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Brief Communication

Seizure occurrence and the circadian rhythm of cortisol: a systematic review

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ABSTRACT

Purpose: Stress is the seizure precipitant most often reported by patients with epilepsy or their caregivers. The relation between stress and seizures is presumably mediated by stress hormones such as cortisol, affecting neuronal excitability. Endogenous cortisol is released in a circadian pattern. To gain insight into the relation between the circadian rhythm of cortisol and seizure occurrence, we systematically reviewed studies on the diurnal distribution of epileptic seizures in children and adults and linked the results to the circadian rhythm of cortisol.
Methods: A structured literature search was conducted to identify relevant articles, combining the terms 'epilepsy' and 'circadian seizure distribution', plus synonyms. Articles were screened using predefined selection criteria. Data on 24-hour seizure occurrence were extracted, combined, and related to a standard circadian rhythm of cortisol.
Results: Fifteen relevant articles were identified of which twelve could be used for data aggregation. Overall, seizure occurrence showed a sharp rise in the early morning, followed by a gradual decline, similar to cortisol rhythmicity. The occurrence of generalized seizures and focal seizures originating from the parietal lobe in particular followed the circadian rhythm of cortisol.
Conclusions: The diurnal occurrence of epileptic seizures shows similarities to the circadian rhythm of cortisol. These results support the hypothesis that circadian fluctuations in stress hormone level influence the occurrence of epileptic seizures.

1. Introduction

The majority of patients with epilepsy report seizures triggered or provoked by endogenous or exogenous factors. The seizure precipitant most often reported is stress [1–7]. The relation between stress and seizures is expected to be mediated by stress hormones like corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, affecting neuronal excitability and seizure threshold [8,9].

Under physiological conditions, cortisol — the 'end product' of the hypothalamic–pituitary–adrenal axis — is released in a distinct circadian pattern [10,11]. These circadian changes in cortisol concentration are likely to affect many important homeostatic processes in the body, including the balance between neuronal excitability and inhibition [12–14]. However, the relationship between circadian fluctuations in cortisol levels and seizure susceptibility is unknown. To provide a first step in exploring this possible relationship, we systematically reviewed the current literature on circadian seizure occurrence in children as well as adults and compared this to the rhythm of cortisol release.

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2. Methods

2.1. Search strategy

To identify studies describing the full 24-hour seizure distribution of seizures in children as well as adults, a literature search was conducted in PubMed and EMBASE on the 30th of July 2014, combining the term 'epilepsy' plus synonyms with a term describing the occurrence of seizures during the day (see supplementary Table 1).

2.2. Article selection

After the exclusion of double publications, titles or abstracts were screened and excluded when no English abstract was available; the study did not report on humans, epilepsy or the circadian occurrence of epileptic seizures; the study did not present original patient data; or when no full text was available. Full texts of the remaining articles were screened and excluded when additional information revealed a conflict with these criteria or seizure occurrence was reported for less than 24 h. References of the remaining articles and articles citing the remaining articles were identified using Web of Science and screened using the same criteria. Only studies reporting results of (video-) scalp electroencephalographic (EEG) or electrocorticographic (ECoG) monitoring

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were included in data aggregation to avoid inaccuracy caused by reporting bias in diary studies. In case of overlapping patient populations, multiple inclusions of data from a single seizure were avoided by excluding one of the two overlapping studies, in favor of the one with the largest patient population.

2.3. Data analysis

Seizure data (i.e., time of occurrence, seizure classification, and localization of the epileptogenic focus) were extracted from the selected articles. Secondary generalized seizures were classified as focal. Data were analyzed for the overall population, as well as for children and adults separately when possible, where the threshold for 'children' corresponded with the threshold used in each individual publication. Data of different studies were combined by calculating the total number of seizures observed in a specific time window. As the time bins in which seizures were measured varied between studies, all results were recalculated into the number of seizures per hour, by dividing the number of seizures observed within a certain time bin by the number of hours in that time window (if time bins comprised two or more hours, seizure frequency in these hours was kept constant).

None of the selected studies measured cortisol in study subjects. Therefore, circadian distribution of epileptic seizures could only be visually compared to a standard circadian cortisol concentration curve in humans. The circadian cortisol rhythm in children develops between 1 month and 2 years of age [15–26]. Although interindividual variability in cortisol levels has been related to age or pubertal status [24,27,28], the overall *circadian pattern* is very robust [25,29]. Therefore, data of children and adults were compared to the same cortisol curve obtained from Weitzman et al. [30].

3. Results

Initially, our search resulted in 2533 titles and abstracts, of which 15 articles fulfilled selection criteria. Reference screening identified one additional article, which did not lead to modification of the query because a term describing circadian seizure distribution in title and abstract was lacking (for a flow chart, see supplementary Fig. 1). Results of the selected studies are described in Table 1.

