

# EPILEPTIC SEIZURE TRIGGERS IN CHILDREN FROM ROMANIA

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## ABSTRACT

**Objectives.** The identification of the types, characteristics and correlations of epileptic seizure triggers in children with epilepsy from Romania.

**Material and methods.** Transversal observational study on 278 children with epilepsy using the questionnaire method, containing questions regarding seizure characteristics, demographical information and medical history.

**Results.** The lot characteristics were average age 9.74 years; 57.2% males; 19.4% positive epilepsy family history; 48.2% late psychomotor development; 54% deficitary neuropsychological development; 25.2% treatment resistant epilepsies; 59.7% of children had focal epileptic seizures, 35.3% had generalized. Average number of triggering factors was 3 and 20.1% of children had no seizure trigger. The most frequently reported factors were: sleep deprivation 39.57%, anxiety 23%, sleep disturbances 22.66%, fever 20.50%, anger 19%, light stimulation 17.27%, crying 16.19%, interrupting antiepileptic medication administration 14.39%, watching too much TV 14.39%, physical fatigue 12.59%. The number of seizure triggers can be mathematically modelled according to age and treatment resistance. Unresponsiveness to treatment of the epilepsy has a few predictors: timing of the seizure occurrence, imaging alterations, late psychomotor development, IQ, the number of seizure triggering factors.

**Conclusions.** There was at least one seizure trigger identified in 79.9% of children with epilepsy. The most frequent reported trigger was sleep deprivation. The number of seizure triggers can be estimated through mathematical modelling. Treatment resistance of epileptic seizures has more predicting factors.

**Keywords:** epilepsy, seizure triggers, children

## INTRODUCTION

Epilepsy is the most common neurological affliction in the world, with a major social impact. The World Health Organisation estimates that there are 2.4 million new cases per year diagnosed, half of which are children or adolescents (WHO, 2012). Most people with epilepsy could lead a normal life with proper treatment, that would efficiently control seizures.

Many epileptic patients recognise certain relationships between their seizures and certain factors, more or less specific. Nonspecific, general factors (such as fever, stress, fatigue, etc.) are not related to the type of epilepsy. Specific factors, such as light or noise, usually identify a reflex epilepsy.

The currently best known triggers in the medical literature are visual stimuli (intermittent light, pat-

terns, video or computer games) (Fisher, Harding et al. 2005), audio stimuli (music, sounds, noise) (Lin, Wang et al. 2003), tactile or somatosensitive stimuli (Hsieh, Chiou et al. 2011), startle (Yang, Liu et al. 2010), reading (Striano and Striano 2011), writing (Chifari, Piazzini et al. 2004), praxia (Glenn, Carazana et al. 2012), eating (Rosenzweig and Manfred 2008), hot water (Yalcin, Toydemir et al. 2006), calculus (Marino, Lanzafame et al. 2009), thinking of a certain subject (Striano, Minetti et al. 2010; Nevler and Gandelman-Marton 2012), board games (Lee, Yoo et al. 2012).

The study of epileptic seizure triggers in children is important and is justified by the limitations of current drug therapy, that does not achieve the optimal seizure control. As a consequence, the prevention of seizures in treatment resistant epilepsies

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is possible only by making lifestyle changes and avoiding seizure triggers.

The objectives of our study were the identification of seizure triggers in children with epilepsy in Romania and the evaluation of their correlations, in the view of improving the current management protocols of epilepsy.

## MATERIAL AND METHODS

The current study is an observational transversal study regarding children with epilepsy who were admitted to the Neuropediatric Clinic of “Prof. Dr. Al. Obregia” Psychiatry Clinical Hospital in Bucharest between 01.01.2013 and 31.12.2013. Ages varied between 1 and 18 years. Babies under 1 year old were excluded due to the fact that epilepsy diagnosis at this age is often uncertain and frequently confused with isolated febrile seizures.

Demographic data, medical history and results of the psychological evaluation were collected from 357 medical files of eligible patients, whose parents were approached to take part in the study. Only 278 parents accepted to participate, answering our custom made questionnaire, 44 refused and 35 could not be contacted.

The questionnaire contained a list of 40 items, out of which parents identified the factors they observed to trigger epileptic seizures in their children. The psychological evaluation used the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003). The results of the test differentiate between average intelligence (IQ 90-110), under average (IQ 80-89), borderline (IQ 70-79) and mental retard (IQ  $\leq$  69).

The obtained data was statistically analyzed using Microsoft Excel XLSTAT Pack and SPSS 15. We described the variables, made Pearson and Spearman bivariate correlations with significance level  $p < 0.05$  and multivariate analysis.

