Psychogenic non-epileptic seizures in Japan: Trends in prevalence, delay in diagnosis, and frequency of hospital visits

Purpose: Psychogenic non-epileptic seizures (PNES) are psychogenic disorders that often resemble epileptic seizures. Herein, we describe the recent clinical trends of PNES by using the data from a large, claims-based Japanese database obtained from the Japan Medical Data Center.

Methods: A 10-year epidemiological study of patients of all ages with newly diagnosed PNES was conducted. Data were extracted using the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes. Prevalence in new epilepsy patients and period of the diagnostic delay of PNES after epilepsy diagnosis were retrieved from the data. The study endpoint was change in frequency of hospital visits. Data of 413 patients with PNES were retrieved using the criterion of “PNES diagnosis after epilepsy diagnosis.”

Results: The highest PNES prevalence in new epilepsy patients was observed in the 40–49 year age group (4.3%) for males, and in the 30–39 age group (4.9%) for females. The ratio of the prevalence in males to that in females was 1:2 for 0–9, 10–19, and >60 age groups, and 1:1 for the other age groups. A significant and positive correlation was found between the frequency of hospital visits and duration of the diagnostic delay of PNES. After PNES diagnosis, the average number of monthly hospital visits decreased over time.

Discussion: The differences in the duration of diagnostic delay of PNES among cases and also a decrease in the frequency of hospital visits after PNES diagnosis highlight the importance of early differentiation between epilepsy and PNES.

Key words: Psychogenic non-epileptic seizure; Diagnostic duration; delay, Epilepsy diagnosis

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Abstract

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Introduction

Psychogenic non-epileptic seizures (PNES) are estimated to occur in 2 to 33 per 100,000 of people; approximately 20% of outpatients visiting an epilepsy clinic for the first time are thought to have PNES [1-8]. The features of PNES occasionally overlap with epilepsy and the two may occur concomitantly in approximately 4 to 60% of PNES cases [9]. Therefore, a definitive diagnosis of PNES is crucial to allow prescription of the appropriate treatment [10]. Monitoring of the ictus using a video electroencephalogram (EEG), a relatively costly and time-consuming examination, is considered the gold standard for distinguishing PNES from epilepsy [11-18]. Treatments for PNES, such as cognitive behavioral intervention, education, psychotherapy, and communication and family therapy, are thought to be effective. However, there is no documented comparison of the effectiveness among those treatments. Part of the clinical outcomes of treatment for PNES is thought to be a decrease in the frequency of hospital visits and/or a decrease in the frequency of seizures [19, 20].

The majority of the literature on the epidemiological and etiological outcomes of PNES is from Europe and USA, although a number of papers from other countries such as Iran have suggested significant differences among patients with PNES from different countries [11]. These are most likely due to the differences in culture, health systems, medical traditions, and communication styles between doctors and patients.

In the present study, the current epidemiological features of PNES in Japan were evaluated from patient data that were extracted from a claims-based database using the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes.

Patients and Methods

We conducted a 10-year retrospective epidemiological study of patients of all ages who were newly diagnosed with PNES, using the large, claims-based database of the Japan Medical Data Center (JMDC). The patient characteristics, PNES prevalence in newly diagnosed epilepsy patients (hereinafter, “prevalence”), the period of delay in diagnosing PNES in each department of the hospital (including departments of psychiatry, internal medicine, neurology, neurosurgery, and pediatrics) and the frequency of hospital admissions were recorded. Also, the frequency of hospital visits before and after PNES diagnosis were recorded to evaluate patient outcomes. Due to the retrospective nature of the study, the need for informed consent was waived. The study protocol was approved by the Ethics committee of Kyoto University (Kyoto, Japan; registration number, E2478).

Data source and analysis

The data analyzed in this study were retrieved from a claims-based database of approximately 1.60 million individuals, which is maintained by a large corporate social insurance system in Japan and comprises data of employees working at middle-to-large-sized companies, and their families; family members who are unemployed are incorporated into the insurance membership of employees, although the majority of members are employed. This database covers nationwide cohorts and includes a wide range of
employers; thus, it is believed to be representative of the overall Japanese population. The records of all medical claims made by these individuals were obtained from the JMDC, which maintains the database [21], and traced using anonymous patient codes.

