

Introduction

Electrographic seizures in the intensive care unit (ICU) are frequent and often subclinical. In a series of 570 patients (495 adults and 75 patients younger than 18 years of age) who underwent continuous EEG monitoring (cEEG), seizures were detected in 110 (19%), and seizures were exclusively nonconvulsive (subclinical) in 101 (92%) [1]. In a series of 550 pediatric patients (ages 1 month to 21 years) who underwent cEEG in the ICU, 162 (30%) had electrographic seizures, and 61 of 162 (38%) had electrographic status epilepticus (SE) [2].

Electrographic seizures and electrographic SE are increasingly recognized, and they are associated with worse outcomes in neonates [3–6], children [2, 4, 5, 7–9], and adults [10–12]. However, it is currently unknown whether they impact outcome or are a biomarker of a more severe underlying etiology, hence the lack of clear guidelines on how aggressively to treat them. This chapter aims to address this gap in knowledge by summarizing currently available literature on how electrographic seizures and electrographic SE influence outcome in different populations of critically ill patients.

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Continuous Electroencephalogram Monitoring

The burden of electrographic seizures in the ICU is increasingly recognized as cEEG becomes more available. cEEG monitoring is growing exponentially at a pace of approximately 30% per year both in adults [13] and children [14]. In a large series of 5949 adults (>17 years of age) with mechanical ventilation in the USA, cEEG use increased by 263%, and the number of hospitals reporting cEEG use nearly doubled from 135 to 244 over the 4-year study period between 2005 and 2009 [13]. cEEG use increased by an average of 33% per year—much more than the average 8% increase per year in routine EEG use during the same period [13]. A survey of pediatric neurologists from 50 US and 11 Canadian leading hospitals showed that cEEG use also increased by approximately 30% from August 2010 to August 2011 [14]. During that 1-year period, the number of patients with cEEG monitoring per month and per site increased from a median [and 25th and 75th percentiles (p_{25} – p_{75})] of 6 (5–15) to 10 (6.3–15) in the USA and from 2 (1–2.5) to 3 (2–4.5) in Canada [14]. ICUs are the main drivers of this increase in cEEG monitoring. A survey of 137 intensivists and neurophysiologists from 97 adult ICUs in the USA reported a 43% increase in the number of cEEG per month during a 1-year period [15]. Further, in an ideal situation with unlimited resources, respondents would monitor between 10 and 30% more patients (depending on specific cEEG indications), and 18% would increase cEEG duration [15].

However, resources are limited and relatively minor changes in cEEG monitoring strategies can lead to major differences in the rate of seizure detection and in costs [16], specifically by identifying patients at greatest risk. Using readily available variables, a proposed model can guide the use of limited resources to those patients who will benefit more from EEG monitoring [17]. In a cost-effectiveness analysis of electrographic seizures in the pediatric ICU, cEEG monitoring for 1 h, 24 h, and 48 h would identify 55%,

85%, and 89% of children experiencing electrographic seizures, respectively [18]. The preferred strategy (specifically, higher cost-effectiveness for detection of a patient with seizures) would be cEEG monitoring for 1 h if the decision-maker was willing to pay <\$1666, for 24 h if willingness to pay was \$1666–\$22,648, and for 48 h if willingness to pay was >\$22,648 [18]. Seizure detection is used as a surrogate end point for the real outcome of interest: outcome improvement. Several studies show that electrographic seizures and electrographic SE are independently associated with worse outcomes in neonates [3–6], children [2, 4, 5, 7–9], and adults [12, 19], but there is no conclusive evidence that early detection and treatment of electrographic seizures improves outcome [16]. However, a study showed that even minor improvements in outcome may make up for the tentative economic burden of cEEG monitoring [20]. If cEEG yielded an increase in quality-adjusted life years (QALYs) of as little as 3%, cEEG monitoring for 24 h would be more cost-effective than not performing an EEG or performing a one-hour EEG [20]. For QALY increases of 3–6%, both 24 h and 48 h monitoring (depending on willingness to pay per QALY) would be cost-effective compared to not performing an EEG or a one-hour EEG [20]. For QALY increases of more than seven percent cEEG monitoring for 48 h would be the more cost-effectiveness strategy [20]. Unfortunately, these cost-effectiveness data cannot be translated into objective clinical decision-making because there is no data on how much—if at all—detection and treatment of electrographic seizures influences outcome. Hence, there is an urgent need for high-quality and quantitative estimates of the influence of electrographic seizures on outcome.

Terminology

For the purposes of this review, we define electrographic seizures as abnormal, paroxysmal electroencephalographic events that differ from the background activity and evolve in frequency, morphology, and spatial distribution on EEG [21]. We classified seizures into electroclinical seizures when there is a clinical correlate and electrographic-only seizures when they are asymptomatic or have very subtle clinical features detected only during video-EEG review [21]. For the purposes of this overview, we refer to electrographic SE as uninterrupted electrographic seizures lasting at least 30 min or repeated electrographic seizures totaling more than 30 min in any 1 h period [2, 6, 9, 22, 23], although lower time thresholds like 5 min are gaining popularity following the literature on convulsive SE [24].

