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Are there physical risk factors for psychogenic non-epileptic seizures in patients with epilepsy?

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Patients with epilepsy may have additional psychogenic non-epileptic seizures (PNES). It has been suggested that PNES are more common if patients with epilepsy are female, develop epilepsy later in life and have right-sided brain lesions. We examine whether these or other physical factors affect the risk of PNES in patients with epilepsy in a controlled study.

Methods: Ninety consecutive patients with PNES and concurrent epilepsy (PNES + E group) and 90 consecutive patients with epilepsy alone (epilepsy group) were compared with regard to the variables sex, age at onset of epilepsy, epilepsy type (focal/generalised), location and lateralisation of epileptogenic zone, aetiology of epilepsy, interictal epileptiform potentials, magnetic resonance imaging (MRI) abnormalities, neuropsychological (NPS) deficits and intelligence quotient (IQ).

Results: Female sex ($P < 0.001$), abnormal visual memory ($P = 0.012$), global NPS impairment ($P = 0.029$), and low IQ category ($P = 0.005$) were associated with a higher risk of PNES. Other variables did not differ between the groups.

Conclusions: In patients with epilepsy, female sex, poor visual memory or global neuropsychological underperformance and low IQ are associated with an increased risk of PNES. MRI changes, epileptiform EEG abnormalities and location of epileptogenic zone do not show a predilection for one hemisphere.

Key words: psychogenic non-epileptic seizures; epilepsy; pseudoseizures; dissociative seizures; MRI; EEG; neuropsychological tests.

INTRODUCTION

Psychogenic non-epileptic seizures (PNES) have been defined as episodes of altered movement, sensation, or experience which mimic those due to epilepsy but which are not associated with abnormal electrical discharges in the brain[1]. Although PNES result from a psychogenic process and psychiatric co-morbidity or a history of traumatic experiences are often found[2–5], it is well recognised that they are commonly associated with physical brain disorder[6–10]. PNES have been reported after head injury[9,11,12], intracranial surgery[13,14], and in mental retardation[15,16]. The risk of PNES is also increased in patients with epilepsy. Although the percentage of patients with concurrent epilepsy has varied from 3.6 to 58% in different series[5,8,15,17–24], it is generally accepted that the prevalence of epilepsy amongst PNES patients is greater than in the general population[23]. Despite this, only a handful of studies have focused on patients with PNES and additional epilepsy (PNES + E)[13,25–27]. These studies of groups of 12–38 patients have suggested that a number of physical or biological factors may predispose patients to the development of PNES: female sex[13,25–27], later onset of epileptic seizures[13,26], and right hemispheric brain lesions[13,25]. Here we describe the clinical characteristics of a group of 90 consecutive patients with PNES and concurrent epilepsy and compare this group with 90 patients with epilepsy alone to determine whether these or other biological or epileptological factors affect the risk of PNES in patients with epilepsy.

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MATERIALS AND METHODS

The computerised database of the Department of Epileptology at the University of Bonn, Germany, was used to identify all patients in whom a diagnosis of PNES was established between 1 April 1991 and 1 April 2001 ($n = 329$). Out of this group, 119 were thought to have concurrent epilepsy (PNES + E) on the basis of a history taken by an expert epileptologist and ancillary tests like EEG, brain imaging and neuropsychological (NPS) testing. However, in this study we only included patients above the age of 16 with (1) a history suggestive of epilepsy, and (2) ictal or interictal epileptiform changes in the EEG ($n = 90$). Patients below the age of 16 were excluded because they would not have been investigated on the adult epileptology ward from which the control group was recruited. In all patients, PNES were documented at our centre by the recording of spontaneous events with video-EEG, EEG, observation and ictal examination, or by the provocation of a typical seizure by suggestive intravenous injection of 0.9% saline under video-EEG surveillance. PNES were categorised as 'convulsive' (including tonic–clonic like), 'tonic', 'flaccid' (including limp collapse) or 'sensory' according to the predominant semiological features. Ninety consecutive patients with epilepsy who were admitted to our ward between 1 January and 4 August 1995, during the middle of the recruitment period for the PNES patient group, served as controls. Reason for admission of these patients included evaluation for epilepsy surgery ($n = 48$), establishment of a clear diagnosis ($n = 32$), reassessment of epilepsy treatment ($n = 9$), or status epilepticus ($n = 1$). Eight patients were excluded from the control group because they had PNES or the diagnosis of epilepsy remained in doubt. Of the 48 patients evaluated for epilepsy surgery, 32 underwent an operation. Epileptic seizures were documented by ictal EEG or video-EEG recordings in 55 of the PNES+E and 48 of the epilepsy-only patients. We did not exclude patients in whom there was no ictal documentation of epileptic seizures as we wanted to reduce the risk of selection bias associated with focusing on a particular subgroup of PNES + E patients (those with frequent epileptic seizures).

