All That Shakes Is Not Status Epilepticus

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Misdiagnosis of Prolonged Psychogenic Non-epileptic Seizures as Status Epilepticus: Epidemiology and Associated Risks

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Objective: This study aims to determine the epidemiology of prolonged psychogenic non-epileptic seizures (pPNES) misdiagnosed as status epilepticus, as well as the risks associated with non-indicated treatment. Methods: We performed an individual patient data analysis from the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) and the Established Status Epilepticus Treatment Trial (ESETT) to assess incidence, patient characteristics, and clinical course of misdiagnosed pPNES. Results: Among 980 patients aged 8 years or older diagnosed and treated for status epilepticus in RAMPART and ESETT, 79 (8.1%) were discharged with a final diagnosis of pPNES. The relative incidence was highest in adolescents and young adults (20.1%). The typical female preponderance seen in that age bracket was not evident in children and older adults. Adverse effects, including respiratory depression and intubation, were documented in 26% of patients with pPNES receiving benzodiazepines in RAMPART and 33% of patients receiving additional second-line medication in ESETT. In ESETT, patients who were treated with benzodiazepines before hospital admission had higher rates of unresponsiveness and severe adverse effects than those treated after admission, suggesting cumulative effects of accelerated treatment momentum. Across trials, one in five patients with pPNES were admitted to an intensive care unit. Conclusions: Misdiagnosis and treatment of pPNES as status epilepticus are a common and widespread problem with deleterious consequences. Mitigating it will require training of emergency staff in semiological diagnosis. Status epilepticus response protocols should incorporate appropriate diagnostic re-evaluations at each step of treatment escalation, especially in clinical trials.

Commentary

Psychogenic non-epileptic seizures (PNES) are frequently encountered in emergency departments (ED). When prolonged (pPNES), they can be misdiagnosed and mismanaged as status epilepticus (SE), frequently with deleterious consequences for these patients. This manuscript[1] analyzed data from the 2 largest SE treatment trials to date (RAMPART: Rapid Anticonvulsant Medication Prior to Arrival Trial[2] and ESETT: Established Status Epilepticus Trial[3,4]) to characterize the epidemiology and risks associated with that phenomenon.

RAMPART was a double-blind, randomized, noninferiority trial comparing the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in SE treated by paramedics. Eligible subjects had convulsions that persisted for more than 5 minutes and were still convulsing after paramedics arrived.[2] ESETT was a randomized, blinded, adaptive trial comparing the efficacy and safety of 3 intravenous anticonvulsive agents (levetiracetam, fosphenytoin, and valproate) in children and adults with convulsive SE unresponsive to treatment with benzodiazepines. Eligible subjects had been treated with a generally accepted cumulative dose of benzodiazepines for generalized convulsions lasting more than 5 minutes and continued to have persistent or recurrent convulsions in the ED between 5 and 30 minutes after the last dose of benzodiazepines.[3,4] Hence, none of these studies required an emergent clinical evaluation by a neurologist nor electroencephalographic (EEG) confirmation. The adjudication of pPNES in both trials was performed post-hoc by expert neurologists based on medical record reviews.

Focusing on children > 8 years old and adults, the investigators of this sub-analysis estimated the cumulative incidence of pPNES as 8.1% in the 980 patients studied, reaching its zenith of 20.1% in adolescents and young adults (15–29 years). Females dominated most age groups aside for the age extremes. In RAMPART, where first-line treatment with benzodiazepines was evaluated, 15% required admission straight to the intensive care unit (ICU) and 26% to the regular nursing floor. 26% of the pPNES patients manifested adverse effects related to their treatment, including respiratory depression and intubation. In ESETT, where second-line treatment with anticonvulsive agents was evaluated, 31% were admitted to the ICU and 36% were

admitted to the floor. Adverse events, including intubation, were seen in 33% of these patients and were overall graded as more severe for those patients (55%) who received benzodiazepines prior to ED arrival, suggestive of cumulative effects of rapid treatment escalation. Jointly in both trials, 30 adverse events were recorded in 29% of patients with pPNES.[1]

