	58	USA (California)	1986-1995	Pediatric	Variable	Anatomical, functional, or modified anatomical hemispherectomy	1 year (minimum)
Di Rocco and Iannelli (2000) (Di Rocco and Iannelli, 2000)	Case series	15	Italy (Rome)	1985-1996	Pediatric	Hemimegalencephaly	Anatomical and functional hemispherectomy	5,5 years (mean)
Schramm et al. (2001) (Schramm et al., 2001)	Cohort study	20	Germany (Bonn)	NR	Mixed	Variable	Transsylvian keyhole hemispherectomy	43 months
Kossoff et al. (2002) (Kossoff et al., 2002a)	Survey	32	USA (Maryland)	1979-2001	Pediatric	Sturge–Weber syndrome	Anatomic and Functional hemispherectomies, and Hemidecortication	NR
Kossoff et al. (2002) (Kossoff et al., 2002b)	Case series	106	USA (Maryland)	1975-2001	Pediatric	Variable	Hemidecortications	NR
Devlin et al. (2003) (Devlin, 2003)	Case series	33	UK (London)	1991-1997	Mixed	Variable	Hemispherectomy	3.4 years (1-8 years)
Cook et al. (2004) (Cook et al., 2004b)	Cohort study	115	USA (California)	NR	Pediatric	Variable	Anatomical hemispherectomy (37), Rasmussen Functional Hemispherectomy (32), Modified Lateral Hemispherotomy (46)	NR
Pulsifer et al. (2004) (Pulsifer et al., 2004)	Case series	71	USA (Maryland)	1968-1997	Pediatric	Variable	Anatomical hemispherectomy	5.4 years
Almeida et al. (2006) (Almeida et al., 2006)	Cohort study	30	Brazil (Sao Paolo)	1987-2003	Mixed	Variable	Anatomical hemispherectomy (3), Functional hemispherectomy, Hemispherotomy (16)	NR
Villemure and Daniel (2006) (Villemure and Daniel, 2006)	Case series	43	Switzerland (City: not reported)	NR	Pediatric	Variable	Peri-insular hemispherotomy (PIH) (43)	9 years
Basheer et al. (2007) (Basheer et al., 2007)	Case series	24	Canada (British Columbia)	1993-2004	Pediatric	Variable	Peri-insular hemispherotomy (PIH) (19), Hemidecortication (5)	7 years
Delalande et al. (2007) (Delalande et al., 2007)	Case series	83	France (Paris)	1990-2000	Pediatric	Variable	Vertical Parasagittal Hemispherotomy	4.4 years (SD, 2.7 yr; range, 0.03–11.3 yr)
Lettori et al. (2008) (Lettori et al., 2008)	Case series	19	Italy (Rome)	1980-1992	Pediatric	Variable	Anatomical hemispherectomy (11), Functional hemispherectomy (5), Hemidecortication (4)	6 years (2-11 years)
Terra-Bustamante et al. (2009) (Terra-Bustamante et al., 2009)	Case series	25	Brazil (Sao Paolo)	1995-2008	NR	Rasmussen encephalitis	Functional hemispherectomy (16), Anatomical hemispherectomy (3), Hemidecortication (1), Partial surgeries (3),	63 months
Marras et al. (2010) (Marras et al., 2010)	Case series	13	Italy (Milan)	NR	NR	Variable	Peri-insular hemispherotomy (PIH)	4.5 years
Kwan et al. (2010) (Kwan et al., 2010)	Cohort study	41	Canada (Ontario)	NR	Pediatric	Variable	Hemidecortication (21) and Peri-insular hemispherotomy (PIH) (20)	72 months
Dorfer et al. (2013) (Dorfer et al., 2013)	Case series	40	Austria (Vienna)	1998-2013	Pediatric	Variable	Vertical perithalamic hemispherotomy	0.1-15 years
Liang et al. (2013) (Liang et al., 2013)	Case series	25	China (Beijing)	2006-2011	Adults	Variable	Functional (9), hemispherectomies, Anatomical hemispherectomies (16)	2 years minimum
Lee et al. (2014) (Lee et al., 2014)	Case series	12	Korea (Seoul)	1997-2005	Pediatric	Variable	Anatomical or Functional hemispherectomy (8) and Hemispherotomy (4)	12.7 years (range, 7.6–16.2 years)
Iwasaki et al. (2015) (Iwasaki et al., 2015)	Cohort study	13	Japan (Sendai)	2001-2012	Pediatric	Variable	Interhemispheric vertical hemispherotomy (IVH) and Peri-insular lateral hemispherotomy	1.5-11 years

