Complications after Anterior Temporal Lobectomy for Medically Intractable Epilepsy: A Systematic Review and Meta-Analysis

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Keywords

Intractable epilepsy · Medically refractory epilepsy · Anterior temporal lobectomy · Complications · Mortality · Morbidity

Abstract

Background: The efficacy of surgery in the management of patients with longstanding temporal lobe epilepsy has been established. Anterior temporal lobectomy (ATL) is the most frequently implemented procedure. However, there is an obvious need to assess its perioperative safety. **Objective:** We conducted a meta-analysis to estimate the postoperative mortality (Q1) and morbidity (Q2) associated with ATL for medically intractable epilepsy. In addition, we tried to identify the most frequent complications after ATL and assess their relative frequency (Q3) in children and adults. **Methods:** Fixed- and random-effects model meta-analysis was conducted to assess the proportion estimate for each outcome individually. **Results:** The postoperative mortality and cumulative morbidity were estimated to be as high as 0.01 (95% CI: 0.01, 0.02) and 0.17 (95% CI: 0.12, 0.24), respectively. Psychiatric disorders were the most common postoperative complications after ATL, with an estimated frequency

as high as 0.07 (95% CI: 0.04, 0.10), followed by visual field defects (0.06; 0.03, 0.11), and cognitive disorders (0.05; 0.02, 0.10). Less frequent complications included hemiparesis and language disorders (0.03; 0.01, 0.06), infections (0.03; 0.02, 0.04), hemorrhage (0.02; 0.01, 0.05), cranial nerve deficits (0.03; 0.02, 0.05), extra-axial fluid collections (0.02; 0.01, 0.03), and medical complications (0.02; 0.01, 0.03). **Conclusions:** Even though the mortality after ATL is minimal, the overall morbidity cannot be ignored. Psychiatric disturbances, visual field defects, and cognitive disorders are the most common postoperative complications, and should be considered during the preoperative planning and consultation.

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Introduction

Epilepsy is a serious worldwide health problem, affecting approximately 1% of the general population [1]. Despite optimal medical treatment, 20–40% of the epilepsy patients continue to have seizures [2]. Temporal lobe epilepsy (TLE) associated with hippocampal sclerosis constitutes the most common cause of focal, intractable epilepsy (IE) among adults [3]. It has been demonstrated,

Table 1. Criteria and definitions for ATL-associated complications reported among eligible studies

Complication	Definition
Infection	Meningitis, wound infection, osteomyelitis, empyema
Hemorrhage	Epidural hematoma, chronic subdural hematoma, intraparenchymal hemorrhage, hemorrhagic infarction
Pyramidal/sensory tract/language deficits	Hemiparesis, monoparesis, aphasia, dysphasia, hemisensory deficit
VFDs	Hemianopsia, quadranopsia
CNDs	Diplopia, paresis of frontal branch of facial nerve
CSF-related	CSF leak, hydrocephalus
Extra-axial fluid collections	Subgaleal fluid collection, subdural collections other than chronic subdural hematoma
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
Morbidity	Cumulative frequency of complications
Mortality	Frequency of death

VFDs, visual field defects; CNDs, cranial nerve deficits; CSF, cerebrospinal fluid.

that children and adults with IE have poor long-term intellectual and psychosocial outcomes, along with a poor quality of life [4–6]. The medical treatment of these patients accounts for as high as 80% of the cumulative cost of epilepsy in the United States [7].

Two randomized controlled trials (RCTs) have well established the efficacy of surgery in the management of patients with longstanding TLE and have ultimately proved that resective surgery along with continued anti-epileptic drug (AED) treatment resulted in a lower probability of seizures during the second year of follow-up than continued AED treatment alone, in selected cases [8, 9]. Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (seAH) are the most commonly employed surgical approaches in the management of medical refractory TLE [10].

While surgical treatment is effective, many patients and their referring physicians consider a potential surgical intervention with a lot of skepticism, due to the absence of robust evidence supporting its safety [3]. A single-center RCT from India concluded that surgery, irrespective of the utilized surgical procedure, results in anticipated neurological deficits, depending on the region of brain resection [2]. In addition, a retrospective, observation study reported that ATL was associated with increased risk of complications when compared to seAH [10]. Therefore, the necessity of accurate evaluation of any ATL-associated complications becomes of paramount importance, especially nowadays with the emergence of many nonresective treatment modalities.