Biographical information, details of medical and seizure history, EEG and MRI reports were retrieved from clinical records. Details of the neuropsychological test performance were obtained from the neuropsychology database. The localisation of the epileptogenic zone was determined by an experienced epileptologist (CE, MR) using all available data with particular emphasis on ictal EEG recordings and MRI appearances.

Routine EEG, lasting at least 25 minutes, was performed on an analogue, 24-channel Schwarzer system with silver/silver chloride bridge electrodes (including T1 and T2) placed according to the international 10–20 system. The examination comprised of recordings at rest using two unipolar montages with ear or vertex electrodes as reference, three bipolar montages (longitudinal, transverse, temporal ring), a unipolar toposelective, and a unipolar Goldmann common reference montage. Provocation methods included hyperventilation (HV) and photostimulation (PS). Reports of routine EEG recordings were available for all patients. All EEGs were reported by EEG-board-certified physicians. If several EEGs were available for one patient, a cumulative report was generated by an EEG-board-certified physician (MR), which incorporated data from ambulatory and video-EEG monitoring if available. Only epileptiform EEG changes were considered for the purpose of this study (spikes, polyspikes, sharp waves, spike wave-, sharp slow wave- and polyspike wave-complexes). EEG changes were categorised as right-sided, left-sided or generalised/bilateral. We did not consider predominance of lateralisation of epileptiform EEG changes—if changes were seen over both hemispheres, they were classed as bilateral.

Ambulatory EEG, lasting 24–48 hours, was performed on an analogue, 8-channel Oxford Medilog System with gold plated, colodium fixated electrodes in bipolar, serial montages using standard electrode positions according to the international 10–20 system.

Synchronous video-EEG was performed by passing continuous video-monitoring and EEG signals to a 128-channel amplifier system using an average common reference. After 12-bit A/D conversion, the data was written onto the disk of a data acquisition computer system with a sampling rate of 180 Hz per channel. EEG was recorded with tin-electrodes embedded in an elastic cap (Electra-Cap International, USA). The electrodes were placed according to the international 10–20 system and the guidelines of the American EEG Society (1991). Video-EEG/ambulatory EEG results were available from 138 of 180 patients (76.7%).

MRI was performed on a 1.5T scanner (Philips Gyroscan, Best, The Netherlands) according to our epilepsy protocol comprising of a sagittal T1-weighted spin echo sequence (5.0 mm slice thickness, 0.5 mm interslice gap, TR 650 milliseconds, TE 16 milliseconds), axial T2-weighted TSE sequence (5.0/1.0/2876/120), coronal T2-weighted TSE sequence (2.0/0.3/3719/120), coronal T1-weighted inversion recovery sequence (6.0/1.2/2300/40/TI 470 milliseconds) and axial FLAIRsequence (5.0/1.0/6000/120/1900). Field of view was 220 mm × 220 mm and matrix was 256 × 256. In most patients, the coronal T2 images were angulated perpendicularly to the longitudinal axis of the hippocampus. Visual analysis was performed by epileptologically experienced

neuroradiologists. For the purpose of further analysis, changes were categorised into right-sided, left-sided and bilateral. If abnormalities were seen in both hemispheres, were generalised or global (for instance in cerebral atrophy), they were classed as bilateral.

Neuropsychological results were derived from a 1- to 2-hour screening examination with assessment of (1) frontal motor skills (finger tapping and Luria sequences)[28], (2) psychomotor speed and attention (d2 letter cancellation)[29], symbol counting interference inhibition (Kurztest für cerebrale Insuffizienz, c.I.-Test)[30], (3) verbal memory (Verbaler Lern- und Merkfähigkeitstest, VLMT)[31], (4) figural memory (Diagnostikum für Cerbralschädigung, DCS)[32], and (5) written phonematic word fluency (Leistungsprüfsystem, LPS-subtest 6)[33]. Raw scores in each of the five domains of assessment were categorised into 'highly abnormal' (>2SD from the norm population), 'abnormal' (>1.5SD from the norm population), 'borderline abnormal' (>1SD from the norm population) and 'normal' performance according to their relation to normative test data. For statistical purposes, result categories were then treated as ordinal variables. A global NPS deficit was defined as an abnormal or highly abnormal performance in all parts of the testing procedure. Intelligence quotient (IQ) was estimated on the basis of a vocabulary test which is highly correlated with full scale IQ and eduction (Mehrfachwortschatz Intelligenztest, MWT-B)[34]. IQ was categorised as 'below average' (<85), 'average' (85–115) and 'above average' (>115), and then treated as an ordinal variable. The neuropsychological test battery employed in the patients described here and its interpretation in patients with frontal and temporal lobe epilepsy has been described in greater detail elsewhere[35].