(*continued on next page*)

Table 3 (*continued*)

Author	Study design	Number of patients	Country (State/City)	Enrolment period	Population	Pathology	Type of surgery	Follow-up
Vedantam et al. (2017) (Vedantam et al., 2018)	NSQIP-P database	50	USA (Texas)	2015	Pediatric	Variable	Hemispherectomies (50)	30 days
Chen et al. (2019) (Chen et al., 2019)	Survey	196	USA (California)	NR	Pediatric	Variable	Cerebral hemispherectomy	92 ± 78 months
Sood et al. (2019) (Sood et al., 2019)	Case series	77	USA (Michigan)	2000-2019	Pediatric	Variable	Anatomical hemispherectomy	5.7 years (range 1–16.84 years)
Weil et al. (2020) (Weil et al., 2020)	Case series	69	USA (Florida)	2000-2014	Pediatric	Variable	Functional hemispherectomy	NR
Iwasaki et al. (2021) (Iwasaki et al., 2021)	Case series	75	Japan (Tokyo)	2006-2019	Pediatric	Variable	Vertical parasagittal hemispherotomy (22), Peri-insular hemispherotomy (PIH) (5)	1 year (minimum)
Vining et al. (1997) (Vining et al., 1997)	Case series	58	USA (Maryland)	1968-1996	Pediatric	Variable	Hemispherectomy	6.2 years
Kestle et al. (2000) (Kestle et al., 2000)	Case series	16	Canada (British Columbia)	1993-1999	Pediatric	Variable	Peri-insular hemispherotomy (PIH) (11), Hemidecortication (6)	3 months to 5.7 years (median 3.0 years)
Shimizu et al. (2005) (Shimizu, 2005)	Case series	44	Japan (Tokyo)	1983-2002	Pediatric	Variable	Functional hemispherectomy	NR
O'Brien et al. (2006) (O'Brien et al., 2006)	Case series	19	UK (Liverpool)	1991-2004	Mixed	Variable	Anatomical hemispherectomy	7 years
Wyllie et al. (1998) (Wyllie, 1998)	Case series	136	USA (Ohio)	1990-1996	Mixed	Variable	Functional hemispherectomy (16)	3.6 years
de Palma et al. (2019) (de Palma et al., 2019)	Cohort study	92	Italy (Multicentric study)	2006-2016	Mixed	Variable	Vertical Parasagittal Hemispherotomy (38), Peri-insular hemispherotomy (PIH) (54)	2.81 years
Gonzalez-Martinez et al. (2005) (Gonzalez-Martinez et al., 2005)	Cohort study	22	USA (Ohio)	1997-2001	Pediatric	Variable	Anatomical hemispherectomy (8), Functional hemispherectomy (14)	34.8 months
Panigrahi et al. (2015) (Panigrahi et al., 2016)	Case series	21	India (Telengana)	NR	Pediatric	Variable	Vertical parasagittal hemispherotomy (VPH) (16), Peri-insular hemispherotomy (PIH) (5)	25.4 months
Chandra et al. (2008) (Chandra et al., 2008)	Case series	19	India (New Delhi)	2001-2007	Pediatric	Variable	Vertical parasagittal hemispherotomy (VPH) (8), Peri-insular hemispherotomy (PIH) (11)	78 weeks

Table 4
Grading of the retrieved articles regarding the Quality of Evidence based on the GRADE (overview of the grade approach, 2023) approach.

Question	Starting grade	Down-grade					Up-grade			Final grade
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Magnitude of effect	Dose response	Confounding factors	
Mortality	2	0	-1	0	0	0	0	0	0	1 (Very low)
Hydrocephalus	2	0	-1	0	0	0	+1	0	0	2 (Very low)
Infection	2	0	-1	0	0		+1	0	0	2 (Very low)
Intracranial hemorrhage	2	0	-1	0	0	0	0	0	0	1 (Very low)
Fever and aseptic meningitis	2	0	0	0	0	0	+1	0	0	3 (Low)
Extra-axial collections	2	0	-1	0	0	0	0	0	0	1 (Very low)
Subgaleal effusions	2	-1	-1	0	0	NT	0	0	0	0 (Very low)
Cranial nerve deficits	2	0	0	0	-1	NT	0	0	0	2 (Very low)
Anemia	2	0	-1	0	-1	NT	+1	0	0	1 (Very low)

Table 5
Summary-of-evidence regarding mortality and morbidity incidence among different surgical techniques and over time.

