CASE REVIEW

PNES – Case Review in Neuroimaging Context

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Abstract

Psychogenic nonepileptic seizures (PNES) – episodic failure of behavioural control – create a heterogeneous group of diseases. There is no common approach in the diagnostics of mentioned diseases. The absence of the common diagnostic approach contributes to a significant delay in the diagnostic process, often up to 7 years. Very important part of this process is neuroimaging. There are quite inhomogenous results in up to date literature review whether in context of morphology or function. The main aim of the presented paper is a review of specific cases in neuroimaging context to collect data for further research. For the review the authors introduce 2 case studies of patients with PNES on different psychopathological background and their representation via EEG – current density maps using eLORETA software. On the basis of the studied literature and analyzed cases, conclusions are drawn and suggestions for further investigation are proposed.

Keywords

PNES, EEG, eLORETA, current density maps, neuronal networks

1. Introduction

Current bio-psycho-social model of PNES depicts the multifactoriality of the disease. Based on previous research (Hingray et al., 2011; Brown & Reuber, 2016; Green, Norman & Reuber, 2017; Dworetzky & Baslet, 2017) certain life events can be considered as causal in the formation of psychogenic nonepileptic seizures. These events include severe trauma in childhood (24–58% sexual abuse, child abuse & neglect (CAN syndrome); adult life trauma (rape, physical abuse, severe accidents); relevant emotional loss (decease of a close person); acute or situational stress (dissonance in the family, developmental unreadiness, insufficient maturity). Motoric and behavioural expressions of PNES are different in different patients (remarkable motoric activity, wil or falling vocalisation or ictal injury). Seizures appear typical in home setting when there are other people present, mostly during the day, typically lasting longer than 2 minutes. Psychogenic nonepileptic seizure is described by patients as out of their willful control. (Brown & Reuber, 2016). Prevalence of PNES is approximately 33 cases on 100 000 people per year. (Green et al., 2017). Manifestation of PNES occurs mostly in the 2nd or 3rd decennium (Asadi-Pooya et al., 2014), predominantly by females (approx. % of all patients) and people with lower education (Brown & Reuber, 2016) or mental issues (Kanemoto et al., 2017). As a comorbidity with epilepsy, a PNES is reported in 10 to 30% of patients. The most common psychiatric conditions in these patients are depressive and anxious disorder, personality disorders (mostly borderline personality disorder) and other somatoform and dissociative disorders. (Dworetzky & Baslet, 2017). Neurologic comorbidities in PNES patients are migraine, other types of headaches, chronic pain, weakness, lowered sensitivity (Mintzer, 2015). Psychofarmacologic treatment is indicated when the patient is diagnosed along with panic disorder, depression, anxious-depressive disorder or psychosis. Most commonly used drugs are antidepressants of SSRI group. Benzodiazepines can be used temporarily. (Dworetzky & Basket, 2017). The mere fact, that from 20% to 25% of pharmacoresistent epilepsy patients suffer from PNES or combination of both, suggests that the process of PNES diagnosis requires improvement. (Schachter & LaFrance, 2010). Proper and early diagnosis can prevent significant damage to istrogen, the inadequate treatment of which can lead to the death of the patient (Asadi-Pooya et al., 2014). Foreign research includes the financial burden of the inadequate therapy. (Magee et al., 2014). Absolute specificity in PNES diagnostic is fundamental taking into account the diagnostic delay reaching up to 5 to 10 years (Alessi & Valente, 2014). „Golden standard“ for the definitive diagnosis of PNES is video EEG monitoring. Psychologic examination consists of neuropsychologic assessment, projective methods, personality questionnaires and tests for simulation and effort. Basics of a neuropsychologic assessment are detailed diagnostic interview, personal history mapping overloading moments and traumatic life experience. It can be stated that in PNES patient group there is maladaptive emotional regulation in their perception (Novakova et al., 2015). Psychogenic nonepileptic seizures can reflect a deficit in recognition, thinking and emotion description. From this perspective can be PNES seen as symptom of emotional discomfort or arousal which person incorrectly attaches to physical cause or as a valve for releasing unrecognised emotional stress. (Brown & Reuber, 2016). Patients with PNES represent a heterogeneous group with various manifestations of psychiatric symptoms and somatic discomfort. Therefore is it less probable that this disorder would be associated with one model of emotional regulation and procession. This is very important for the need of individual approach in psychotherapy with these patients. Therapy of this
The key structures in neuroimaging of functional movement disorder (FMD) in affective and regenerative states, including prefrontal cortex (PFC) and ventral striatum (VST), are interconnected with PNES. This finding corresponds to its hyperactivity in patients with fibromuscular dysplasia (FMD) in affective and regenerative tasks.

