Received: 17 July 2023 | Accepted: 12 December 2023

DOI: 10.1002/epd2.20192

Epileptic Disorders

REVIEW ARTICLE

Does the absence or presence of sleep spindles on EEG have prognostic value for cognitive outcome in children with infantile epileptic spasms syndrome? A systematic literature review

Jaana Lähdetie[1] | **Miguel Muñoz-Ruiz**[2] | **Hannu Kokki**[3]

[1]Department of Child Neurology, University of Turku and University Central Hospital of Turku, Turku, Finland

[2]Department of Clinical Neurophysiology, Central Finland Welfare District, Nova Hospital, Jyväskylä, Finland

[3]Department of Anesthesiology, University of Eastern Finland and University Central Hospital of Kuopio, Kuopio, Finland

Correspondence
Jaana Lähdetie, Department of Child Neurology, University of Turku, P.B. 52, FI-20521 Turku, Finland.
Email: jaana.lahdetie@utu.fi

Funding information
Aivosäätiö (Finnish Brain Foundation), Grant/Award Number: 20220170

Abstract

Infantile Epileptic Spasms Syndrome (IESS) is an epileptic encephalopathy in childhood that affects infants under the age of two years. When spasm series occur, prognosis for cognitive outcome is poor in the majority of cases. The encephalopathy in IESS includes delayed maturation of normal sleep phenomena in the EEG, such as sleep spindles. Children with intellectual disabilities often have abnormal sleep, and children with sleep problems have difficulties learning at school. We examined whether there is evidence of prognostic value of detection of sleep spindles in the EEG of children with IESS on their future cognitive development. A systematic literature search yielded five studies touching this question. They were evaluated by two scorers independently. The lack of normal sleep patterns including lack of sleep spindles was used as a biomarker of poor cognitive outcome. Positive (PPV) and Negative (NPV) prognostic values were calculated. A summary of all five studies indicates a PPV of 82% and an NPV of 45%. Given the small amount of data, the retrospective quality of most studies, and the differences in the outcome parameters reported, it is prudent to say that currently available data do not allow us to conclude whether spindles have a specific and independent role in the cognitive prognosis of affected children. Since sleep spindles are needed for memory consolidation and demonstrate the active role of sleep for learning and memory, the hypothesis remains that their absence in the EEG may indicate an increased risk of cognitive delay, but more supporting data are needed to reach such a firm conclusion.

KEYWORDS

cognitive development, epileptic spasms, prognosis, sleep spindles

Registration: This research was not registered. The literature review protocol is available from J.L. and M.M.R.

1 | INTRODUCTION

1.1 | Infantile epileptic spasms syndrome and cognitive outcome

Epilepsy in infancy can be detrimental to the rapidly growing brain of the baby.[1] One of the best known epileptic encephalopathies is West syndrome, now renamed as Infantile Epileptic Spasms Syndrome (IESS) by The International League Against Epilepsy.[2] This peculiar encephalopathy can result from structural, genetic, metabolic, immunologic or unknown comorbid disorders. There is a sensitive period of brain maturation, so IESS starts most often between 3 and 8 months of age. Normal development prior to IESS onset, short lag time to treatment, and prompt response to treatment by resolution of spasms are good prognostic indicators for seizure outcome.[3] Symptomatic etiology, pre-existing developmental delay, ongoing spasms, persistent hypsarrhythmia, persistent seizures of any kind and evolution to Lennox–Gastaut syndrome predict poor outcome.[3]

Infantile epileptic spasms and spasm series are easiest visualized after awakening. The common mechanisms remain enigmatic, even though imaging and genetics have increased the knowledge of associated, possibly causally important, disorders and syndromes. Focal dysgenesis of cortical tissue, migration disorders, hypoxic–ischemic brain damage and stroke, Down syndrome, tuberous sclerosis complex, mutation of *ARX* and *CDKL5* genes, and channelopathies are just some examples of more than 200 etiologies that exist for IESS. Patients with structural brain damage and IESS are often intellectually severely handicapped and show increased mortality.[3–5]

The risks of IESS on cognitive development exist in all etiology groups. Patients without known etiology, previously called "cryptogenic",[6] represent usually 20%–30% of all IESS patients in hospital material. It is important to consider the proportion of this group when comparing studies on IESS outcome because of the substantially better cognitive and seizure outcome than in IESS overall.[3] Still many children in this subcategory suffer from learning problems and poor developmental outcome. What destroys the possibilities of normal brain maturation and cognitive development in about 85% of IESS patients and yields intellectual disability?