Categorical variables were compared using the χ^2-test or the Mann–Whitney *U*-test as appropriate, normally distributed continuous variables using the Student *t*-test after applying Levene's test for equality of variance. Continuous variables with unequal variance were treated as non-parametric. A two-tailed $P < 0.05$ was considered significant.

RESULTS

Psychogenic seizure disorders

Of the 329 patients in whom a diagnosis of PNES was established between April 1991 and April 2001, 68 women and 22 men fulfilled our diagnostic criteria for additional epilepsy. The mean age at onset of PNES was 26.8 years (SD 11.1 years). PNES started after epileptic seizures in all cases. The semiology of PNES was convulsive in 61.1%, tonic in 23.3%, flaccid in 10.0% and sensory in 5.6% of patients. Attacks involved apparent loss of consciousness in 64.4% of patients. The semiology was similar to the patient's epileptic seizures in 40.0%. 16.7% of patients with PNES and epilepsy had had at least one proven episode of PNES status. PNES occurred after epilepsy surgery in 14 patients and after intracranial surgery for other indications in 13 patients. Thirty-eight patients with PNES and epilepsy underwent epilepsy surgery evaluation, 13 were operated on. This patient group has been described in detail elsewhere[36].

Epileptic seizure disorders

Patient sex and clinical details of epilepsy onset and syndromes, epileptogenic regions and lesions in the PNES + E and epilepsy groups are summarised in Table 1. Of all the biologic and epileptologic variables examined by univariate comparison, only the difference of sex distribution achieved significance, women were over-represented amongst patients with additional PNES (75.5% vs. 45.5%, $\chi^2 = 16.956$, $P < 0.001$). Neither age at epilepsy onset nor lateralisation or localisation of epileptogenic region differed between the two groups.

Investigations

Of the patients with PNES + E, 100% had at least one EEG examination, 71 (78.9%) had undergone MRI, 58 (64.4%) NPS testing, and 30 (33.3%) determination of IQ. Of those with epilepsy, 83 (92.2%) had had an MRI, 65 (72.2%) NPS testing and 44 (48.9%) determination of IQ. Details of EEG changes, MRI abnormalities and NPS deficits are presented in Table 2. Of the results, only abnormal visual memory (Mann–Whitney $U = 1100.5$, $P = 0.112$), global NPS impairment (19.6% vs. 6.2%, $\chi^2 = 5.040$, $P = 0.029$) and lower IQ (Mann–Whitney $U = 466.0$, $P = 0.005$) were found more frequently in patients with additional PNES. Visual memory was compared on the basis of categorised performance (see Section 'MATERIALS AND METHODS' for a definition of performance categories). As visual memory has been shown to be poorer in women[37], we also compared visual memory test results in males with those in females. Although we also found that women did less well, the difference was not significant. Performance in the other areas of the neuropsychological test battery did not differ between the two groups. IQ was compared on the basis of categorised IQ values of all patients tested (using the categories 1: <85; 2: 86–115; 3: >116).

Table 1: Characteristics of epilepsy in patients with epilepsy alone and patients with epilepsy and additional PNES.

	Epilepsy plus PNES	Epilepsy	Significance
Female sex	75.5%	45.5%	χ^2=16.956; $P < 0.001$
Age at onset of epilepsy (mean/SD)	12.9 (9.3)	13.7 (11.2)	n.s.
Age at examination (mean/SD)	34.3 (10.7)	33.1 (11.2)	n.s.
Epilepsy type			
Focal	71.1%	84.4%	n.s.
Idiopathic generalised	10.0%	4.4%	n.s.
Cryptogenic or unclassified	18.8%	11.1%	n.s.
Epileptogenic zone			
Frontal	13.3%	17.7%	n.s.
Temporal	56.6%	66.7%	n.s.
Unclear/other	30.0%	15.5%	n.s.
Side of focus			
Right	31.1%	30.0%	n.s.
Left	30.0%	43.3%	n.s.
Bilateral or unclear	38.8%	26.7%	n.s.
Aetiology			
Hippocampal sclerosis	25.5%	27.7%	n.s.
Tumours	8.8%	18.8%	n.s.
Cortical malformation	8.8%	8.8%	n.s.
Trauma	7.7%	5.5%	n.s.
Ischaemia	5.5%	7.7%	n.s.
Idiopathic	10.0%	4.4%	n.s.
Unclear	26.7%	22.2%	n.s.
Other	6.7%	4.4%	n.s.

