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a controlled national study

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Morbidity and mortality of nonepileptic seizures (NES): A controlled national study☆,☆☆,★

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ABSTRACT

Nonepileptic seizures (NES, psychogenic NES-PNES) are associated with significant morbidities. We evaluated the morbidities and mortality in a national group of children, adolescent, and adult patients before and after a first diagnosis of PNES.

Methods: From the Danish National Patient Registry (1998–2013), we identified 1057 people of all ages with a diagnosis of NES and matched them with 2113 control individuals by age, gender, and geography. Comorbidities were calculated three years before and after diagnoses.

Results: Patients with PNES showed increased comorbidities 3 years before and after diagnosis in almost all the diagnostic domains.

The strongest associations were identified with other neurological diseases (after diagnosis, Hazard Ratio (HR): 38.63; 95% Confidence Interval (CI): 21.58–69.13; $P < 0.001$), abnormal clinical and laboratory findings (HR: 46.59; 95 CI: 27.30–79.52; $P < 0.001$), other health-related factors (HR: 12.83; 95%CI: 8.45–19.46; $P < 0.001$), and psychiatric comorbidities (HR: 15.45; 95% CI: 9.81–24.33). Epilepsy was identified in 8% of the patients with PNES. We found especially frequent comorbidity involving overweight, depression, anxiety, dissociative somatoform condition, other convulsions, lipothymias, reports of pain and other symptoms in several organ systems, and several reports of minimal traumas to the head, trunk, and extremities. Mortality was higher in patients with NES than in controls (HR: 3.21; 95% CI: 1.92–5.34; $P < 0.001$).

Conclusion: Morbidity is more frequent in several domains, including neurological, psychiatric, and other diseases, before and after a diagnosis of NES. Mortality is significantly higher in patients with PNES as compared to controls.

Epilepsy affects approximately 1% of children and adults, and is associated with significant comorbidities and mortality, and personal, familiar, and societal consequences [1]. Episodes with transient behavioral abnormalities or changes in consciousness may be different in nature, e.g., as if they are different events neurological, cardiovascular, or psychological. Diagnosing epilepsy may be difficult due to the complex nature of the disorders, the occurrences of seizures, the timing, and reports from patients and witnesses. Other causes of ictal events include episodes of nonepileptic seizures (NES), e.g., other pathological conditions (cardiac and vasovagal disorders) and other neurological (e.g., cataplexy in narcolepsy) and malingering or psychogenically induced seizures (psychogenic NES [PNES]).

Diagnosing PNES is challenging, which, due to the potential risk of incorrect diagnosis, should depend on positive criteria, including witnessed of clinical episodes and/or long-term video-electroencephalographic (vEEG) recordings [2–4]. Despite the application of these criteria, there is still a degree of uncertainty about diagnoses.

The cause and etiologies of PNES include complex mechanisms, such as constitutional, psychological, social, familiar, and other complex pathways. Patients with PNES may suffer from several other comorbidities. Previous studies have focused on psychopathology and comorbid psychiatric disorders which occur in a significant proportion of patient with PNES [5–11], and PNES may occur in patients with epilepsy [5,7,12,13]. A systematic approach to the evaluation of PNES with respect to all other comorbidities is yet to be adopted, as compared with control

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subjects. There is currently very limited long-term follow-up data regarding morbidities and mortality in patient with PNES.

In Denmark, the diagnosis of PNES depends on careful diagnostic procedures, including several nonictal and ictal vEEGs. In this study, we aim to present the results of the comparison of all identified national cases of PNES cases with matched controls regarding comorbidities and mortality.

1. Methods

1.1. Patients and controls

The methods used in this study follow those of two previous studies [14,15]. Our current study is based on reports from all Danish clinics and hospitals registered in the Danish National Patient Registry (NPR). The NPR is a time-based national database of administrative information, diagnoses, and diagnostic and treatment procedures that uses several international classification systems, including the International Classification of Disorders (ICD-10). This is possible because all Danes are registered using social security codes, enabling the collection of linked data, including health information. Data on the time and type of health contacts cover those related to the hospital sector, including diagnostic and treatment procedures at the time of diagnosis. Thus, it is a complete national sample containing the dates of contact and diagnoses of all patients.

Since April 1968, all Danish citizens have been assigned a unique identifier (Central Personal Registration [CPR] number), which is recorded in the Danish Civil Registration System along with information about place of birth and residence and vital and marital status [16]. Denmark includes approximately 5.8 mill citizens; almost all citizens have a patient contact with the healthcare system and are consequently registered in the NPR.