In an obvious need to assess the safety of ATL for the management of IE of temporal origin, we conducted a meta-analysis to estimate the postoperative mortality (Q1), overall morbidity (Q2), and individual complication rate (Q3) associated with ATL. The results were stratified according to the targeted population. The final results were interpreted by taking into consideration the overall quality of the available evidence.

Methods

Search Strategy

We prospectively designed the search methods, eligibility criteria, and data extraction process. The working definition of the complications associated with ATL is summarized in Table 1. The search strategy is displayed in Table 2, while the summary of the protocol is presented thereunder. This meta-analysis was conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocol) [11], and it has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42018102297.

Information Sources

Two review authors (T.G. and A.G.B.) independently identified candidate studies through an electronic search of five databases: PubMed, Cochrane Library, ClinicalTrials.gov, Web of Science, and Scopus. They used the following MeSH terms: “drug-resistant epilepsy,” “intractable epilepsy,” “medical refractory epilepsy,” “temporal lobe epilepsy,” “anterior temporal lobectomy,” “anterior temporal lobe surgery,” “complications,” “visual field defects,” “aphasia,” “hemiparesis,” “cranial nerve palsy,” “psychiatric disorders,” “memory,” “cognitive,” “deficit,” “hemorrhage,” “psychological,” and “infections” in any possible combination. The search period extended from 1964 until July 2018. The literature was last

Table 2. Search strategy

Frame	Mesh terms	Search	Inclusion criteria	Exclusion criteria	Sources
P (patients, participants, population)	#1. "Adults," OR "Pediatric," #2. "Drug-resistant epilepsy," OR "Medically refractory Epilepsy," OR "Intractable Epilepsy," OR "Temporal lobe epilepsy"	#1 AND #2 AND #3 AND #4	Articles reporting at least three different complications Published in peer-review journals English language	Irrelevant title or abstract Irrelevant full text Non-English Editorial, reviews, meta-analysis Studies with less than 5 subjects Experimental/nonhuman studies Interventions other than ATL Indications other than epilepsy Total number of patient sample not obvious	Databases (PubMed, Cochrane Library, Clinical-Trials.gov, Web of Science, and Scopus)
I (intervention)	#3. "Anterior temporal lobectomy", OR "Anterior temporal lobe surgery"				
C (reference test)	–				Reference list
O (outcome)	#4. "Complication," OR "Visual field defects," OR "Aphasia," OR "Hemiparesis," OR "Cranial nerve palsy," OR "Psychiatric disorders," OR "Memory," OR "Cognitive," OR "Deficit," OR "Hemorrhage," OR "Psychological," OR "Infections"				
Time	Search period: 1964 until August 2018 Last search: August 2018				