The study was approved by the Hospital Ethics Committee.

## RESULTS

The age of the patients varied between 2 and 18 years old. The average age was 9.47 years with the standard deviation of 4.645 years and the median age was 9.81 years.

The demographic characteristics of the children included in the study are found in Table 1.

The epilepsy diagnoses were very diverse and the epilepsy classification system changed often in the last decades, thus we preferred to take note of

**TABLE 1.** Demographic characteristics of children with epilepsy in Romania

	Number	Percent	P	CI 95%
Gender				
M	159	57.2%		
F	119	42.8%	0.016	0.51-0.63
Living area				
Urban	147	52.9%		
Rural	131	47.1%	0.337	0.46-0.58
Child Rank				
I	151	54.3%	0.150	0.48-0.60
II	84	30.2%	<0.001	0.24-0.35
$\geq$ III	43	15.5%	<0.001	0.11-0.19
IQ				
Low	150	54%	0.187	0.48-0.59
Normal	127	45.6%	0.150	0.39-0.52
Superior	1	0.4%		

the types of seizures: 59.7% (N=166) focal, 35.3% (N=98) generalized and 5% (N=14) unclassified, both focal and generalized.

The type of epileptic seizure correlated with the weight at birth category ( $p=0.039$ ). Children under 2,500 g at birth, as well as those over 4,000 g, had in a significantly greater number focal seizures. The greatest percent of children with normal weight at birth was observed in children with generalized seizures (87.75% vs. 74.7% focal seizures and 78.57% unclassified seizures).

The timing of seizure occurrence was noted, 56.1% (N=156) of the children having their seizures predominantly when awake and approx. 25% (N=68) having seizures regardless of the moment of the day. A correlation with the number of reported seizure triggers was observed ( $p=0.044$ ). The children with seizures anytime in the day have a high number of seizure triggers (average:  $2.74 \pm 1.663$ ), probably due to excessive reporting, the parents interpreting as seizure trigger any incidental factor, without any real correlation. Children with seizures when falling asleep or waking up have an average of seizure triggers of  $3.15 \pm 2.544$ , the highest average with the highest standard deviation. Children with seizures while awake have an average of  $2.81 \pm 2.094$  potential triggers, while children with seizures during sleep have the least average in the lot, 1.66 seizure triggers, as expected taking into account the difficulty in relating anything with the seizures.

Another correlation was observed, between timing of the seizures and treatment resistance ( $p<0.001$ ), children with seizures anytime in the day being less responsive to antiepileptic drugs in terms of seizure control, while children with seizures when waking up or falling asleep having better outcome.

**TABLE 2.** Similar studies on epileptic seizure triggers

Study	Country	% of patients who identified epileptic seizure triggers
(Konishi, Naganuma et al. 1992)	Japan	51.5%
(Nakken, Solaas et al. 2005)	Norway	53%
(Chowdhury, Hasan et al. 2014)	India	62%
(Frucht, Quigg et al. 2000)	USA	62%
(Sperling, Schilling et al. 2008)	USA	65%
(Spatz, Langbauer et al. 1998)	Austria	71%
(Tan, Wilder-Smith et al. 2005)	Singapore	75%
(Lunardi Mdos, Sukys-Claudino et al. 2011)	Brazil	84.5%
(Spector, Cull et al. 2000)	Great Britain	90%
(da Silva Sousa, Lin et al. 2005)	Brazil	92%
(Ferlisi and Shorvon 2014)	Italy	97%
<i>Present study (2014)</i>	<b>Romania</b>	<b>79.9%</b>

Treatment resistance was identified in 25.2% (N= 70) of the cases. Among the resulting correlations, worth mentioning are the positive associations with late psychomotor development ( $p<0.001$ ), the presence of imaging abnormalities ( $p=0.012$ ) and low IQ ( $p<0.001$ ), mainly because a higher seizure frequency profoundly affects the child's development and intellect, the presence of a distinctive lesion indicating a clear source of a more difficult to control seizure onset zone. As expected, the number of seizure triggers was significantly higher ( $p=0.029$ ) in the case of children with treatment resistant seizures in comparison with responsive children (averages 3.11 vs 2.48).

