Pediatric RESEARCH

POPULATION STUDY ARTICLE

Incidence rates and characteristics of pediatric onset psychogenic nonepileptic seizures

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BACKGROUND: Pediatric onset psychogenic nonepileptic seizures (PNES) is a highly disabling disorder and potentially misdiagnosed as epilepsy. Still, knowledge regarding PNES in children and adolescents is limited and data on both incidence and characteristics are scarce. This study investigated the incidence rate (IR) and clinical characteristics of pediatric onset PNES, including possible differences when having comorbid epilepsy.
METHODS: A population-based study of children and adolescents aged 5–17 years with an incident diagnosis of PNES in the Danish healthcare registries between 1996 and 2014. In total, 386 children and adolescents were included after assessment of diagnostic validity using medical record data.
RESULTS: The IR increased during the study period with the maximum IR observed in 2014 (7.4 per 100,000 person-years). A history of both neurologic and psychiatric problems as well as negative life events was identified. Comorbid epilepsy was confirmed for 55 cases (14.2%) and was associated with intellectual disabilities, school support and prolonged delay in PNES diagnosis.
CONCLUSIONS: PNES are increasingly diagnosed in children and adolescents, and the clinical profile of both neurologic and psychiatric health problems underscores the need for collaborative pediatric and mental healthcare. These findings provide important information for future healthcare planning in this area.

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IMPACT:

- This nationwide study is the first to report population-based incidence rates of pediatric onset PNES documenting markedly increasing incidence rates between 1996 and 2014.
- A history of both neurologic and psychiatric problems as well as negative life events was identified for pediatric onset PNES.
- Comorbid epileptic seizures were associated with intellectual disabilities, school support and prolonged delay in PNES diagnosis.
- The clinical profile of both neurologic and psychiatric health problems underscores the need for collaborative pediatric and mental healthcare.
- The increasing number of children and adolescents diagnosed with PNES is important information for future healthcare planning in this area.

INTRODUCTION

Pediatric onset psychogenic nonepileptic seizures (PNES) are a challenge in the pediatric setting.[1,2] Diagnostic difficulties can lead to unnecessary investigations, improper treatment with antiepileptic drugs, emotional distress and financial consequences for both the child, the family, and the healthcare system.[2–7]

The diagnostic challenge is often to recognize PNES, since the seizures may mimic epileptic seizures with changes in behavior or consciousness, however, without the associated electroencephalographic (EEG) findings characteristic of epileptic seizures.[8] The gold standard for diagnosing PNES includes a video-EEG recorded during a seizure, though this is not always a viable clinical option.[9] Thus, a staged approach to the PNES diagnosis is recommended based on characteristics and witnessed semiology consistent with PNES, while taking into account the availability of an EEG result[10]. Such an approach can nonetheless be hampered by the limited existing knowledge regarding characteristics of children and adolescents with PNES and with comorbid epileptic seizures being reported in 12–44% of pediatric PNES with possible associated differences regarding characteristics.[11–16]

PNES is a conversion disorder, where the recommended treatment is psychiatric management including psychoeducation and psychotherapy.[2,17] Nevertheless, these children and adolescents are often neglected as a result of a treatment gap between pediatric and mental health care.[18–21] Numbers on the occurrence of pediatric onset PNES could inform future strategies for proper healthcare planning, but no population-based study has reported this in pediatric PNES, as most prior studies have investigated

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adult populations or small samples of children from tertiary hospital care.[22,23]

This study is the first to establish a population-based cohort of children and adolescents with incident PNES across hospital settings. The aim is to describe the incidence rate and clinical characteristics of pediatric patients diagnosed with PNES, including a comparison between patients with and without comorbid epilepsy.

METHODS

Study design

This is a nationwide study of incident pediatric onset PNES diagnosed in Denmark between 01 Jan 1996 and 31 Dec 2014.

Registers utilized

Every person born or immigrating into Denmark receives a unique identification number (the Civil Person Registration number, CPR),[24] which allows information linkage across different registries. The Danish National Patient Registry (DNPR)[25] contains data on diagnoses at discharge for somatic inpatient hospital contacts since 1977. The Danish Psychiatric Central Research Registry (DPCRR)[26] was established in 1969 to register psychiatric inpatient hospital contacts, and was merged with the DNPR in 1995. From 1995 and onwards the DNPR included all somatic and psychiatric in- and outpatient hospital contacts.

