Semiologic analysis and classification of childhood psychogenic non-epileptic seizures based on Video-EEG monitoring data

Doctoral theses

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1. Introduction

Psychogenic non-epileptic seizures (PNES) are sudden paroxysmal changes in behavior or consciousness, that resemble epilepsy but are not accompanied by the electrophysiological changes that characterize an epileptic seizure.

Although the absolute incidence of PNES is not high (estimated as 1.5-3 / 100,000 citizens) it can account for up to 20-24% of therapy resistant epileptic patients showing up for video-EEG and up to 50% among therapy resistant epileptic patients. Females make up for the majority of patients (67-74%). Disease diagnosis is usually reached 7.2 years on average after initial symptoms. According to Reuber et al the first seizure occurs between 10-19 years of age, while diagnosis is usually reached only at 20-40 years of age. These data underline the responsibility of pediatric epilepsy specialists in reaching PNES diagnosis.

Frequent triggers of PNES include a sort of trauma (mourning, physical or sexual abuse). Along with trauma also dysfunctional family structure, critical parents and strong somatisation tendency can also provide its ground. PNES is often accompanied by anxiety, depression, somatoform disorders, dissociative disorders, post-traumatic stress and also some sort of identity disorder. Several studies have described inefficient fight strategy, high degree of anger and inhospitality in PNES patients. Stress and unresolved problems may aggravate seizures not only instantly, but also months or years later.

Reaching diagnosis of psychogenic seizures is primarily reached due to Video-EEG monitoring. It is challenging to discriminate from childhood parasomnia and epileptic seizures especially as one third of PNES patients have GM-like seizures. The appearance of characteristic seizure semiology features aid differential diagnosis.

The first element of therapy is to communicate the correct diagnosis to the patient. It discontinues seizures in at least 10% of patients. It is especially true for freshly diagnosed cases. Several psycho-therapeutic methods have been trialled in PNES with good experience including cognitive behavioral therapy (CBT), personalized psychotherapy, exercise therapy, the method of operative conditioning, dynamic oriented psychotherapy. The efficiency of CBT vs. conventional therapy was proved by class III evidence. Mayor et al described that the immediate suspension of anti-epileptic therapy has not increased risks but ameliorated the outcome.

PNES prognosis is highly variable among various studies but recovery rate is between 29-50%. Prognosis also depends on what type of outcome indicators is used. Seizure frequency may easily be used but it does not reflect changes in other psycho-pathological features (i.e. employment, degree of disability, healthcare burden). Better outcome is expected for patients with high IQ, good social status, higher education and young age. Non-severe seizures and the absence of further diseases were also associated with better prognosis. Male gender, increased dissociative tendency, significant identity disorder and multiple symptoms are associated with poor prognosis.

Semiology classification

The semiology classification of psychogenic seizures appears to be a good method as usually a single type of seizure appears in both adult and pediatric patients. The most frequently used classification directives are based on dominant symptoms thus differentiating seizures with loss of consciousness or motoric symptoms. Certain authors classify pseudo-seizures based on the lateralization of symptoms. Seneviratne et al classified psychogenic seizures into six groups based on 330 seizures of 62 patients: 1. rhythmic tremor, 2. hyperkinetic or hypermotoric form, 3. complex motoric form, 4. dialeptic seizure (prolonged, motionless, coma-like state), 5. non-epileptic aura and 6. mixed (mixture of the above forms).

Among children seizures were classified into prominent motoric, subtle motoric and mixed seizures based on their kinetic range.

Selwa et al have found correlation between prognosis and the form of the seizure. Complete remission occurred more frequently among patients with catatonia (53%) than among patients with serious kinesis (21%). Betts et al have found correlation between disease etiology and seizure type: seizures with collapse were more frequently associated with sexual abuse.

Based on these data it is clear that seizure form often provides aid identifying etiology, prognosis or therapy. It would be important to unite the various classification systems so that results would be easily applicable.

2. Goals

My studies had two goals: to analyze 10 years of examinations of the Bethesda Pediatric Hospital video-EEG laboratory and the detailed semiology analysis of childhood psychogenic non-epileptic seizures recorded during monitoring.