In Japan, only a few hospitals specialize in the treatment of epilepsy or PNES. The treatment of PNES is conventionally performed across various departments, but the majority of the patients are treated in the departments of neurology and psychiatry. Although data for any particular disease in the database can be retrieved using an ICD-10 code, there is no specific code designated for PNES. For instance, PNES is preliminarily represented by the ICD-10 code F44, but both PNES and dissociative (conversion) disorders are included in this code [20]. Therefore, we attempted to extract data for patients with PNES by using the following criterion: a new diagnosis of epilepsy that was eventually changed to a diagnosis of dissociative (conversion) disorder from 2005 to 2014. We expected this criterion to identify dissociative disorders that resembled epilepsy at initial diagnosis, but would eventually progress to PNES. This criterion was based on the PNES diagnostic guidelines published by the Japan Epilepsy Society in 2009. These guidelines define PNES as a psychogenic disorder that resembles epilepsy, although the two are different. They only recommend video-EEG recording to differentiate PNES from epilepsy; therefore, the diagnosis of PNES is usually carried out by physicians. Of note, data from 2005 were used to identify new patients with epilepsy from 2006 onward, and the data of patients who had been diagnosed with epilepsy during the data period but with no record of epilepsy in 2005, and who had no record of dissociative (conversion) disorder before the initial diagnosis of epilepsy were extracted as the data of new epilepsy patients. From these new patients with epilepsy, new patients with PNES were defined as those who were diagnosed with dissociative (conversion) disorder after being diagnosed with epilepsy. We believed that this criterion would allow us to identify a new PNES patient cohort after 2006. The patient characteristics were summarized, and the prevalence of PNES in the JMDC database from 2006 to 2014 was calculated for each 10-year age group up to and including the age of 59 years, and for another age group of individuals >60 years, using the new epilepsy patients in each age group. Chi-square analysis was used to calculate the difference in prevalence between males and females. In addition, as communication between patient and physician regarding the relatively less severe manifestations of PNES (compared to epilepsy) may ease the psychological triggers that induce seizures [5, 19], we recorded the frequency of hospital admissions before and after the diagnosis of PNES.

Duration of diagnostic delay of PNES after epilepsy diagnosis

The duration of the diagnostic delay of PNES was calculated as the number of months between the initial diagnosis of epilepsy and a definitive diagnosis of PNES. A multivariate logistic regression analysis was conducted to examine whether the variables identified as significant factors in a prior univariate logistic regression analysis [variables examined: sex (male, female), age (age groups), frequency of hospital visit before
diagnosis of PNES (0–1 and 2–3 times per month), and hospital transfer between epilepsy and PNES diagnosis (transferred and not transferred)] influenced the duration of the diagnostic delay of PNES. The cutoff period of diagnostic delay was set between <10 months and ≥10 months, because the majority of diagnosis delay was observed to be <10 months. As PNES may be diagnosed or distinguished from epilepsy based on the specific period of disease development and the particular specialty of each doctor (including neurologists and psychiatrists), we used monthly data from the period between the initial diagnosis of epilepsy and the subsequent diagnosis of PNES at each department visit. We assessed the period between the initial epilepsy diagnosis and the diagnosis of PNES among departments from the first hospital visit. If records of department were not available for the first hospital visit, we used the earliest available record of a visit to the department that could be confirmed in the database after the initial epilepsy diagnosis. Additionally, we tried to assess whether the duration of the diagnostic delay of PNES correlates with the frequency of hospital visits before the diagnosis of PNES among departments in which the diagnosis of epilepsy was made.

**Frequency of hospital visits before and after PNES diagnosis**

Variation in the frequency of hospital visits is a possible outcome of the diagnosis of PNES. We compared the number of hospital visits before and after a definitive diagnosis of PNES (for cases diagnosed before January 2014 with available records of hospital visits for 1 year after PNES diagnosis) as the study endpoint. All statistical analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY). The level of significance was set at 5%.