Study participants

We defined pediatric as children and adolescents aged 5–17 years[2,22] and included all registered with an incident diagnosis of "Dissociative Seizures" (ICD-10; F44.5) or "Other and Unspecified Convulsions, Non-Epileptic Seizures" (ICD-10; R56.8G) in the DNPR between 1996 and 2014. The diagnosis of F44.5 was ranked to have the highest specificity to identify PNES cases compared to R56.8G, and participants registered with both inclusion diagnoses were included at time of first given F44.5 diagnosis. To ensure inclusion of incident cases only, participants diagnosed prior to the study period with a possible PNES condition (ICD-8; 300, 305, 306, 307, 308, 780 and/or ICD-10; F44.5, F91.8, F98.9, R56.8) were excluded. Furthermore, we excluded participants only registered at an emergency department.

The inclusion and exclusion diagnoses were selected in collaboration with a panel of Danish neuropediatric experts and based on a recent Danish survey study.[9] All included participants were subsequently rated for case validity as described below.

Medical record data

All notes and any relevant clinical test results available were retrieved from the medical records of the participants. A case report form was developed containing a diagnostic rating scale for case validation (described below) and a list of clinical variables to be extracted from the medical records. The clinical variables were defined based on the existing literature on pediatric onset PNES[2,10,22,27] and included: clinical examinations, hospital information, seizure characteristics, seizure semiology, history of illness, prior treatment, level of functioning, family characteristics and negative life events (Supplementary Table S1(online)). The data were managed using REDCap electronic data capture tools hosted at the North Denmark Region.[28]

Case validation and final study population

The primary investigator (ASH) performed the case validation. An initial consensus rating was conducted on five participants between ASH and two co-raters; a consultant child and adolescent psychiatrist (CUR) and a consultant neurologist (JC). Secondly, to test inter-rater reliability a random subsample of 60 participants was rated by the two co-raters as well.[29]

To assess case validity, we utilized an adapted version of the staged approach to diagnosing PNES outlined by the International League Against Epilepsy (ILAE) in 2013.[10,30] The ILAE approach is based on history characteristics, the witnessed event and EEG result (Supplementary Fig. S1 (online)). The ILAE criteria were adapted regarding EEG result due to pragmatic considerations, as the EEG availability differed across the country, over the study period and across hospital settings. Thus, an ictal video-EEG was necessary to achieve the highest level of diagnostic certainty ("Documented"), whereas the three subsequent levels ("Clinically Established", "Probable" and "Possible—likely yes") could be achieved based on an ictal/interictal EEG without epileptiform activity or without an EEG (missing or not performed). Participants achieving these four levels of diagnostic certainty were rated with confirmed PNES and included in the final study population. Another three diagnostic levels were defined for participants not achieving a validated PNES diagnosis ("Possible – likely no", "Not PNES" and "Insufficient information to perform rating").

A condition of co-morbid epilepsy (termed mixed PNES) was confirmed, if an EEG showed epileptiform activity together with clinical information supporting an epilepsy diagnosis in patients also fulfilling the above PNES criteria.

Finally, we assessed whether the participants also fulfilled the criteria for a diagnosis of "Conversion Disorder; Functional Neurological Symptom Disorder" (DSM-V; 300.11).[17]

Statistical analyses

Continuous variables were summarized by the median and range while categorical variables were presented as frequencies and percentages. Comparisons between groups were made using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The groups were: PNES without comorbid epilepsy ("pure PNES") vs PNES with comorbid epilepsy ("mixed PNES"), age at diagnosis (preteens (<12 years of age) vs teens (≥12 years of age)) and sex.

Statistical analyses were performed using Stata15. Results with p values below 0.05 were considered statistically significant.

Ethics

The Danish Data Protection Agency (ID: 2016–164), the Danish Health Data Authority (FSEID: 00002709), and the Danish Health Authority (ID: 3-3013-1859) approved the study and data use.

