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Circadian patterns of generalized tonic–clonic evolutions in pediatric epilepsy patients

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ABSTRACT

Objective: To investigate the sleep/wake, day/night, and 24-h periodicity of pediatric evolution to generalized tonic–clonic seizures (GTC).
Methods: Charts of 407 consecutive patients aged 0–21 years undergoing continuous video-EEG monitoring for epilepsy were reviewed for the presence of GTC evolution. Seizures were characterized according to 2001 ILAE terminology. Charts were reviewed for EEG seizure localization, MRI lesion, and for seizure occurrence in 3-h time blocks, out of sleep or wakefulness, and during the day (6 AM–6 PM) or night. Analysis was done with binomial testing. Regression models were fitted using generalized estimating equations with patients as the cluster level variable.
Results: 71 patients (32 girls, mean age 12.63 ± 5.3 years) had 223 seizures with GTC evolution. Sleep/wake seizure distribution predicted tonic–clonic evolution better than time of day, with more occurring during sleep ($p < 0.001$). Tonic–clonic evolution occurred most frequently between 12–3 AM and 6–9 AM ($p < 0.05$). Patients with generalized EEG onset had more tonic–clonic evolution between 9 AM and 12 PM ($p < 0.05$). Patients with extratemporal focal seizures were more likely to evolve during sleep ($p < 0.001$); this pattern was not found in patients with temporal or generalized seizure onset on EEG. Patients without MRI lesions were more likely to evolve between 12 AM and 3 AM ($p < 0.05$), in the sleeping state ($p < 0.001$), and at night ($p < 0.05$). Logistic regression revealed that sleep and older patient age were the most important predictors of GTC evolution.
Conclusion: GTC evolution occurs most frequently out of sleep and in older patients. Our results may assist in seizure prediction, individualized treatment patterns, and potentially complication and SUDEP prevention.

1. Introduction

Sleep, time of day, and likelihood of seizure occurrence are linked to each other in patients with epilepsy.[1] More recently, the description of circadian patterns of seizures has become more feasible as seizure tracking has improved, particularly with the aid of electronic and online seizure diaries. The coupling of seizures to a circadian phase in individual patients has direct implications for the clinical management of epilepsy, most notably in chronotherapeutics, i.e. the differential dosing of medications based on circadian seizure patterns. Improved granularity in seizure tracking data offers new and potentially lifesaving approaches to seizure prevention and early treatment.[2]

There is no detailed analysis of the relationship of evolution to generalized tonic–clonic seizures to time of day and wakefulness or sleep.[3,4] Tonic–clonic seizures are risk factors for accidents and may be associated with sudden unexpected death in epilepsy (SUDEP).[5] While a few studies have identified secondary generalization to occur more frequently during sleep, exact description of timing and seizure onset is limited. No data on differential likelihood of tonic–clonic seizure evolution across the 24-h or sleep/wake cycles in the pediatric population has yet been published. We investigate whether the evolution of a single seizure from subclinical or partial to generalized tonic–clonic is more likely in daytime vs. nighttime, in sleep vs. waking state, or at a particular time of day in children and adolescents.

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2. Methods

2.1. Patient population

Medical records of 955 consecutive patients from our tertiary care center admitted for continuous video-EEG (V-EEG) monitoring during a five-year period were reviewed for recorded electroclinical seizure data. Patients between the age of 0 and 21 years with recorded epileptic seizures were included. 407 (42.6%) patients met inclusion criteria for the study. Patients were allowed to adjust their sleep/wake pattern at their own discretion. Antiepileptic medications were tapered in a patient-specific pattern. Patients' MRIs during the testing period were reviewed for the presence of MRI lesions. Patient selection and data acquisition was done following approval of the study by an institutional review board.

2.2. Continuous video-EEG monitoring

Patients were monitored around the clock with continuous V-EEG by a closed-circuit television system and dedicated technologists. EEG leads were placed based on the 10–20 international system of electrode placement, with additional anterior temporal electrodes. Patients underwent continuous V-EEG monitoring for a period ranging from 1 to 10 days. Patients and/or caretakers were also instructed to press the seizure alarm bell during manifestation of clinical seizures. All EEG and video data were later reviewed by a board-certified clinical neurophysiologist.