**Results**

**Baseline patient characteristics**

We obtained data from 413 patients (males: females, 200:213) who were newly diagnosed with PNES, which accounted for approximately 1.6% of all patients newly diagnosed with epilepsy (Figure 1). Epilepsy patients comprised 4.4% of the average population of the cohorts in the database during the period. The baseline characteristics of these PNES patients (at the initial diagnosis of epilepsy) are presented in Table 1. Notably, the age range of females was slightly higher than that of males (1–74 years vs. 1–72 years, respectively), whereas the mean and median ages of females were relatively lower than those of males (34.5 and 34 years vs. 37.0 and 39 years, respectively).

**PNES prevalence in new epilepsy patients by age group and potential comorbidity with epilepsy**

The prevalence of PNES among new male and female epilepsy patients was relatively high (≥3.0%) in the age groups 10–59 years (Table 2). The prevalence of PNES in males was relatively higher (≥3.0%) in the 20–59 age group, whereas in females, the prevalence was relatively higher in the 10 to >60 age groups. For males, the highest prevalence was observed in the 40–49 age group (4.3%). For females, the highest prevalence of PNES was noted in the 30–39 age group (4.9%).
PNES prevalence was higher among females than males (ratio between 1:1.1 to 1:2.3) for all the age groups, except the 40–49 age group, and these differences were found to be significant for the 10–19 (p = 0.01) age group.

After PNES diagnosis, 63.5% of males and 56.3% of females were re-diagnosed with epilepsy as a potential comorbidity with PNES.

**Table 1.** Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Male patients (n = 200)</th>
<th>Female patients (n = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) age (yrs.)</td>
<td>37.0 (34.9–39.0)</td>
<td>34.5 (32.4–36.7)</td>
</tr>
<tr>
<td>Median age (yrs.)</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Minimum age (yr.)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum age (yrs.)</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>SD</td>
<td>14.7</td>
<td>16.0</td>
</tr>
</tbody>
</table>

PNES prevalence was higher among females than males (ratio between 1:1.1 to 1:2.3) for all the age groups, except 40–49 age group, and these differences were found to be significant for the 10–19 (p = 0.01) age group.

After PNES diagnosis, 63.5% of males and 56.3% of females were re-diagnosed with epilepsy as a potential comorbidity with PNES.

**Frequency of hospital admission**

A total of 37 patients were admitted to the hospital once, 6 patients were admitted to the hospital twice, and one was admitted three times for epilepsy. For PNES, 55 patients were admitted to the hospital once, and 5 patients were admitted twice.

**Duration of the diagnostic delay of PNES and frequency of hospital visits after PNES diagnosis**

Among the 413 patients diagnosed with PNES, 201 (48.7%) were diagnosed with both epilepsy and PNES at the same hospital, although the diagnosis was being based on a coding for epilepsy or dissociative (conversion) disorders. The mean duration of the diagnostic delay of PNES was 12 months (95% confidence interval [CI]: 10–14 months, median: 4 months) and <10 months for the majority of patients (257, 62.2%) as shown in Supplementary Figure S1. In the group that was diagnosed with PNES within 10 months of an epilepsy diagnosis, the highest proportion of patients were diagnosed in the same month of the first epilepsy diagnosis.
A univariate logistic regression analysis identified a significant association (p<0.01) of PNES diagnostic delay with higher frequency of hospital visit before the diagnosis of PNES and hospital transfer between epilepsy and PNES diagnoses. Sex and age were not significantly associated with late PNES diagnostic delay. Odds ratios from a multivariate logistic regression analysis of late PNES diagnosis (≥10 months) were 2.03 [95% CI: 1.52–2.7] (p<0.001) for patients with more frequent hospital visits (2–3 times per month) before the diagnosis of PNES, and 2.26 [95% CI: 1.48–3.46] (p<0.001) for patients who transferred hospital between epilepsy and PNES diagnoses. Among the 224 records obtained from various medical departments, most patients were diagnosed in the psychiatry department. The frequency of hospital visits per month before PNES diagnosis was highest in the psychiatry department and lowest in the pediatrics department. There was a relatively large difference in the duration between diagnoses among departments in which the diagnosis was confirmed. The shortest duration was found in the neurology department (8.94 months [95% CI: 5.69–12.18]) and the longest was in the psychiatry and neurosurgery departments (15.25 months [95% CI: 12.00–18.50], and 15.89 months [95% CI: 3.88–27.91], respectively) (Supplementary Table S1). In these departments that had longer periods of diagnostic delay, there might be more patients who were misdiagnosed. The diagnostic period of PNES and frequency of hospital visits per month (before PNES diagnosis) were compared between the patients who did (or did not) transfer to other hospitals between the diagnoses of epilepsy and PNES, new patients with the diagnosis of dissociative (conversion) disorders after the first epilepsy diagnosis. P values were calculated using chi square analysis. (**p<0.01, *p<0.05)
PNES among departments (Supplementary Table S1). The ratios of the number of those who transferred to other hospitals to those who did not were similar in all departments. Also, a relatively longer diagnostic period for PNES was observed in those who transferred to other hospitals (except for the pediatrics, neurosurgery, and other departments which had no significant difference in the diagnostic period compared to those who did not transfer).