Performing data analysis recorded during 10 years I have examined the indications of monitoring, their characteristics, the diagnoses, the benefit of the examination, the difficulties and the epidemiological features of the patients. I wish to summarize and help to define childhood video-EEG monitoring indications based on national experience to assist early diagnosis, early recognition of epileptic cases requiring surgical intervention and early execution of pre-operative examination.

Several studies have described various semiology characteristics of psychogenic seizures, but only few have attempted to classify psychogenic seizures based on seizure characteristics and only one has examined the semiology of childhood psychogenic seizures. The current study fills this gap by re-analyzing all PNES-diagnosed childhood psychogenic seizures, their detailed semiology description and classification. The other goal was to study the utility of the adult PNES classification system in the pediatric population.

3. Methods

We have analyzed the database and detailed summaries of continuous VEM examinations performed during the 10 years between 1st June 2001 and 31st May 2011 at MRE Bethesda Pediatric Hospital's Epilepsy Diagnostic Unit. Data of patients with min. 24 hours of VEM examination have been processed.

All children underwent 24h continuous video-EEG monitoring. Scalp electrodes were placed in accordance with the 10-20 international electrode system EEG and audio visual signals were acquired and analysed using Brain Quick (Micromed S.p.A) video EEG system and System Plus software. Accessory electrodes (ECG or EMG) have also been placed as necessary.

Besides the recorded video and EEG material the most important characteristics of the patients, clinical examinations and specialist records were also collected in a database. The database contains patient age at disease appearance and initial monitoring, number of seizures prior to examination, the presence or absence of ictal or inter-ictal epileptic signs, the duration of the examination, the number of seizures recorded during examination and their duration. We have also recorded VEM indication and the decision based on the examination i.e. if pre-operative examination supported epileptic surgery or not. In the case of epilepsy as a diagnosis the database contains syndrome category and etiology, or the diagnosis if other than epilepsy.

I have further analyzed the records of children (18 years or younger) diagnosed with PNES. Epilepsy as an accompanying disease was not an exclusion criterion. The semiology of each psychogenic non epileptic event was visually analyzed in detail and entered into a statistical database. Type and anatomic distribution of the movement (extremities, head, trunk, pelvis), synchrony, symmetry, eye movement, responsiveness, vocalization, hyperventilation, vegetative signs, presence of emotional signs and aura, onset (abrupt or gradual), course, presence of eyewitness and duration of the event were recorded and tabulated. We used the results of Seneviratne et al to classify events into distinct group: 1. Rhythmic Motor PNES, 2. Hypermotor PNES, 3. Complex motor PNES, 4. Dialeptic PNES, 5. Non-epileptic Aura, as well as 6. Mixed PNES.

Statistical analysis was made by STATISTICA (StatSoft, Inc. (2010) version 9.1. www.statsoft.com.). Non parametric tests (Mann-Whitney U test or Kruskal-Wallis test) were used to compare groups.

Informed consent was obtained from each patient and their parents before VEM. Our study was authorized by the Ethical Committee of the Bethesda Children's Hospital.

4. Results

4.1 Experience with Video-EEG monitoring

During the past 10 years 597 VEMs (longer than 24h) were performed in 541 patients (280 males). The examination had to be repeated for 46 patients (twice for six patients and thrice for three patients). The indication of repeated examination were mostly differential diagnostic problems and also repeated examination was often required to confirm surgical indication.

The average age of the patients examined was 9.27 years (0-36 years, SD 6.02). Only 5% of the patients (32 people) were older than 18 years.

Average time between disease initiation and examination was 4.7 years (0-26 years, SD 4.7; median 3) for the overall population.

The event could be recorded in 80% of the examinations (477 examinations), there was no significant difference between efficacy of monitoring with respect to indication.

Success rate was much higher if the event occurred at least once a week prior to monitoring.