2.3. Seizure semiology

Seizures were analyzed based on International League Against Epilepsy (ILAE) seizure terminology.[6,7] Two independent investigators, who were blinded to the patient's clinical history and EEG findings, analyzed and categorized each seizure. In rare cases of disagreement final categorization of seizures was decided by a third reviewer (<5%). Seizures were divided into clinical phases, and separated into seizures with clinical evolution to generalized tonic–clonic semiology and those with other evolution patterns. Only patients with seizures consisting of clinical evolution into generalized tonic clonic seizures after another different semiological seizure phase and regardless of generalized or focal EEG onset were included. Seizures that presented solely as generalized tonic clonic seizures have been analyzed previously.[8] The term "secondarily generalized seizure" was defined as a focal seizure that was preceded by any other semiological phase, and then evolved into a generalized tonic–clonic seizure.[9] Notably, this expression is now being replaced by the term "bilateral convulsive evolution" according to the most recent 2010 ILAE report on classification and terminology.[10]

2.4. EEG analysis

All EEG data were reviewed by two independent board-certified clinical neurophysiologists who were blinded to the patient's clinical history and EEG findings. Data were analyzed based on occurrence of tonic–clonic evolution during the day (6 AM–6 PM) or night (6 PM–6 AM), based on seizure relationship to wakefulness and sleep, and within 3-h time blocks throughout a 24-h cycle. Further data analysis was also based on ictal EEG seizure onset localization. We specifically compared tonic–clonic evolutions from temporal, extratemporal, and generalized ictal onset patterns. EEG was used to determine seizure occurrence during wakefulness or sleep as well as time of onset. Seizures that involved several lobes based on ictal EEG recordings were classified under a multifocal extratemporal category.

2.5. Statistical analysis

Statistical analysis was performed utilizing binomial testing. SPSS version 16.0 was used for the analysis (SPSS Inc., Chicago, IL, USA). In addition, patients with tonic–clonic evolutions were compared to patients with alternative seizure evolutions by means of generalized estimating equations using patients as a cluster and an unstructured correlation matrix. This analysis adjusted for multiple seizures from individual patients. This model was used to identify predictors of seizure evolution. Candidates for predictors included brain lesion on MRI, seizure localization, sleep/wake status leading to seizure, occurrence of seizure out of day or night, and patient age. *P* values less than 0.05 were considered significant.

3. Results

3.1. Patient population and demographics

Out of 955 patients, 407 patients (213 boys, 194 girls) presented with epileptic seizures. Of these, 71 patients (32 girls, 39 boys) had evolution to generalized tonic–clonic seizures. Demographics are depicted in Table 1.

3.2. Description of seizure semiology and evolution patterns including tonic–clonic evolution

A total of 223 tonic–clonic evolutions were seen. Of these, 139 (62.3%) seizure evolutions occurred out of sleep and 84 (37.7%) out

Table 1
Descriptive table of patient population.

Total patients (tonic–clonic evolutions)	71 (223)
Number of girls	32 (45.1%)
Mean age (SD; range)	12.63 (5.3; 0.17–21)
Mean V-EEG duration (SD; range)	6.05 (2.5; 1–14)

	Patients	Seizures
Seizure localization		
Generalized	17	32
Frontal	2	6
Temporal	18	55
Parietal	3	8
Occipital	1	5
Multilobar	30	117
MRI findings		
Normal	33	94
Lesional	33	121
No MRI	5	8
MRI site of lesion		
Frontal	1	1
Mesial temporal	6	17
Parieto-occipital	2	8
Perirolandic	1	2
Temporo-occipital	9	25
Other lesion	14	68
MRI side of lesion		
Left	16	56
Right	7	29
Bilateral	6	15
Diffuse	4	21
MRI type of lesion		
Cortical dysplasia	6	23
Hippocampal sclerosis	7	15
Tumor	5	19
Encephalomalacia	2	5
Volume loss, unspecified	2	10
Other lesion	11	49
AEDs		
None	13	46
One	16	37
Two	23	78
Three	14	45
Four or more	5	17