RESULTS

Case validity and the final study population

In total, 464 eligible participants were identified in the health registers, and 451 participants remained after exclusion due to a prior PNES condition or only being registered at an emergency department. Medical records were available for 426 participants of which 386 participants were rated PNES cases and included in the final study population (Supplementary Fig. S2 (online)). The inter-rater reliability test showed an agreement between the primary rater and the two co-raters on 100 % (rater CUR; Cohen's kappa = 1.0) and 93.3 % (rater JC; Cohen's kappa = 0.76), corresponding to an agreement level of almost perfect and substantial (Cohen's kappa range: 0.81–1.0 and 0.61–0.80). The diagnostic levels for the final study population were; "Documented": $N = 90$ (23.3%), "Clinically established": $N = 173$ (44.8%), "Probable": $N = 23$ (6.0%), "Possible – likely yes": $N = 100$ (25.9%). EEG information was retrieved for 336 (87.0%) of the PNES cases. (Supplementary Table S2 (online)). The positive predictive value (PPV) of the two inclusion diagnoses was 94.4% for ICD-10 F44.5 and 75.9% for ICD-10 R56.8 G. Every PNES case fulfilled the diagnostic criteria for Conversion Disorder; Functional Neurological Symptom Disorder

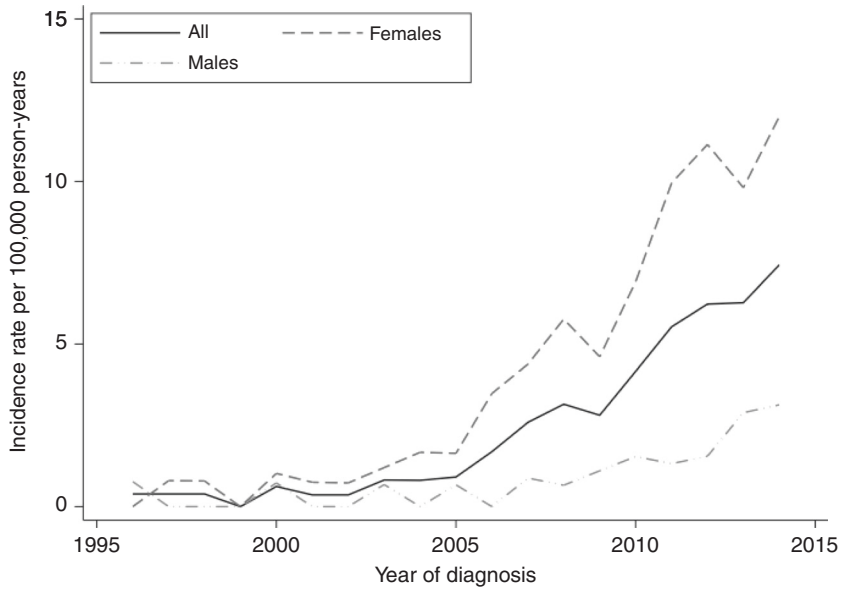

Fig. 1 Annual incidence rates of PNES among 5- to 17-year-old children and adolescents in Denmark during the period 1996–2014. In years where the number of cases was above 0 but below 3, the number of cases was automatically set to 3 due to data protection rules in Denmark.

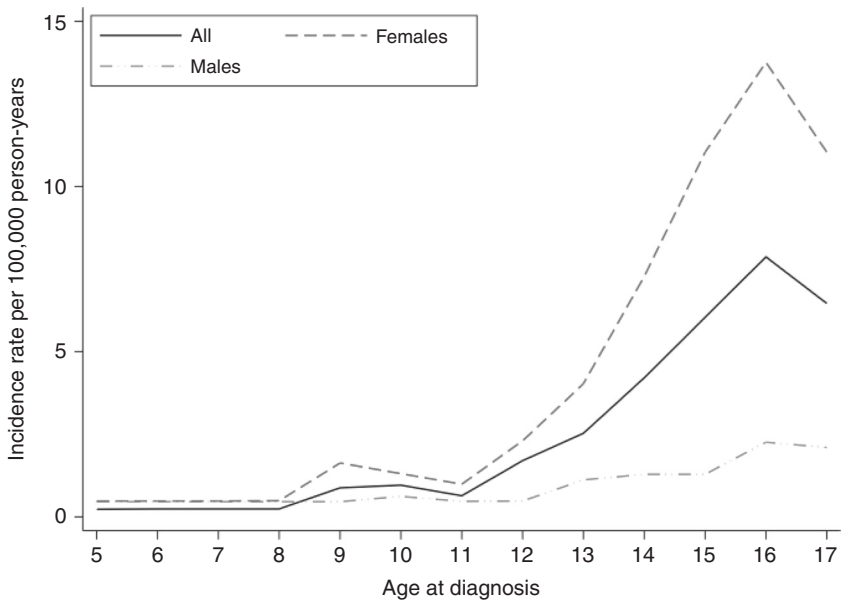

Fig. 2 Incidence rates of PNES based on age at diagnosis among 5- to 17-year-old children and adolescents in Denmark for the period 1996–2014. In age groups where the number of cases was above 0 but below 3, the number of cases was automatically set to 3 due to data protection rules in Denmark.