After excluding the pediatrics department, which had a relatively long diagnostic delay of PNES and the lowest frequency of hospital visits, a significantly positive correlation \( (r = 0.82, p = 0.045) \) was found between the diagnostic duration and frequency of hospital visits (Supplementary Table S1).

**Frequency of hospital visits after PNES diagnosis**

On average, the patients visited the hospital less than once per month for 1 year before a diagnosis of PNES was made (Figure 2). On the other hand, in the period following PNES diagnosis, the frequency of hospital visit per month increased for the first 3 months, then declined continuously from months 4 to 6. The frequency of hospital visit was less than one visit per month at 7-9 months and 10-12 months after PNES diagnosis.

**Discussion**

To the best of our knowledge, this is the first study on the trends of PNES based on a massive database of more than 1.60 million patients in Japan. This large-scale study analyzed the epidemiological features of patients with PNES from a sample population in Japan using a new patient identification method. Our data included patients with PNES who were diagnosed at many departments and hospitals, which may provide a better representation of patients with low disease severity as compared to patient cohorts recruited from a traditional single center. PNES cases accounted for 1.6% of patients with epilepsy, and the proportions with epilepsy as a potential comorbidity with PNES were 63.5% for males and 56.3% for females. The PNES prevalence was calculated based on new epilepsy patients (observed over a period of 10 years). However, given that the PNES diagnosis was made within 10 months for the majority of patients, and the frequency of hospital visits decreased within 1 year after PNES diagnosis, we assume that this 10-year observation would suffice for the detection of general PNES prevalence in epilepsy patients. Although a few population-based studies on PNES prevalence have been reported, particularly outside the US and Europe, the preva-
lence of PNES reported in epidemiological studies was 4% of epilepsy patients, and 4 to 60% having epilepsy as a comorbidity [1, 9]. In these epidemiological studies, the prevalence was assessed at epilepsy centers and may differ from our calculation of prevalence from data extracted from the general population. However, the overall prevalence of PNES by age group, and the rate of having epilepsy as a potential comorbidity were similar to the prevalence reported in previous studies. The disparity in the relatively lower prevalence of PNES among epilepsy patients in our study may be attributable to a wider detection of epilepsy in the overall cohort compared to tertiary care centers, which were used in most previous studies to assess the prevalence of PNES among epilepsy patients. Our data analysis was based on the PNES diagnostic guidelines of Japan and limited to clinical observations, which may have differed from the diagnostic methods and tests conducted for patients in previous studies.

This study had a few limitations. First, it was conducted by extracting data on PNES using ICD-10 codes. In some instances, the ICD-10 code may have been applied less rigorously in clinical practice. Also, the third data selection criterion of “no record of dissociative conversion before epilepsy diagnosis” was expected to exclude cases with an initial diagnosis of dissociative conversion that was not PNES and a second diagnosis of epilepsy as a comorbidity, or epilepsy as the correct diagnosis, and also to identify PNES cases that were not diagnosed or initially misdiagnosed as epilepsy. However, the data were limited with regard to differentiating the comorbidity of epilepsy from PNES. Some patients may have had a diagnosis of epilepsy and then developed a form of somatization that was not PNES. Second, patients who were diagnosed with PNES without a previous diagnosis of epilepsy may have been overlooked. Therefore, the certainty of PNES diagnosis should be examined in further studies.