We only considered outcomes that were objectively defined in the primary studies such as in-hospital death, death at 30 days after an index event (such as stroke or sepsis), or functional outcomes defined with a widely used scale

such as the Glasgow Outcome Scale. The literature is skewed toward short-term outcomes, and this review reflects the available data. We focused our review on outcome data from adult studies.

Literature Search Methods

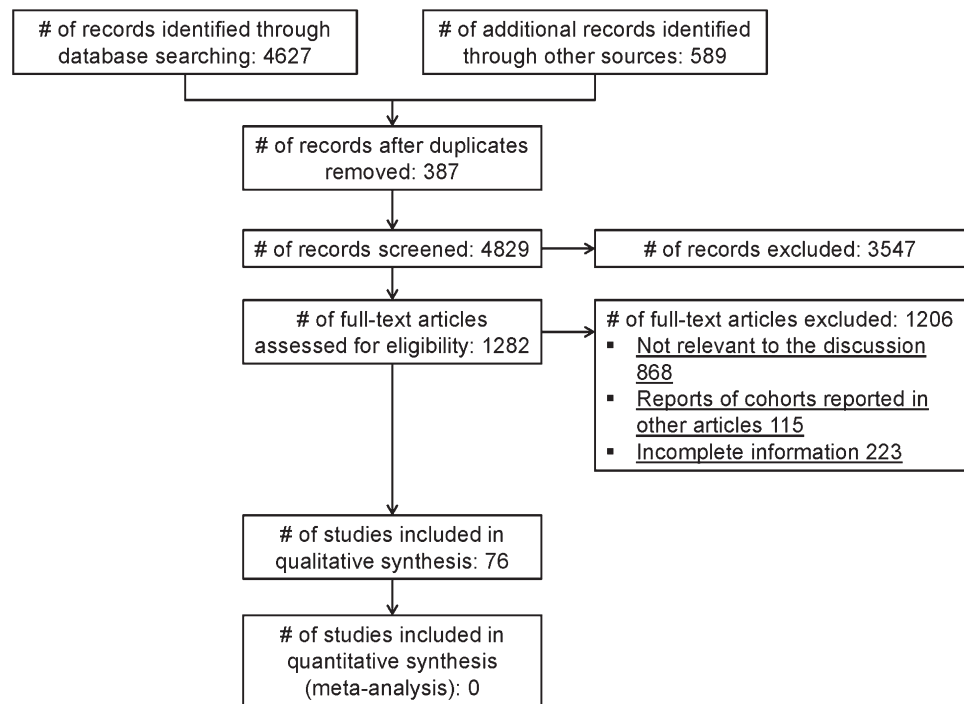
We performed a PubMed search up to September 2015 using different combinations of the following terms: “seizures,” “nonconvulsive seizures,” “electrographic seizures,” “epilepsy,” “critical,” “intensive care unit,” “sepsis,” “septic shock,” “traumatic brain injury,” “subarachnoid hemorrhage,” “stroke,” “brain infarct,” “intracranial bleeding,” “cardiac surgery,” “cardiac arrest,” and “brain tumor.” The initial searches returned 4627 articles. Additional 589 papers were identified from relevant articles from a manual search of cited references. After screening and exclusion of abstracts (and when relevant, full-text manuscripts), 76 articles were included in this literature review (Fig. 2.1).

Electrographic Seizures in the Intensive Care Unit

Electrographic seizures and electrographic SE are frequent and are often associated with poor outcome in critically ill patients [11]. In a study of 201 adults in a medical ICU without known acute neurologic injury, 21 patients (10%) had electrographic seizures, 34 (17%) had periodic epileptiform discharges, 10 (5%) had both, and 45 (22%) had either electrographic seizures or periodic epileptiform discharges [12]. Electrographic seizures were electrographic-only (not clinically detectable) in most patients (67%) [12]. After controlling for age, coma, renal failure, hepatic failure, and circulatory shock, the presence of electrographic seizures or periodic epileptiform discharges was associated with death or severe disability, with an odds ratio of 19.1 (95% CI, 6.3–74.6) [12]. In a large series of 5949 adult (>17 years) patients who underwent mechanical ventilation (as a proxy for ICU stay) and in whom a routine EEG or a cEEG was performed, the use of EEG was independently associated with lower in-hospital mortality (OR = 0.63, 95% CI, 0.51–0.76) with no significant difference in cost or length of stay [13].