(DSM-V; 300.11), and 55 (14.2%) had a comorbid diagnosis of epilepsy confirmed.

Incidence rates

The incidence rate (IR) of pediatric onset PNES in Denmark was 2.4 per 100,000 person-years for the total study period. The IR increased between 2005 and 2014, with a maximum IR of 7.4 per 100,000 person–years in 2014 (Fig. 1). Considering IRs based on diagnostic level of certainty, the "Clinically Established" cases had the highest IR with a maximum of 2.7 per 100,000 person-years in 2014 (Supplementary Table S3 (online)). The increase was primarily observed in females with an IR of 12.0 per 100,000 person-years in 2014, while the IR in males was 3.1 per 100,000 person-years. The IR for the total study period stratified on age at diagnosis was highest for the 16-year-old adolescents with an IR of 7.9 per 100,000 person-years (Fig. 2).

Clinical characteristics

Most patients were females (83.4%) and the median age at diagnosis was 15.7 years. Characteristics for the final study population and divided by pure PNES (PNES without epilepsy) and mixed PNES (PNES with comorbid epilepsy), respectively, are shown in Table 1. In the mixed PNES group a higher proportion reported intellectual disabilities and established support in school. In total, 210 patients (54.4%) reported one or more negative life events with the highest proportion among the pure PNES group.

Table 1. Patient Characteristics[a].

Characteristic	Final study population, $N = 386$	Pure PNES, $n = 331$ (85.8)	Mixed PNES, $n = 55$ (14.2)	P value
Female sex	322 (83.4)	274 (82.8)	48 (87.3)	0.41
Age at diagnosis, median (Q1-Q3)	15.7 (14.2–16.9)	15.7 (14.2–16.9)	15.3 (13.8–16.5)	0.37
Diagnosed before 12 years of age	37 (9.6)	30 (9.1)	7 (12.7)	0.39
Type of hospital department				0.30
Pediatric	175 (45.3)	150 (45.3)	25 (45.5)	
Neurology	164 (42.5)	143 (43.2)	21 (38.2)	
CAMHS	40 (10.4)	31 (9.4)	9 (16.4)	
Other	7 (1.8)	7 (2.1)	0 (0.0)	
Diagnosis given as inpatient	314 (81.3)	266 (80.4)	48 (87.3)	0.22
Reason for referral to hospital[b]				
Seizures	356 (92.2)	301 (90.9)	55 (100.0)	0.02
Fainting or dizziness	50 (13.0)	50 (15.1)	0 (0.0)	0.002
Other	6 (1.6)	6 (1.8)	0 (0.0)	0.31
Patient history of illness				
Epilepsy	67 (17.4)	15 (4.5)	52 (94.5)	<0.001
Psychiatric disorder	78 (20.2)	64 (19.3)	14 (25.5)	0.30
Self-harm behavior	62 (16.1)	57 (17.2)	5 (9.1)	0.13
Family history of illness				
Epilepsy	32 (8.3)	25 (7.6)	7 (12.7)	0.20
Psychiatric disorder	62 (16.1)	52 (15.7)	10 (18.2)	0.64
Prior treatment				
Psychotherapy	98 (25.4)	82 (24.8)	16 (29.1)	0.50
Antiepileptic drugs	112 (29.0)	64 (19.3)	48 (87.3)	<0.001
Psychopharmacological medicine	48 (12.4)	39 (11.8)	9 (16.4)	0.34
Level of functioning				
School problems	133 (34.5)	105 (31.7)	28 (50.9)	0.006
Support in school	105 (27.2)	76 (23.0)	29 (52.7)	<0.001
Low IQ (IQ < 70)	31 (8.0)	16 (4.8)	15 (27.3)	<0.001
Specific learning difficulties	94 (24.4)	64 (19.3)	30 (54.5)	<0.001
Family characteristics				
Living with parents	339 (87.8)	290 (87.6)	49 (89.1)	0.76
Living in foster care/children's institution	20 (5.2)	13 (3.9)	7 (12.7)	0.006
Parents divorced	143 (37.0)	124 (37.5)	19 (34.5)	0.68
Support at home	68 (17.6)	54 (16.3)	14 (25.5)	0.10
Negative life events experienced, any type	210 (54.4)	189 (57.1)	21 (38.2)	0.009
Seizure in context with described stress	117 (30.3)	101 (30.5)	16 (29.1)	0.83
Specific trigger in context with onset[c]	54 (14.0)	53 (16.0)	<5	<0.001