The potential predictors of treatment resistance were associated in blocks in a multiple hierarchical regression. In accordance with the level of statistical correlation with treatment resistance the following variables were introduced: psychomotor development ( $p<0.001$ ), seizure timing ( $p<0.001$ ), IQ ( $p<0.001$ ), imaging abnormalities ( $p=0.012$ ) and the number of reported seizure triggers ( $p=0.022$ ). Other studies also identified some of these factors as predictors: late psychomotor development and imaging abnormalities (Gururaj, Sztriha et al. 2006; Seker Yilmaz, Okuyaz et al. 2013). The final model indicated that the psychomotor development is a negative predictor ( $B= -0.07$ ), so as timing of the seizures ( $B= -0.11$ ) and IQ ( $B= -0.17$ ), while imaging abnormalities ( $B=0.05$ ) and the number of reported seizure triggers ( $B=0.02$ ) were found as positive predictors.

The number of seizure triggers identified by parents varied between 0 and 10, with median 3 and average 2.64. A percentage of 20.1% (N=56) of children had no observed seizure trigger, the rest of 79.9% having reported at least one. We identified only one similar study in the available literature, with a lot made up exclusively of children (Konishi, Naganuma et al. 1992). Out of all the children with epilepsy, 50% (N=139) had between 1 and 3 potential seizure triggers and 29.9% (N=83) had more than 3.

The first important correlation observed was between the number of triggers and the age ( $p<0.001$ ), the number of observed factors increasing proportionally with age, most likely due to the increase in observational and expressive capacity, but also because parents could easier identify seizures as the epilepsy evolved or the number of recognized seizures increased. On the other hand, adolescents frequently have more risk behaviours, being predisposed to more frequent seizures caused by alcohol, drugs, caffeine, lack of sleep and stress.

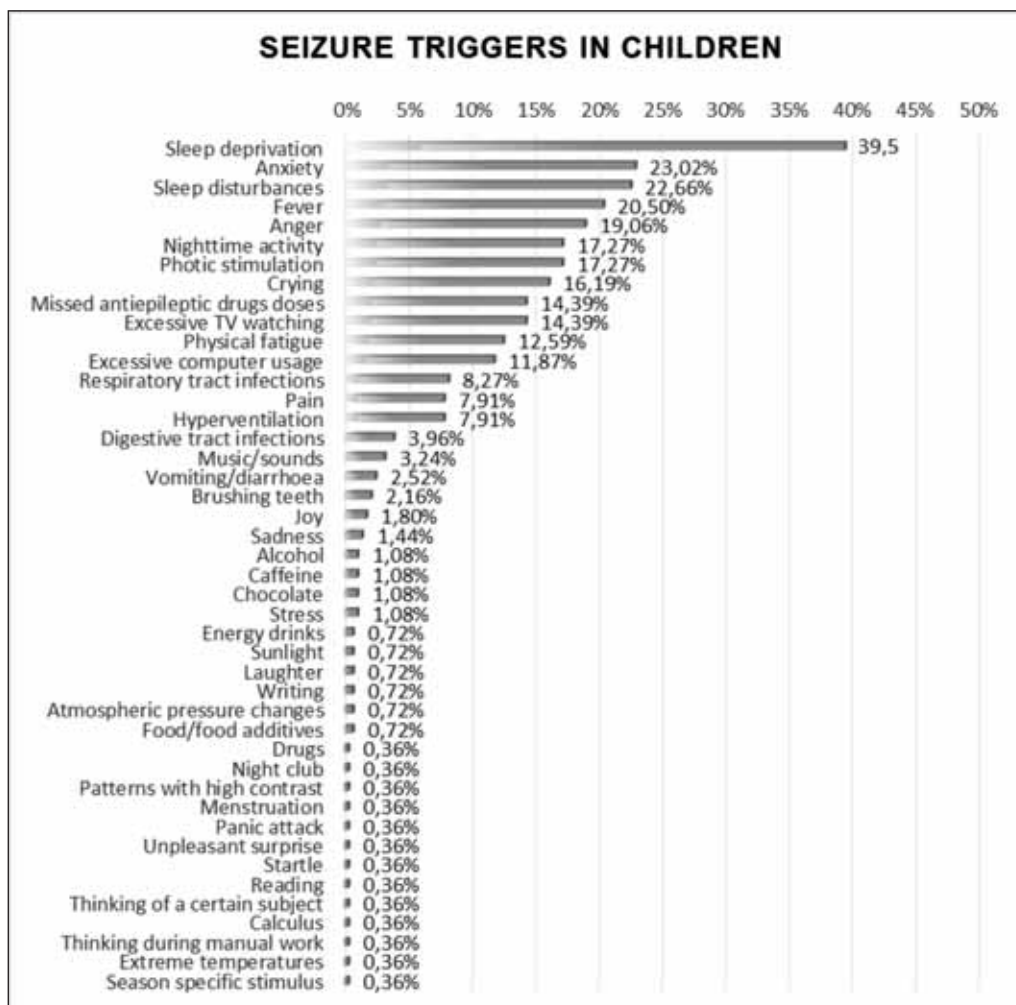
The correlation with treatment resistance ( $p=0.022$ ) adds another problem to the unresponsiveness to antiepileptic drugs: sensitivity towards a larger number of triggers means a greater risk of having a seizure, thus a greater number of seizures, entering a vicious circle. At the same time, treatment resistance means an increased number of seizures, thus a bigger risk of falsely identifying potential triggers.