The trend of PNES prevalence among young and elderly patients is unknown. Among a few studies that examined the PNES epidemiological trend, the prevalence of PNES was similar in young and elderly patients, although the clinical background of PNES was thought to differ between these cohorts [22-24]. In the present study, the youngest patient was 1 year of age. As diagnosis of PNES would be more difficult for infants, further analysis of younger age groups is needed [25]. PNES prevalence was higher in age groups older than 10 years. It was interesting to find significant differences in the prevalence between males and females, particularly in those aged 10-19 years. The reason for this is unknown. However, it may indicate that the lifestyle or psychological circumstances in males and females may differ in these age groups. The round-up ratio of the prevalence in males to that in females was 1:2 for 0–9, 10–19, and ≥60 age groups, which is consistent with the results of previous studies [4, 11]. In the 20–29, 30–39, 40–49, and 50–59 age groups, the round-up ratio of the prevalence in males to that in females was 1:1. These results may suggest a possible difference in the male-to-female prevalence among the age groups, as well as a difference in behavior regarding the frequency of hospital visits between females and males. Further
studies are needed to clarify these trends. Nevertheless, the difference in the PNES prevalence between males and females and among different age groups suggests that the patient’s clinical background is highly associated with a diagnosis of PNES. The frequency of hospital admission was relatively low for both epilepsy and PNES, and the diagnosis of the selected PNES cohort was mostly performed without video-EEG recording that is usually needed for hospital admission. In Japan, the diagnosis of PNES is often based on a clinician’s clinical judgment without video-EEG confirmation, and this is a major limitation of the large claims-based data used in our study. Although the data could cover a wide range of patients and cohorts, without information from chart review and video-EEG confirmation, it may be difficult to diagnose or confirm a case of PNES accurately.

The largest number of cases was diagnosed in the psychiatry department, probably because epilepsy is often treated in the psychiatry department in Japan. The largest number of PNES cases were diagnosed with epilepsy and PNES within the same month. Since the data used in this study were only retrieved from monthly records, the order of those diagnoses with both epilepsy and PNES remain unknown. Nevertheless, the duration of the delay in diagnosis of clinical PNES observed for the majority of cases in our study was relatively short compared to those in previous studies, which reported 1.5–9 years for the diagnosis delay [1, 26-29]. One of these studies reported an average duration of 7 years calculated from the period between the mean age at PNES onset and the mean age at PNES diagnosis at the department of epilepsy in a university hospital in Germany observed for a 10-year period [1]. The data in the present study were also collected from a relatively wide range of institutions and departments and potentially included less severe cases, which is important because the period for differentiation of PNES from epilepsy may depend on the severity of the case.

The duration of the diagnostic delay of PNES was shortest in the neurology department, which also had a relatively low frequency of hospital visits during the diagnostic duration. Interestingly, the psychiatry and neurosurgery departments had relatively long diagnostic delay of PNES, and the latter showed a wider 95% CI range. Although this trend may depend on the condition and severity of seizure in each patient, these findings suggest that the standard of diagnostic criteria varies among doctors, and diagnostic boundaries may exist between departments. A significant positive correlation between the frequency of hospital visits and duration of diagnostic delay of PNES indicates that the severity may be higher in patients with a higher frequency of hospital visits. Therefore, the diagnostic duration tended to be longer in those who visited the psychiatry and neurosurgery departments more frequently. A multivariate logistic regression analysis of PNES diagnostic delay showed a significant association with more frequent hospital visit as well as hospital transfer before the diagnosis of PNES. These results potentially indicate patient status or characters that make diagnosis more difficult.