CAMHs child and adolescent mental health services, *IQ* intelligence quotient.
[a]Data are presented as number (percentage) unless otherwise indicated.
[b]More than one referral type possible.
[c]Due to data protection rules in Denmark, numbers above 0 but below 5, are set to <5.

Comparing the pure and mixed PNES subgroups regarding subtype of negative life event, the only statistically significant difference was observed for child neglect (4.5 vs 14.6%, $P = 0.004$) (Fig. 3).

Seizure characteristics are presented in bar charts in Fig. 4. The distribution of time from PNES onset to diagnosis was statistically significantly different between the groups ($P = 0.03$) with the mixed PNES group having a longer diagnostic delay of PNES. Still, most were diagnosed within 0–6 months in both the pure (43.5%) and mixed (25.9%) PNES groups. The frequency of seizures was most often reported as weekly (pure: 61.5% vs mixed: 50.6%) and the duration of seizures to last 5–30 min (pure: 61.2% vs mixed: 49.7%). The seizure semiology as divided by pure and mixed PNES is shown in Fig. 5.

The female preponderance was lower in the preteens compared to the teens (70.3 vs 84.8%, $P = 0.02$). Regarding seizure semiology, the teens presented more "Asynchronous movements" (81.1 vs 51.4%, $P < 0.001$) and "No incontinence/tongue biting" (58.7 vs 37.8%, $P = 0.02$) compared to the preteens, whereas the preteens presented more "Emotional features" (24.3 vs 10.9%, $P = 0.02$) compared to the teens. Furthermore, the teens had received more psychotherapy compared to the preteens (27.2 vs 8.1%, $P = 0.01$). Comparing groups divided by sex, males showed a higher proportion of support in school (39.1 vs 24.8%, $P = 0.02$)

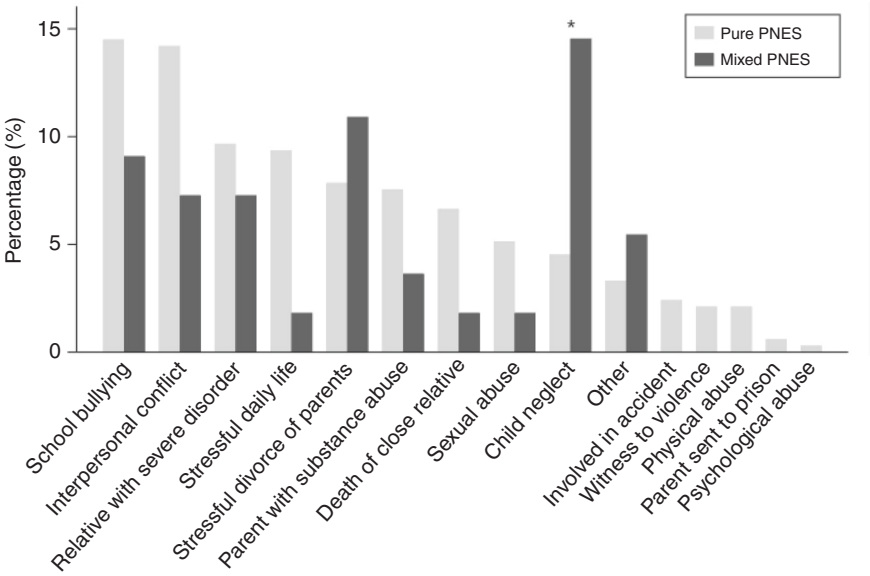

Fig. 3 Negative Life Events in Pediatric Onset PNES. Subtype of negative life event with statistically significant difference (*) ($P = 0.004$) between the pure PNES and mixed PNES groups. Definition: 'Relative with severe disorder' was defined as having a family member (parent/sibling/grandparent) with a severe mental (e.g., bipolar disorder, depression or schizophrenia) or somatic disorder (e.g., cancer or stroke) evaluated as leading to a stressful impact on the family functioning.

