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Original article

The prognostic value of sleep spindles in long-term outcome of West Syndrome

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ABSTRACT

Objective: There is a high risk for a profound developmental disorder in West Syndrome. However, a prognostic biomarker for neurodevelopmental outcome does not exist. Hypsarrhythmia disturbs normal EEG sleep patterns and hence sleep spindles, which are thought to be important for memory consolidation and learning. We postulated that the early recurrence of sleep spindles as well as an early resolution of hypsarrhythmic patterns after onset of West Syndrome lead to a favourable long-term outcome.

Method: 448 sleep EEGs recorded during the first two years of life in 44 patients with newly diagnosed West Syndrome between 1980 and 1989 were reviewed retrospectively. Long-term outcome was assessed in 2015–2016 by the Functional Independence Measurement Score as an indicator for coping with everyday situations. EEG-data were correlated with long-term outcome by Fisher's Exact Probability Test or Kruskal–Wallis H test.

Results: There were no statistically noticeable differences between time to cessation of hypsarrhythmia and long-term outcome. In a subgroup analysis of patients with cryptogenic etiology only (n = 13) recurrence of sleep spindles correlated with better long-term outcome ($p = 0.038$). In this subgroup 11/13 showed recurrence of sleep spindles in childhood, 10 of which had a good or intermediate outcome. Considering the whole patient cohort, recurrence of sleep spindles showed a statistically non-significant better long-term outcome.

Conclusion: Recurrence of sleep spindles and cessation of hypsarrhythmia cannot be used as a valid prognostic biomarker of neurodevelopmental outcome in non-cryptogenic West Syndrome.

Glossary: EEG, electroencephalogram; FIM, Functional Independence Measurement; ILAE, International League Against Epilepsy; PFU, primary follow up; SD, standard deviation; sEEG, sleep EEG; SFU, secondary follow up; SPSS, Statistical Package for Social Sciences; vs., versus; wEEG, waking EEG; WS, West Syndrome.

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1. Introduction

Epileptic spasms, hypsarrhythmia and mental retardation are the cardinal symptoms of West Syndrome, an epileptic encephalopathy in early childhood.[1,2] Hypsarrhythmia, the electroencephalographic key feature of West Syndrome, can occur during all sleep stages and also during wakefulness.[3] Consequently, it disturbs sleep patterns such as the emergence of sleep spindles. Sleep spindles are a characteristic electroencephalographic feature of sleep stage 2 (N2), consisting of oscillating waves with a frequency of 7–14 Hz.[4] They are believed to have a positive effect on memory consolidation and learning[4] and in consequence are important for brain development in childhood. We postulated that sleep spindles can be used as an electrophysiological biomarker to predict the long-term outcome in West Syndrome.

2. Patients

88 children with onset of West Syndrome during the years 1980–1989 were identified in the University Children's Hospital of Muenster database. Patients were included if reported onset of West Syndrome was under the age of two years and if they were diagnosed and treated in the Neuropediatric Department of the University of Muenster. Onset was defined as the initial documentation of hypsarrhythmia in a waking or sleep EEG.

3. Methods

Microfilmed sleep EEGs from 1980–1991 were reanalyzed in 2015 by a single observer blinded to the patients' long-term outcome. The following data were extracted from the patients' files and EEGs:

- Reported age of onset (defined as the first appearance of hypsarrhythmia in waking or sleep EEG)
- Dates of sleep EEGs with and without sleep spindles
- Dates of onset and cessation of hypsarrhythmia, defined as beginning of hypsarrhythmia in waking or sleep EEG and termination of hypsarrhythmia in sleep EEG.
- Sex
- Etiology. Old Dichotomous classification as proposed by the ILAE[5] was used (symptomatic with an underlying cause vs. cryptogenic without a clear cause)
- Preterm birth (before gestational age of 37 + 0 weeks)

For each child primary follow up was defined as period between date of age at onset and date of last sleep EEG on or before the age of two years. Secondary follow up was defined as long-term follow up (24–34 years later).

Long-term outcome was measured by the Functional Independence Measurement (FIM) score as an indicator for quality of life, as it projects the ability to cope with everyday life situations independently. The FIM is an ordinal scoring system originating from medical rehabilitation with 18 items and six areas of evaluation (self-care, sphincter control, transfers, locomotion, communication and social cognition) and a range of 18–126 points[6] thus assigning the patients to one of the following groups:

Group A) Independent (108–126 pts.) = no support is needed in everyday life matters = good outcome.
Group B) Partly dependent (54–107 pts.) = supervision and up to 50% assistance = intermediate outcome.
Group C) Fully dependent (18–53 pts.) = assistance up to 100% = poor outcome.