Table 3. Characteristics of studies included in the analysis

First author [Ref.]	Year	Country	Study design	Recruitment period	Population	Intervention	Alternative treatment	Outcome
Erba [16]	1992	US	R, case series	1972–1987	Mixed	ATL	–	Q1, Q2, Q3
Jacobson [25]	1995	US	R, case series	1987–1993	Adult	ATL	–	Q3
Popovic [26]	1995	Australia	R, case series	1969–1991	Adult	ATL	–	Q3
Adam [41]	1996	France	R, case series	1991–1994	Pediatric	ATL	–	Q2, Q3
Wiebe [8]	2001	Canada	RCT	1996–2000	Adult	ATL + AH	Antiepileptics	Q1, Q2, Q3
Salanova [27]	2002	US	P, case series	1984–1999	Mixed	Temporal resective surgery	–	Q1, Q2, Q3
Sinclair [28]	2003	Canada	R, case series	1988–2000	Pediatric	ATL	–	Q1, Q2, Q3
Oertel [14]	2004	Germany	R, case-control	1995–2000	Adult	ATL + neuro-navigation	ATL – neuro-navigation	Q3
Sindou [29]	2006	France	R, case series	1994–2003	Adult	ATL +/- AH	–	Q1, Q2, Q3
Grivas [30]	2006	Germany	R, case series	1991–2002	Adult	ATL / SelAH	–	Q1, Q2, Q3
Bate [15]	2007	UK	R, case-control	1996–2004	Adult	ATL	AH	Q1, Q2, Q3
Lee [31]	2008	Korea	R, case series	1997–2006	Mixed	ATL	Various (110 pts)	Q3
Kim [32]	2008	Korea	R, case series	1993–2005	Pediatric	ATL	Various	Q1, Q2, Q3
Heller [17]	2009	US	R, case series	1998–2005	Adult	ATL	–	Q3
Tanriverdi [18]	2009	Canada	R, case series	1976–2006	Adult	ATL +/- AH	–	Q3
Ipekda [19]	2010	Turkey	R, case series	2000–2010	Adult	ATL +/- AH	–	Q1, Q3
Srikijvithaikul [13]	2011	Thailand	R, case-control	2004–2009	Adult	ATL + AH	–	Q1, Q2, Q3
Engel [9]	2012	US	RCT	2003–2007	Adult	ATL	Medications	Q2, Q3
Lopez-Gonzalez [20]	2012	US	R, case series	1996–2006	Pediatric	ATL +/- AH	–	Q2, Q3
Falowski [21]	2012	US	R, case series	–	Adult	ATL +/- AH	–	Q1, Q2, Q3
Iachinski [22]	2014	Brazil	R, case series	1998–2010	Adult	ATL / SelAH	–	Q3
Jayalakshmi [23]	2016	India	R, case series	2005–2014	Adult	ATL + SelAH	–	Q3
Nascimento [10]	2016	Canada	R, cohort	2005–2012	Adult	ATL (33)	SelAH	Q1, Q2, Q3
Pauli [24]	2017	Brazil	P, case series	2008–2014	Adult	ATL	–	Q3
Mathon [3]	2017	France	R, case series	1990–2015	Adult	ATL	SAH	Q2, Q3

R, retrospective; P, prospective; RCT, randomized control trial; ATL, anterior temporal lobectomy; AH, amygdalohippocampectomy; SelAH, selective amygdalohippocampectomy; Q1, mortality; Q2, seizure freedom; Q3, complications.

accessed in August 2018. Finally, the references of the resulting full texts were searched for further relevant citations.

Eligibility Criteria

We focused on RCTs, observational studies, and case series studies reporting at least four different types of complications after ATL for IE. The review process was limited in the English literature. In addition, we discarded editorials, reviews and meta-anal-

yses, underpowered studies (<5 patients), and studies focusing on specific complications (Table 3).

Study Selection

After duplicate removal, the two review authors (A.G.B. and T.G.) assessed the retrieved articles for title and abstract relevance, independently. Then, they evaluated their full texts, according to the eligibility criteria. Disagreement between the reviewers was re-

Table 4. Grading of the retrieved articles with regard to the quality of evidence

Question	Starting grade	Downgrade					Upgrade			Final grade
		risk of bias	inconsistency	indirectness	imprecision	publication bias	magnitude of effect	dose response	confounding factors	
Morbidity	4	-1	-1	0	0	-1	+1	0	0	2
Infection	4	0	-1	0	0	-1	0	0	0	2
Hemorrhage	2	0	0	0	0	-1	+1	0	0	2
Pyramidal/sensory tract/ language deficits	4	0	0	0	0	-1	+1	0	0	4
CSF-related	4	-1	0	0	0	-1	+1	0	0	3
Cranial fluid collections	2	0	0	0	0	0	0	0	0	2
VFDs	4	-1	-1	0	0	-1	0	0	0	1
CNDs	2	0	0	0	0	-1	+1	0	0	2
Cognitive deficits	4	-1	-1	0	0	-1	0	0	0	1
Psychiatric disorders	4	-1	0	0	0	-1	0	0	0	2
Medical complications	2	0	0	0	0	0	0	0	0	2
Other	4	-1	0	0	0	0	0	0	0	3
Mortality	2	0	0	0	0	-1	0	0	+1	2

VFDs, visual field defects; CNDs, cranial nerve deficits; CSF, cerebrospinal fluid.

Fig. 1. Study PRISMA flow diagram.

solved through discussion with the senior author (K.N.F.). The remaining studies formed the basis of our systematic review and meta-analysis. The process of study selection was outlined in a flowchart (Fig. 1).