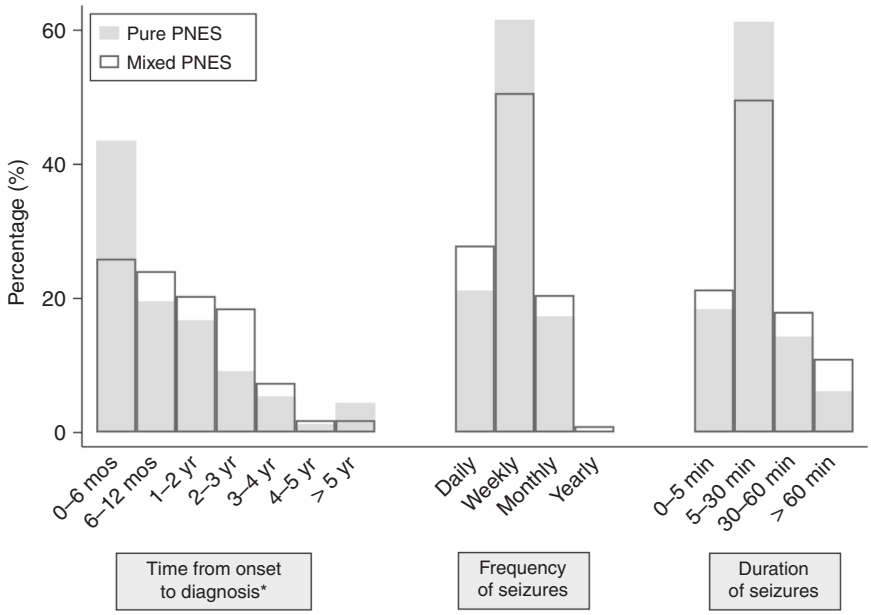

Fig. 4 Seizure Characteristics in Pediatric Onset PNES. Statistically significant difference (*) ($P = 0.03$) between the two groups. mos. months, yr. years, min. minutes.

(Supplementary Tables S4, S5 and Supplementary Figs. S3, S4, S5, S6, S7, S8 (online)).

DISCUSSION

This is the first population-based study of the incidence rate and clinical characteristics of PNES in children and adolescents. We found that the IR of pediatric onset PNES increased between 1996 and 2014 with the maximum IR observed in 2014.

The study revealed new findings demonstrating differences between PNES with and without comorbid epilepsy, while prior findings regarding neurological, psychiatric and socioenvironmental dimensions were replicated.

Incidence rates

Only five prior studies have reported the IR of PNES of which two studies reported on children and three studies on adolescents and adults. A UK study and an Australian study reported the IR of children (age range 7–15 years) with PNES, though not using clear case criteria and having short study periods (i.e., maximum 2 years), showing IRs of 0.4 to 0.5 per 100,000 person-years.[31,32] An Icelandic study on adolescents and adults found an IR of 1.4 per 100,000 person-years for the age group 15–54 years between 1992 and 1996,[33] and the highest IR was for individuals aged 15–24 years of 3.4 per 100,000 person-years. Two non-nationwide studies (i.e., a US study between 1995 and 1998 and a Scottish study between 2006 and 2008) reported on adult populations