		Studies	Complicated Cases/Study Population	Pooled proportion estimate (95% CI)	Subgroup analysis based on surgical technique	Subgroup analysis over time	Conclusions
Mortality	Overall	24	36/1060	5 (3-16)	0.521	**<0.001***	Decreased mortality over time
	AH	15	25/342	7 (4-15)			
	FH	9	1/207	4 (2-8)			
	HDC	3	3/122	5 (2-8)			
	TFKH	1	1/20	5 (1-34)			
	HT	13	6/379	3 (2-6)			
Hydrocephalus	Overall	28	197/1228	16 (12-22)	**0.026***	0.285	Hydrocephalus was low in a statistically significant fashion when using hemispherotomy techniques compared to hemispherectomy
	AH	16	96/357	26 (17-39)			
	FH	10	23/194	14 (10-20)			
	HDC	6	28/140	21 (15-29)			
	TFKH	1	0/20	–			
	HT	19	50/517	13 (9-18)			
Infection	Overall	17	64/847	11 (8-16)	0.550	0.06	No difference was observed either between different surgical techniques, or over time with the evolution of each technique
	AH	12	33/315	14 (9-22)			
	FH	6	8/144	11 (4-27)			
	HDC	3	10/112	11 (6-19)			
	TFKH	1	2/20	10 (3-37)			
	HT	7	10/256	6 (2-15)			
Intracranial hemorrhage	Overall	6	22/288	9 (4-22)	0.156	**0.006***	The incidence of intracranial hemorrhage significantly decreased over time
	AH	4	17/146	9 (2-44)			
	FH	1	1/3	33 (7-99)			
	HDC	–	–	–			
	TFKH	–	–	–			
	HT	5	4/139	6 (2-13)			
Fever and aseptic meningitis	Overall	8	80/305	33 (24 - 46)	**0.003***	0.238	Fever and aseptic meningitis were low in a statistically significant fashion when using hemispherotomy techniques compared to hemispherectomy
	AH	6	38/73	51 (37-71)			
	FH	5	22/118	22 (9-53)			
	HDC	4	6/33	43 (16-99)			
	TFKH	–	–	–			
	HT	5	14/81	19 (21-29)			
Extra-axial collections	Overall	9	12/358	8 (5-13)	0.719	0.681	No differences were observed either between different surgical techniques or over time
	AH	6	7/157	8 (3-22)			
	FH	6	3/125	5 (2-12)			
	HDC	2	0/7	13 (2-79)			
	TFKH	–	–	–			
	HT	5	2/69	8 (4-27)			
Subgaleal effusions	Overall	4	9/147	8 (3-19)	0.127	**0.043***	The incidence of subgaleal effusions presentation significantly decreased over time
	AH	1	2/19	11 (3-39)			
	FH	1	1/67	1 (0-10)			
	HDC	1	1/21	5 (1-32)			
	TKFH	1	1/20	5 (1-34)			
	HT	1	4/20	20 (8-48)			
Cranial nerve deficits	Overall	3	3/139	11 (5-23)	0.861	**0.01***	Cranial nerve deficits presentation significantly decreased over time
	AH	3	2/50	7 (2-23)			
	FH	3	1/37	13 (2-37)			
	HDC	1	0/2	–			
	TFKH	–	–	–			
	HT	3	0/50	–			
Post-operative anemia	Overall	10	88/371	28 (18-43)	0.222	0.195	No differences were observed either between different surgical techniques or over time
	AH	4	26/72	41 (27-62)			
	FH	4	22/72	34 (11-99)			
	HDC	3	4/28	37 (11-99)			
	TFKH	1	3/30	15 (5-43)			
	HT	6	29/188	16 (6-40)			

4. Discussion

Our analysis demonstrates that less invasive HT was associated with fewer complications. Interestingly, based on the reported mortality and morbidity rates, hemispherotomy seems to be safer than it used to be.

Anatomical hemispherectomy was associated with significant mortality (Fountas et al., 2006). The extensive nature of AH, the removal of multiple lobes, and the intra-operative blood loss were a few of the causes of the increased mortality. However, more recent series, as well as our current analysis, have demonstrated that the mortality associated with HT is minimal. Schramm et al., 2012a, 2012b, reported in a pediatric series mortality of 1.0%, while in their adult series their mortality was zero. Likewise, several recent pediatric series have reported zero mortality (Dorfer et al., 2013; Ye et al., 2020; Moosa et al., 2012). The transformation of the procedure from extensive resection to minimal disconnection, as well as the advances in neuroanesthesia, may well explain the minimalization of the associated mortality.