One study was excluded from data aggregation because seizure occurrence was only reported in a seizure diary [31], as opposed to EEG or ECoG in the other studies. Of the 14 studies remaining, seven focused on children, one on adults, two described results for children and adults separately, and four provided results without this distinction. All studies that provided separate data for adults focused on focal seizures. For two of the studies, only data for specific generalized seizure types could be included in our analysis, because of possible overlap in patient populations with other studies of the same research group [32,33]. Epileptic seizures were monitored by scalp EEG in 12 studies and intracranial ECoG in two. The number of recorded seizures per study varied between 80 and 1350, within a period ranging from 24 h to 16 days. Information on the number of seizures per patient was only reported in eight of the original articles. Combined data resulted in a total of 5700 seizures, of which 2074 could specifically be attributed to children, 1393 to adults, and the other 2233 were reported in studies not distinguishing between adults and children.

3.1. Circadian seizure distribution

Circadian seizure distribution varied between studies (Table 1). Most of the original studies described an increased seizure occurrence in the (early) morning compared to the rest of the day, both in epilepsy populations of all ages [31,34,35] and in cohorts including children [32,33,36–39] or adults separately [40]. Many also reported a peak at varying times in the afternoon or the evening [32–37,39–45].

The aggregated seizure data showed a steep increase in seizure occurrence in the early morning, starting around 4h (military time), following the rise in plasma cortisol with a time lag of roughly 1 to 2 h (see Fig. 1). The seizure occurrence reached a plateau level around 6h, approximately the moment in time when plasma cortisol showed its awakening response. During the next 3 h, seizure occurrence and cortisol both stayed high. During the day, additional peaks were observed in seizure occurrence (11–12h and 15–17h), that were not observed in cortisol level. At the end of the day, both seizure occurrence and cortisol levels dropped to reach a nightly quiescence. Few differences were observed in seizure occurrence between children and adults (Fig. 1). Seizure occurrence in children follows the same pattern as overall seizure occurrence, with an additional increase in the evening (21–22h). In adults, from whom only data on focal seizures were available, an additional increase in seizure occurrence can be observed between 13 and 17h, followed by a steady decrease during the evening and early night.

3.2. Specific localizations and seizure types

Circadian seizure distribution varied with localization of the epileptic focus in patients with focal seizures and between seizure types (Fig. 2). Both seizures with a focal ($n = 3783$) and primarily generalized ($n = 575$) onset showed a clear increase in occurrence in the early morning (4–7h resp. 6–8h), after a nightly quiescence. Where focal seizures showed an additional peak in the afternoon, occurrence of generalized seizures gradually declined throughout the day, following the circadian rhythm of cortisol (Fig. 2A). Although no EEG based data on seizures with a generalized onset were available for adults, a diary study by Le et al. [31] also reported these seizures to mainly occur in the morning.

Subdivision of focal seizures based on the localization of the epileptic focus showed that associations with the circadian rhythm of cortisol existed especially for seizures with a parietal onset ($n = 250$) (Fig. 2B). These seizures showed a clear peak in occurrence in the early morning and an afternoon decline, although an additional peak was observed in the evening. While the occurrence of seizures with a frontal onset ($n = 752$) and seizures with a temporal onset ($n = 2008$) showed the least circadian variation, both showed an increase in seizure frequency in the early morning, with an additional peak in the afternoon. Seizures from the occipital lobe showed a strong afternoon preference. Some studies suggested differences in circadian seizure occurrence between neocortical temporal lobe epilepsy and mesial temporal lobe epilepsy, with a morning peak especially for mesial temporal lobe seizures [34,40].

Subdivision of generalized seizures based on seizure type showed that seizure occurrence increased in the early morning (resembling the rising phase in the circadian cortisol rhythm) for myoclonic ($n = 89$), clonic ($n = 297$), tonic ($n = 201$), and atonic ($n = 55$) seizures (Fig. 2C). Most of these seizure types showed a morning peak, except for atonic seizures that peaked in the early afternoon. Although tonic–clonic seizures ($n = 230$) also often occurred in the early morning, similarity to the cortisol rhythm was less striking because their occurrence was already high during the night and showed a downward trend during the day. Absences ($n = 47$) and epileptic spasms ($n = 299$) showed a different rhythm.

4. Discussion

This review summarized the circadian rhythmicity of seizure occurrence by pooling the data of previous studies and enabled visual comparison with circadian cortisol rhythmicity. The overall circadian occurrence of epileptic seizures resembles the circadian rhythm of cortisol, especially the increase in seizure occurrence in the early morning and the state of quiescence at night. This similarity was observed both in children and adults but varied between different seizure types and localizations of the epileptic focus.