Data Collection

Each study was identified by the name of the first author and the year of publication. Then we collected the following data: (1) the hosting country, (2) the type of study, (3) the size of patient sample and its demographic characteristics, (4) the number of patients who presented complications, including death, (5) patient characteristics related to their clinical status, and (6) technical details regarding the surgical procedure.

Quality Appraisal in Individual Studies and Overall Evidence

Two other review authors (E.K. and E.D.) performed the quality appraisal of the collected articles, independently, based on the type of the study. Thus, case series, observational studies, and RCTs were considered as “low,” “moderate,” or “high” quality studies, respectively. The quality of the overall body of evidence was assessed on each question, according to the GRADE working group as “high,” “moderate,” “low,” or “very low.” In the case of disagreement, the authors reached a consensus after consulting the senior author (K.N.F.).

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 interstudy heterogeneity was measured by the I^2 statistic. A value of I^2 less than 25% was regarded as low heterogeneity, 25–75% as moderate, and greater than 75% as severe heterogeneity. The results were visualized in forest plots. We estimated the risk for publication bias using the Egger’s regression test and “trim-and-fill” funnel plots. Subgroup analysis and meta-regression was used to identify differences between adults and children.

Table 5. Summary of evidence

	Studies (eligible population), <i>n</i>	Cases	Quality of pertinent evidence (GRADE)	Pooled proportion estimate (95% CI)	Rank	Pediatric considerations	Conclusions	Future recommendations
Morbidity	25 (2,842)	458	Low quality (⊕⊕○○)	0.17 (0.12, 0.24)	1	There is no difference between adult and pediatric series	There is a large body of low-quality evidence that there is a moderate risk for major of minor morbidity after ATL	Further evidence from high-quality studies is needed
Infection	20 (2,695)	60	Low quality (⊕⊕○○)	0.03 (0.02, 0.04)	8	There is no difference between adult and pediatric series	There is a large body of low-quality evidence that there is a minor risk for infections after ATL	Further evidence from high-quality studies is needed
Hemorrhage	9 (1,244)	18	Low quality (⊕⊕○○)	0.02 (0.01, 0.05)	9	Data is limited to adult population	There is a small body of low-quality evidence that there is a minor risk for hemorrhage after ATL	Further studies are needed to clarify the incidence of hemorrhage in pediatric populations
Pyramidal/sensory tract/language deficits	21 (2,345)	90	High quality (⊕⊕⊕⊕)	0.04 (0.03, 0.06)	5	There is no difference between adult and pediatric series	There is a large body of high-quality evidence that there is a minor risk for long tract signs and or language disorders after ATL	Further studies are needed to clarify the occurrence of language disorders and long tract signs independently
CSF-related complications	8 (991)	11	Moderate quality (⊕⊕⊕○)	0.02 (0.01, 0.04)	11	There is no difference between adult and pediatric series	There is a small body of moderate-quality evidence that there is a minor risk for CSF-related complications after ATL	Further evidence from high-quality studies is needed, especially in pediatric populations
Cranial fluid collections	5 (595)	11	Low quality (⊕⊕○○)	0.02 (0.01, 0.03)	12	Data is limited to adult population	There is a small body of low-quality evidence that there is a minor risk for extra-axial collections after ATL	Further evidence from high-quality studies is needed
VFDs	13 (1,608)	129	Very low quality (⊕○○○)	0.06 (0.03, 0.11)	3	There is no difference between adult and pediatric series	There is a moderate body of very-low-quality evidence that there is a moderate risk for VFDs after ATL	Further evidence from high-quality studies is needed
CNDs	14 (1,815)	36	Low quality (⊕⊕○○)	0.03 (0.02, 0.05)	7	Data is limited to adult population	There is a moderate body of very-low-quality evidence that there is a moderate risk for CNDs after ATL	Further evidence from high-quality studies is needed, especially in pediatric populations
Cognitive deficits	5 (825)	47	Very low quality (⊕○○○)	0.05 (0.02, 0.10)	4	Data is limited to adult population	There is a small body of very-low-quality evidence that there is a moderate risk for cognitive disorders after ATL	Further evidence from high-quality studies is needed, especially in pediatric populations
Psychiatric disorders	9 (836)	53	Low quality (⊕⊕○○)	0.07 (0.05, 0.09)	2	There is no difference between adult and pediatric series	There is a small body of low-quality evidence that there is a moderate risk for psychiatric disorders after ATL	Further evidence from high-quality studies is needed
Medical complications	8 (1,181)	17	Low quality (⊕⊕○○)	0.02 (0.01, 0.03)	13	There is no difference between adult and pediatric series	There is a small body of low-quality evidence that there is a minor risk for medical disorders after ATL	Further evidence from high-quality studies is needed
Other	4 (459)	17	Moderate quality (⊕⊕⊕○)	0.04 (0.02, 0.06)	6	Data is limited to adult population	There is a small body of low-quality evidence that there is a minor risk for other unclassified complications after ATL	Further evidence from high-quality studies is needed, especially in pediatric populations
Mortality	16 (2,382)	19	Low quality (⊕⊕○○)	0.01 (0.01, 0.02)	10	There is no difference between adult and pediatric series	There is a small body of low-quality evidence that there is a minor risk for death after ATL	Further evidence from high-quality studies is needed