Recent neuroimaging results show a connection between dissociation and increased resting-state perigenual ACC activity. This seems important taking into account that psychotraumatization in childhood, PTSD, dissociation are very common in patients with PNES.

From the structural point of view – volumetric findings in patients with PNES show reduction of grey matter in dorsal ACC and SMA areas, reduced cortical thickness in paracentral and precentral gyrus. Described structural alteration in dorsal ACC-SMA parts can lead to abnormal behavioural expression. Reciprocal ventral and dorsal ACC connection can mediate interactions between impaired emotional regulation and expression (Perez, 2015).

Recent studies (Szaflarski, 2018) imply causal relationship between altered brain connectivity and formation and maintenance of PNES (Figure 1).

![Figure 1 Neuronal network scheme by PNES formation. TPJ, Pl, dlV, vlV, P/ACC LN VM/PC V/LPFC (Szaflarski, 2018)](image)

3. Material and methods

In this chapter, study material collected from 2 cases of patients diagnosed per exclusionem with PNES is presented, as well as the description of the methods for the processing of obtained data.

Case No.1.

Patient – female, 2 yrs.

Personal History: Seizures in diff. Dg. Process – PNES, Canabinoid Misuse, St.p. TS with medication 02/20, St.p. Nephrostomy

Family History: no neuropsychiatric burden found

Social History: parents have lived separated since she was 3 years old, father pays alimony, communication with father via grandfather, patient studies 3rd year of opera singing, acting and piano at musical academy, after the 1st year of studies she changed the school for bullying; for the last couple of months she has lived in a rented flat, after school classes she works as a student job receptionist in a fitness centre, she lives of the alimony and money she earns, after paying her bills she is left over with ca 60 euro for a...
month, as 16 yrs old she had a relationship, which ended with an unpleasant experience in a park where her drunk boyfriend sexually harassed her and gossiped on her afterwards, at the time being she has had a 19yrs old boyfriend for 4 months, she is happy in this relationship.

Seizure semiology: Seizure starts with a sudden fall, the patient imposes atonic, lays without moving with closed eyes and calm breathing. Ca after 2.5 min she suddenly sits up, begins to hyperventilate and cough, cries for the next 3-4 minutes until she calms down.

Diff. Dg. Procedure:

EEG–background activity occipital, less regular with frequency 8–9 Hz, amplitude up to do 50uV, less modulated, Berger reaction is present. In frontal electrodes beta activity, frequent muscle and ocular artifacts, patient lays herself to sleep stands afterward up, sits and plays with her mobile phone. Often IRDA discharges, bilaterally FT. At 14:16 she falls asleep until 14:51 with appearance of K-complexes, after waking up she repeatedly falls asleep until the end of recording at 19:31. In video recording IRDA without ocular artifacts. Night: awake state until falling asleep at 21:47 with typical course of nonREM and REM sleep. Conclusion: EEG without specific abnormality.

Brain MRI: no significant morphologic abnormality

Psychodiagnostic Examination: ROR, Figure Drawing Test, Baumtest, Association experiment, WAIS-R; Personality in maturation process, at the moment immature with average intellect. Autonomy tendency dominates by difficult self-enforcement. Orientation in own experiences imposes limited. As problematic seems the acceptance of the female role.

Conclusion: PNES based on PTSD

Case No.2

Patient – female, 41 yrs.

Personal history: Brain MRI 12/2017 – P1 part ACP bilat. Hypoplasia, since 2017 diagnosed with hyperventilation tetany – seizure regulation by breathing, subsequently no effect of Diazepam per Rectum, EEG after sleep deprivation - negative result, 03/2020 neurological hospitalisation with record of tetanic seizure with atenoid movements of upper and lower extremities, opistotonus – concluded as susp. PNES; Vertebralagnic syndrome of cerebral spine, Micronodular Struma, St.p. Appendectomy, St.p. Tonsilectomy, St.p. Curetag for a Myoma, St.p. H.pylori Eradication

Family History: Father committed a suicide by strangulation in his 47 yrs. "he felt like he cannot earn for the living of the family", brother of the father with posttraumatic epilepsy, otherwise no neuropsychiatric burden found.