However, electrographic seizures are not always an independent predictor of poor outcome. In a series of 247 adult (>17 years) patients presenting to the emergency department with seizures who either died in the emergency department or were admitted to the ICU, ten patients died in hospital, and nine were discharged to hospice for a total of 19 (7.7%) patients with a poor prognosis [25]. The causes of death (septic shock in three patients, cocaine-associated intracranial hemorrhage in two, cardiac death in two, ruptured

Fig. 2.1 PRISMA flowchart of the literature search methods and results



cerebral aneurysm in one, acute ischemic stroke in one, and ethylene glycol ingestion in one) suggest that the primary etiology and not the seizures was largely responsible for mortality [25]. Independent risk factors for poor outcome were early intubation (OR 6.44, 95% CI, 1.88–26.6) and acute intracranial disease (OR 5.78, 95% CI, 1.97–18.6) [25]. In contrast, presence of SE was not associated with a poor outcome in this series [25].

Whether electrographic seizures worsen outcome independent of the underlying etiology or whether they are just a biomarker of a more severe underlying lesion is a matter of ongoing discussions and study, and there are significant hurdles to appropriately answer this question best. First, the frequency of electrographic seizures reported in the literature is inherently biased due to confounding by indication as most patients only undergo cEEG when clinically indicated. A survey of 330 neurologists showed that the most common indications for performing cEEG monitoring in critically ill patients were altered mental status with or without seizures, subtle eye movements, acute brain lesion, and paralyzed patient in the ICU [26], but indications vary between and within centers. Second, patients might be misclassified as not having electrographic-only seizures because they occur prior to initiation of monitoring or after cEEG is discontinued. cEEG is most commonly used for at least 24 h if there are no electrographic seizures and, when detected, maintained for at least 24 h after the last seizure [26]. However, in certain populations such as patients with non-traumatic subarachnoid hemorrhage, the first seizure can occur later than 48 h [27] and might be missed when monitoring routinely for

24–48 h. Last, the impact of seizures on outcome might be etiology specific; electrographic seizures might cause marked outcome worsening in subarachnoid hemorrhage but not in brain tumors. Studies that analyze heterogeneous and broad etiologic categories jointly might bury associations in individual subgroups. In the following sections, we summarize the impact of electrographic seizures on outcome in different subgroups of critically ill patients (Tables 2.1 and 2.2).

Outcome in Sepsis

EEG background abnormalities and electrographic seizures are common in patients with sepsis [28]. In a series of 71 adults with septic shock, 43 patients underwent EEG for clinical signs of coma, delirium, or seizure, and 13 (30.2%) had electrographic seizures [29]. Based on the limited literature available, sepsis is a risk factor for electrographic seizures, and when patients present with seizures and sepsis, outcomes are poor. In a series of 201 patients admitted to the ICU for acute neurologic injury, sepsis on admission was the only independent predictor of electrographic seizures, and electrographic seizures were independent predictors of death or severe disability at hospital discharge with an OR of 19.1 (95% CI, 6.3–74.6) [12]. In another series, 100 of 154 adults in a surgical ICU developed sepsis, and among these patients 24 (15.6%) had electrographic seizures and 8 of 24 (33.3%) patients had electrographic SE [30]. Electrographic seizures (including electrographic SE) were independently associated with poor outcome (death, vegetative state, or severe

Table 2.1 Summary of studies that suggest that electrographic seizures independently worsen outcome

Author and year	Population	Main finding
Glass et al. [3], Lambrechtsen et al. [4], McBride et al. [5], Pisani et al. [6]	Neonates	Electrographic seizures and electrographic SE are independent predictors of poor outcomes
Abend et al. [2], Lambrechtsen et al. [4], McBride et al. [5], Gwer et al. [7], Payne et al. [8], Topjian et al. [9]	Children	Electrographic seizures and electrographic SE are independent predictors of poor outcomes
Oddo et al. [12], Foreman et al. [11], Claassen et al. [10]	Adults	Electrographic seizures and electrographic SE are independent predictors of poor outcomes
Vespa et al. [36]	Adults with TBI	Increase in brain extracellular glutamate during electrographic seizures
Vespa et al. [37]	Adults with TBI	Patients with electrographic seizures had higher elevations of intracranial pressure and lactate/pyruvate ratio than matched controls
Ko et al. [79]	Single adult post-cardiac arrest	Electrographic seizures were time-locked with reductions in brain tissue oxygen tension, increases in cerebral blood flow, and increases in brain temperature

SE Status epilepticus, TBI Traumatic brain injury

disability) at hospital discharge, with an OR of 10.4 (95% CI, 1–53.7) [30]. Further data are needed to evaluate the impact of electrographic seizures during sepsis on long-term outcome and to elucidate whether treatment modifies outcome.

Outcome in Traumatic Brain Injury

Electrographic seizures are frequent following traumatic brain injury (TBI) and are often associated with poor outcomes. In a series of 94 adults with moderate to severe TBI, electrographic seizures occurred in 21 (22.3%) patients including 6 with electrographic SE [31]. In this study, 11 of 21 (52.4%) patients had electrographic-only seizures [31]. Patients with electrographic seizures had similar outcomes as compared to patients without electrographic seizures, but the six patients with electrographic SE died (100% mortality), compared to 24% mortality in the non-seizure group [31], suggesting that the presence of SE (and not only the presence of seizures) was associated with worse outcomes.