60% of the examinations (356 examinations) were carried out to perform differential diagnosis while 40% (241 examinations) as epileptic pre-surgical examinations. As a result of epileptic pre-surgical examinations 84 surgeries were performed in 74 patients.

Only one non-habitual seizure occurred during 10 years of VEM due to drug therapy withdrawal.

Of the 356 VEMs performed due to differential diagnosis 191 cases (53.6%) lead to the diagnosis of epilepsy. The event was not due to epilepsy in 165 cases (28% of overall examinations and 46% of all differential diagnostic examinations) and the diagnosis of epilepsy could be excluded in 124 cases. The event has not occurred during 41 cases (24%) and hence the diagnosis of epilepsy could not be verified. Based on medical history, the events described and the observed awake and sleep EEGs these were likely not be of epileptic origin. The other non-epileptic events were motion disorders (33), behavioral disorders (11) or psychogenic disorders (47).

4.2. Characteristics of non-epileptic psychogenic seizures

In the examined period PNES diagnosis was reached in 27 cases (21 females), in whom altogether 275 psychogenic seizures were recorded (1-92 /child, median: 3), and 75 were archived (1-8, median: 2/child). Average age at the time of VEM was 14.8 years for children, significantly higher ($Z= -6.21$ p<0001) than with other patients undergone VEM (7.9 years). In nine children (33.3%) PNES was accompanied with an epilepsy diagnosis at the same time or in the past.

The mean duration of PNES was 269 ±549 (1-3417) seconds compared to seizures of the epileptic group 83.2 ±222.4 seconds ($Z= -3.72$ p=0.002).

At the start of PNES episodes, there was an eyewitness (mostly parents) in the VEM room in 89% of cases. 80% of events had an

abrupt start, with 68% also ending abruptly. In 15% of events, the patients had their eyes closed at the beginning and 22 % had their eyes closed during the whole attack. Patients were unresponsive during 34% of all events. The most frequent motor sign was tremor (25%) involving the upper limbs more frequently than the lower. Pelvic thrusting was only seen in two attacks.

Mostly negative emotional signs were observed during 32 attacks (43%).

Based on Seneviratne's classification in our cohort, 18 events (24%) were classified as rhythmic motor PNES, only half the frequency of that previously described in adults. No hypermotor PNES was found. The frequency of complex motor PNES (13%) and mixed PNES (4%) showed similar frequency in children as in adults. Dialeptic PNES was found more frequently in children (29%) then in adults (11%). In 23 patients (85%) all PNES belonged to the same semiologic type.

In altogether 14 cases was the etiological parameter discovered, usually some sort of anxiety. Call for attention and secondary disease benefits were found in the case of two children. In two cases depression requiring drug therapy were discovered. In one case pathological relation between mother and child was observed that played a role in maintaining seizures.

5. Conclusions

5.1. Experience based on Video-EEG monitoring

The appearance of video-EEG monitoring reshaped our view of epilepsy. Differential diagnostics have become easier including syndrome classification and therapy.

- Based on our data the VEM seems to be safe examination in paediatric population

- The efficacy of our laboratory is appropriate the international data, the addressed event could have been recorded in 80% of VEM.

- Based on our experience the indications of childhood video-EEG monitoring may be summarized by the following:

- Every case that raises the possibility of surgical intervention of epilepsy.

- If seizures are not accompanied by epileptic EEG signs, or those are not synchronized with seizure description.

- In the case of therapy resistant epilepsy with no rational explanation.

- If symptoms refer to PNES, motion disorder or sleep disorder but medical history does not allow for identification.

- If patient has epileptic seizures or inter-ictal epileptic signs that accompany PNES, sleep disorder or motion disorder.

- The examination may be required if subtle, difficult to recognize seizures are suspected.

5.2. Psychogenic non-epileptic seizures

- We found that both the prevalence of PNES among children undergone VEM (4.8%) and the male / female ratio of our patinet (78% were females) and the frequency of coexisting epilepsy (33%) correspond with previous adult data.

- We found that PNES typically lasts longer than epileptic seizures and the episodes frequently start abruptly.

