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Interobserver reliability of a recently proposed semiological classification in psychogenic nonepileptic seizures in children

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ABSTRACT

Background: The aim of this study is to examine the semiological features of Psychogenic Nonepileptic Seizures (PNES) in children and to evaluate interobserver reliability (IR) of two different classifications. to identify the sources of any variance in agreement and to estimate the IR of the classification systems
Methods: Semiological features of 137 pediatric patients with PNES with and without epilepsy were analyzed. Two different, blinded observers evaluated these semiological features according to A. Asadi-Pooya and Seneviratne et al. classifications. The interobserver reliability was measured using a kappa (κ) coefficient for each PNES classification.
Results: The mean age of patients with PNES was 14.3 (SD: 2.9) years. Ninety five patients were female (69.3 %), 42 were male (30.6 %). Ictal eye closure (n:109, 79.5 %), was the most common seizure semiology. Asymmetric limb movements (n: 71, 51.8 %), motor phenomenon lasting> two minutes (n:69, 50.3 %), and closed mouth (n:53, 38.6 %) were other common seizure semiologies of PNES. Kappa value was higher in A. Asadi-Pooya classification than Seneviratne classification ($k = 0.697$ and $k = 0.433$; $p < 0.05$). Kappa values were higher in the motor and non-motor categories of A. Asadi-Pooya classification than in the mixed category ($k = 0.713$, $k = 0.799$ and $k = 0.455$; $p < 0.05$).
Conclusion: The added value of the new classification scheme with respect to uniform application by experienced pediatric neurologists seems to be reliable and influential, as interobserver reliability of the new classification system was higher than the early classification. Our findings suggest that a simple but comprehensive classification would be useful in the management of PNES.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysmal changes in responsiveness, movements, or behavior which resemble epileptic seizures in appereance but lack a neurobiological origin similar to epileptic seizures and are not associated with electrophysiological epileptic changes. PNES has psychological foundations and causes (LaFrance et al., 2013a). Management of patients with PNES starts with correct diagnosis (LaFrance et al., 2013b).

Misdiagnosis of PNES leads to iatrogenic unnecessary medication for patients and inappropriate treatment, which also significantly increases the cost to the healthcare system (LaFrance et al., 2013b; Reuber, 2008). However, the lack of a classification system for PNES is a major disadvantage in its recognition and management. Classification of PNES plays an important role in the clinical approach as well as in scientific research with respect to inclusion criteria. Semiology-based classifications may facilitate in suspicion, diagnosis, management and also homogenize the studies describing PNES events in the future. However there is still no universally accepted terminology, definition and semiological classification system for PNES. Over the years, some experts have attempted to make various classifications for PNES (LaFrance and Benbadis, 2006; Meierkord et al., 1991; Betts and Boden, 1992; van Merode et al., 1997; Hubsch et al., 2011; Seneviratne et al., 2010; Gröppel et al., 2000; Selwa et al., 2000; Magaudda et al., 2016; Asadi-Pooya, 2019).

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Until very recently, one of the most accepted and commonly used classification scheme is the one by Seneviratne et al. (2010). In Seneviratne et al., PNESs were separated into six subtypes: "rhythmic", "hypermotor", "complex motor", "dialeptic PNES", "nonepileptic auras", and "mixed PNES". After the publication of this expanded classification, many neurology clinicians around the world had responses about this classficiation (Asadi-Pooya, 2019). Doubts mainly exist on whether the implemenation of this expanded classification scheme in clinical practice will succeed or not. Recently, A. Asadi-Pooya proposed a new semiological classification system for PNES. This includes three major classes of "motor", "nonmotor", and "mixed" semiology (Asadi--Pooya, 2019). There is a need for the applicability of this new clasification system for future clinical practice and research. Duwicquet et al. looked at the interrater reliability of five different classification systems in 2017 (Duwicquet et al., 2017). However this particular study did not use the more recent classification proposal by Asadi-Pooya. To be able to appreciate the value of this new classification, studies of inter-observer reliability or agreement help to identify this in decision-making. A short time consuming semiological classification of PNES can help address appropriate diagnosis and management, and also provide standardization for future studies.

Recently Garg et al. retrospectively classified and analysed PNES semiology based on video-electroencephalography (VEEG) using Hubsch, Dhiman, Wadwekar, and Asadi-Pooya's classification systems. They concluded that all events could be classified using the schemes by Asadi-Pooya and Wadweker et al (Garg et al., 2021).

The first objective of this study to establish a comparison between the semiological classifications recommended by Seneviratne et al. and A. Asadi-Pooya to identify the sources of any variance in agreement and to estimate the IR of the classification systems. Secondly, we aimed to provide a descriptive profile of patients with (PNES) in children in Turkey who have been evaluated in a tertiary epilepsy monitoring unit.