ATL, anterior temporal lobectomy; VFDs, visual field defects; CNDs, cranial nerve deficits; CSF, cerebrospinal fluid.

Sensitivity analysis was performed after rerunning the meta-analysis without the “low” quality studies. We used the statistical environment R for all statistical analyses [12]. Significance was set at $p < 0.05$, and for complications associated with zero events, we used a continuity correction equal to 0.5.

Results

Literature Search

The literature search identified 25 studies with 2,842 patients that fulfilled our eligibility criteria (Fig. 1; Tables 4, 5). There were 2 RCTs [8, 9] (8%), 4 observational studies [10, 13–15] (16%), and 19 case series [3, 16–32] (76%)

among the retrieved articles. Eighteen studies (72%) concerned adults, 4 studies concerned children (16%), while 3 (12%) reported on mixed populations. Most studies came from the US and Canada, with 7 (28%) and 4 (16%) studies, respectively. The median length of follow-up was 3 years (IQR: 2, 5 years).

Quality Assessment (Individual Studies/Overall Evidence)

The quality of the gathered individual studies was “high” in 2 studies (8%), “moderate” in 4 (16%), and “low” in 19 (76%). In addition, the overall body of evidence was found to be of “low” quality according to the GRADE recommendations [33]. Despite the presence of

Fig. 2. The mortality associated with anterior temporal lobectomy is estimated to be as high as 0.01 (95% CI: 0.01, 0.02). There is strong evidence that there is a high risk of publication bias in the pertinent literature.

Fig. 3. The postoperative morbidity was estimated to be as high as 0.17 (95% CI: 0.12, 0.24), in the presence of significant publication bias.

Fig. 4. Psychiatric disorders were the most common postoperative complication after anterior temporal lobectomy for intractable temporal lobe epilepsy, followed by visual field defects (VFDs) and cognitive disorders. CSF, cerebrospinal fluid; CNDs, cranial nerve deficits.

2 RCTs among the examined studies, the quality of the evidence was frequently downgraded after the identification of significant publication bias.

Mortality (Q1)

Sixteen eligible studies with 2,382 patients described 19 deaths after ATL for IE. The heterogeneity between studies was moderate ($I^2 = 48\%$, $p = 0.02$), while the postoperative mortality was estimated to be as high as 0.01 (95% CI: 0.01, 0.02). This result was based on a small number of low-quality studies; however, it was robust, since it did not change after eliminating the “low”-quality studies ($p = 0.486$). There were no differences in terms of mortality between adult and pediatric series ($p = 0.79$) (Table 5; Fig. 2).

Morbidity (Q2)

There were 458 complications recorded among the examined studies. There was significant interstudy heterogeneity ($I^2 = 92\%$, $p < 0.01$). The postoperative morbidity was estimated to be as high as 0.17 (95% CI: 0.12, 0.24).

However, this result was not robust, according to our sensitivity analysis ($p = 0.03$), and after stratifying it by study quality. Once again, the incidence of the postoperative complications showed no difference between adults and children ($p = 0.91$) (Table 5; Fig. 3, 4).