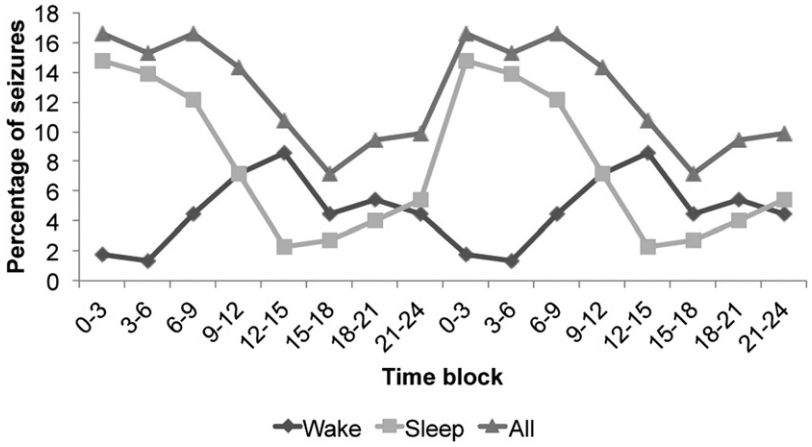

Fig. 1. Diurnal variations of tonic–clonic seizure evolutions out of sleep and wakefulness over a 48-h period. Graphs are plotted as a percentage of total seizures. Maximal seizure activity was seen between 12 AM and 9 AM during sleep ($p < 0.001$).

of wakefulness. 114 (51.1%) of tonic–clonic evolutions occurred at night and 109 (48.9%) occurred during the day.

3.3. Relationship between tonic–clonic evolution, time of day, and state of alertness

Analysis of 3-h time blocks irrespective of sleep/wake status revealed that tonic–clonic evolutions occurred most frequently between 12 AM and 3 AM and between 6 AM and 9 AM ($p < 0.05$, Fig. 1). Evolutions occurred more frequently during sleep ($p < 0.001$). There was no overall difference between daytime or nighttime occurrence of seizure evolution.

3.4. Relationship of tonic–clonic evolution to EEG seizure onset

Patients were also analyzed according to focal or generalized EEG seizure onset during seizures with secondary generalization. Seventeen patients (23.9%, 32 seizures) presented with generalized EEG seizure onsets, and 54 (76.1%, 191 seizures) had focal EEG seizure onsets. There were no patients in our series with both focal and generalized EEG onsets. Patients with generalized EEG seizure onset had most evolutions to tonic–clonic semiology between 9 AM and 12 PM ($p < 0.05$). Patients with focal EEG onsets were more likely to have secondary generalization between 12 AM–3 AM and 6 AM–9 AM ($p < 0.05$) (Fig. 2) and were more likely to generalize out of sleep ($p < 0.001$). Sleep/wake variations were not seen in patients with generalized EEG seizure onset (Table 2). Differentiation of secondary generalization based on localization of extratemporal or temporal EEG onset provided further information on diurnal and sleep/wake patterns. Fifty-five secondary generalizations (29.0% of focal secondary generalizations) occurred in 18 patients with temporal lobe seizures and 136 secondary generalizations occurred in 36 patients with extratemporal lobe seizures. In temporal lobe seizures, occurrence of secondary generalization had a peak between 3 AM and 6 AM ($p < 0.05$). Secondary generalization in extratemporal lobe seizures was most frequently seen between 12 AM and 9 AM out of sleep ($p < 0.001$), and occurred more frequently out of sleep. This pattern was not seen in secondarily generalized temporal lobe seizures. Secondary generalizations in temporal lobe seizures were 2.4 times more likely to occur out of wakefulness compared to those in extratemporal lobe seizures (95% confidence interval: 1.26–4.57).

3.5. Relationship of tonic–clonic evolution and MRI lesion

Sixty-six out of 71 patients had an MRI available for review. Among 33 patients with MRI lesion 121 tonic–clonic evolutions (54%) were seen. In 33 patients without MRI lesions 94 tonic–clonic evolutions (42.2%) were seen. Patients with MRI lesions were more likely to present with seizure evolutions between 12 AM and 6 AM out of sleep ($p < 0.01$), 6 AM–9 AM out of sleep ($p < 0.05$) and between 12 AM and 3 PM out of wakefulness ($p < 0.01$) Patients without MRI lesions were more likely to have evolutions between 12 AM and 9 AM out of sleep, with the lowest p