We used the multiple hierarchical regression in which we introduced age as the first independent variable and treatment resistance as the second. Age significantly contributes ( $p<0.001$ ) to the prediction of the number of triggers with 4.9%. If we add antiepileptic drugs resistance, the variance in the number of seizure triggers increases to 6%, with a significance of  $p=0.041$ . Thus we can calculate the number of potential seizure triggering factors in a child with epilepsy using the formulas:

$$\begin{aligned} \text{No. seizure triggers} &= 1.673 + \text{Age} * 0.099 \\ \text{No. seizure triggers} &= 1.572 + \text{Age} * 0.095 + \\ &\quad \text{Treatment resistance} * 0.555 \end{aligned}$$

Figure 1 illustrates the frequency of all the reported seizure triggers by the parents of children with epilepsy included and willing to take part in the study.

Numerous correlations between different seizure triggering factors and other data (clinical, anamnestic, psychological, imaging data), and also with other triggers. The results were concentrated



**FIGURE 1.** Frequencies of epileptic seizure triggers in children

in a few observations and logical schemes (*Figures 2 a, b, c*) about the modality of questioning patients about epileptic seizure triggers.

## DISCUSSIONS

Among the children who took part in the study, parents identified at least one seizure trigger in 79.9% of cases, the percentage being similar to other studies, although most included adults and only one included adults and children when questioning about seizure triggers. Sleep deprivation was also identified as a very frequent trigger, but other triggers that we asked about were not included in the questionnaires.

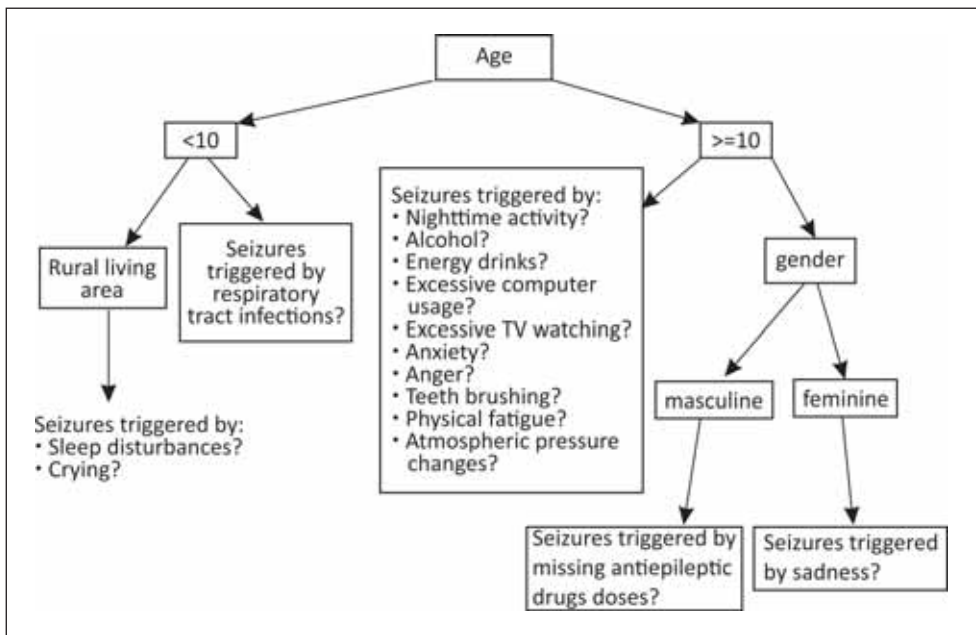
When a treatment resistant epilepsy is diagnosed in a child, parents and patient, when old enough, should be questioned on the reaction to fury or intense anger, reaction to fatigue, to music or sounds. The first correlation can be explained by the fact that children with treatment unresponsiveness live more often the frustration of lack of results in spite

of optimal conduct and efficient drugs prescribed. These negative feelings can increase and cause a negative output on life and loss of tolerance to other negative situations, such moments becoming seizure triggers. Another correlation to take into account is that between anger/fury and fatigue ( $p=0.003$ ), explained by their interdependence, biochemical stress in the body predisposing to irritability, the seizures being easier provoked by negative emotional states.