The frequency of hospital visits continued to decrease over time after PNES diagnosis, but in the first 3 months of PNES diagnosis, the overall frequency increased. This result suggests that during the first 3 months after
PNES diagnosis, increased communication of doctors with patients about PNES may have contributed to a decrease in the frequency of hospital visits after the first 3 months. In addition, previous studies have reported that the frequency of emergency room visits decreased as a consequence of routine consultations and the diagnosis of PNES. Also, communication between doctors and patients may have effectively decreased the need for treatment and PNES recurrence [30-35]. These results further highlight the importance of differentiating PNES from epilepsy as early as possible.

Previous epidemiological studies of PNES were generally conducted at one center. Thus, patients with PNES who were not referred to this center would not have been included in the study. As previous studies lacked useful data, further studies on this topic are needed. The findings of the present study highlight the usefulness of existing large databases in further elucidation of the epidemiology of PNES.

Conclusions
This study examined the epidemiological and clinical trends of PNES cases in Japan. The prevalence of PNES was highest in age groups older than 10 years. The differences in the diagnostic delay of PNES among cases and departments, and also a decrease in frequency of hospital visits after PNES diagnosis suggest the importance of early differentiation between epilepsy and PNES. Further studies to clarify these trends are necessary.

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Conflicts of interest
The authors declare that they have no conflicts of interest.

References


Supplementary Materials

**Figure S1.** Duration of the diagnostic delay of psychogenic non-epileptic seizures

The duration of diagnostic delay of psychogenic non-epileptic seizure (PNES) was calculated as the number of months between the initial diagnosis of epilepsy and a definitive diagnosis of PNES.

**Table S1.** Case distribution, frequency of hospital visit, and duration for PNES diagnosis by department according to hospital transfer status between epilepsy and PNES diagnoses

<table>
<thead>
<tr>
<th>Frequency in distribution ranking</th>
<th>Department</th>
<th>n (proportion within 224)</th>
<th>Frequency of hospital visit (per month) before diagnosis of PNES (95% CI)</th>
<th>Average period (months) between diagnosis of epilepsy and PNES (95% CI)</th>
<th>N: transfer* / no transfer*</th>
<th>Average period (months) between diagnoses of epilepsy and PNES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Psychiatry</td>
<td>97 (0.433)</td>
<td>1.32 (0.37–1.88)</td>
<td>15.25 (12.00–18.50)</td>
<td>48/49</td>
<td>17.81 (11.10–24.53)</td>
</tr>
<tr>
<td>2</td>
<td>Internal medicine</td>
<td>47 (0.210)</td>
<td>1.31 (0.35–1.02)</td>
<td>12.26 (7.47–17.04)</td>
<td>25/22</td>
<td>13.88 (5.40–22.36)</td>
</tr>
<tr>
<td>3</td>
<td>Neurology</td>
<td>32 (0.143)</td>
<td>0.69 (0.29–1.81)</td>
<td>8.94 (5.69–12.18)</td>
<td>14/18</td>
<td>15.56 (7.13–23.98)</td>
</tr>
<tr>
<td>4</td>
<td>Neurosurgery</td>
<td>19 (0.085)</td>
<td>1.05 (0.21–1.52)</td>
<td>15.89 (3.88–27.91)</td>
<td>11/8</td>
<td>20.36 (1.12–39.6)</td>
</tr>
<tr>
<td>5</td>
<td>Pediatrics</td>
<td>14 (0.062)</td>
<td>0.57 (-0.1–1.24)</td>
<td>14.21 (3.74–24.69)</td>
<td>9/5</td>
<td>11.22 (0.77–21.68)</td>
</tr>
<tr>
<td>6</td>
<td>Other</td>
<td>15 (0.067)</td>
<td>0.87 (0.21–1.52)</td>
<td>11.27 (2.81–19.73)</td>
<td>5/10</td>
<td>16.20 (3.28–29.12)</td>
</tr>
</tbody>
</table>

| Total                            | 224            | 1.09 (0.86–1.32)          | 9.46 (8.23–10.69)                                                        | 116/108                                                                 | 16.28 (12.41–20.15)        | 8.32 (5.26–11.39)                                                     |

*No significance
PNES, psychogenic non-epileptic seizure; CI, confidence interval
Transfer*: change of hospital in between the diagnoses of epilepsy and PNES