2. Methods

2.1. Patients and methods

Video-EEG recording and medical files of all patients, who underwent video EEG monitorization between 1997 and 2022 at Gazi University Hospital Video EEG Monitorization Unit were reviewed retrospectively. All patients underwent a 32-channel video-EEG monitoring (Nihon-Kohden) with 10–20 system electrode placement, plus anterior temporal electrodes. Prolonged Video-EEG monitorization was performed for a mean time of three days, ranging from one to five days. All patients who were included had at least one typically characterized event during monitorization. For the diagnosis of PNES, an epileptologist (EA, AS) experienced in the diagnosis of seizures confirmed the diagnosis when semiology was typical of PNES while on video-EEG monitoring, and no epileptiform activity before, during or after the seizure was captured on ictal video-EEG recording of the patients. Patients included in this study presented a normal or non epileptiform EEG during the event. The typical event was defined by reviewing the episode with a person who has witnessed such events before. We required more than one episode in doubtful cases.

Semiological features of all pediatric patients with PNES both with and without epilepsy were analyzed. We included the PNES events captured in patients with coexistent true epilepsy who were referred to our Epilepsy Unit for drug resistance and in patients referred due to the presence of recurrent paroxysms or transient neurological events with a suspicious diagnosis of epilepsy.We excluded patients with non epileptic paroxysmal disorders captured during video EEG monitorization (syncope, tics, paroxysmal choreoathetosis, dystonia, parasomnia). Detailed clinical and demographic data of the patients were obtained from the medical records. All episodes of PNES that were recorded during the video-EEG monitoring were re-evaluated by two pediatric neurologists (H.E(Observer 1) and E.A (Observer 2)) as retrospectively. Each clinical event was visually analyzed in detail by H.E. and E.A. Final decisions were based on the agreement of findings by both physicians. These clinical episodes were compared according to the semiological classifications proposed by Seneviratne et al. and recently proposed classification system by A. Asadi-Pooya.

2.2. Statistical analysis

Initially, descriptive analyzes were conducted. Prepubertal (< 12 years of age) and postpubertal groups (>12 years of age) were compared using a Pearson chi-square test with a significant alpha level of 0.05. Cohen's kappa (κ), a chance-corrected measure of IR, was computed for each tested classification system. Values of κ were interpreted via guidelines suggested by Landis & Koch, which rate themas follows: 0.80–1.00, almost perfect; 0.60–0.80, substantial; 0.40–0.60, moderate; 0.20–0.40, fair; 0.00–0.20, slight; and 0.00, poor (Landis and Koch, 1977). We also reported class specific values within each classification. Data were analyzed using SYSTAT (version 12; Systat Software, Inc., U. S.A.). Confidence interval (CI) estimation for proportions was calculated according to the method described by Fleiss, Cohen, and Everitt (Fleiss et al., 1969). We also compared two classification systems using the McNemar's chi-square test with a p value of < 0.05 was considered statistically significant.

3. Results

One thousand two hundred eighty seven children underwent prolonged Video EEG monitoring at Gazi University Hospital Video EEG Monitorization Unit with the purposes of presurgical workup, clinical seizure definition, or differentiation between epileptic and non-epileptic paroxysmal events between 1997 and 2022. One hundred thirty seven children were diagnosed with PNES, with or without epilepsy, by the clinical assessment and long-term video-EEG monitoring with ictal recording of their spontaneous seizures during this period.

In this study, the prevalence of PNES in children evaluated with video-EEG was 10.64 % (137/1287). The mean duration of video EEG monitoring was 3.7 ± 0.8 days.

The mean age of patients with PNES was 14.3 (SD: 2.9) years. Ninety five patients were female (69.3 %), 42 were male (30.6 %). Ninety one (66.4 %) patients were postpubertal, 46 (33.5 %) patients were prepubertal. The mean time until diagnosis of PNES patients was 23 ± 20 months (min: 2 months, max: 82 months). The mean time to diagnosis in patients with PNES+ epilepsy was found to be 79.4 ± 48.3 months.