Table 2: Results of investigations in patients with epilepsy and additional PNES and patients with epilepsy alone.

		Epilepsy plus PNES (%)	Epilepsy (%)	Significance
Epileptiform interictal EEG changes *n* (E + PNES) = 90, *n* (E) = 90	Right hemisphere	27.6	23.3	n.s.
	Left hemisphere	27.6	34.4	n.s.
	Bilateral/multiregional	31.0	37.8	n.s.
	Generalised	13.8	4.4	χ^2 = 4.390, P = 0.064
MRI abnormalities *n* (E + PNES) = 71, *n* (E) = 83	Right hemisphere	35.2	30.1	n.s.
	Left hemisphere	29.6	38.6	n.s.
	Bilateral/global	12.7	12.0	n.s.
	None	22.5	19.3	n.s.
NPS deficits *n* (E + PNES) = 58, *n* (E) = 65	Motor	51.2	36.0	n.s.
	Attention	44.0	33.9	n.s.
	Verbal fluency	40.5	43.8	n.s.
	Verbal memory	67.9	67.2	n.s.
	Visual memory	74.5	51.6	U = 1100.5, P = 0.012*
	Global	19.6	6.2	χ^2 = 6.524; P = 0.015
	None	1.7	4.6	n.s.
IQ *n* (E + PNES) = 30, *n* (E) = 44	Below average (<85)	30.0	6.8	U = 466.0, P = 0.005*
	Average (85–115)	70.0	93.2	
	Above average (>116)	0.0	0.0	

All patients underwent EEG, MRI reports were available on 154 of 180 patients (89.5%), NPS results were known in 123 patients (68.3%), and an IQ category in 74 patients (41.1%). (∗) See Section 'MATERIALS AND METHODS' for statistical details of the comparison.

DISCUSSION

As in other somatoform disorders[10, 38, 39], there is evidence that brain abnormality, especially epilepsy, is a risk factor for PNES[5–9, 12, 15, 19, 22, 24]. In our patient population, the clinical history suggested additional epilepsy in 119 of 329 PNES patients (36.2%). Of these, 90 (27.4% of all PNES patients) also had ictal or interictal EEG changes and were included in this study. This proportion is considerably higher than that reported by some investigators[18, 21, 23], who found evidence of concurrent epilepsy in 3.6–10% of their

PNES patients. However, it is low in comparison to other reports which found that 28–58% of patients with PNES also had epilepsy[5, 15, 19, 22, 40, 41]. One important reason for this variability is that the former studies required evidence of ictal epileptiform activity for a diagnosis of concurrent epilepsy during a relatively short period of monitoring whereas most of the latter accepted interictal EEG changes, credible accounts of epileptic seizures, or evidence of remote epileptic events as sufficient for the diagnosis. If we had required ictal EEG documentation of an epileptic seizures for the diagnosis, 58 of 329 (17.6%) would have been classed as having PNES with concurrent epilepsy. Another important factor which may influence the number of PNES+E patients found by different investigators is the setting of the study. The present study was undertaken at a tertiary referral centre with a large epilepsy surgery programme, which may have attracted a greater number of patients with concurrent epilepsy.

As noted in previous studies of patients with PNES + E, PNES were always preceded by epilepsy[13, 25–27]. In our patients, convulsive PNES (including tonic–clonic-like attacks) were most common. However, it has been pointed out that the semiology of PNES is difficult to categorise as many patients exhibit a continuum of different movements[42]. In line with one study, the semiology of PNES mimicked that of epileptic seizures in only about one third of cases[27].

Previous investigators have identified a number of specific physical or biological factors which may predispose patients with epilepsy to develop PNES, namely female gender, later onset of epilepsy and right hemispheric brain lesions[13, 25–27]. Our considerably larger, controlled study only demonstrated significant effects of female sex, visual memory or global NPS impairment and lower IQ.