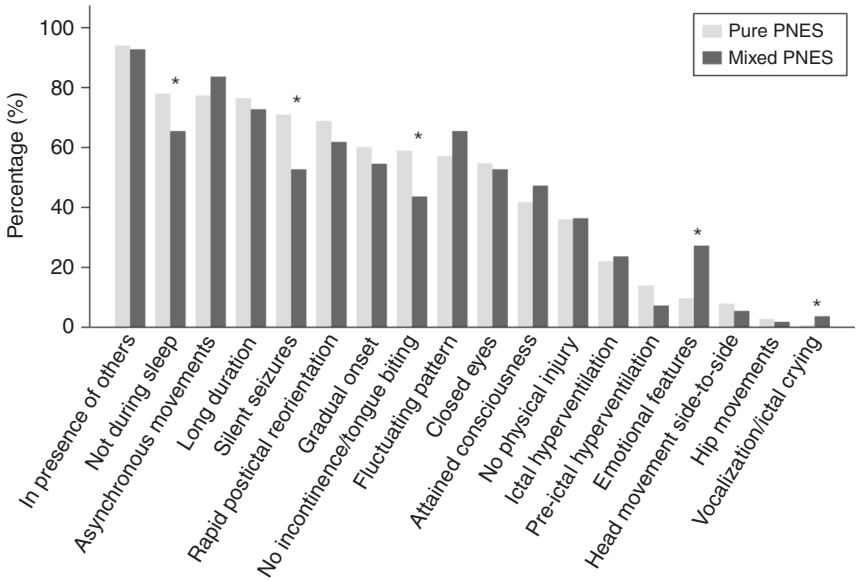

Fig. 5 Seizure Semiology in Pediatric Onset PNES. Semiology subtypes with statistically significant differences (*) ($P < 0.05$) between the pure PNES and mixed PNES groups.

referred to epilepsy specialist centers showing IRs of 3.03 to 4.9 per 100,000 person-years.[34,35] Thus, no prior study has investigated IRs for children and adolescents with PNES utilizing nationwide data over a study period spanning almost two decades. In the current study, the IR for the total study period (i.e., 2.4 per 100,000 person-years) corresponded to the ranges prior reported, but an increase was shown reporting the highest IR of PNES to date (i.e., 7.4 per 100,000 person-years in 2014).

The increasing IRs reported over the last decades in this study are similar to the findings for several psychiatric disorders in children and adolescents, e.g., depression, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD).[36] This could indicate children and adolescents having an increased risk of psychiatric disorders possibly due to increased levels of stress in society, or it could reflect an improved recognition of psychiatric disorders in the pediatric population. Though we are not able to ascertain the reason behind the increasing IRs, our finding of the highest IRs in the "Clinically established" cases could indicate an increasing awareness of conversion disorders among health clinicians.

Clinical characteristics

Prior studies have reported a prevalence of comorbid epilepsy in pediatric PNES ranging from 12 to 44%.[12,13,37] In our study population 14% had comorbid epilepsy. Higher numbers previously reported could result from more selected study samples, e.g., more complex cases recruited from highly specialized epilepsy units. Our results resemble the prevalence of comorbid epilepsy reported in the adult population,[38] thereby contradicting prior suggestions of children and adolescents having higher rates of comorbid epilepsy than adults.[23]

In general, we found a spectrum of semiology manifestations very similar to prior studies including a lower prevalence of asynchronous movements in preteens compared to teens.[2,39] However, asynchronous movements were more prevalent overall in our study population than previously reported[40,41] and at a level comparable to adult PNES.[10] When comparing seizure semiology between pure and mixed PNES some significant differences were found (Fig. 5), which may be explained by the clinicians having difficulties distinguishing between PNES and epileptic seizures in cases with mixed PNES. Time from onset to diagnosis differed between groups with mixed PNES having a prolonged delay to PNES diagnosis, again likely explained by the more complex clinical presentation in these patients. Still, time from onset to diagnosis and duration of seizures for the total study population resembled previous research results,[40,42] while frequency of seizures were lower (weekly) in our study,[3,43] possibly due to less complex cases included across hospital settings as prior mentioned.

Regarding level of functioning, school related difficulties and academic difficulties have been reported in 9–46% of patients with pediatric PNES,[2] with one study describing learning difficulties in 60% of pediatric PNES.[44] Most prior studies have reported normal IQ levels in pediatric PNES,[45,46] while one study found mixed PNES to be associated with intellectual disability.[47] In our study, patients with mixed PNES had a higher proportion of established support in school, reported school problems, learning difficulties and reported low IQ as compared to pure PNES. Since children with epilepsy have been reported to have lower IQ and more frequent learning difficulties than children without epilepsy,[48,49] the higher proportion of school difficulties and intellectual disability found in our study among children with mixed PNES could be explained by the comorbid epileptic disorder or underlying neurological condition, emphasizing the importance of screening for cognitive disabilities especially in these patients.

Besides academic difficulties, PNES is commonly associated with negative life experiences. In our study population, 54.4% reported negative life events, which is similar to rates reported in prior studies.[38,50] The pure PNES group had more negative life events than the mixed PNES group. Likewise, we found more reported triggers and described stress in context with seizures in the pure PNES group. This may stem from clinicians being more prone to seek a psychosocial explanation, when managing pure PNES, and thus recording this information more frequently in the medical notes, but still, this needs further investigation.