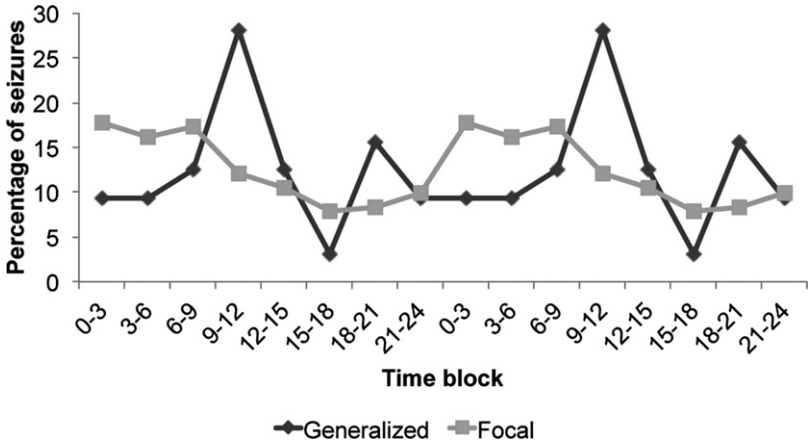

Fig. 2. Diurnal variations of tonic–clonic seizure evolutions based on electrographic localization over a 48-h period. Evolutions are displayed as a percentage of total seizures for the respective type (focal or generalized). Patients with generalized seizures had more events between 9 AM and 12 PM and patients with focal lesions had more events between 12 AM–3 AM and 6 AM–9 AM ($p < 0.05$).

Table 2
Diurnal and sleep/wake patterns of tonic–clonic seizure evolutions based on EEG localization and presence of MRI lesion.

	12 AM–3 AM	3 AM–6 AM	6 AM–9 AM	9 AM–12 PM	12 PM–3 PM	3 PM–6 PM	6 PM–9 PM	9 PM–12 AM	Wake	Sleep
Temporal	4	10	7	9	8	4	3	10	28	27
Extratemporal	30**	21	26**	14	12	11	13	9	41	95***
Generalized	3	3	4	9*	4	1	5	3	15	17
With MRI lesion	17	16	20	17	17	13	9	12	55	66
Temporal	3	4	5	5	5	4	2	6	20	14
Extratemporal	13**	12*	14**	8	10	8	7	5	28	49
Generalized	1	0	1	4	2	1	0	1	7	3
Without MRI lesion[a]	19*	16	15	15	6	3	12	8	29	65***
Temporal	1	5	2	4	3	0	1	4	8	12
Extratemporal	16***	8	10	6	1	3	6	2	13	39***
Generalized	2	3	3	5	2	0	5	2	8	14
All GTC evolutions	37*	34	37*	32	24	16	21	22	84	139***

[a] A small fraction of patients ($n = 5$, 8 seizures) did not have MRI data available for review and are not included in the above table.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

value between 12 AM and 3 AM ($p < 0.001$). Patients with lesional MRIs did not exhibit any particular day/night or sleep/wake patterns. Patients without MRI lesions had more tonic–clonic evolutions out of sleep as compared to wakefulness ($p < 0.001$), and more evolutions during the nighttime as compared to day ($p < 0.05$) (Fig. 3, Table 2).

3.6. Predictive modeling

Upon comparing tonic–clonic evolutions to evolutions of other seizures semiologies, the regression model identified two significant predictors of secondary generalization: patient age and sleep. The odds of having a seizure with tonic–clonic evolution increased by a factor of 1.07 for each year of age increase ($p < 0.05$). Tonic–clonic evolution was found to occur more frequently during sleep than wakefulness (odds ratio 1.82, $p < 0.05$). Analysis of tonic–clonic evolution occurrence during day (6 AM–6 PM) and nighttime (6 PM–6 AM) did not reveal this factor to be a significant predictor.

4. Discussion

4.1. Summary

Evolution to generalized tonic–clonic seizures occurred most frequently in the early morning hours, predominantly out of sleep. Specifically focal seizures in patients with extratemporal epilepsy and in patients without MRI lesions were found to generalize more frequently out of sleep. Tonic–clonic evolution was more likely in older children.

4.2. Sleep/wake patterns of tonic–clonic evolutions

We found tonic–clonic evolution to occur more frequently in sleep. Our findings are in keeping with a prior prospective study performed in adults undergoing V-EEG that also found partial seizures to more likely generalize during the sleeping state.[3] Another prospective study, analyzing the relationship between sleep and epilepsy performed on adults prior to epilepsy surgery, similarly noted that both secondarily generalized and complex partial seizures occurred more frequently out of sleep.[4]

4.3. Diurnal patterns of tonic–clonic evolutions

Our study also indicates that tonic–clonic evolutions occur more frequently in the early morning hours. This early morning occurrence of generalized seizures has been acknowledged in previous ILAE descriptions, and a separate syndrome of idiopathic epilepsy with generalized tonic–clonic seizures has been described.[11]

4.4. Tonic–clonic evolutions based on EEG-onset

Focal seizures were more likely to generalize to tonic–clonic seizures out of sleep in our series. This finding was particularly notable in extratemporal seizures. While the above-mentioned