- We showed that the frequency of negative emotional signs (weeping, crying, painful facial expression, fear or laughing) were relatively high (43%) during paediatric PNES, verbal communication was present in 32%.

- We found that tremor is the most frequent ictal motor sign of paediatric PNES, appearing in 25% of all seizures

- Pelvic thrusting is rarely seen in children

- In children the loss of responsiveness has occurred less frequently as in adults, only in 34% of seizures, most often during dialeptic seizures (100%) and complex motoric seizures (67%).

- Also in children in a given patient, all PNES belonged to the same semiologic type in almost all cases (85%).

- We have found that the frequency of different form of seizures is different in children

- Our clinical study also supported that the motion-deprived, dialeptic form is characteristic for young children as dialeptic PNES is twice as

frequent in childhood than in adulthood. Besides, in the examined population the average age of children with dialeptic form was the lowest, significantly lower than with non-epileptic aura or complex motoric seizure.

- We have created a proposal of some modification on PNES classification in children. Based on the attacks observed in children, we subcategorized the mainly motor PNES to *minor motor* and *major motor* seizures. The classification was created based on motion quantity and dissemination, the presence or absence of responsiveness rather than symmetry or synchronicity. The minor motor seizure is characterized by a homogenous motor activity (mainly tremor but also tonic like movement could be observed), which is localized, mainly synchronized, and more often involves the upper limb accompanied by retained responsiveness. Seizures with more complex movements involving several limbs or migrating and appear as various types, are classified as major motor seizures. Disturbed consciousness is often seen in this group. The major motor group could be subdivided based on movement synchrony as *asynchron motor* and *synchron rhythmic motor* group.

6. Publications

6.1. Publications related to the thesis

1. Siegler Zs, Hegyi M, Jakus R, Neuwirth M, Paraicz É, **Szabó L**, Fogarasi A. (2013) 10 év- 600 vizsgálat – gyermekek video-EEG monitorizálásával szerzett tapasztalataink. Ideggyogy Sz 66:107-114.   IF: 0,488

2. **Szabó L**, Siegler Z, Zubek L, Liptai Z, Körhegyi I, Bánsági B, Fogarasi A. (2012) A detailed semiologic analysis of childhood psychogenic nonepileptic seizures. Epilepsia. 53:565-70.
                            IF: 3,961

3. Constantin T, Kalovics T, Ponyi A, Nagy E, Sallai K, **Szabo L**, Garami M, Muller J, Gergely P, Danko K, Fekete G, Kalmanchey R.(2009) Prevalence of antiphospholipid and antinuclear antibodies in children with epilepsy. Medical Science Monitor. 15:CR164-9.   IF: 1,543

6.2 Publications not related to the thesis

1. Zubek L, **Szabó L**, Diószeghy Cs, Gál J, Élő G.(2011) End-of-life decisions in Hungarian intensive care units. Anaesth Intens Care 39:116-121.   IF 1,279

2. Zubek L, **Szabo L**, Lakatos PL, Papp J, Gal J, Elo G. (2010) Double balloon enteroscopy examinations in general anaesthesia. World J Gastroenterol 16:3418-3422.   IF: 2,240

3. Zubek L, **Szabó L**, Gál J, Lakatos PL, Papp J, Élő G. (2010) Kettősballon-enteroszkópiás vizsgálatoknál végzett altatások során szerzett hazai tapasztalatok. Beteg-autonómia az anesztéziában. Orvosi Hetilap 151:1976–1982.

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7. Gács Zs., **Szabó L**., Kovács G. (2006) Methaemoglobinaemia – ritka vagy gyakori – oka. Gyermekgyógyászat 57: 160-164.

8. **Szabó L**., Polgár P., Gerevich J. (2005) Metadonkezelés: Egy ártalomcsökkentő módszer meghonosodása Magyarországon. Orvosi Hetilap 146:1685-161.

9. Gerevich J., **Szabó L**., Polgár P., Bácskai E. (2006) Methadone Maintenance in Europe and Hungary: Degrees of Sociocultural Resistance. Psychiatric Sevices 57:776-778   IF: 2,430