Since the NPR contains details of all patient contacts, the data may be representative of all patients in Denmark who have received a diagnosis of (psychogenic) NES (DR568G, DF445, or DF449) in the secondary sector and in public and private hospitals. The year of diagnosis was defined as the first time a patient was registered with the diagnosis of PNES (index date) in the NPR between 2011 and 2016 (calendar year). Patients were followed until death, emigration, or 31st December 2016.

We identified all patients when they received their first diagnosis. We set up a control group that was randomly selected but matched by age, gender, and geography (county) at the time of the initial diagnosis. The controls had no diagnosis of NES but may have suffered from other diseases. Each patient was matched with four controls. Information about health was obtained from the NPR, which we used to estimate the total morbidity and mortality of the cohort. The study was approved by the Danish Data Protection Agency. The study was register-based so no approval from the ethics committee was needed.

1.2. Comorbidity and mortality after diagnosis (postindex)

A postindex measure of patient comorbidity in the first three years before and after the initial PNES diagnosis was calculated for the cohort. The index of PNES diagnosis was not included in the calculation of comorbidity, but subsequent contacts due to NES were included in the analysis, as were those due to other neurological disorders.

Pre- and postindex comorbidity for the 21 WHO chapters was analyzed by examining the odds ratios (conditional logit model). A more detailed analysis of the ICD-10 diagnoses that typically occur in patients with PNES is provided. The diagnoses were calculated based on the first three digits, and only those occurring in at least 3% of the patient or control group were included in this analysis. Logistic regression was used to examine the included diagnoses, controlling for the level of parental education.

We also evaluated annual all-cause mortality after the initial PNES diagnosis.

Table 1
Basic descriptive statistics.

	NES		Control	
	N	%	N	%
Total	1057		2113	
Age (years)				
0–10	240	22.7	479	22.7
11–20	246	23.3	492	23.3
21–30	167	15.8	334	15.8
31–40	120	11.4	240	11.4
41–50	89	8.4	178	8.4
51–60	82	7.8	164	7.8
61–70	63	6.0	126	6.0
71–80	32	3.0	64	3.0
>80	18	1.7	36	1.7
Gender				
Male	325	30.7	650	30.8
Female	732	69.3	1463	69.2
Marital status				
Married	630	59.6	1259	59.6
Not married	427	40.4	854	40.4

Statistical analyses were performed using SAS 9.1.3 (SAS, Inc., Cary, NC, USA).

2. Results

One thousand fifty seven patients with PNES were identified and compared with 2113 matched controls. Forty six percent were children (0–20 years old) (Table 1). The number of identified patients per year was about the same for the period (2011: 81; 2012: 185; 2013: 206; 2014: 180; 2015: 221 2016: 184). Four hundred fifty five patients with PNES and 912 controls were identified who had prediagnosis information, and 472 patients with PNES and corresponding 974 controls were selected who had postdiagnosis information for at least three years, estimated from the date of diagnosis. All patients showed significantly higher frequencies in several disease areas, as documented in the 21 chapters of the WHO classification before, and particularly after, diagnosis (Table 2). The analysis of the separate diagnoses for diseases that occurred in more than 3% of patients is presented in Table 3. It is notable that there is a significant and overwhelming number of patients with PNES: both before and after diagnoses of overweight, psychiatric diseases, but also following a diagnosis of other types of convulsion (not recorded as psychogenic or epileptic), lipothymias, and other abnormal movements are reported. Moreover, patients with PNES report several additional somatoform symptoms from the head, trunk, extremities, and pain complaints. Patients with PNES have significantly more contact with health services for minor traumas affecting all body parts. As we only included occurrences with a frequency of more than 3% for each diagnosis, almost none of these reports were identified in the controls (Table 4).

Mortality was greater in patients with PNES than in controls (HR: 3.21; 95% CI: 1.92–5.34; $P < 0.001$) (Fig. 1).

3. Discussion

We prospectively evaluated the comorbidity rates in childhood, adolescence, and adult PNES in a national sample with matched controls. The study made several important novel findings: 1) patients with PNES showed elevated comorbidities in several of the 21 WHO disease groups; 2) the associations included overweight, psychiatric diseases, other types of nonepileptic convulsion, lipothymias, abnormal movements, somatoform symptoms, pain, and minor traumas; and 3) the mortality rate was significant and 3 times higher in patients with PNES this small population. Thus, PNES is associated with a wide range of comorbidities but is dominated by unspecific health contacts

Table 2
Comorbidities (WHO 21 Chapters) of patients three years before their initial NES diagnosis.