A multifactorial morbidity has also been associated with hemispherectomy/hemispherotomy, compromising its safety, and limiting its clinical usage. Superficial cerebral hemosiderosis, significant intra-operative blood loss, development of post-operative hydrocephalus, hematoma formation, persistent post-operative fever, and infection represent the most common surgical complications. However, the existence of superficial cerebral hemosiderosis has been questioned by many authors (Schramm et al., 2012a; Di Rocco and Iannelli, 2000). All recently published series, pediatric or adult, have reported no such cases, making the discussion only of historical value (Fountas et al., 2006; Schramm et al., 2012a, 2012b; Sood et al., 2019; Di Rocco and

Table 6
Motor, cognitive, and visual deficits after hemispherectomy/hemispherotomy.

Author	Tool-Instrument	Findings/motor deficit
Wilson et al. (1970) (Wilson, 1970)	Clinical examination	8 patients had useless arm and hand on the affected side 15 patients were able to walk
Davies et al. (1993) (Davies et al., 1993)	NR	None of the patients experienced worsening of their pre-operative hemiparesis
Peacock et al. (1996) (Peacock et al., 1996)	Five- point scale, interview of the patients' parents in the outpatient clinic or by telephone	Of the 50 patients evaluated, 27 (54%) showed improvement in their pre-operative hemiparesis at their pos-toperative follow-up, while 11 (22%) remained unchanged. Nine patients (18%) had a worsening of their pre-operative hemiparesis, and additional three (6%) had improvement in one hemiparetic limb with worsening in the other ipsilateral limb
Di Rocco and Iannelli (2000) (Di Rocco and Iannelli, 2000)	Neurological examination	Two children showed a temporary worsening of their pre-operative hemiparesis. However, the motor performance of both patients appeared to be significantly improving over a 6 month period.
Devlin et al. (2003) (Devlin, 2003)	NR	The pre-existing hemiplegia and fine finger movements deficits remained unchanged in 48 patients, improved in 7 and deteriorated in 11 patients, following hemispherectomy
Lettori et al. (2008) (Lettori et al., 2008)	NR	Pre-existing hemiparesis improved in 12 and remained unchanged in 6 patients after surgery
Terra-Bustamante et al. (2009) (Terra-Bustamante et al., 2009)	NR	Worsening of the neurological deficits with complete hemiplegia
Marras et al. (2010) (Marras et al., 2010)	NR	The pre-exixsting hemiparesis of the affected upper extremity transiently worsened; 11 patients were able to independently walk, while spasticity improved in all cases
Kwan et al. (2010) (Kwan et al., 2010)	NR	All patients (41) exhibited post-operative hemiparesis
Dorfer et al. (2013) (Dorfer et al., 2013)	NR	All patients (40) had pre-existing hemiparesis (with no useful hand function) and 4 of them presented with worsening of their motor skills after surgery
Liang et al. (2013) (Liang et al., 2013)	Both post-operative scores of Full—Meyer assessment-movement subscales for upper and lower limbs and aphasia quotient	The majority of the patients presented unchanged upper and lower limb movement post-operatively
Lee et al. (2014) (Lee et al., 2014)	NR	No changes of the pre-existing hemiparesis
Shimizu et al. (2005) (Shimizu, 2005)	NR	Psychomotor improvement
de Palma et al. (2019) (de Palma et al., 2019)	NR	Hemiparesis, spastic quadriparesis, facial palsy, hypotonia were observed
Gonzalez-Martinez et al. (2005) (Gonzalez-Martinez et al., 2005)	NR	Contralateral hemiplegia, recovery of motor function
Panigrahi et al. (2015) (Panigrahi et al., 2016)	NR	Further deterioration of motor weakness of the hemiparetic side
Chandra et al. (2008) (Chandra et al., 2008)	Comparison to pre-operative	Worsening of pre-operative motor weakness