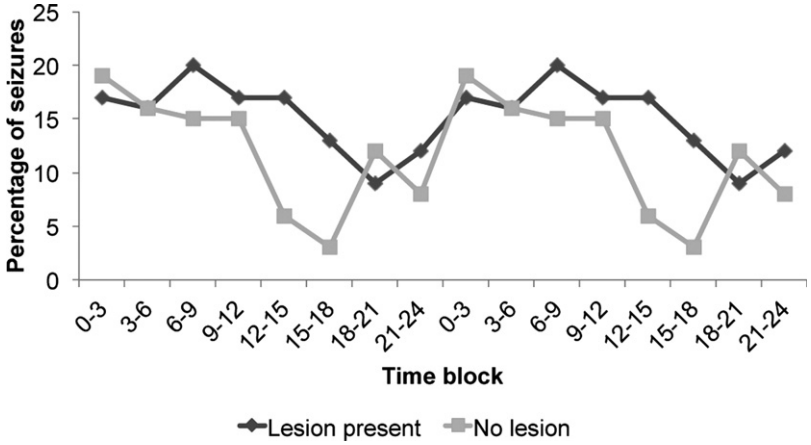

Fig. 3. Tonic–clonic seizure evolutions based on the presence or absence of an MRI-identifiable lesion over a 48-h period. Patients without MRI lesions had significantly increased seizure activity between 12 AM and 3 AM ($p < 0.05$).

adult study of partial seizures found an exception to this in regards to frontal lobe seizures, it otherwise obtained similar results.[3] Another retrospective pediatric study analyzing the sleep/wake occurrence of seizures based on EEG found that focal seizures, with the exception of frontal lobe seizures, occurred more frequently out of wakefulness.[12] We did not have sufficient patients with secondarily generalized frontal lobe seizures to perform this sub-analysis in our series.

4.5. Tonic–clonic evolutions in relation to MRI lesion

The absence of MRI lesions is associated with occurrence of tonic–clonic seizure evolution during sleep and in the early morning. This finding may assist in seizure prediction in this subgroup of patients. No previous studies, analyzing the occurrence of secondary generalization,[3,4] considered the presence or absence of an MRI lesion in their analyses.

4.6. Age and tonic–clonic evolutions

When comparing tonic–clonic evolution to other seizure evolutions using predictive modeling, we found a relationship between age and tonic–clonic evolution. To date, there is no published analysis of timing of tonic–clonic evolution in young children and adolescents, in part due to lack of generalized tonic clonic seizures in infants.[13]

4.7. Limitations

The findings from this study must be interpreted within the setting of data acquisition and subsequent analysis. The retrospective analysis of data derived from a tertiary care center may have led to referral and information bias. Though patients were permitted to maintain their own sleep/wake patterns, these may have been influenced by factors such as nursing schedules, meal times, and physician rounds. The study was done with V-EEG data: EMG, eye-leads, and sleep logs were not used. Medication taper may have had an influence on the frequency of generalized tonic clonic seizures in our series. Details of the individual medication taper were not available, although medications were cut by 50% during the first night and discontinued the following day in most patients. Complete cessation of seizures following localized resection is considered the gold standard of localization diagnosis in surgical patients with refractory focal epilepsies. There were too few of these patients in our study to allow for confirmation of seizure localization. It is difficult to disentangle the relationship between night/day and circadian rhythms based on our retrospective data, and prospective studies are underway to provide additional information on these relationships.

5. Conclusion

Evolution to generalized tonic–clonic seizures in pediatric seizures is influenced by time of day and state of arousal. This observation may assist in the prevention of sudden unexpected death in epilepsy. While much of the data concerning SUDEP is anecdotal, witnessed reports suggest that 90% of cases occur during sleep and in relation to primary or secondarily generalized seizures.[5] The relationship and interactions between SUDEP, sleep and secondarily generalized seizures merit further investigation.[14]

Knowledge of a circadian pattern in epilepsy can also facilitate localization and estimation of secondary generalization risk. Management of epilepsy may be improved in light of these findings via improved approaches to timing of dose regimens (chronotherapy). Higher doses may be considered several hours prior to peak seizure onset in patients with tonic–clonic evolution patterns; this technique has been shown to work in a pilot study in patients with known nocturnal and early morning seizures.[2] Furthermore, this technique may allow for lower-dosing during low seizure intervals, decreasing adverse effects and improving compliance. Alternative therapeutic methods that may be improved by consideration of seizure timing include light therapy and electrical stimulation.

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