Descriptive statistics were used to delineate characteristics of the study group. Fisher's Exact Test and Kruskal–Wallis Test were used to compare differences in variables among the groups. Statistical analyses were done using IBM's SPSS 24 for Windows (SPSS, Chicago, IL, U.S.A). Analyses were explorative and thus not adjusted to multiple testing. P-values are considered as descriptive measures, with p-values $p \leq 0.05$ considered as statistically noticeable. Medians and interquartile range (IQR) were used to express continuous variables, frequencies and percentages for categorical ones. This study was approved by the Ethics Committee of the medical faculty of the University of Muenster.

4. Results

31 of the initially identified 88 patients (35%) were deceased in 2014, six patients (7%) were lost to follow up. Of the remaining 51 patients, 44 (86%) participated via phone and personal interview either by themselves or via carers in 2014–2015.

Patient's clinical data extracted from their medical records are shown in Table 1. Retrospective analyses of long-term outcome were summarized in Table 2. Female (17, 38.6%) to male (27, 61.4%) ratio was 1:1.6. 13 patients (29.5%) had cryptogenic, 31 (70.5%) symptomatic etiology, nine of these were premature infants. Median age of onset of hypsarrhythmia was 7.4 (IQR 3.0) months, median time until first sleep EEG after onset was 0 (IQR 22) days. Median primary follow up duration was 8.7 (IQR 8.6) months. Median secondary follow up duration was 28.4 (IQR 4.3) years. Median age at last sleep EEG was 16.3 (IQR 8.0) months, median age at last sleep or waking EEG was 21.8 (IQR 3.1) months. We found no statistical differences among the three outcome groups and sex distribution, etiology and age at onset (cf. Table 1). Additionally there were no statistical differences concerning time until first sleep EEG after onset, time until last sleep or waking EEG during primary follow up, primary follow up duration and secondary follow up duration (cf. Table 1).

Analysis of 448 sleep EEGs was performed. On average 11 (Median; IQR 8) sleep EEGs per person were recorded. In 11 patients sleep architecture was permanently disturbed as they never developed sleep spindles during primary follow up. In contrast, eight subjects showed sleep spindles from disease onset and retained them throughout. In 25 patients sleep architecture normalized and sleep spindles recurred after initiation of anticonvulsive treatment. In the latter group there was no statistical difference among the three outcome groups and mean time until development of the first sleep spindle ($p = 0.581$). The eight patients with continuous evidence of

Table 1 – Summary of demographic data and key EEG-features.

	Total ($n = 44$)	Group A ($n = 11$)	Group B ($n = 16$)	Group C ($n = 17$)	p-value[a]
Sex (male/female)	27/17	8/3	7/9	12/5	0.206[b]
Etiology (cryptogenic/symptomatic)	13/31	4/7	6/10	3/14	0.414[b]
Preterm birth[d] (yes/no)	9/35	1/10	3/13	5/12	0.463[b]
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Age at onset of WS in months	7.4 (3.0)	8.3 (2.5)	7.0 (4.0)	7.4 (3.4)	0.830[c]
Primary follow up in months	8.7 (8.6)	8.7 (5.6)	9.6 (7.9)	7.9 (9.2)	0.652[c]
Secondary follow up in years	28.4 (4.3)	28.3 (7.6)	28.5 (4.6)	28.1 (4.0)	0.777[c]
Number of sEEGs, total number = 448	11.0 (8.0)	11.0 (6.0)	11.5 (9.0)	11.0 (9.0)	0.449[c]
First sEEG after onset of WS in days	0.0 (22.0)	7.0 (38.0)	0.5 (13.0)	0.0 (25.0)	0.680[c]
Age at last sEEG in months	16.3 (8.0)	15.6 (9.3)	17.5 (5.2)	16.2 (8.8)	0.700[c]
Age at last sEEG or wEEG in months	21.8 (3.1)	22.9 (2.8)	22.2 (2.5)	20.4 (5.3)	0.068[c]
Number of patients with sleep spindles	33	9	14	10	
First sleep spindle after onset of WS in days	23 (122)	117 (235)	22.5 (54)	19 (92)	0.581[c]

sEEG = sleep EEG; wEEG = waking EEG; WS = West Syndrome.
[a] Group A vs. group B vs. group C.
[b] Fisher's Exact test.
[c] Kruskal–Wallis H test.
[d] Before gestational age 37 + 0 weeks.

sleep spindles all had a symptomatic etiology. Within this subgroup there was no noticeable difference among the three outcome groups.