Author	Tool-Instrument	Findings/cognitive deficits
Wilson et al. (1970) (Wilson, 1970)	Clinical examination	Roughly 42% of patients assessed before operation as being of borderline or severely subnormal intellect proved to some degree educable or employable after hemispherectomy Low-level language disorder (clinical nominal or receptive dysphasia) Mental deficiency, anomia and alexia
Davies et al. (1993) (Davies et al., 1993)	NR	Ten patients have become employable since surgery, usually in a sheltered setting. Six patients have lived independent lives, and six have lived protected existences with their families. Three have been semi- independent, living in community homes with other disabled people. Dysphasia
Devlin et al. (2003) (Devlin, 2003)	NR	The overall cognitive behavior was unchanged in 23 and improved in 4 patients after surgery Intellectual deterioration and loss of language Language function
Pulsifer et al. (2004) (Pulsifer et al., 2004)	Comprehensive set of cognitive tests to patients before surgery and at follow-up	General intelligence, receptive language, expressive language, visual-motor, developmental functioning IQ and language skills, receptive-expressive language
Basheer et al. (2007) (Basheer et al., 2007)	SIB-R scale scores, PPVT-III Social/ Communication scale	Broad independence, motor, social/communication, personal living, community living Borderline to mild impairment in language skills
Delalande et al. (2007) (Delalande et al., 2007)	Vineland Adaptive Behavior Scale	Communication, Daily living skills, socialization, motor skills, global score
Lettori et al. (2008) (Lettori et al., 2008)	NR	The majority of the patients presented an unchanged cognitive assessment (IQ measurement)
Terra-Bustamante et al. (2009) (Terra-Bustamante et al., 2009)	NR	No cognitive modification, cognitive decline, cognitive improvement, aphasia, aphasia, language dysfunctions, normal language
Liang et al. (2013) (Liang et al., 2013)	Full—Meyer assessment- movement subscales for upper and lower limbs and aphasia quotient	Improved verbal IQ and performance IQ, speech function impairment
de Palma et al. (2019) (de Palma et al., 2019)	NR	Psychomotor delay21
Panigrahi et al. (2015) (Panigrahi et al., 2016)	IQ test, QOLIE test	Average mental age, social age, social quotient and developmental quotient
Chandra et al. (2008) (Chandra et al., 2008)	NR	Cognitive profile improved post-operatively

Author	Tool-Instrument	Findings/visual deficits
Wilson et al. (1970) (Wilson, 1970)	Clinical examination	All patients had a complete contralateral homonymous hemianopia
Devlin et al. (2003) (Devlin, 2003)	NR	Visual fields deficits remained unchanged in 17 and deteriorated in 13 patients who underwent hemispherectomy
Terra-Bustamante et al. (2009) (Terra-Bustamante et al., 2009)	NR	Hemianopsia
Marras et al. (2010) (Marras et al., 2010)	NR	Hemianopia
Dorfer et al. (2013) (Dorfer et al., 2013)	NR	Homonymous hemianopia
Chen et al. (2019) (Chen et al., 2019)	NR	Post-operative strabismus
de Palma et al. (2019) (de Palma et al., 2019)	NR	Hemianopsia, strabismus and other visual disturbances occurred post-operatively
Gonzalez-Martinez et al. (2005) (Gonzalez-Martinez et al., 2005)	NR	Homonymous contralateral hemianopsia, and gaze preference toward the surgical side