Electrographic seizures following TBI are also frequent in children, especially during the first 2 years of life [32, 33]. In a series of 144 children with TBI and cEEG, 43 (29.9%) patients had electrographic seizures, 17 of whom had electrographic-only seizures [33]. The presence or absence of electrographic seizures or status epilepticus did not correlate with discharge outcome, classified in only three broad categories: death, discharge to rehabilitation facility, and discharge to home [33]. In a series of 87 children with TBI and

Table 2.2 Summary of the association of seizures with worse outcomes in different conditions

	Experimental models	Clinical studies: short-term outcomes	Clinical studies: long-term outcomes	Comments
Sepsis	?	+	?	Unclear whether electrographic seizures impact outcomes or just reflect a more severe underlying lesion
Traumatic brain injury	+	+	–	Unclear whether electrographic seizures impact outcomes or just reflect a more severe underlying lesion
Subarachnoid hemorrhage	+	+	+	The inflammatory cascade of blood products in the brain causes worse outcomes through electrographic seizures
Stroke (ischemic or hemorrhagic)	?	–	–	Electrographic seizures are not independent predictors of outcome in most studies
Cardiac surgery	?	+	+	Heterogeneous group with multiple potential confounders
Cardiac arrest	+	+	+	Electrographic seizures cause additional damage in the human brain
Tumor	–	–	–	Electrographic seizures more frequent in slow-growing tumors

+ Data supporting a positive association, – Data supporting lack of an association, ? Unknown/limited evidence

cEEG admitted to the ICU, 37 (42.5%) patients had electrographic seizures, 14 of whom had electrographic-only seizures [32]. Outcomes at hospital discharge—measured more precisely with the King's Outcome Scale for Childhood Head Injury—were worse in patients with clinical and subclinical SE, electrographic-only seizures, and electrographic SE [32].

Worse outcomes might simply reflect a more severe underlying etiology. However, some studies suggest that electrographic seizures contribute to poor outcomes. In a series of 140 patients with moderate to severe TBI and cEEG, 32 (22.9%) patients had electrographic seizures [34]. A subgroup of patients had volumetric MRI at baseline (within 2 weeks of TBI) and 6 months after TBI [34]. Among these, six had electrographic seizures and were compared with a control group of ten patients matched by Glasgow Coma Scale, CT lesion, and occurrence of surgery [34]. Patients with electrographic seizures had greater hippocampal atrophy on follow-up as compared to those without seizures (21% vs 12%, $p = 0.017$) [34]. Further, hippocampi ipsilateral to the electrographic seizure focus demonstrated a greater degree of atrophy as compared with contralateral hippocampi (28% vs 13%, $p = 0.007$) [34]. These data suggest that post-TBI electrographic seizures cause long-term anatomic damage [34].

The underlying mechanism by which post-TBI electrographic seizures cause worse outcomes may be related to the dysregulation between excitation and inhibition. In a mouse model of TBI, glutamate signaling was elevated and GABAergic interneurons were reduced following controlled cortical impact—an experimental equivalent to moderate to severe TBI [35]. In parallel, spontaneous excitatory postsynaptic current increased, and inhibitory postsynaptic current decreased after controlled cortical impact [35]. Similar dysregulation is described in humans. In a series of 17 adults with severe TBI, a microdialysis probe measured extracellular glutamate during the first week post-TBI [36]. Transient elevations in extracellular glutamate occurred during periods of decreased cerebral perfusion pressures of less than 70 mmHg, but also during seizures with normal cerebral blood perfusion [36]. Dysregulation of brain metabolism may elevate intracranial pressure and may lead to worse outcomes. A study in adults with moderate to severe non-penetrating traumatic brain injury evaluated cEEG and cerebral microdialysis for 7 days after the traumatic brain injury [37]. Matched for age, CT lesion, and initial Glasgow Coma Scale, ten patients with electrographic-only seizures (seven with electrographic SE) were compared with ten patients without electrographic seizures [37]. Patients with post-traumatic electrographic-only seizures experienced a higher mean intracranial pressure, a greater percentage of time of elevated intracranial pressure, and a more prolonged elevation of intracranial pressure beyond post-injury hour 100 as com-

pared with patients with no post-traumatic electrographic seizures [37]. Similarly, the lactate/pyruvate ratio was elevated for a longer period of time and more often in patients with post-traumatic electrographic-only seizures [37]. In ten patients with electrographic-only seizures, a within-subject design compared the time periods 12 h before seizure and 12 h after seizure onset within the same patients [37]. Seizures led to episodic increases in intracranial pressure, in lactate/pyruvate ratio, and in mean glutamate level [37]. These findings have been confirmed on a series of 34 patients with severe traumatic brain injury in whom brain microdialysis showed that the lactate/pyruvate ratio increased during seizures and pseudoperiodic discharges, but not during non-epileptic epochs [38]. These results suggest that intracranial pressure and lactate/pyruvate ratio go up in response to electrographic-only seizures, and not vice versa. Electrographic-only seizures may therefore not only represent a simple biomarker of brain damage, but may contribute to further brain damage, at least in the context of traumatic brain injury.