Social History: she considers her childhood as very good, her parents didn’t argue, she has 2yrs younger sister, high school – hairdresser, she didn’t finish the school because she got a job, 1 marriage which lasted 2 yrs, her husband didn’t have much interest in the family, he does not have interest on their daughter (16yrs), after divorce she returned back to her mother where she opened her own hairdresser studio. She met her 2nd husband 8 years ago, she has been married for 5 years, her 2nd husband has 2 children from an earlier marriage, problematic relationship with his ex-wife. These children are staying with the patient and her 2nd husband weekends and all holidays. They live in a house of her husband parents. They have altogether good relationships. As an investment she bought her own flat.

Seizure semiology: series of habitual movements (confirmed by the patient who communicates easily during the seizure), semiology of incongruent and inconsistent movements – atetoid movements in quadrudistribution of crescendo-decrescendo type, turning over, interponed voluntary movements – patients makes up her pillow, recorded opistotonus, duration several tens of minutes.

Diff-dg. Procedure:

Long-term video-EEG monitoring - nocturnal recording – modulated basic activity with amplitude up to 9 Hz, in sleep stages I-III, 4 cycles of REM and nonREM, no epileptic activity in EEG or in video recording. Regular rhythm found in EEG. Daily record: during recording at 6:53 am. a seizure – movement in lying with opistotonus indicated, movements of upper and lower limbs, in EEG muscle and electrode artifacts, before or after seizure no epileptic activity. The seizure was terminated by conversation. Seizure manifestation imposes as psychogenic. No epileptic process in EEG or clinically proven. Recommendation: Control according to clinical course, psychological treatment.

Psychodiagnostic examination. –Personality, Intellect - ROR, AE, PSSI, WAIS-R; Personality with dominant histronic traits. The actual intellectual performance is in lower average range. The performance appears underneath the ability level. A good readiness and concentration ability were observed by easy tasks. Subjectivistic, intuitive thinking. Critical-analytical thinking is reduced. Contact with reality is preserved, however, there were some distortions based on emotional repression observed. Tendency to negative emotion attenuation and self-focusing affections are present.

Conclusion: Dissociative seizures based on personality disorder.

3.1 EEG Data Acquisition and Postprocessing

EEG Data recording was performed on a standard 19-channel digital EEG amplifier BrainScope EADS with 19 Ag/AgCl surface electrodes placed according to the international 10/20 system. The data-sampling rate was 1000 Hz and the acquired signals were filtered with digital high- and low-pass filters at 0.15 and 70 Hz, respectively. Our selected data were a part of the video-EEG examination in duration of several hours.

Prior to data analysis artifact detection was visually performed to exclude all epochs containing eye blink, eye-rolling artifact, head movements, muscle artifacts. Thus, from each EEG at least 60 sec of resting state, artifact-free, and highly reliable data were subjected to further analysis. The number of epochs, as well as the length of the samples processed, did not differ between the patients and the healthy control.
Data analysis was performed using the exact low-resolution electromagnetic tomography - eLORETA an inverse solution technique that estimates the intracranial distribution of electrical activity (current density) in the cortex based on a three-shell spherical head model co-registered with Talairach coordinates (Pascual-Marqui, 2002). We used the eLORETA-Keyp software (Key Institute for Brain-Mind Research, Zurich, Switzerland), available at http://www.uzh.ch/keyinst/loreta.htm. Using the eLORETA transformation matrix, cross spectra of each subject and for each frequency band were transformed to eLORETA files. This resulted in a corresponding 3D cortical distribution of the electrical neuronal generators for each subject. The computed eLORETA images reflect the cortical current density distribution in 6,239 voxels with a spatial resolution of 5 × 5 × 5 mm. The eLORETA algorithm has no localization of bias even in the presence of structured noise, which allows us to increase the localization accuracy, compared to the previous version of sLORETA (54). The advantage of eLORETA is that it belongs to a reference-free method of EEG analysis, therefore, determining the source distribution for EEG data is not affected by the selected electrode reference. Current density values were computed in eight frequency bands delta (0.5–3.5 Hz), theta (4–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz), beta-3 (21.5–30 Hz), and omega (0.5–30 Hz).

3.2 Statistical Analysis

For the statistical analysis e.loreta data were used. We performed no normalisation of the data. Our data were approached as paired groups. No baseline correction was computed. Tests were performed for all timeframes/frequencies. For the analysis the F-Test – Log of F-Ratio was chosen. In the eLORETA analyses, the localization of the differences in baseline activity between the group of responders and non-responders was assessed using a voxel-by-voxel unpaired t-test of the eLORETA images, based on the power of estimated electric current density. In the resulting statistical three-dimensional images, cortical voxels showing significant differences were identified using a nonparametric approach (statistical nonparametric mapping or SnPM) via randomizations. This randomization strategy determined the critical probability threshold values for the actual observed t-values, with correction for multiple comparisons across all voxels and all frequencies. A total of 5,000 permutations were used to determine significance for each randomization test.