Limitations of the study are the post-hoc adjudication of pPNES from descriptions provided in medical records, often by non-neurologists, without available video or EEG recordings, which has been previously shown to suboptimally distinguish between epileptic and psychogenic (or other) non epileptic events.[5] The possibility that some patients with pPNES may have had a placebo response to administered anticonvulsants cannot be excluded. While all these might have resulted in misclassification, it represents the harsh reality of unavailable clinical and neurophysiological expertise in most emergency settings. It is also possible that some of the admission decisions and adverse events observed were related to institutional resources and practices, but both studies exhibited broad enrollment. The somatization tendency in PNES makes patients more prone to report allergies and comorbidities[6] which could have played a role in the high rate of identified adverse events. While certain demographic variables were collected, the available data cannot adequately provide a comprehensive profile of this subgroup, though this was not the primary intent of the original trials nor the current sub-analysis. Finally, the focus of this investigation was on convulsive pPNES, while hypomotoric pPNES can also pose a diagnostic dilemma; yet, hypermotoric pPNES are overwhelmingly more common[7] and provoke a treatment imperative.

These limitations notwithstanding, this study highlights that pPNES are frequently encountered in the emergent setting and that they are commonly misdiagnosed and mismanaged. PNES status, arbitrarily defined as > 30 minutes duration, has been described in up to 78% of patients with PNES, and it is commonly recurrent.[8] There are no robust data that these patients are demographically and phenomenologically different than those with short-lasting PNES, aside for an earlier and more dramatic presentation[9] and a higher tendency to self-harm.[8] PNES status is typically an escalation of a pre-existing diagnosis of PNES and tends to be semiologically alike.[7] To complicate matters more, 12% of them have comorbid epilepsy,[7] akin to the overall population with PNES. Adverse effects can occur in the acute setting as part of unnecessary interventions (e.g., lumbar punctures, placement of central lines, intubation, and drug administration).[7] That results in unnecessary hospitalizations, some of which include an ICU stay, with substantial somatic, psychological, and financial repercussions to the patients, their families, and the health system, in terms of resource allocations.[9]

What can we do though to mitigate these repercussions? First, we need to raise awareness in first responders and ED healthcare providers and instill in them the possibility of PNES when they encounter a shaking patient.[1] In simple words, "all that shakes is not status epilepticus." Second, we need to educate them on the value of careful semiological analysis at the bedside that includes key phenomenological features (e.g., closed eyes, side-to-side head movements, asynchronous limb movements, rotation in bed, opisthotonus, and fluctuating course).[10] In an era where smart phones provide instant access to video recordings and telemedicine is rapidly occupying a bigger share of medical practice worldwide, acquiring an expert opinion by a neurologist in a SE scenario similar to acute stroke codes should not be a far-fetched goal. The use of quickly applicable probability scores[6] to differentiate PNES from epileptic seizures (ES) based on pre-existing characteristics may further assist in decision making and facilitate the creation of medical-alert tags in the electronic records of patients with recurrent admissions. Where available, the application of rapidly applied by untrained personnel limited EEG recordings that can be wirelessly transmitted or automatically interpreted through reliable algorithms may add further value to avoid unnecessary initiation or escalation of treatment. Postictal laboratory biomarkers such as prolactin, creatine kinase, and leukocytosis that tend to be normal in PNES could be used as an adjunct,[7] though their collection and elevation is often delayed. Most importantly, patients with PNES should be diagnosed promptly and treated appropriately in the outpatient setting, so that this diagnostic dilemma does not cross the ED doors.[7] On the research realm, the misclassification of patients provides an impetus for redesigning future SE trials,[1] but also focusing on this subset of patients with pPNES, with a goal to proactively distinguish them from the overall population with PNES, to highlight those more vulnerable to iatrogenic harm, and to identify their optimal treatment plan.

By Ioannis Karakis

ORCID iD

Ioannis Karakis https://orcid.org/0000-0001-5122-7211

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