



Can Treating Patients With PNES Lower the Risk of Sudden Unexpected Death?

Epilepsy Currents

2021, Vol. 21(2) 87-89

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DOI: 10.1177/1535759720988544

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Mortality in Patients With Psychogenic Nonepileptic Seizures

Nightscales R, McCartney L, Auvrez C, et al. *Neurology*. 2020;95(6):e643-e652. doi:10.1212/WNL.0000000000009855

Objective: To investigate the hypothesis that patients diagnosed with psychogenic nonepileptic seizures (PNES) on video-EEG monitoring (VEM) have increased mortality by comparison to the general population. **Methods:** This retrospective cohort study included patients evaluated in VEM units of 3 tertiary hospitals in Melbourne, Australia, between January 1, 1995, and December 31, 2015. Diagnosis was based on consensus opinion of experienced epileptologists and neuropsychiatrists at each hospital. Mortality was determined in patients diagnosed with PNES, epilepsy, or both conditions by linkage to the Australian National Death Index. Lifetime history of psychiatric disorders in PNES was determined from formal neuropsychiatric reports. **Results:** A total of 5508 patients underwent VEM. A total of 674 (12.2%) were diagnosed with PNES, 3064 (55.6%) with epilepsy, 175 (3.2%) with both conditions, and 1595 (29.0%) received other diagnoses or had no diagnosis made. The standardized mortality ratio (SMR) of patients diagnosed with PNES was 2.5 (95% CI: 2.0-3.3). Those younger than 30 had an 8-fold higher risk of death (95% CI: 3.4-19.8). Direct comparison revealed no significant difference in mortality rate between diagnostic groups. Among deaths in patients diagnosed with PNES ($n = 55$), external causes contributed 18%, with 20% of deaths in those younger than 50 years attributed to suicide, and “epilepsy” was recorded as the cause of death in 24%. **Conclusions:** Patients diagnosed with PNES have a SMR 2.5 times above the general population, dying at a rate comparable to those with drug-resistant epilepsy. This emphasizes the importance of prompt diagnosis, identification of risk factors, and implementation of appropriate strategies to prevent potential avoidable deaths.

Commentary

Psychogenic nonepileptic seizures (PNES), functional seizures, or dissociative seizures are all names in consideration to define a presentation of functional neurologic symptom disorder (FND) with seizures or attacks. The prevalence of PNES is reported to be 2 to 33 per 100 000¹ but they represent about a third of patients with intractable seizures seen in epilepsy clinics and epilepsy units.

Although our understanding of the physiopathology of PNES is still in an infant state, over recent years neurologists, psychiatrists, and epileptologists alike have learned to recognize its presentation, risk factors, premorbid conditions, and triggering events. We started to recognize this condition, as well as other FND, as brain network integration disorders with a biologic basis and a common presentation.²

Patients with PNES share multiple similarities with patients with epilepsy (PWE). Both groups have sudden, mostly unpredictable, episodes of loss of voluntary control of their actions often with altered awareness or responsiveness which severely impair their social functioning. These episodes often come with limitations on education and employment opportunities as well

as driving restrictions. Both groups live with the impending threat of a seizure or attack at almost any time in their life and both are associated with increased risk of psychiatric comorbidities such as depression and anxiety.^{3,4}

As an epileptologist, my goals of treatment are also similar for PWE and persons with PNES. My patients and I work together, aiming to achieve complete control of all episodic events, identify and manage comorbid conditions, minimize medication side effects, improve quality of life, and support social and emotional life goals including education, employment, and emotional functioning to the best of our abilities.

Some risks, however, we thought were different such as the risk of dying from the primary condition. The elevated risk of sudden unexpected death in PWE (SUDEP) and other potentially preventable causes of epilepsy-related deaths (status epilepticus, drowning, accidental death, and medication overdose),⁵ but specially SUDEP, have become an enormous call to action for controlling all seizures in PWE. Considerations such as early intervention with epilepsy surgery, use of neuromodulation, polytherapy, and other nonpharmacological





treatments for seizures are motivated often by the goal of controlling all seizures and by doing so, decreasing the risk of premature death.

The present study by Nightscales et al⁶ highlights a new and striking similarity between the 2 groups of concern by bringing attention to the elevated mortality rate among patients with PNES which this group found to be 2.6 times higher than the general population and up to 8.3 times the risk in younger adults. This death rate is comparable to patients with intractable epilepsy, making a strong case for the need of recognizing, studying, and treating PNES at least as purposefully and aggressively as we do for PWE. Prior smaller scale studies had found similar increased mortality ratios in younger patients with PNES relative to the general population.^{7,8}

Nightscales' group conducted a thorough retrospective review of all cases admitted to their inpatient video EEG unit in 3 hospitals over 20 years (5508 patients) and compared their data to the national death registries, pulling the records for cause of death (COD) as documented by the medical examiner's report. Following definite video EEG results patients were classified as having the diagnosis of Epilepsy, PNES, both or none. The first 3 groups were subsequently studied for overall mortality and COD. Of note, patients with neoplastic lesions and epilepsy were excluded from analysis.

The COD analysis for patients with PNES reported "epilepsy" in 23.6% of patients, but subsequent review of these cases found no basis to support the diagnosis of epilepsy, raising the question of death-related to acute functional seizures, but the coexistence of undiagnosed epileptic seizures could not be completely ruled out in 7 of 13 cases.

Suicides and accidental poisonings accounted for 18.2% of deaths and were strongly related to having history of substance abuse. Sudden unexpected death (SUD) was determined after careful review in 21.7% of deaths in patients with PNES, which is double the expected rate for the general population.

The urgency for making the diagnosis of PNES is further supported by the existence of evidence-based treatment for this condition. Studies of both cognitive behavioral therapy informed psychotherapy⁹ and mindfulness-based therapy¹⁰ have shown improvement in seizure frequency and quality of life for this population. These interventions can be offered from the epilepsy clinic and even remotely, using Telehealth. A recent study by Goldstein et al¹¹ reported better quality of life, less bothersome events, longer seizure-free periods, and other improvements in social functioning when CBT was provided in addition to "standard of care" alone but no difference in absolute seizure count or severity. However, it is worth noting that both groups showed improvement in seizure frequency, likely due to successful trial interventions provided to both treatment groups such as education about the condition, medical support by an expert on the field, and active follow-up which is not really "standard of care" for most PNES patients.


There are a lot of questions following this large and thorough retrospective analysis on mortality: What was the cause of those "epilepsy" related deaths in patients with no evidence of epilepsy? Why would patients with PNES have double the risk of SUD than the general population? We have learned the best way to prevent SUDEP is achieving seizure control. Could it be possible that successfully identifying and treating patients with PNES would result in lowering the risk for SUD? Autonomic changes described in patients with PNES are starting to show possible contributors such as heart rate variability during PNES.¹² Prospective studies in this population may be able to answer these questions in the future.

A history of substance abuse was clearly identified as the only psychiatric diagnosis related to an increased risk for death due to medication and drug poisoning. Lowering and discontinuing ASM in patients with PNES should be a goal of care in the clinic. Fewer medications may reduce the possibility of accidental overdosing and recognizing the risk posed by substance abuse should facilitate the process as well.

This information on mortality risk should be a call for action for neurologists and epilepsy specialists to make the diagnosis, institute treatment, and follow-up patients with PNES. Although we have a lot to learn about the pathophysiology, presentation, and best therapy for this condition, the reward for taking this task will be no less than the one we get from adequately treating our PWE: fewer or no seizures, appropriate medications with fewer side effects, better treated comorbidities, improvement in quality of life, and reduced mortality: what more could we ask for?


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