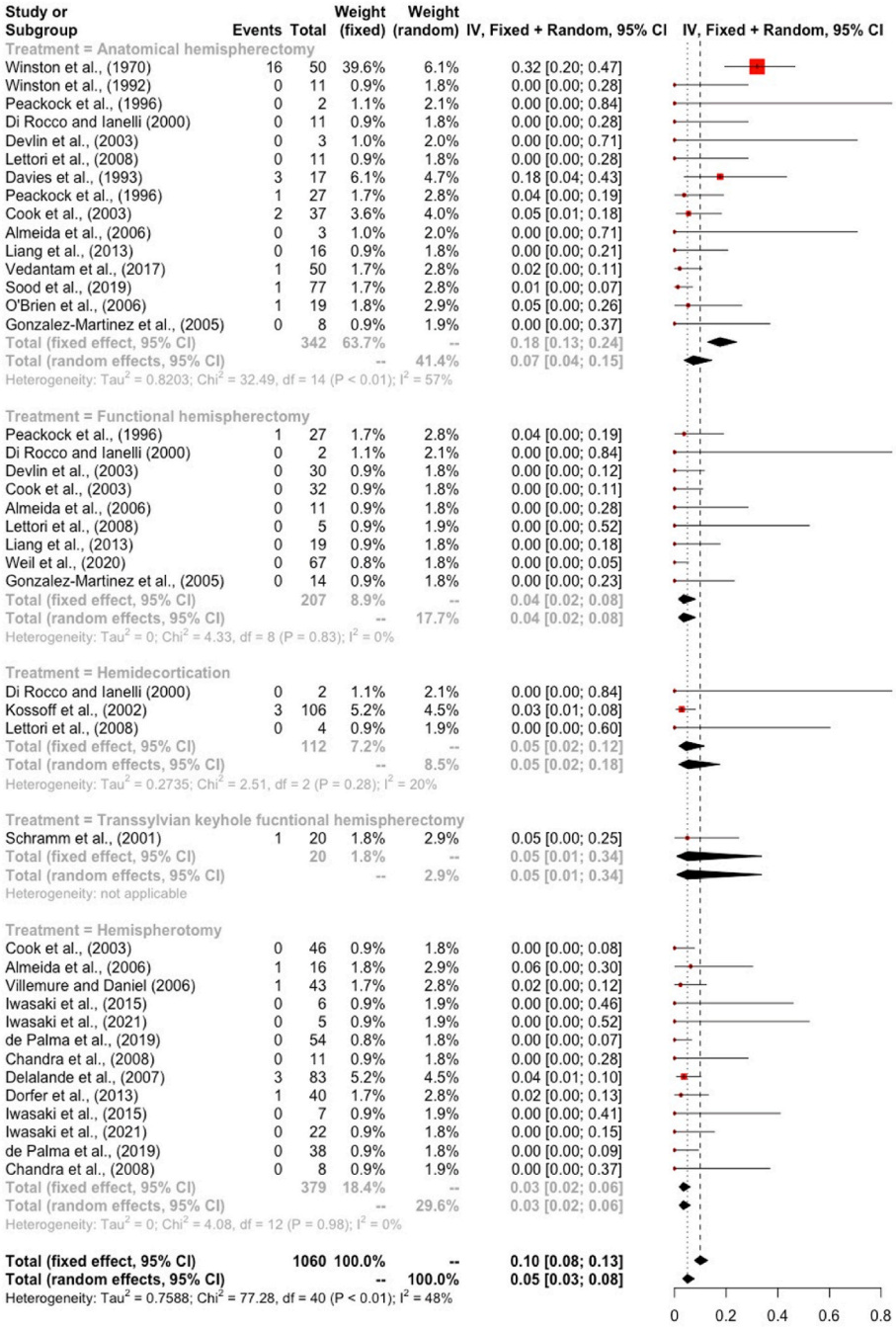

Fig. 2. Mortality occurs with an estimated frequency of 5% (95% CI: 0.03-0.08) after hemispherectomy/hemispherotomy. Although there was a trend for higher mortality associated with hemispherectomy compared to hemispherotomy, the observed difference did not reach the level of statistical significance.

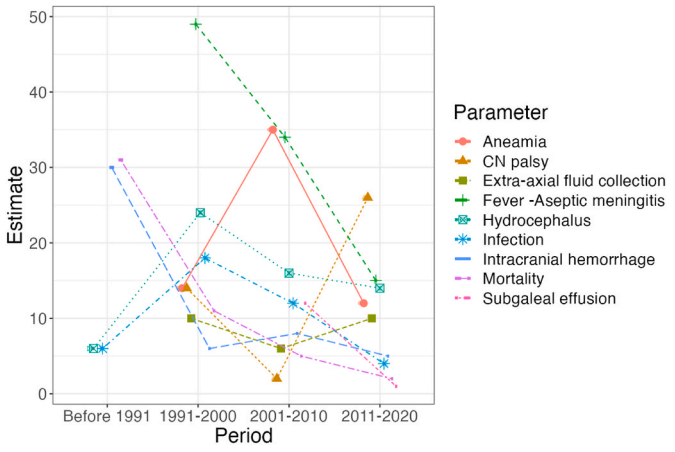

Fig. 3. A plot depicting the temporal evolution of mortality and morbidity. The hemispherectomy/hemispherotomy mortality significantly dropped from 32% (95% CI: 0.21-0.48) in the 1970's to 2% (95% CI: 0.01-0.05) in the 2020's. Similarly, the incidence of intracranial hemorrhage ($p = 0.006$), subgaleal effusions ($p = 0.043$), and cranial nerve deficits ($p = 0.01$) significantly decreased over time.

Iannelli, 2002).

A major concern regarding hemispherectomy has been the intra-operative blood loss and the necessity for transfusion. Brian et al. (1990), reported that all their cases required blood transfusion. Similarly, Gowda et al. (2010), reported that a transfusion was necessary in all their cases. It has to be pointed out, however, that their series included pediatric patients aged less than six months. On the other hand, Dorfer et al. (2013), reported that only 5% of their pediatric patients had to be transfused.

The incidence of post-operative hydrocephalus comprises another worrisome complication. Lee et al. (2014), reported hydrocephalus incidence 9-81% in adult and pediatric populations, while the respective percentage in a solely pediatric series was 23%. Likewise, Brotis et al. (Brotis, 2015), reported hydrocephalus incidence 2-26%. Recently published pediatric series reported lower incidence (13-14%) (Weil et al., 2020; Volpon Santos et al., 2020), while Lopez et al. (2021b), reported incidence of 19%. It has been postulated that certain pathologies such as hemimegalencephaly or cortical dysplasia are more frequently associated with hydrocephalus. However, this association could not be verified in our analysis.