Our finding that women were over-represented in the PNES group is in accord with practically all previous studies of unselected patients with psychogenic seizures or other somatoform disorders[43, 44]. Of course, female sex could simply be an organic marker for environmental or experiential factors such as a history of sexual or physical abuse, which have been shown to be highly relevant in the context of PNES[45]. Abnormal illness behaviour in women could be a culturally determined exaggerated expression of 'normal' feminine helplessness[43]. However, several mechanisms for a genetic or gender-related predisposition to complex behaviours have been described and genetic–environmental interaction must at least be possible[44, 46–48]. A better characterised example for this would be post-traumatic stress disorder which has been found to affect twice as many women as men exposed to similar levels of psychological trauma[49].

Other physical factors identified in this study as associated with an increased risk of PNES were a low IQ or global NPS deficits. Reasons for the association could include limitations of problem-solving and communication skills or the ability to verbalise emotional distress[16]. However, it is also possible that our findings are related to the high risk of sexual and physical abuse in people with learning disability[50, 51]. It should be pointed out in this context that the majority of patients with PNES and epilepsy had a normal IQ.

At first glance our finding that visual memory deficits were more common in patients with PNES and epilepsy than in those with epilepsy alone could be interpreted as evidence of an increased prevalence of non-dominant hemisphere dysfunction in PNES patients. As the right hemisphere is thought to be involved in emotional processing, this finding could make some sense[52, 53]. However, we did not find a predilection of MRI abnormalities or EEG changes for the right-side of the brain. Neither did we find a predominance of right hemispheric epilepsy in our patients with PNES when all clinical results were considered together. Unfortunately, the lateralising value of figural memory deficits is limited because they are not only observed in right temporal lobe epilepsy but also in dominant hemisphere epilepsies with a degree of interhemispheric language shift[54]. Moreover, figural memory was poorer in women than in men. Although the difference was not significant in our study, this finding is in line with previous studies of sex differences in material-specific cognitive functions[37], and diminishes the lateralising value of the observed figural memory deficits further. Lastly, NPS data were available on fewer patients than EEG and MRI results. Overall we therefore do not think that our study provides evidential support for the suggestion from two previous studies, that PNES are associated with right hemispheric brain abnormalities[13, 25]. In the wider context of somatoform illness, our results are in keeping with the two most comprehensive studies of this issue which did not confirm the traditional neurological belief that conversion disorder favours the left-side of the body (and arises from the right hemisphere of the brain)[55, 56].

Our study did not confirm a later epilepsy onset in patients with additional PNES, which was noted in one previous study of patients undergoing pre-surgical evaluation and which had significant discriminating value in a study of patients who developed PNES after epilepsy surgery[13, 26].

Unfortunately, due to the retrospective nature of our study, the clinical data were incomplete and we were unable to perform any meaningful logistic regression analysis to assess the predictive value of the variables examined. A complete set of clinical, EEG, MRI, NPS and IQ data was only available on 30 patients

with PNES and epilepsy and 44 patients with epilepsy alone. Most of these patients were undergoing epilepsy surgery evaluation and would not have been representative of the whole group. However, it does not appear that the limited number of physical risk factors identified could fully explain the occurrence of PNES in patients with epilepsy, and it is likely that psychiatric co-morbidity and personality play an important role[2, 57, 58]. An alternative explanation for the failure of an association of PNES with a particular type of brain pathology would be that PNES could be caused by a variety of different brain lesions. This would be consistent with the observation that PNES do not represent a single psychopathological syndrome but are seen in many different psychiatric conditions[2].

Our results should not be extrapolated to all patients with PNES as there may be important aetiological differences between patients with PNES alone and those with PNES + E. However, the preponderance of women in the great majority of patient cohorts with somatoform disorders has already been discussed. There is also evidence that neuropsychological deficits are common in patients with PNES—even if they do not have concurrent epilepsy or other recognised brain pathology[21, 59].

CONCLUSIONS

This controlled study shows that in patients with epilepsy, female sex, global NPS impairment, visual memory deficits and lower IQ are associated with an increased risk of PNES. Other organic or biological factors, especially lateralisation of the epileptogenic lesion and age at epilepsy onset, are not associated with a higher risk of additional PNES. Although we characterised a number of physical differences between patients with PNES and epilepsy and patients with epilepsy alone these probably do not fully explain the occurrence of PNES in patients with epilepsy. Psychological, personality and biographical factors are likely to play an important role in the causation of PNES in this patient group.

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