Prior studies suggest that seizures contribute to worse outcomes by causing additional damage. Therefore, prophylactic AED use to reduce seizure burden, and to improve outcomes, has been contemplated. However, a Cochrane review of randomized clinical trials found that AED prophylaxis in TBI reduced the risk of early seizures (within 1 week of TBI) but not late seizures or mortality [39]. In summary, post-TBI electrographic seizures lead to further brain damage, but to date there is lack of evidence that electrographic seizure control after TBI improves outcomes.

Outcome in Subarachnoid Hemorrhage

Electrographic seizures are particularly frequent and appear relatively late in patients with subarachnoid hemorrhage. Electrographic seizures occurred in 8 of 69 (11.6%) patients with non-traumatic high-grade subarachnoid hemorrhage [27]. In this study, the initial 17 patients underwent cEEG for clinical suspicion of electrographic seizures, which occurred in 3 (17.7%) patients [27]. The following 52 patients underwent cEEG as part of a protocol for subarachnoid hemorrhage, regardless of clinical suspicion, and electrographic seizures occurred in 5 (9.6%) patients [27]. Among the 35 patients monitored per protocol and without a clinical suspicion of seizures, electrographic seizures occurred in 3 (8.6%) patients [27]. While high clinical grade of the subarachnoid hemorrhage was associated with poor outcome, the presence of electrographic seizures was not [27]. In a series of 402 patients with subarachnoid hemorrhage, seizure burden was independently associated with outcome so that every hour of seizure on cEEG was associated with an OR of 1.1 (95% CI, 1.01–1.21) to 3-month disability and mortality [40].

In contrast, other studies showed an association between electrographic seizures and poor outcome. In a series of 479 adult patients with subarachnoid hemorrhage, 53 (11%) had electrographic seizures [10]. Patients with electrographic seizures had increased clinical and laboratory inflammatory biomarkers, and the degree of inflammation was an independent predictor of electrographic seizures [10]. On univariate analysis, both inflammatory burden during the first 4 days and the presence of electrographic seizures were associated with poor outcome [10]. But after correction for other potential confounders, only electrographic seizures remained a predictor of poor outcome [10]. Further, mediation analysis showed that the effect of inflammation on outcome was mediated through the presence of electrographic seizures [10]. In summary, this study suggests that blood products in the brain may trigger an inflammatory cascade which causes electrographic seizures and, eventually, poor outcomes [10].

The concept that inflammatory cascades cause or contribute to seizures, and these impact outcome, is clinically relevant because it implies that anti-inflammatory products may reduce seizures. In fact, targeted anti-inflammatory treatments have controlled seizures or brain damage in animal models. In a rat model of inflammation—induced either by intestinal inflammation which increases tumor necrosis factor alpha (TNF α) or by direct infusion of TNF α —neuronal excitability increased with severity of inflammation. Central antagonism of TNF α prevented increase in seizure susceptibility [41]. Further, in a rat model of subarachnoid hemorrhage, the administration of IL-1RA—an interleukin-1 (IL-1) antagonist—reduced blood-brain barrier breakdown and the extent of brain injury [42].

Despite promising animal models, anti-inflammatory therapy for seizure prevention in subarachnoid hemorrhage is not ready for clinical use. A more realistic goal in subarachnoid hemorrhage may be outcome prediction based on cEEG results. In a series of 116 patients on cEEG following subarachnoid hemorrhage and with 3 months functional follow-up (measured with the modified Rankin Scale), the absence of sleep architecture (OR, 4.3) and the presence of periodic lateralized discharges (OR, 18.8) independently predicted poor outcome [43]. Additionally, outcome was poor in all patients with lack of EEG reactivity or state changes within the first 24 h, generalized periodic epileptiform discharges, or bilateral independent periodic lateralized epileptiform discharges and in 92% of patients with nonconvulsive SE [43].

cEEG may not only predict, but it may also modify outcome in patients with subarachnoid hemorrhage by early detection of delayed cerebral ischemia. In a series of 34 patients with subarachnoid hemorrhage, 9 (26.5%) patients developed delayed cerebral ischemia [44]. Visual analysis of cEEG demonstrated new onset slowing or focal attenuation

in seven of nine patients with delayed cerebral ischemia (77.8%) [44]. Further, decreases in alpha power to delta power ratio identified patients with delayed cerebral ischemia with a very high sensitivity and a reasonable specificity: a cutoff of six consecutive recordings with more than 10% decrease in alpha power to delta power ratio from baseline yielded a sensitivity of 100% and a specificity of 76%; a cutoff of any single measurement with more than 50% decrease in the ratio yielded a sensitivity of 89% and a specificity of 84% [44]. In summary, cEEG detects electrographic seizures and/or delayed cerebral ischemia in patients with subarachnoid hemorrhage and in the appropriate clinical setting may improve outcomes.