There were 61 (44.5 %) patients with PNES+epilepsy. Twenty seven (44.2 %) of PNES+epilepsy patients were prepubertal and 34 (55.3 %) were postpubertal, nineteen (26 %) of patients with PNES were prepubertal and 57 (75 %) were pubertal. The age and gender of the patients did not show any significant difference between the prepubertal and postpubertal groups of PNES and PNES+epilepsy patients ($p = 0.48$). Fifty two (37.9 %) patients had a family history of epilepsy. Fifty nine (43 %) patients were receiving two or more antiepileptic drugs whereas nine (6.5 %) were not receiving any antiepileptic drugs. 14 (23.7 %) of 59 patients receiving antiepileptic drugs were diagnosed as PNES by video EEG monitorization did not have epilepsy. Eight (5.8 %) patients were receiving psychotropic drugs, ECT was applied to one patient due to severe depression.

Ictal eye closure (n:109, 79.5 %), was the most common seizure semiology. Asymmetric limb movements (n: 71, 51.8 %), motor phenomenon lasting> two minutes (n:69, 50.3 %), and closed mouth (n:53, 38.6 %) were other common seizure semiologies of PNES (Table 1).

The overall κ value for interobserver reliability was 0.697 (95 % confidence interval) for the A. Asadi-Pooya classification, indicating substantial agreement (Table 2).

The overall κ value for interobserver reliability was 0.433 (95 % confidence interval) for the Seneviratne et al. classification, indicating fair agreement (Table 3).

Table 1
Clinical characteristics (semiology) of PNES in relation to with or without epilepsy.

	n:137		Total n:137
	With epilepsy n = 61	Without epilepsy n = 76	
Closed mouth	17	39	53 (38,6 %)
Eyelid flutter	2	7	9 (6.5 %)
İctal eye closure	52	57	109 (79.5 %)
Asymmetric limb movement	24	27	71(51.8 %)
Pelvic thrusting	13	16	29 (21.1 %)
Undulating motor activity	17	24	41 (29.9 %)
Pseudosleep	7	10	17 (12.74 %)
Hyperventilation before event	2	10	12 (8.7 %)
Rapid postictal Reorientation	10	23	33 (24,08 %)
İctal stuttering	6	3	9 (6.5 %)
Motor phenomen lasting >two minutes	34	35	69 (50.3 %)
İctal crying	8	12	20 (14.5 %)
Prolonged ictal atonia	9	6	15 (10.9 %)
Resisted lid opening	2	3	5 (3,6 %)
Staring blankly	11	8	19 (13,8 %)
Vocalization during tonic clonic phase	6	11	17 (12.4 %)
Opisthotonos	8	13	21(13,5 %)
Trembling	12	19	31 (22.6 %)
Side to side head shaking	6	14	20(14.5 %)
Loss of responsiveness	11	7	18(13,1 %)
Ictal grasping	2	7	9 (6.5 %)
Urinary incontinance	1	2	3 (2.1 %)

Table 2
Interobserver reliability for the A. Asadi-Pooya classification.

		Motor	Non-Motor	Mixed		
Observer1	Motor	67	11	1	79	
	Non-Motor	9	26	2	37	Kappa= 0.697 **p:0.0001**
	Mixed	11	6	4	21	
TOTAL		87	43	7	137	

In the A. Asadi-Pooya classification, there is a statistically significant and substantial agreement in motor and non-motor sub-categories (k = 0.713 and k = 0.799 (95 % confidence interval); $p < 0.05$). Statistically significant and moderate agreement is in the mixed sub-category (k = 0.455 (95 % confidence interval); $p < 0.05$).

In the Seneviratne classification, there is statistically significant and moderate, fair and slight agreement in the mixed, complex motor and rhytmic motor sub-categories (k = 0.455, k = 0.36 and k = 0.157(95 % confidence interval), $p < 0.05$).

We compared proportions of events which may be successfully classified using each of the semiology-based classification systems using the McNemar's chi-square test. Significantly more events could be classified using the Asadi-Pooya (100 % classified) ($p < 0.05$) system compared to the classification by Seneviratne (90.5 % classified).

4. Discussion

There are many patients with PNES who are truly 'difficult' to have video EEG monitorization and get the exact diagnosis. Many examinations in child neurology practice are time consuming. The patients and parents may give various and dissimilar histories. There is a need for the applicability of a simple semiological classification system as efficient as a detailed one (Garg et al., 2021; Subramanian Muthusamy et al., 2022; Dhiman et al., 2014). Our study describes the semiological characteristics of patients with PNES referred to a specialized epilepsy center and demonstrated that significantly more events could be classified using the A. Asadi-Pooya.

The results of this study shows that the interobserver reliability of the newly proposed classification scheme by A. Asadi-Pooya is higher than the interobserver reliability of the scheme proposed by Seneviratne. Interobserver reliability was much more high especially in motor and non-motor sub-categories whereas was moderate in mixed sub-category of A. Asadi-Pooya. The fact that the CIs for κ for the detailed and semiological classification system by A. Asadi-Pooya do not overlap indicating that they are significantly different at least $P < 0.05$. The percent agreement is higher in the new classification system, indicating that it may be used for the classification of PNES in children.