To summarize, the pure PNES and the mixed PNES group appeared to some extent quite similar regardless of co-existing epilepsy. Albeit, regarding seizure characteristics, we showed a longer diagnostic delay in the mixed PNES group. In Table 1, outlining patient characteristics, the mixed PNES group showed a higher proportion of intellectual disabilities and school support. Thus, these characteristics were more frequent, when having co-existing epileptic seizures in patients with PNES, and appeared to

increase the complexity of PNES. Similarly, epilepsy is associated with learning difficulties and psychiatric disorders.[51] Thus, factors predisposing to PNES may be the same in patients with pure PNES and patients with mixed PNES, as also suggested in prior research.[52,53] Future research should explore the differences between pure PNES and mixed PNES as well as the possible linkage between these two disorders.

Strengths and limitations

The main strength of this study was the population-based design, the long study period, and the systematic case validation. However, the study also had some limitations.

First, two ICD-10 diagnoses were chosen to define PNES as the main inclusion criteria. The lack of consensus regarding use of register diagnosis for PNES leads to the use of a broad range of less specific codes.[9,26] Thus, we may have missed pediatric PNES cases registered under other diagnostic codes not included in this study, resulting in a conservative but uncertain bias regarding incidence rates.

Second, we adapted the staged diagnostic approach for PNES outlined by the ILAE with a primary focus in the case validation on characteristics and witnessed semiology. Most prior studies have included patients from tertiary epilepsy centers with ictal video-EEG as a main inclusion criteria, which could possibly result in highly selected study samples representing more complex cases leading to a bias regarding disease severity and morbidity. Conversely, our adapted staged approach could lower the diagnostic validity of the PNES cases. Still, only including patients with gold-standard diagnosis of PNES could potentially have decreased the representativeness of our sample due to differing EEG availability over the study period and across hospital settings.

Finally, data on clinical characteristics were based on medical notes. We therefore had to assume that the examining medical doctors performed a thorough history taking and medical examination with all abnormal findings reported in the medical record. Again, this may cause the prevalence of the various items to be underestimated.

CONCLUSION

This population-based study is the first to describe pediatric onset PNES in a nationwide sample of validated cases. We found increasing incidence rates of PNES in the number of children diagnosed during the last two decades. Regarding clinical characteristics, comorbid epileptic seizures increased the complexity of PNES, and prior knowledge regarding neurological, psychiatric and socioenvironmental dimensions were replicated. These findings highlight a need for collaborative care pathways between the pediatric and psychiatric setting and can inform future service planning.

Future research on the characteristics of pediatric onset PNES should include control groups of children with epilepsy not having PNES in order to gain further knowledge on characteristics essential to differentiate between these two mimicking disorders and to help clarify the possible linkage between epilepsy and PNES. This could help in the development and improvement of clinical guidelines on how to recognize and manage pediatric onset PNES.

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AUTHOR CONTRIBUTIONS

A.S.H. contributed to the conception and design of the study, the collection of data, the analysis and interpretation of data and the drafting as well as revision of the manuscript. R.E.N., C.U.R. and J.C. contributed to the conception and design of the study, the interpretation of data and the drafting as well as revision of the manuscript. M.R.D. and S.G.P. contributed to the conception and design of the study, the data analysis, the interpretation of data and revision of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-0945-z) contains supplementary material, which is available to authorized users.

Competing interests: J.C. has received honoraria for serving on the Scientific Advisory Board of Union Chimique Belge (UCB) Nordic and Eisai AB and for giving lectures for UCB Nordic and Eisai, as well as travel funds from UCB Nordic and funding by the Novo Nordisk Foundation (grant number: NNF16OC0019126), the Central Denmark Region and the Danish Epilepsy Association. R.E.N. has received research grants from H. Lundbeck and Otsuka Pharmaceuticals for clinical trials, has received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, H. Lundbeck, Servier, Otsuka Pharmaceuticals, Teva and Eli Lilly, and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda and Medivir. The remaining authors have no financial relationships relevant to this article to disclose. All authors have no competing interests relevant to this article to disclose.

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Patient consent: Not required. The Danish Data Protection Agency (ID: 2016–164), the Danish Health Data Authority (FSEID: 00002709), and the Danish Health Authority (ID: 3–3013–1859) approved the study and data use.

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