Outcome in Stroke

Seizures occur frequently after stroke, particularly when it involves a hemorrhagic component or conversion from ischemic to hemorrhagic. In a study of 6044 patients with stroke, 190 (3.1%) patients experienced clinical seizures within the first 24 h, and these were more frequent in hemorrhagic than in ischemic stroke [45]. On univariate analysis, patients with seizures had a higher 30-day mortality rate than patients without seizures (32.1% vs 13.3%) [45]. Clinical seizures might represent only “the tip of the iceberg” as electrographic-only seizures might be overlooked without cEEG monitoring. In a series of 109 patients with stroke, electrographic seizures within 72 h occurred in 21 (19.3%) patients: 18 of 63 (28.6%) patients with intracranial hemorrhage, and in 3 of 46 (6.5%) patients with ischemic stroke [46]. On univariate analysis, posthemorrhagic seizures worsened the NIH Stroke Scale and increased midline shift [46]. However, on multivariate analysis, seizures did not independently predict outcome [45, 46]. Similarly, clinical seizures within 30 days of non-traumatic supratentorial hemorrhage occurred in 57 of 761 (7.5%) patients, but seizures were not independent predictors of in-hospital mortality [47]. In concordance with these results, electrographic seizures occurred in 32 of 102 (31%) adults with non-traumatic intracerebral hemorrhage who underwent cEEG monitoring [48]. In this series, 20 (20%) patients died in the hospital, and 5 patients had poor neurological outcome including coma, persistent vegetative state, or minimally conscious state [48]. Independent factors associated with poor outcome (defined as death, vegetative or minimally conscious state) at hospital discharge were coma at the time of hospital admission (OR 9, 95% CI, 2.4–34.3), intracranial hemorrhage volume of 60 ml or more (OR 4.4, 95% CI, 1.2–15.7), presence of periodic epileptiform discharges (OR 7.6, 95% CI, 2.1–27.3), periodic lateralized epileptiform discharges (PLEDs) (OR 11.9, 95% CI, 2.9–49.2), and focal stimulus-induced rhythmic, periodic, or ictal

discharges (SIRPIDs) [48]. In this series, lower systolic blood pressure on admission was protective (OR 0.9, 95% CI, 0.9–1 per mmHg), but the presence of electrographic seizures did not influence outcome [48]. In summary, after non-traumatic intracranial hemorrhage, clinical seizures occur in approximately 3–8% of patients, but many seizures are subclinical, and EEG detects electrographic seizures in approximately 20–30% of patients. However, based on available data, seizures were not independent predictors of outcome.

Further, seizures were also not clearly associated with acute deterioration following stroke. In a series of 266 patients with non-traumatic intracranial hemorrhage, early neurological deterioration occurred in 61 (22.9%) patients and was associated with an eightfold increase in poor outcome; however, seizures were not a predictor of early neurological deterioration [49].

Considering more detailed outcome features, late seizures are weakly associated with subsequent development of epilepsy. In a series of 1897 patients with stroke, seizures occurred in 168 (8.9%) patients: 28 of 265 (10.6%) patients with hemorrhagic stroke and 140 of 1632 (8.6%) patients with ischemic stroke [50]. Recurrent seizures occurred in 47 of 1897 (2.5%) patients with late first seizure onset as sole risk factor for epilepsy following ischemic stroke. In this series, the authors did not find risk factors following hemorrhagic stroke [50]. Mechanistically, early seizures may frequently reflect brain irritation by blood products, while late seizures may often be related to gliosis and scarring [51]. In a series of 110 patients who underwent clot evacuation after intracerebral hemorrhage, the frequency of seizures was particularly high, occurring in 41%: early-onset seizures (within 2 weeks) in 31% and late-onset seizures in 10% [52]. Independent predictors of early-onset seizures were volume of hemorrhage, presence of subarachnoid hemorrhage, and subdural hemorrhage, and independent predictors of late-onset seizures were subdural hemorrhage and increased admission international normalized ratio (INR) [52]. These results suggest that the severity of the bleeding is related to seizure development. Therefore, these authors recommended prophylactic antiepileptic therapy for patients with severe intracranial hemorrhage [52]. However, the value of AEDs in intracranial hemorrhage remains unclear. In a study where 5 of 295 (1.7%) patients with intracranial hemorrhage had seizures, the use of AEDs was an independent risk factor for poor outcome after 90 days [53]. The deleterious effects of stroke and SE appear to act synergistically, so that mortality is three times higher when there is SE on an ischemic stroke compared to when there is only an ischemic stroke [54]. In summary, poststroke seizures are not independent predictors of outcome [50, 51], and their treatment does not necessarily improve prognosis [53]. However, the presence of SE may worsen prognosis, especially in ischemic stroke [54].