Classifications group			Share of classification group			95% confidence interval		
	NES N	Control N	PNES N = 472 %	Control N = 944 %	Odds ratio	Lower 5%	Upper 90%	P
Infectious and parasitic diseases	32	41	6.8	4.3	**1.62**	1.00	2.62	0.051
Neoplasms	25	42	5.3	4.5	1.21	0.72	2.02	0.473
Blood and immunological diseases	12	11	2.5	1.2	2.18	0.96	4.94	0.062
Endocrine, nutritional and metabolic diseases	73	52	15.5	5.5	**3.15**	2.15	4.61	<0.001
Mental and psychiatric disorders	142	30	30.1	3.2	**12.95**	8.18	20.49	<0.001
Nervous system disorders	193	22	40.9	2.3	**33.90**	18.45	62.29	<0.001
Diseases of the eye and adnexa	35	28	7.4	3.0	**2.83**	1.65	4.87	<0.001
Ear, nose, and throat diseases	24	12	5.1	1.3	**4.24**	2.07	8.68	<0.001
Circulatory/cardiovascular diseases	79	56	16.7	5.9	**3.83**	2.54	5.78	<0.001
Respiratory diseases	64	51	13.6	5.4	**2.75**	1.86	4.07	<0.001
Gastrointestinal diseases	62	70	13.1	7.4	**1.92**	1.33	2.78	0.001
Skin and subcutaneous tissue diseases	24	25	5.1	2.7	**2.02**	1.13	3.63	0.018
Musculoskeletal system and connective tissue diseases	103	116	21.8	12.3	**2.08**	1.53	2.82	<0.001
Genito-urinary diseases	53	58	11.2	6.1	**1.94**	1.31	2.88	0.001
Pregnancy, childbirth, and puerperium	29	60	6.1	6.4	**0.95**	0.57	1.61	0.860
Certain conditions originating in the perinatal period	24	43	5.1	4.6	1.20	0.63	2.27	0.584
Congenital malformations, deformations, and chromosomal abnormalities	28	19	5.9	2.0	**3.04**	1.68	5.50	<0.001
Abnormal clinical and laboratory findings	286	115	60.6	12.2	**9.50**	7.03	12.84	<0.001
Injury, poisoning, and certain other external causes	223	223	47.3	23.6	**3.30**	2.54	4.29	<0.001
External causes of morbidity and mortality	77	125	16.3	13.2	**6.10**	2.07	17.93	0.001
Other factors influencing health status and contact with health services	428	517	90.7	54.8	**9.79**	6.70	14.31	<0.001

Bold values statistically significant at P < 0.01.

due mostly to psychiatric, nonspecific symptoms, and somatoform complaints.

By using a national dataset in which all health contacts are recorded, we found a striking feature of PNES in this study whereby the disorder was associated with more disease consequences in several disease domains. Psychogenic NES comorbidities were observed before the initial diagnoses. Increased morbidity with long delays are noted in many other diseases and conditions [17].

We found that PNES is associated with elevated rates of metabolic disease (overweight, diabetes type II, and hypercholesterolemia), which makes it possible that PNES is linked to poor lifestyles and sedentary behavior, although no data are currently available to support this inference.

The strongest and most important finding in this study is the raised prevalence of comorbidities involving psychiatric diseases (depression, anxiety) and in dissociative and somatoform conditions. Case-based observations have highlighted the high frequency of specific psychological profiles [5,18–21], and the high rates of depression, anxiety, and somatoform conditions [18,22,23]. Somatoform patterns are also evident in this study as more patients showed a greater number of contacts with the healthcare system due to lipothymias, abnormal nonepileptic movements, symptoms of multiple organ system and minor traumas. Patients with epilepsy suffer from high rates of traumas and falls, although only one study has identified a higher risk of injury [24]. The higher rate of epilepsy is well-known; patients with epilepsy may also suffer from PNES

Table 3
Comorbidities (WHO 21 Chapters) of patients three years after their initial NES diagnosis.

