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Effect of epileptic activity on outcome for critically ill patients



Continuous electroencephalography (EEG) recordings of critically ill patients commonly show epileptiform activity. Such continuous EEG recordings have shown frequency of seizures to vary between 8% and 34%, most of which are non-convulsive.¹⁻³ Other subtypes of epileptiform activity are also common in critically ill patients, including periodic and rhythmic patterns (eg, generalised and lateralised periodic discharges, generalised and lateralised rhythmic delta activity, and bilateral independent periodic discharges).⁴ Generalised epileptic seizures should be promptly and effectively treated to prevent escalation into status epilepticus, but treatment decisions for short-lasting epileptiform bursts or milder epileptic activities are not always straightforward.⁵ Several factors affect the decision making process regarding treatment intensity, including patient's age and previous diseases, cause of presenting disease, present general clinical condition, and duration of intensive care. The decisions are often made case-by-case on the basis of all forementioned factors.⁶ Growing evidence suggests that the presence of epileptic activity is associated with worse outcome,^{7,8} but it is not clear whether this is due to severity of underlying illness, medication side-effects, or worsening of epileptiform activity per se.⁹ The role of epileptiform activity in neurological outcome is very challenging to study, mostly due to a plethora of confounding factors and the complex interaction between the underlying disease, type of epileptiform activity, and antiepileptic medication.

The study by Harsh Parikh and colleagues¹⁰ in *The Lancet Digital Health* takes an important step forward in clarifying this clinically highly relevant question. Parikh and colleagues did a retrospective cross-sectional study with 995 patients, using a novel causal inference approach to adjust the treatment effect of antiseizure medication and to evaluate the effect of epileptiform activity on neurological outcome. Epileptiform activity was detected from continuous EEG with an automated algorithm, and several confounding factors were considered in the analysis, including pharmacokinetics and pharmacodynamics models. The patients' drug responsiveness was estimated with a pharmacokinetic model adjusted for fixed drug half-lives, and with a pharmacodynamic model using the Hill coefficient and the dose to reduce epileptiform activity burden by

50%. All covariates (ie, demographics, clinical factors, admission diagnosis, and drug response parameters) were used for matching each patient to patients with similar covariates. Importantly, the matching was not based on proxies as is the case in the propensity-score approach, but rather based directly on these covariates. Although the approach of Parikh and colleagues might appear somewhat complicated, it allowed physicians to verify the quality of every analysis step instead of relying on purely data-driven models.

The results of this study show that epileptiform activity burden correlates to neurological outcome after adjusting for antiseizure medications.¹⁰ These results are in line with existing data showing that extensive epileptiform activity is associated with poor outcomes and provides outcome estimation based on quantification of the burden of epileptiform activity, which is clinically very useful. Patients with high levels of epileptic activity had a 22.27% (SD 0.92) increased chance of severe disability or death, and patients with moderate but long-lasting epileptic activity had a 13.52% (1.93) increased risk of a poor outcome. Subgroup analysis showed that the type of brain lesion mattered. Namely, patients with hypoxic-ischaemic encephalopathy or brain trauma were at higher risk of the worse outcome in response to a large maximum epileptiform activity burden.

Parikh and colleagues included several confounding factors in their analysis, although it is very challenging to account for all possible confounding factors in this type of study. For example, possible spread and type of epileptiform activity is likely to be associated with the outcome. Here, all subtypes of epileptiform activity were included in evaluation of epileptiform activity burden, although, for example, lateralised periodic discharges have been shown to have a high association with seizures, whereas generalised rhythmic delta activity has not.⁴ Furthermore, in critically ill patients, several antiepileptic medications and anaesthetics are often used, particularly if EEG shows extensive epileptic activity. Interaction of different antiepileptics is common, and it might profoundly affect drug elimination and efficacy.

Nevertheless, this study gives important insight to the complex association between epileptiform activity, drug effect, and neurological outcome. The results underline

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the importance of continuous EEG monitoring in patients in the intensive care unit and encourages timely treatment decisions in case short-lasting extensive or longer-lasting moderate epileptiform activity is observed. These promising results hopefully make way for larger, multicentre studies that would help to develop different treatment protocols tailored for patient groups with different CNS pathologies and other covariant factors.

We declare no competing interests.

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