The formation of post-operative hematoma, the development of infection, and/or the occurrence of post-operative fever are frequently reported as cumulative surgical morbidity among many series. Schramm et al., reported a cumulative morbidity of 7.4% in their adult patients (Schramm et al., 2012b), while it was somewhat higher, 9.7%, in their pediatric series (Schramm et al., 2012a). Likewise, Ye et al. (2020), reported a 10% incidence, while in Weil et al. (2020), pediatric series the respective percentage was 14.8%. Interestingly, Santos et al. (Volpon Santos et al., 2020), reported 28.5% of such surgical complications. It has to be pointed out that their series included solely re-operations, which may well explain their increased complication rate. Lopez et al. (2021b), found that the incidence of hematoma varied between 10 and 36%, of infection ranged from 2 to 7%, while post-operative fever observed in up to 83%. They also found that certain pathological entities such as hemimegalencephaly and Sturge-Weber syndrome were more frequently associated with hematoma formation, while Rasmussen's encephalitis might predispose to post-operative fever. Di Rocco et al. (Di Rocco and Iannelli, 2000), had postulated that younger age in children might predispose to surgical complications. The lack of robust data in our meta-analysis could not prove the validity of any of these associations.

Despite the extent of disconnection or resection, the incidence of neurological complications is quite low. Worsening of a pre-existing or de novo hemiparesis has been reported in 8-21% (Gowda et al., 2010; Ramantani et al., 2013; Ghatan et al., 2014; Schusse et al., 2018; Liang et al., 2013). More specifically, Gowda et al. (Sood et al., 2019), reported a worsening of hemiparesis in 8% of their pediatric cases, while Ramantani et al. (2013), found a worsening in 10%, as well as Ghatan et al. (2014). This percentage was higher in the adult series of Schusse et al. (2018), who reported a 21% incidence. It has to be mentioned however, that even in those cases that there was a worsening of the pre-operative hemiparesis, the patients remained ambulatory post-operatively. Post--operative worsening of speech was observed in 10% of Schusse et al. (2018), adult cases. There are also reports of post-operative temporary mutism (Schusse et al., 2018; Liang et al., 2013). These symptoms were more frequent in cases of dominant hemisphere involvement.

Moreover, post-operative visual field and/or visual acuity worsening has been demonstrated in pediatric series (Chen et al., 2019; Meer et al., 2021). Chen et al. (2019), demonstrated that 49% of their cases developed de novo or had worsening of their preoperative strabismus. It is of interest that the majority of these patients developed constant head tilting for compensating their visual deficits. Similarly, Meer et al. (2021), reported that 56% of their cases had decreased visual acuity, while 71% had some type of visual field deficits. It has to be emphasized, however, that the development of visual deficits post-operatively may be indicative of complete resection or disconnection, raising thus the question if visual deficits have to be considered as a complication.

The effect of hemispherotomy on the post-operative neurocognitive status of these patients has not been adequately explored. However, the absence of such reports cannot be considered as lack of proof. Several series have reported some post-operative improvement in the learning abilities of their patients (Villemure and Daniel, 2006; Schramm et al., 2012b; Lopez et al., 2021b; Ramantani et al., 2013; Schusse et al., 2018; Kwan et al., 2010; Iwasaki et al., 2015, 2021; Hwang and Kim, 2019). This issue remains to be more accurately outlined in future studies.

Our current data confirmed that the incidence of aseptic meningitis/fever, as well as hydrocephalus was significantly lower in hemispherotomy compared to hemispherectomy. The role of the type of hemi-deafferentation technique in the development of certain complications is of great interest. Although the comparison between the existent series is extremely difficult due to the mixed populations, different time periods, various underlying pathologies, and the utilization of various surgical techniques even in the same clinical series, there are very few reports comparing different HT techniques (Limbrick et al., 2009; Kwan et al., 2010; Iwasaki et al., 2015) (Kwan et al., 2010; Iwasaki et al., 2015; Limbrick et al., 2009). Limbrick et al. (2009), found no difference in the incidence of complications between the various employed surgical techniques. On the other hand, Kwan et al. (2010), reported that the lateral, peri-insular technique was associated with fewer complications. Contrariwise, Iwasaki et al. (2015), concluded that the vertical HT technique was associated with fewer complications. Fallah et al. in their multicenter, international, retrospective post hoc analysis found that vertical parasagittal technique maintained higher seizure freedom rates throughout a 10-year follow-up period compared to the lateral peri-insular technique (Fallah et al., 2021). They concluded that the lateral approach had shorter time to seizure recurrence, and increased seizure recurrence after the first post-operative year (Fallah et al., 2021). It is apparent that the extraction of any statistically powerful conclusions from these series would be quite risky.