Classifications group			Share of classification group			95% confidence interval		
	NES N	Control N	PNES N = 472 %	Control N = 944 %	Odds ratio	Lower 5%	Upper 90%	P
Infectious and parasitic diseases	51	38	10.8	4.0	**3.08**	1.95	4.88	<0.001
Neoplasms	32	54	6.8	5.7	1.22	0.76	1.97	0.409
Blood and immunological diseases	22	14	4.7	1.5	**3.14**	1.61	6.14	0.001
Endocrine, nutritional, and metabolic diseases	75	67	15.9	7.1	**2.52**	1.76	3.60	<0.001
Mental and psychiatric disorders	168	29	35.6	3.1	**15.45**	9.81	24.33	<0.001
Nervous system disorders	241	36	51.1	3.8	**38.63**	21.58	69.13	<0.001
Diseases of the eye and adnexa	44	40	9.3	4.2	**2.40**	1.52	3.80	<0.001
Ear, nose, and throat diseases	23	20	4.9	2.1	**2.44**	1.31	4.56	0.005
Circulatory/cardiovascular diseases	80	57	17.0	6.0	**4.13**	2.70	6.31	<0.001
Respiratory diseases	83	71	17.6	7.5	**2.75**	1.93	3.92	<0.001
Gastrointestinal diseases	102	89	21.6	9.4	**2.75**	1.99	3.79	<0.001
Skin and subcutaneous tissue diseases	39	32	8.3	3.4	**2.52**	1.56	4.06	<0.001
Musculoskeletal system and connective tissue diseases	111	132	23.5	14.0	**1.93**	1.44	2.57	<0.001
Genito-urinary diseases	83	86	17.6	9.1	**2.23**	1.59	3.13	<0.001
Pregnancy, childbirth, and puerperium	29	77	6.1	8.2	0.69	0.42	1.12	0.132
Certain conditions originating in the perinatal period	–	–						
Congenital malformations, deformations, and chromosomal abnormalities	19	18	4.0	1.9	**2.11**	1.11	4.02	0.023
Abnormal clinical and laboratory findings	412	139	87.3	14.7	**46.59**	27.30	79.52	<0.001
Injury, poisoning, and certain other external causes	219	244	46.4	25.9	**2.55**	2.00	3.24	<0.001
External causes of morbidity and mortality	7	15	1.5	1.6	0.92	0.35	2.44	0.870
Other factors influencing health status and contact with health services	420	473	89.0	50.1	**12.83**	8.46	19.46	<0.001

Bold values statistically significant at P < 0.01.

Table 4
Comorbidities on selected diagnoses grouped into major symptoms or groups. All identified by occurrence of at least 3% of each diagnose.

Disease group	Before		After	
	PNES, N (%)	Control, N (%)	NES, N (%)	Control, All N
Total N	Total 455	912	472	974
Overweight and metabolic diseases	7 (1.5)	0	13 (2.8)	0
Depression, anxiety, and OCD	10 (2.2)	0	12 (2.5)	0
Dissociate and somatoform conditions	51 (11.2)	0	67 (12)	0
Epilepsy, including status epilepticus	36 (7.9)	0	42 (8.9)	0
Lipothymias	18 (3.9)		15 (7.2)	0
Unclassified convulsions	18 (3.9)	0	79 (16.3)	0
Other abnormal movements	16 (3.5)		12 (2.5)	0
Migraine, Horton headache, other chronic headaches	8 (1.8)	0	9 (1.9)	0
Unclassified CNS symptoms	18 (3.9)	0	29 (6.1)	0
Cardiovascular, bronchitis, and asthma	20 (4.8)	0	21 (4.4)	0
Symptoms from abdominal or urogenital system without specific somatic diagnosis	16 (3.5)	4 (0.4)	30 (6.8)	5 (0.5)
Rheumatism, pain	19 (4.2)	0	26 (5.5)	0
Lesion to the thorax, abdomen, or extremities	60 (13.6)	0	51 (10.8)	0

and vice versa [25,26]. Patients with PNES are more likely not only to suffer from personal problems but also to have a lower quality of life [5,27]. The multiple contacts with the healthcare system, the lower educational level and poorer job adherence increase total welfare costs [28,29].

As the aim of the study was to identify the total health-related comorbidities of PNES, we included all the cases in the national sample with a first diagnosis of PNES but did not consider the criteria for any other verification of the diagnoses. A diagnosis of PNES in Denmark generally requires an extensive evaluation based on clinical history, several EEGs, and ictal vEEG. The diagnosis is generally sensitive to misdiagnoses and careful evaluation of patients is needed, especially to avoid that of a different physiological/pathological PNES. In this study, we primarily aimed to evaluate the pattern of comorbidity, but not the underlying causes involving constitutional, familiar, educational, psychological, psychiatric, somatic, and social factors [5,30,31]. A number of interventions for PNES have been proposed [32,33], including those involving psychological management, but we have not evaluated the effect of these factors during the course of the disease in this population because it is too small to do so adequately.