Individual Complications (Q3)

Frequently, there was inconsistency among the authors in reporting postoperative complications. However, we grouped them under eleven subheadings: infections, hemorrhage, hydrocephalus, hemiparesis and language deficits, visual field defects (VFDs), cranial nerve deficits (CNDs), hematomas, cognitive disorders, psychiatric disorders, medical complications, and other (Table 5, Fig. 2–6). Psychiatric disorders were the most common postoperative complication group, with an estimated frequency as high as 0.07 (95% CI: 0.04, 0.10), followed by visual field defects (0.06; 0.03, 0.11), and cognitive disorders (0.05; 0.02, 0.10). Less frequent complications included hemiparesis/hemiplegia and language disorders (0.03; 0.01, 0.06), infections (0.03; 0.02, 0.04), hemor-

Fig. 5. There has been a steady improvement in both mortality and morbidity after anterior temporal lobectomy for temporal lobe intractable epilepsy since its initial description. CNDs, cranial nerve deficits; VFDs, visual field defects.

rhage (0.02; 0.01, 0.05), cranial nerve deficits (especially trochlear nerve) (0.03; 0.02, 0.05), hydrocephalus and cerebrospinal fluid (CSF)-related disorders (0.02; 0.01, 0.04), extra-axial fluid collections (0.02; 0.01, 0.03), and medical complications (0.02, 0.01, 0.03).

Discussion

The present systematic review aimed to summarize the complications associated with ATL for IE, based on an electronic search of the pertinent literature. The latter was often of low reporting quality and characterized by significant clinical heterogeneity regarding the definitions of complications and the adopted screening tools.

Summary of Our Findings

Two RCTs have already proved the effectiveness of ATL in the management of patients with temporal IE [8, 9]. With the current meta-analysis, we demonstrated that it is also a safe procedure, with an estimated mortality and cumulative morbidity rate as high as 1 and 17%, respectively. In addition, the majority of the complica-

tions are limited to temporary psychiatric disturbances, cognitive disorders, VFDs, hemiparesis, hemiplegia, sensory deficits, or speech disorders. Another important finding of our current meta-analysis is that there are no significant differences with regard to the mortality and the cumulative morbidity between pediatric and adult populations.

Comparison with Other Studies

The findings of the present meta-analysis are comparable to the pertinent literature. Tebo et al. [34], performed a meta-analysis of 61 articles with a total of 5,623 patients, and reported that the overall neurological deficits, infections, and hemorrhages accounted for the majority of the postoperative complications, with a reported proportion estimate as high as 19, 1.4, and 1.3%, respectively. In addition, the authors have noticed that the complication rates had dramatically decreased over time (from 1980 to 2012), but unfortunately they remain an unavoidable consequence of resective epilepsy surgery. More specifically, neurological deficits progressively decreased from 41.8 to 5.2% among patients undergoing ATL or selAH. However, it is of note that

Fig. 6. The literature depicts global variations in the mortality and morbidity after anterior temporal lobectomy for temporal lobe intractable epilepsy. These differences might be confounded by the local registration systems, cross-cultural variations, and patient follow-up. VFDs, visual field defects; CNDs, cranial nerve deficits; CSF, cerebrospinal fluid.

the majority of the meta-analytic works focus on the effectiveness of the epilepsy surgery, rather than its safety [35–38].

Implication of our Findings in the Daily Practice

Knowledge of the perioperative mortality and morbidity is important for both the referring neurologist and the operating surgeon, when discussing with the candidate patient. Equally important is the familiarity of the epilepsy surgeon with the relative frequency of each of the potential complications, their preoperative screening examinations, and the basic modes to timely diagnose and promptly treat them. The best available evidence, together with the surgeon's experience, should be individually tailored to the surgical planning of each patient in order to achieve the optimal outcome [39, 40].

Hemiparesis and language disorders are the most serious complications after ATL, as they affect the quality of life and the patient's independence and occur with an estimated frequency as high as 4% (95% CI: 3, 6) [3, 8–10, 13, 14, 16, 17, 20–30, 32, 41]. They have been attributed to either direct intraoperative injury of the pyramidal tract, causing hemiparesis, and of the arcuate and/or the uncinate among other fasciculi resulting in speech difficulties, or to the development of vasospasm secondary to manipulation of the adjacent vessels (middle cerebral artery, and/or anterior choroidal artery) [42]. The importance of employing advanced MR imaging techniques, such as diffusion tensor imaging (DTI) and fractional anisotropy, may help in outlining the corticospinal tract and the speech-involved fasciculi, preoperatively [43]. In addition, the selective employment of intraoperative micro-

Doppler in high-risk patients may identify those who are predisposed to vasospasm development [44]. The early pharmacological treatment of these patients with nimodipine or other vasodilators could prevent the development of clinically symptomatic vasospasm, and thus prevent further neurological deterioration [45].