A subgroup analysis of the 13 patients with cryptogenic etiology revealed a noticeable difference regarding development of sleep spindles during primary follow up among the three outcome groups (cf. Table 2).

A subgroup analysis of male and female patients revealed no statistically noticeable sex difference regarding the recurrence of sleep spindles, cessation of hypsarrhythmia and outcome.

Time to cessation of hypsarrhythmia was divided into intervals of 15 days after onset of this EEG pattern. In all children who showed cessation of hypsarrhythmia this could be detected in sleep EEG except for 2/44 cases, where it was observed in waking EEG only. A statistically noticeable correlation with long-term outcome could only be found for cessation of hypsarrhythmia 30 days after onset of West Syndrome (cf. Table 2). Five patients (11.4%) demonstrated no termination of hypsarrhythmia within primary follow up, two of these were assigned to group B and three to group C in secondary follow up. Six patients had a relapse, with one

Table 2 – Summary of statistical analysis of recurrence of sleep spindles, cessation of hypsarrhythmia and long-term outcome.

	Total ($n = 44$)	Group A ($n = 11$)	Group B ($n = 16$)	Group C ($n = 17$)	p-value[a,c]	p-value[b,c]
Patients with recorded sleep spindles	n/total[d] (%)	n/total[d] (%)	n/total[d] (%)	n/total[d] (%)		
within 0 days	8/23 (35)	2/5 (40)	3/8 (38)	3/10 (30)	1.000	1.000
within 30 days	18/36 (50)	4/8 (50)	8/14 (57)	6/14 (43)	0.733	0.754
within 60 days	21/41 (51)	4/9 (44)	11/16 (69)	6/16 (38)	0.119	0.228
within 90 days	24/43 (56)	4/10 (40)	12/16 (75)	8/17 (47)	0.112	0.539
at all during PFU	33/44 (75)	9/11 (82)	14/16 (88)	10/17 (59)	0.162	0.075
Development of sleep spindles at all during PFU (cryptogenic etiology only, $n = 13$)	11/13 (85)	4/4 (100)	6/6 (100)	1/3 (33)	0.038	0.038
Cessation of hypsarrhythmia after onset	n (%)	n (%)	n (%)	n (%)		
within 15 days	7 (16)	1 (9)	2 (13)	4 (24)	0.664	0.402
within 30 days	17 (39)	6 (55)	2 (13)	9 (53)	0.025	0.203
within 45 days	22 (50)	7 (64)	6 (38)	9 (53)	0.409	1.000
within 60 days	24 (55)	8 (73)	7 (44)	9 (53)	0.327	1.000
within 90 days	30 (68)	9 (82)	9 (56)	12 (71)	0.389	1.000
at all during PFU	39 (89)	11 (100)	14 (88)	14 (82)	0.415	0.359

PFU = primary follow up.
[a] Group A vs. group B vs. group C.
[b] Group A + B vs. group C.
[c] Fisher's exact test.
[d] total number of patients with a recorded sleep EEG at that point of time.

patient suffering from a continuing hypsarrhythmia during primary follow up.

A subgroup analysis of all those children with at least a total number of 3 sleep EEGs (n = 42), of those having a sleep EEG at least at the age of 18 months (n = 18) or of those having both (n = 17) did not change the results stated in Tables 1 and 2 and thus were not stated.

Combining group A and B and testing against group C did not change any of the results stated above (cf. Table 2).

5. Discussion

In general outcome in West Syndrome is poor,[1] so it is important to find early prognostic factors determining long-term neurodevelopmental outcome. Prognostic factors would facilitate treatment decisions as well as counselling parents of children affected by West Syndrome. Some factors associated with a positive outcome have previously been published, specifically a cryptogenic etiology of West Syndrome, an expeditious initiation of anticonvulsive treatment (<4 weeks), onset of West Syndrome at an age >4 months and an early response to treatment.[1,7] Hypsarrhythmia disturbs normal sleep patterns such as sleep spindles during a period of time in which increase of brain volume and gain of function usually is enormous in a healthy brain.[8] Also sleep is most important for brain maturation and sleep spindles are thought to be essential for learning.[4] As there is a paucity of data in the epilepsy literature on early prognostic biomarkers in West Syndrome, we hypothesized that sleep spindles could be utilized as a new prognostic biomarker for long-term outcome.