We found a higher mortality rate in this small population of patients with PNES than in controls. Several factors are responsible for the elevated mortality rates found in childhood, adolescent, and adult epilepsy [1,34], including seizure severity, underlying diseases, medication, comorbidities, and life-style factors [35–37]. A previous study also reported greater mortality in PNES [38]. The effect was relatively strong, with an HR greater than 3, but the cause and etiology of the mortality effect cannot be determined from this study, beyond being able to establish that the patients have higher rates of epilepsy, several comorbidities, medication use (data not shown), and are likely to have a more sedative lifestyle. Epilepsy cannot explain the higher mortality rates in the study as relatively few patients suffered from epileptic seizures.

The strength of our study is that we were able to identify all patients with a diagnosis of PNES and to establish controls based on demographic variables. In this study, the control group was selected based on age,

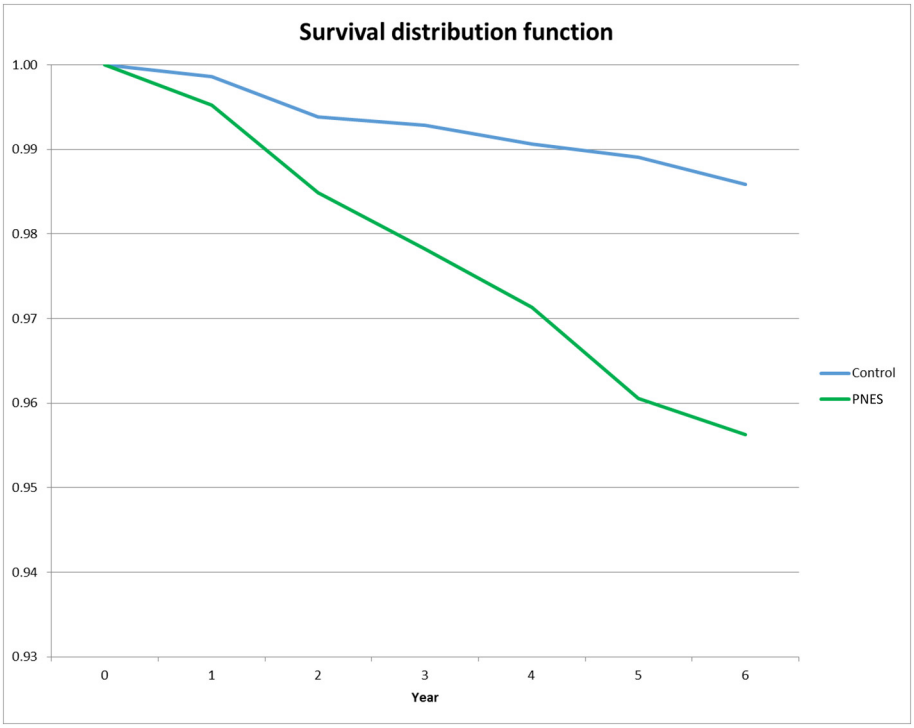

Fig. 1. Mortality in PNES.

gender, and geography (the latter to allow adjustment for social factors); it was not selected to be a group of healthy subjects. If we had compared patients with PNES with healthy members of the general population, the differences and morbidities would have been more pronounced.

The study is limited by our inability to evaluate the criteria by which the individual diagnoses were made; e.g., whether they were based on clinical information or if episodes were classified based on ictal vEEG recordings. We selected only four controls per patient to reduce the variance among controls. To be included as a control, they could not have a diagnosis of PNES, or be suspected of having PNES, although they may well have had other disorders. We did not control for parental social factors. It is likely that this would be of relevance since PNES is probably influenced by social rank [39]. However, the data here were insufficiently complete to enable the familiar analysis that would ideally be required.

In conclusion, the current study found that PNES was associated with significantly more numerous health-related consequences, and that the morbidities extended to several comorbidities other than brain diseases. Healthcare professionals should be aware of the possibilities for detecting, diagnosing, and managing PNES and epilepsy, and should ensure that patients receive adequate information about their disorders. Future research should evaluate the importance of these findings including understanding the etiology and importance for management of PNES.

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