Postoperative cognitive [8, 15, 23, 26, 27] and psychological/psychiatric disorders [8, 15, 19, 26, 27, 29, 30, 32] are among the most common complications after ATL and occur with an estimated frequency as high as 5% (95% CI: 2, 10) and 7% (95% CI: 4, 10), respectively. However, we believe that this figure underestimates the incidence of any postoperative psychological/psychiatric disorders, as this meta-analysis excludes series focusing on specific complications. Of note, some aspects like neuropsychological side effects have been studied quite seriously only in topic-specific publications [46–48]. This complication subgroup includes the decline of preoperative verbal and visual memory (especially on dominant hemisphere cases) [48], as well as exacerbation of a pre-existing or de novo development of psychosis, depression, obsession-compulsion, and anxiety disorders [49–51]. Early diagnosis of postoperative psychological and cognitive disturbances may help in their more efficacious management, and thus may improve the patients' overall outcome.

A thorough clinical psychiatric evaluation along with the employment of the proper neuropsychological battery should be considered preoperatively in order to detect any clinically occult cases. Proper preoperative identification of any predisposing to psychopathology factors (positive family history, mood disturbances, social adjustment difficulties) may help in the early diagnosis of such psychiatric complications and may help in their prompt treatment. Previous studies have identified as predisposing factors: patient's gender and laterality of resection, positive history of anxiety and/or depression disorders, positive family history for psychiatric disorders, presence of mood disturbances preoperatively, postoperative continuation of seizures, difficulty in postoperative psychosocial adjustment, diffuse preoperative epileptogenic area, and presence of secondary generalized, tonic-clonic seizures preoperatively [52]. The exact role of the side of resection, the extent of the mesial and neocortical temporal resection, the underlying histopathology, and the presence of previous temporal surgeries in the development of postoperative cognitive and psychiatric complications remains to be accurately defined in the future. Finally, these patients may benefit from tailored social and work therapy by improving their functional in-

dependence, thus minimizing their postoperative psychological distress.

Symptomatic homonymous quadrantanopsia is another side effect of ATL with an estimated frequency as high as 6% (95% CI: 3, 11) [3, 8, 15–17, 20, 23, 25–27, 30, 32]. Admittedly, this number seems to be a conservative representation of the actual VFD incidence. This is due to an observed heterogeneity of the definitions of the VFDs, a variability of the adopted screening tools in the pertinent literature, and an inherent weakness of our meta-analysis. The definition of VFDs was inconsistent in the literature, ranging from serious symptomatic homonymous quadrantanopsia to minor asymptomatic defects. In addition, early studies used manual kinetic perimetry examination, including Goldmann and Haimark examinations for the diagnosis of VFDs. Both allowed for a detailed mapping of the visual fields but are subjective and observer dependent. Later studies adopted automated static perimetry studies, either monocular or binocular [53–56]. The latter are more reproducible and easier to assess quantitatively [57, 58]. Finally, our meta-analysis excluded topic-specific series. The reported frequency of VFDs in these reports may be as high as 50%; however, with only 8% being symptomatic [58, 59].

The importance of symptomatic homonymous quadrantanopsia is related to difficulties in spatial orientation and particularly to driving issues. It occurs after injury to the anterior and inferior fibers of the Meyer's loop. Avoidance of extensive posterior dissection may minimize the occurrence of this complication, but at the expense of the effectiveness of surgery. On the other hand, preoperative advanced MR imaging, such as DTI, may identify the visual pathway and intraoperatively protect it without compromising the extent of resection [53–55]. Additionally, the intraoperative employment of visual evoked potential monitoring and application of direct subcortical electrical stimulation may further increase the accuracy of resection along the visual pathway, and thus may minimize the chance of postoperative VFDs [60].