We reanalyzed sleep EEGs of 88 children at the onset of West syndrome, 44 of these patients were eventually included into this study. Recurrence of sleep spindles was correlated with long term outcome, measured by FIM, a score used to describe coping with everyday life situations. Statistically no noticeable correlation between long-term outcome and sleep spindles was found in this study, thus refuting our hypothesis of sleep spindles being a prognostic biomarker for long term outcome in West Syndrome.

Children who developed sleep spindles after onset of West Syndrome did not have a noticeably better outcome than those who did not, no matter how early (30 days) or late (up to 17 months) after onset the recurrence occurred. However, our data suggests that there might be a connection between sleep spindles and a good or intermediate outcome as more children who developed sleep spindles during primary follow up had a good (9/11, 82%) or intermediate (14/16, 88%) outcome than those who had a poor one (10/17, 59%; cf. Table 2).

Nevertheless this finding must be regarded critically, as in more than 1/3 of these children (12/33, 36%) sleep spindles recurred more than 60 days after onset of West Syndrome. Potentially, development of sleep spindles and outcome are less correlated after a duration of active hypsarrhythmia of two months.

In group A (good outcome) 4/11 children showed recurrence of sleep spindles 30 days after onset of West syndrome and in an additional 5/11 children sleep spindles recurred after this time period. In group B (intermediate outcome) findings were similar. Hypothesizing that early recurrence of sleep spindles would lead to a favourable long-term outcome, one would have expected earlier recurrence of sleep spindles in both group A and B.

In the subgroup analysis of all those children with cryptogenic etiology a statistically noticeably result was found. All patients with a good or intermediate outcome showed recurrence of sleep spindles more often during PFU than those in the poor outcome group. The findings of Lee et al.[9] are consistent with these findings. They solely described 66 patients with non-lesional (cryptogenic) West Syndrome, a patient cohort which in general is thought to have a better outcome.[1] They found recurrence of normal to borderline sleep spindles significantly more often in the seizure free group, while finding abnormal or no sleep spindles at all in the non-seizure free group ($p = 0.0002$) over a period of 4.5 years. As a limitation of our study only 13 patients belonged to the cryptogenic group in total.

On the contrary Kramer et al.[10] and Schuh et al.[11] found no correlation between a good outcome in patients with hypsarrhythmia and the appearance of sleep spindles. All three studies had a retrospective design, defined a good outcome as freedom of seizures and had a follow-up duration of approximately 3–5 years. As these are rather short follow up periods and the subjects' brains were still in the process of maturation, statements about the prognostic value of sleep spindles concerning outcome are limited.

Cessation of hypsarrhythmia 30 days after onset showed a statistically noticeable difference regarding long-term outcome (cf. Table 2). Nevertheless the proportions of patients with cessation of hypsarrhythmia are similar in group A and C, but lower in group B, thus a legitimate prognostic benefit cannot be inferred from this statistically significant P-value.

The old ILAE classification[5] (1989) was applied since it was in use at the time our patient cohort was treated for West Syndrome from 1980 to 1991.

The limitations of this study are its retrospective design and thus the variable number of sleep EEGs recorded per patient as well as a strong fluctuation in duration between single observations (days to months). Also, because of our retrospective design, not every potential patient participated in our study, which leads to a loss of information. Our cohort was rather small, but as West Syndrome is a rare disease (incidence of 2–3.5 : 10.000 live births)[1] our findings add substantial information on EEG biomarkers in West Syndrome. To corroborate our hypothesis, a prospective study design with a sufficient number of patients under controlled circumstances would be necessary. In further prospective studies also duration, symmetry or synchrony of sleep spindles should be analyzed, as this could yield interesting information.

Another limitation of this study is the fact, that there are relatively long time-spans between diagnosis of hypsarrhythmia in waking EEGs and conduction of the first sleep EEG, thus plausibly attenuating the correlation between sleep patterns (such as recurrence of sleep spindles) and long-term outcome.

6. Conclusion

We found no correlation between recurrence of sleep spindles or cessation of hypsarrhythmia and long-term outcome in West Syndrome except for patients with cryptogenic West Syndrome. Whether the recurrence of sleep spindles in cryptogenic West Syndrome is an independent prognostic factor or interwoven with the non-lesional etiology could not be determined in our study. Especially for patients with cryptogenic West Syndrome further studies with a prospective design should be carried out to re-evaluate these findings.

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Conflicts of interest

G. Kurlemann received personal fees from UCB Pharma, Desitin Arzneimittel, Zogenix, LivaNova, Eisai, GW Pharma, Bial, Dibropharma, Novartis, Biogen, Actelion and Shire.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.09.003.

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