Outcome After Cardiac Surgery

Seizures after cardiac surgery are relatively frequent, especially in neonates, and are associated with worse short-term outcome in most studies. In a series of 2578 patients who underwent cardiac surgery, clinical seizures occurred in 31 (1.2%) cases [55]. Compared to patients without seizures, patients with seizures experienced an almost fivefold increase (29% vs 6%) in in-hospital mortality, a higher incidence of all major postoperative complications, and a lower one-year survival rate (53% vs 84%) [55]. In contrast, a study of 101 adult patients (>18 years) who underwent subhairline cEEG after cardiac surgery found that 3 (3%) had electrographic seizures—two electroclinical and one electrographic-only—but the presence of electrographic seizures did not affect morbidity or mortality [56]. Of note, lack of correlation between electrographic seizures and outcome in this particular study may have been related to a limited EEG montage utilizing a four-channel subhairline EEG applied in the frontal and temporal regions with a typical sensitivity of 68% (95% CI, 45–86%) and a specificity of 98% (95% CI, 89–100%) for detecting seizures as compared to a regular 10–20 electrode placement [56, 57]. Further, only three patients had seizures, limiting statistical analyses in the series [56].

In newborns, electrographic seizures following cardiac surgery are particularly frequent and associated with worse short-term outcomes. Thirteen of 161 (8%) neonates undergoing cardiac surgery had seizures, and these were electrographic-only seizures in most patients (11; 85%) [58]. Acute mortality was higher among neonates with seizures (38% vs 3%) [58]. In contrast, the effect of electrographic seizures on more subtle outcomes, such as neurodevelopmental outcomes, remains to be defined. From a series of 164 survivors of neonatal cardiac surgery, 114 underwent developmental evaluation utilizing Bayley Scales of Infant Development II at 1 year of age [59]. Electrographic seizures occurred in 15 of 114 (13%) patients, but developmental outcomes were not different in patients with and without a history of seizures [59]. However, cEEG after cardiac surgery might help in delineating short-term outcomes. In a series of 723 adults who underwent cardiac surgery, neurological dysfunction within 24 h after surgery occurred in 12 patients: five did not regain consciousness after surgery, four had a clinical event suspicious for seizure, and three had neurological deficits [60]. Among the five patients who did not regain consciousness, two (40%) were in electrographic-only SE: one died during hospitalization, and the other received aggressive treatment for electrographic-only seizures and was discharged to an acute rehabilitation facility [60]. Among the 12 patients with neurological dysfunction, 5 (42%) patients died during the admission, 4 (33%) were dis-

charged home, and 3 (25%) were discharged to an acute rehabilitation facility [60]. Numbers are small to evaluate whether cEEG results can reliably predict outcomes, but among the five patients with an EEG reactive to noxious stimuli, some were discharged home (three patients) or to an acute rehabilitation facility (two patients), while among the seven patients with a nonreactive EEG, five (71%) patients died [60]. It is likely that some of these poor outcomes can be attributed to relatively high frequency of stroke in children undergoing cardiac surgery [61, 62].

Outcome After Cardiac Arrest

Electrographic SE is common after cardiac arrest. A study of 101 adults on therapeutic hypothermia and cEEG following cardiac arrest found that electrographic SE occurred in 12 (12%) patients [63]. In this series, electrographic SE marked a poor prognosis with only 1 of 12 (8%) patients surviving—in a vegetative state [63]. In a study of children with therapeutic hypothermia after cardiac arrest, 9 of 19 (47.4%) children had electrographic seizures, of whom 6 had electrographic SE [64]. In this study five patients died: three with severely abnormal EEG backgrounds and electrographic seizures and two with mild/moderate EEG backgrounds and without seizures [64]. In a series of 106 adults on therapeutic hypothermia and cEEG after cardiac arrest, 33 (31%) patients had electrographic SE [65]. One year after cardiac arrest, 31 (29%) patients had favorable outcomes, and electrographic SE was the most relevant predictive factor of poor outcome [65]. cEEG helps to predict both good and poor outcome after cardiac arrest: in a series of 56 adults on therapeutic hypothermia and cEEG after cardiac arrest, 27 (48%) patients had a good neurological outcome, and 29 (52%) patients had a poor neurological outcome [66]. Low-voltage or isoelectric EEG patterns within 24 h of cardiac arrest predicted poor neurological outcome with a sensitivity of 40%, a specificity of 100%, a negative predictive value of 68%, and a positive predictive value of 100% [66]. Low-voltage or isoelectric EEG patterns predicted poor neurological outcome better than bilateral absent N20 responses with a sensitivity of 24%, a specificity of 100%, a negative predictive value of 55%, and a positive predictive value of 100% [66].

However, cEEG is resource-intensive. Therefore, reduced EEG montages and automated EEG analyses are being evaluated as a cheaper approach for outcome prediction after cardiac arrest [67]. Reduced versions of the EEG such as continuous amplitude-integrated EEG predict outcome as demonstrated by a series of 95 adults on therapeutic hypothermia, regular cEEG, and amplitude-integrated cEEG after cardiac arrest [68]. In this series, an initial flat amplitude-integrated EEG did not have prognostic value, but a continuous EEG pattern at the start of the recording was associated

with recovery of consciousness in 87% of the patients, a continuous EEG pattern at normothermia was associated with recovery of consciousness in 90% of the patients, and suppression burst was always associated with eventual death [68]. Myoclonic SE after cardiac arrest has been classically considered incompatible with good outcome. However, in the era of therapeutic hypothermia, a growing body of evidence shows that some patients may recover after myoclonic SE following cardiac arrest [69–78].