The importance of the selection of the surgical candidates for HT cannot be overemphasized. A thorough, multi-disciplinary (including but not limited to epileptologist, neuro-pediatrician, neuroradiologist, nuclear medicine specialist, neurophysiologist, specially trained neurosurgeon, neuropathologist, and psychiatrist) pre-operative evaluation of the surgical candidates is of paramount importance for achieving a good surgical and functional outcome (Bartoli et al., 2017). The implementation of predictive models and scales may further increase the safety and the efficacy of HT. Weil et al. have introduced the

Hemispheric surgery Outcome Prediction Scale (HOPS), which takes into consideration parameters such as the patient's age at seizure onset, the presence of generalized seizures, the presence of contralateral hemisphere hypometabolism on 18-fluoro-2-deoxyglucose positron emission tomography, the underlying pathology, and the performance of a previous non-hemispheric resective surgery (Weil et al., 2021). Such predictive scales may further minimize the associated to the HT morbidity while at the same time may increase its overall efficacy (Weil et al., 2021). These predictive scales may facilitate the decision-making process not only in first time HT, but also in redo HT in cases of previously failed procedures (Bartoli et al., 2017).

4.1. Future developments

Certain actions may be taken for increasing HT utilization and further minimizing its associated complications and improving its overall efficacy, in the near future. The application of strict selection criteria among surgical candidates for undergoing HT may further enhance its efficacy. A thorough, pre-operative work up by a multidisciplinary team of highly trained experts, with special emphasis on the neurocognitive and psychological status of these patients may minimize surgical failures, further improve the safety profile of HT, and facilitate a good functional outcome. The adaptation of unanimously accepted surgical and functional outcome criteria, along with the development of international registries of the HT performed cases may allow a more solid, from methodological standpoint, approach to the evaluation of the overall efficacy of this technically demanding procedure. This will accurately outline HT's actual role in the management of patients with catastrophic DRE.

4.2. Limitations

The current study is characterized by some important limitations. Firstly, the current evidence is based on a limited number of heterogeneous, low-quality studies. Secondly, we cannot rule out overlapping of study populations among the included studies, despite our copious efforts. Equally important, several studies failed to provide extractable data. The single most common reason was that several studies reported their complications on more than one technique under a common heading without providing specific data for each technique independently. Thirdly, there is a lack of consistent complication reporting, which prohibits us from registering frequent and important complications. Fourthly, the protocol of our study was not registered in any relevant registry. Furthermore, there is substantial variation in the length of follow-up. Indeed, the currently available studies focus on short- and intermediate-term complications. In addition, the available studies did not permit any further subgroup analysis according to the involved population, since solely adults were involved in only one study. Likewise, subgroup analysis according to the underlying pathology was impossible due to the limited data and the mixed series. Finally, numerous studies with multiple treatment arms were excluded since the reported results were presented without any stratification.

5. Conclusions

Our current systematic review and meta-analysis demonstrate that HT constitutes a valid surgical treatment option in the management of catastrophic DRE. Undoubtedly, HT remains a technically demanding procedure, requiring extremely careful selection of the surgical candidates, as well as meticulous, multidisciplinary, pre-operative work up. Moreover, our analysis demonstrated that the evolution from a resective to a disconnecting procedure, along with advances in neuroanesthesia, had a tremendous impact on the associated mortality and morbidity. Hydrocephalus remains the most common surgical complication. Surgical intervention is required in another 16% of the cases for the evacuation of either extra-axial hematomas or subdural effusions. Aseptic meningitis/post-operative fever manifests in a third of the cases, while infections requiring intravenous antibiotics occur in 11% of the cases. The reported neurological complications associated with hemispherotomy are rare and of low clinical significance in the majority of cases.

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Author contributions

The authors confirm contribution to the paper as follows:study conception and design: Maria D. Karagianni, Alexandros G. Brotis, Konstantinos N. Fountas; data collection: Maria D. Karagianni, Alexandros G. Brotis; analysis and interpretation of results: Alexandros G. Brotis, Maria D. Karagianni, Anastasia Tasiou, Konstantinos N. Fountas; draft manuscript preparation: Alexandros G. Brotis, Maria D. Karagianni, Anastasia Tasiou, Konstantinos N. Fountas, Daniel Delev, Marec von Lehe, Olaf E.M.G. Schijns, All authors reviewed the results and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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