5. Discussion

In our patient with PNES based on PTSD we found significant baseline activity difference - decrease in primary somatosensory cortex (postcentral gyrus) which plays important role in each stage of emotional processing, including identification of emotional significance in a stimulus, generation of emotional states, and regulation of emotion. Furthermore there was decrease of baseline activity found in area involved in the analysis and integration of higher order visual, auditory and somesthetic information, area in parietal cortex where translation and interpretations of visual impressions take place. Increased baseline activity was found in subgenual area, part of the ventromedial prefrontal cortex implicated in a variety of social, cognitive, and affective functions that are commonly disrupted in mental illness.

Patient with PNES based on personality disorder had their baseline activity significantly decreased in postcentral gyrus of primary somatosensory cortex taking part in emotional processing, in primary motoric cortex, in area in parietal cortex playing role in visuo-motor coordination and in secondary visual cortex. Baseline activity increase was seen in associative visual cortex.

As shown by our results it is inevitable to take into account the psychopathological background of PNES formation. It can be stated that precisely this aspect is a condition by which the patient population can be subdivided where certain similarity of results can be expected.

Further moment would be targeting of neuroimaging - neuronal connectivity for instance – according to up to date neuroimaging results.

One quite remarkable design for subsequent research would be comparison of neuroimaging of PNES patient with a group of patients with the same psychiatric condition without seizure manifestation. Perhaps, it would be this approach which will bring us closer to the neurophysiological correlate of PNES.

4. Results

Case No.1

Baseline activity decrease in Alpha 1 frequency band in BA 2 – postcentral gyrus, parietal lobe (Fig.1), alpha 2 in BA 7 – superior parietal lobule, parietal lobe (Fig.2), beta 2 in BA 19 – precuneus (Fig. 3), parietal lobe, beta 3 in BA 19 – precuneus, parietal lobe (Fig 4). Baseline activity increase in delta frequency band in BA 25 – anterior cingulate, limbic lobe (Fig.5).
Case No.2

Baseline activity decrease in delta frequency band in BA 7 – precuneus, parietal lobe (Fig 6), theta in BA 3 – postcentral gyrus, parietal lobe (Fig 7), alpha 2 frequency band in BA 4 – precentral gyrus, frontal lobe (Fig 8), beta 1 in BA 4 – precentral gyrus, frontal lobe (Fig 9), beta 2 in BA 4 – precentral gyrus, frontal lobe (Fig 10), beta 3 in BA 18 – cuneus, occipital lobe (Fig 11.).

Baseline activity increase in alpha 1 frequency band in BA 19 – ligual gyrus, occipital lobe (Fig 12).

6. Conclusion

Neuroimaging studies present the next step in understanding of formation and maintenance processes of PNES. Considering the multifactoriality of this disease the subdivision of patient group into subpopulations depending on psychopathological background appears inevitable. Some other diagnostic tools like psychodiagnosis seem quite helpful. However, PNES cannot be seen as a homogenous disease which corresponds with the heterogeneity of results found in recent neuroimaging studies. In this context, the authors of the presented paper agreed that further comparison of neuroimaging of PNES patients with a group of patients with the same psychiatric condition without seizure manifestation and targeting of neuroimaging are crucial for better understanding of the PNES disease and optimization of the treatment options for the affected group of patients.

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Figure 1 Neuronal network scheme by PNES formation. TPJ, PI, dAI vAI P/ACC LN VMPC VLPFC (Szaflarski, 2018)

FIGURE. Schematics of possible nodes of the network underlying development and maintenance of psychogenic nonepileptic seizures (PNES) derived from structural neuroimaging studies of patients with PNES and other functional neurological disorders/conversion disorders (FND/CoDs) and possible connections between those nodes derived from functional and structural connectivity studies. Colors indicate from which studies the connections were derived: BLUE = resting state connectivity; BLACK = structural findings/structural connectivity (dashed line around vAI is derived from the meta-analysis of some of the neuroimaging studies of PNES); GRAY = task-related functional connectivity; DASHED BLUE = connectivity noted in other FND/CoDs in addition to the connectivity in PNES; DASHED ORANGE = task-related functional connectivity (various tasks).

Figure 8 Alpha 1

Figure 9 Alpha 2
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