Electrographic seizures, as well as abnormal EEG background patterns, may simply be a marker of severity for the underlying encephalopathy. However, some results suggest that electrographic seizures independently contribute to brain damage and worse outcomes. In an 85-year-old patient who underwent hypothermia and multimodality monitoring after cardiac arrest, 17 electrographic seizures were time-locked with reductions in brain tissue oxygen tension, increases in cerebral blood flow, and increases in brain temperature [79]. These metabolic derangements normalized during interictal periods and after AED treatment stopped the seizures [79]. Therefore, electrographic seizures may impose an increase metabolic demand which cannot be met in the already damaged brain leading to further tissue damage. More importantly, these findings suggest that timely treatment of seizures might halt additional damage.

Outcome in Tumors

Clinical seizures are one of the most common presenting symptoms of intracranial tumors. Seizures occur more frequently in slow-growing tumors than in aggressive tumors—hence the fact that seizures may sometimes be actually considered to be a marker of good prognosis in brain tumors [80]. Seizures are also a marker of tumor recurrence after surgical resection. In a series of 332 adults who underwent initial surgery for low-grade gliomas, 269 (81%) had at least one clinical seizure before surgery [81]. Seizure freedom after resective surgery occurred in 67% of patients and was more frequent among those with gross-total resection than after subtotal resection or biopsy [81]. Seizure recurrence after initial postoperative seizure control was a marker of tumor progression with a proportional hazard ratio of 3.8 (95% CI, 1.74–8.29) [81].

It is unclear how aggressive electrographic-only seizures should be treated. In a series of 947 EEGs in 658 patients with tumors, 26 episodes of electrographic SE were found in 25 patients [82]. Among these, 11 (44%) patients had a primary brain tumor, 12 (48%) patients had a systemic tumor, and 2 (8%) had both [82]. Fifteen of 25 (60%) patients with electrographic SE had a new intracranial lesion defined as progression of neoplastic disease or a new unrelated lesion [82]. In this series, 3 of 25 (12%) patients died during

electrographic SE, but more aggressive AED treatment was not pursued as the patients received comfort care in a terminal disease [82]. Based on limited literature, electrographic seizures associated with tumors likely represent a marker of the underlying pathology and do not significantly alter outcome.

Pediatric Outcome

Electrographic seizures are frequent in critically ill children, occurring with a frequency of 7–46% depending on indications and clinical settings [8, 83–87]. However, it remains unclear whether electrographic seizures worsen outcome or they are mere biomarkers of a more severe underlying etiology. In a study of children in coma, 74 of 204 (36.3%) had electrographic seizures, and they independently predicted poor outcome with an OR of 15.4 (95% CI, 4.7–49.7) [88]. In a series of children who underwent cEEG, 84 of 200 (42%) had electrographic seizures, and 43 had electrographic SE [9]. In this study, electrographic seizures were not an independent predictor of mortality, but electrographic SE was with an OR of 5.1 (95% CI, 1.4–18) [9]. Therefore, the presence of SE may be independently associated with worse outcomes. In particular, in a series of 259 children with EEG monitoring, electrographic seizures occurred in 93 (35.9%) and electrographic SE in 23 patients [8]. Above a maximum seizure burden threshold of 20%—12 min—per hour, both the probability and the magnitude of neurological decline rose sharply [8]. On multivariable analysis, the odds of neurological decline increased by 1.13 (95% CI, 1.05–1.21) for every 1% increase in maximum seizure burden per hour [8].

Seizure burden or severity is also associated with poor outcomes in newborns [5]. In a series of 77 term newborns at risk for hypoxic-ischemic brain injury, the presence and severity of clinical seizures was an independent predictor of motor and cognitive poor outcome [3]. In a series of 56 newborns treated with hypothermia, seizures occurred in 17 (32.7%) and electrographic SE in 5 [89]. Moderate to severe brain injury was more common in newborns with seizures with a relative risk of 2.9 (95% CI, 1.2–4.5), and electrographic-only seizures were associated with injury as electroclinical seizures [89]. In a series of 218 term infants with moderate to severe neonatal encephalopathy, children with no seizures on amplitude-integrated EEG had a higher incidence of death and severe neurodevelopmental disability at 18 months of age with an OR of 1.96 (95% CI, 1.02–3.74) [90].

Conclusions

Electrographic seizures are common (10–40%) in critically ill newborns, children, and adults, and most cannot be detected without an EEG. It remains unknown whether elec-

trographic seizures worsen outcomes independently from the underlying cause, but available literature to date suggests an independent impact on outcome. Treatment may also have to be tailored taking underlying etiology into consideration.

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