Surgical complications are not very common after ATL, and include postoperative hematoma formation, hydrocephalus, CSF leakage, and procedure-related medical problems. They occur with an estimated cumulative rate of 1–2%. Although these complications are rare, improvement of the surgical technique, and proper patient selection may further decrease their incidence. Moreover, early mobilization of the patient, along with deep vein thrombosis prophylaxis may further minimize the incidence of any medical complications.

During our meta-analysis, we observed significant geographical variations of the postoperative mortality and morbidity (Fig. 5). Countries with high-volume centers reported significant complication rates, while their low-volume counterparts presented a safer profile. This paradox is partially explained by the retrospective nature of the recruited studies, which is associated with a significant information bias (including recall, attrition, and misclassification). In addition, our results were largely based on simple epidemiological studies, which are characterized by important selection bias (such as patient selection and selective referral). Finally, the presence of significant publication bias draws our attention to the selective reporting of positive outcomes; a fact that contradicts complication reporting. The role of sophisticated imaging techniques and intraoperative neurophysiological monitoring in optimizing the patient's outcome cannot be overemphasized. Likewise, surgical expertise and experience, which are associated with high-volume practice, may further mitigate the incidence of any procedure-associated complications. Thus, it would not be an overstatement that high-volume facilities are required for the safe management of these patients. It becomes evident that as global knowledge gradually accumulates, the overall morbidity after ATL decreases, a finding that supports our previous postulation (Fig. 5).

Study Limitations

The present meta-analysis has some important limitations. As the number of RCTs on ATL was very limited, we broadened our eligibility criteria in order to include observational studies and case series as well. In contrast to the traditional two-arm meta-analysis, the proportional meta-analysis summarizes a phenomenon related to a single parameter. Thus, all three of the above-stated study types could be safely used for extracting our conclusions. Nevertheless, we performed a sensitivity analysis after re-running our meta-analysis without the "low"-quality studies. The results were taken into consideration, while we evaluated the overall quality of evidence according to the GRADE recommendations. In addition, it needs to be emphasized that our results come from low-quality evidence.

Another limitation of this study was the presence of significant clinical heterogeneity, which was mainly related to the differences in the underlying pathology, target population, and extent of ATL among the included studies. This was verified by the identification of significant statistical heterogeneity, and interestingly, it persisted after stratifying our results according to the target pop-

ulation. Finally, there was no standardized method to report complications after ATL, and as a result, there were large variations among the definitions of each complication among the eligible studies. Thus, in order to deal with this form of heterogeneity, we had to redefine all complications, as presented in Table 1. However, this led to a necessity of listing heterogeneous complications as a common category. Hence, hemiparesis, hemianesthesia, and language disorders were presented as a single category, attributed to lesions of the central and speech-associated cortical areas. Similarly, there is another broad category of complications termed "CSF-related complications," which included both CSF leakage and hydrocephalus.

Future Perspectives

The need for consistent and uniform reporting of complications after ATL became evident during the current meta-analysis. Further evidence from high-quality studies is of paramount importance in order to improve the quality of the overall evidence, especially in pediatric populations. Finally, additional studies are needed to identify high-risk populations and technique modifications for complication prevention, timely diagnosis, and proper management.

Conclusions

ATL constitutes an extremely safe procedure, with mortality rates approaching zero. Postoperative cognitive and psychological deficits are the most common causes of morbidity after ATL and include a decline in the preoperative verbal and visual memory as well as exacerbation of a preexisting or a de novo development of psychosis, depression, obsessive-compulsive, and/or anxiety disorders. Their early detection may help in their more efficacious management and may improve the patients' overall outcome. Finally, proper identification of any factors preoperatively predisposing to psychopathology may help in the early diagnosis of such psychiatric complications and may assist in their prompt treatment. Postoperative VFDs represent another common ATL-associated complication, which is systematically underreported. Application of advanced MR imaging techniques, such as DTI and fractional anisotropy, and intraoperative neurophysiological monitoring may decrease their incidence. Neurological complications, including hemiparesis, and dysphasia/aphasia occur less frequently. The employment of advanced imaging modalities for delineating major sub-

cortical white matter tracts and intraoperative micro-Doppler for early detection of cerebral vasospasm may prevent or minimize the incidence of adverse postoperative neurological events. The importance of minimal and gentle manipulation of the adjacent vascular structures during resection cannot be overemphasized.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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