In the study by Garg A. et al., the classification systems of Hubsch, Dhiman, Wadwekar and A. Asadi-Pooya were compared and concluded that the A. Asadi-Pooya classification, which evaluated only three categories, was inclusive (Garg et al., 2021). In the study by Duwicquet et al. (2017), Magaudda et al. (2016) and Gröppel et al. (2000). also found that the classifications were more reproducible than the others, as they included fewer subcategories (Reuber and Elger, 2003). It should be noted that a classification system that takes into account too many clinical signs can cause confusion for clinicians and lead to poor interobserver reliability.

The difficulty in establishing a timely correct diagnosis is a relevant matter of concern for PNES in children. Diagnosing PNES is important avoiding unnecessary use of antiepileptic drugs, possible side effects and cost burden (Bhatia and Sapra, 2005). It is a well known fact that there is a delay between the onset of seizures and the diagnosis of PNES (Paolicchi, 2002; Alsaadi et al., 2004). In the video-EEG monitorization performed in epilepsy centers, it was found that one fourth of the

Table 3
Interobserver reliability for the Seneviratne et al. classification.

		Observer 2					Total	
		Mixed	Rhytmic Motor	Hypermotor	Complex motor	Dialeptic		
Observer1	**Mixed**	5	10	0	0	4	19	
	Rhytmic Motor	0	16	10	14	0	40	Kappa= 0.433
	Hypermotor	0	0	6	0	0	6	**p:0.001**
	Complex motor	2	21	2	16	0	41	
	Dialeptic	0	9	0	0	22	31	
TOTAL		7	56	18	30	26	137	

patients whose seizure control could not be achieved after the use of two or more antiepileptic drugs (AEDs) did not have epileptic seizures (Verrotti et al., 2009).

One of the most astonishing finding of this study is the long duration of the time lag occurring between the onset of PNES and the correct diagnosis of PNES in our children, which resulted to elapse for a maximum period of almost one decade in particular patients.This might be due to teh fact that our video-EEG monitoring unit is part of a huge metropolitan tertiary care center that services a diverse patient population with more complicated cases. The difficulty in obtaining the correct diagnosis proved to represent a dramatic barrier for most PNES patients. This long-lasting search for correct diagnosis causes numerous referrals to various specialists as well as several instrumental examinations, representing a time-consuming process which is frequently inconclusive since patients often receive incorrect diagnoses and over-treated as epilepsy (Asadi-Pooya and Sperling, 2015). This frustrating delay and treatment failure considerably affect the patients' quality of life, with a subsequent worsening of their clinical status and remarkable psychological distress, for both children and their families. One of the hopes of this recent classification is that it will allow a model of care in the correct and timely diagnosis of PNES in children.

The semiological classifications of PNESs are important for categorizing these events in clinicians' daily practice, taking into account semiological features. Asadi-Pooya classification was found to be easier to apply since it had fewer categories and also made provisions for mixed semiology when compared with classification by Seveniratne et al. The system by Seveniratne et al. due to multiple categories, were more challenging to apply. Despite this, we could not classify all events with this system.

It is not yet clear how these classification systems finally affect patient management and final outcomes in a comparative way and this need needs to be assessed in future studies.

Our study has a few limitations. The first and most important limitation is the small number of patients which do not show the exact incidence of PNES in the pediatric population. This gives rise to the thought that mild or definite cases were probably not monitored due to limited access to the monitoring. Secondly, because of the retrospective manner of the study our data is constrained by the information from the medical records.

The added value of the new classification scheme with respect to uniform application by experienced pediatric neurologists seems to be reliable and influential, as interobserver reliability of the new classification system was higher than the early classification.

5. Conclusion

Our study yields the following conclusions.

1. Recognition of the clinical aspects of PNES plays a key role in diagnosing PNES in clinical practice. Due to the inconsistent manifestations, long-term VEM can be very useful in differentiating epileptic from nonepileptic events to prevent overmedication and guide proper treatment.
2. However due to the limited availibility of VEM, it is necessary to classify PNES into different semiological categories by a less time consuming and practical classification system with a moderate to substantial interrater reliability.
3. Significantly more events could be classified using the Asadi-Pooya system. We recommend the use of A. Asadi-Pooya classification system with only three categories including mixed semiology for PNES in children, facilitating a greater interobserver reliability and a comprehensive identification.

Key message

Simple but comprehensive classification would be useful in the management of PNES.

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Conflicts of interest

There are no conflicts of interest.

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