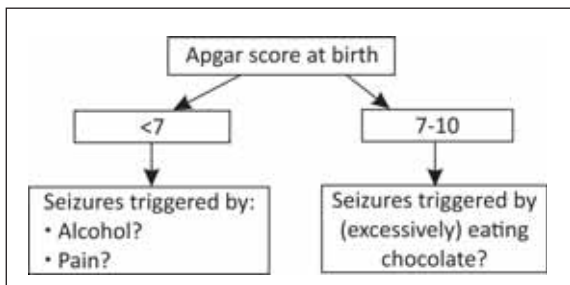
A surprising correlation found was between anxiety as triggering factor and type of seizure ( $p=0.047$ ), children with focal seizures having anxiety significantly more frequent as trigger. This correlation can occur possibly due to more frequent involvement of mesial structures in focal epilepsy, superimposing with the networks responsible for fear and anxiety perception. Moreover, caffeine and chocolate consumption provoked significantly more frequent focal seizures.

Another interesting relationship was found between anxiety and excessive computer use as sei-

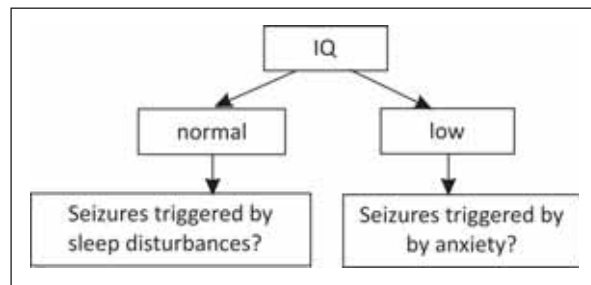




a)



b)



c)

**FIGURE 2.** Logic schemes of structured anamnesis on seizure triggers according to: a) age, gender and living area; b) Apgar score at birth; c) IQ.

zure triggers ( $p=0.043$ ), children having seizures after spending too much time in front of a computer having significantly less frequent seizures when feeling anxious and viceversa. A possible explanation would be that violent games (first person shooter, horror, thriller), often played by children these days, by sending visual impulses first through the amygdala, then to the optical perception areas, hyperstimulate the amygdala due to the threatening visual content. The vegetative answer to fear is the increase of heart beats, respiratory frequency and body temperature, leading to the association with hyperventilation and extreme temperatures as seizure triggers ( $p<0.001$  and  $r=0.006$ ) in these children. In time, the fear response attenuates and tolerance appears, anxiety having not enough effect to cause seizures.

Small weight at birth of a child with epilepsy should lead to questioning about the susceptibility to high contrast patterns or light, surprising touch.

Premature birth predisposes children with epilepsy to seizure triggers such as excessive crying and sleep disturbances, which are metabolic stressful situations that easily cause an imbalance in susceptible neuronal zones.

If the epileptic child has a positive family history, epilepsies with genetic components should be investigated, such as epilepsies which have pain, reading, mathematical calculus and music as seizure triggers.

When the child had febrile convulsions in his/her personal history, stroboscopic lights and extreme happiness can be among their seizure triggers, also suggesting the implication of the amygdala in the epileptogenesis.

Head trauma was correlated with many seizure triggers: panic attacks, unpleasant surprise, voluntary lack of sleep, reading, eating and certain foods, all of these indicating the corresponding affected cortical areas by the trauma or preexistent lesions aggravated by the trauma.

## CONCLUSIONS

Epileptic seizure triggers in children represent a practical subject of interest regarding optimal seizure control, especially due to the negative effects of frequent seizures on a developing brain, during the most important period in learning and acquiring basic skills. Avoiding seizure triggers can be of great help in epilepsy management, especially when treatment resistance occurs.

Taking into account that 79.9% of children with epilepsy included in the study identified at least one seizure trigger, extensive research of triggers represents an important subject for future studies.

The results of the present study were synthesized in a few probability schemes for different sei-

zure triggers according to different parameters and can be seen in *Figures 2 a, b, c*. These schemes can further be used to elaborate an anamnesis protocol for children with epilepsy, as well as a more comprehensive lifestyle advice sheet.

More detailed studies on a greater number of children could validate these schemes for clinical use, aiding in the identification and control of triggering factors, especially when dealing with treatment resistant epilepsies.

We consider that more studies are needed on the subject, with the possible inclusion in the questionnaire of questions regarding possible seizure inhibiting factors.

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