1.2 | Sleep and sleep spindles

The lack of normal sleep phenomena may offer a clue about the mechanisms causing permanent damage to cognition. Slow-wave sleep (SWS) has long been known to preferentially consolidate declarative memories, whereas rapid eye movement (REM) sleep primarily supports procedural memories.[7] Consolidation of memories during sleep is an active process. Abnormalities in sleep may be associated with poor cognitive development of a child with epilepsy.[8,9]

Key points

- The systematic literature review resulted in five relevant papers.
- Lack of sleep spindles had a positive prognostic value of 82% for poor cognitive outcome.
- Currently available data are scarce and more data are needed to reach a conclusion of the prognostic significance of sleep spindles.

Sleep spindles are an EEG event characterizing stage 2 sleep. They increase in number after learning and are correlated with intellectual performance. They play a role in hippocampal-neocortical dialogue necessary for memory consolidation.[10] In the maturing brain of the healthy infant, spindles start to be observed between 6 weeks and 3 months age.[11] Spindles originate in the thalamus and involve an interaction of the GABAergic neurons of the nucleus reticularis, the pacemaker, to widespread thalamocortical projections so that they function in a synchronized manner. Spindles occur preferentially in networks that have potentiated synapses.[12] In general, they oscillate at frequencies of 10–15 Hz and last 0.5–3 s.

Two types of spindles exist: fast spindles (13–15 Hz) with centroparietal prevalence, and slow spindles (10–13 Hz) with frontal predominance. The latter appear only around 1 year of age. In contrast, the fast spindles exist in typically developing infants from 4 months to 1 year, interestingly concomitantly with the sensitive period for IESS. During the first 6 months, spindles are mostly asymmetric and unilateral. Around 1 year of age bilateral synchrony of spindles increases.[11] Spindle activity has been suggested to have important links to cortical development and to serve as a maturation indicator[13,14] but a consensus on the role of specific spindle types is still lacking.[8]

1.3 | Intellectual disability and sleep

Intellectual disability, usually defined by an Intelligence Quotient (IQ) less than 70, is linked with shorter duration of sleep.[15] A meta-analysis shows that people with intellectual disability sleep, on average, 18 min less per day than people without intellectual disability.[15] Also,

the quality of sleep is worse in individuals with intellectual disability. Children with intellectual disability frequently have no sleep spindles in EEG, and compared to those who do have sleep spindles, they tend to have a lower Developmental Quotient (DQ).[16,17] In Shibagaki and Kiyono's study there was a significant decrease in DQ in children with short spindles or no spindles compared to those with many long spindles.[17] A positive correlation between IQ scores and the number of sleep spindles was reported by Fogel and Smith.[10]

1.4 | Rationale for the present study

Different scoring systems[18–21] have been suggested as tools in the treatment of IESS in order to decide about type and duration of treatment or to predict seizure outcome or development.[22] Their use has, however, not become a widespread clinical guideline. The absence of normal sleep phenomena has been known to correlate with outcome. In 2008 Guzzetta et al.[23] speculated that lack of sleep spindles may be a stronger marker of basal abnormal electrographic activity than hypsarrhythmia itself.

In this systematic literature review we asked whether there is evidence in the literature that sleep spindles or deep sleep markers including sleep spindles could serve as biomarkers of good cognitive outcome in IESS and, vice versa, whether lack of sleep spindles might be a biomarker for poor cognitive outcome.

2 | MATERIALS AND METHODS

2.1 | Systematic review protocol

A systematic literature search was conducted in May–June 2023 using EMBASE, PubMed (Medline), ScienceDirect and PsychINFO (EBSCOhost) databases with search phrases infantile spasm* or West syndrome, sleep or sleep spindle*, and intellectual or cogniti* without limits for years nor language of publication (Figure 1). Searches yielded 501 results. Two authors (JL and MMR) checked the lists independently based on titles and abstracts. Duplicates were removed. Research papers with data about spindles in EEG in SWS and cognitive outcome were included irrespective of the etiology of infantile epileptic spasms. Studies on the Hypsarrhythmia Index[22] or related constructed EEG-based measures, which contained "the absence of normal sleep phenomena such as spindles" were included. If spindles were not mentioned, the study was excluded. We excluded animal experiments, conference abstracts, single case reports, papers reporting patients whose epileptic spasms started after 1 year of age or who were having ESES, CSWS, status epilepticus, Lennox–Gastaut syndrome, Dravet syndrome or concerned neonates. To be included in this review, papers had to contain original data on the following three aspects (1) infantile epileptic spasms, (2) sleep EEG and spindles, and (3) cognitive or general developmental outcome. EEG registrations had

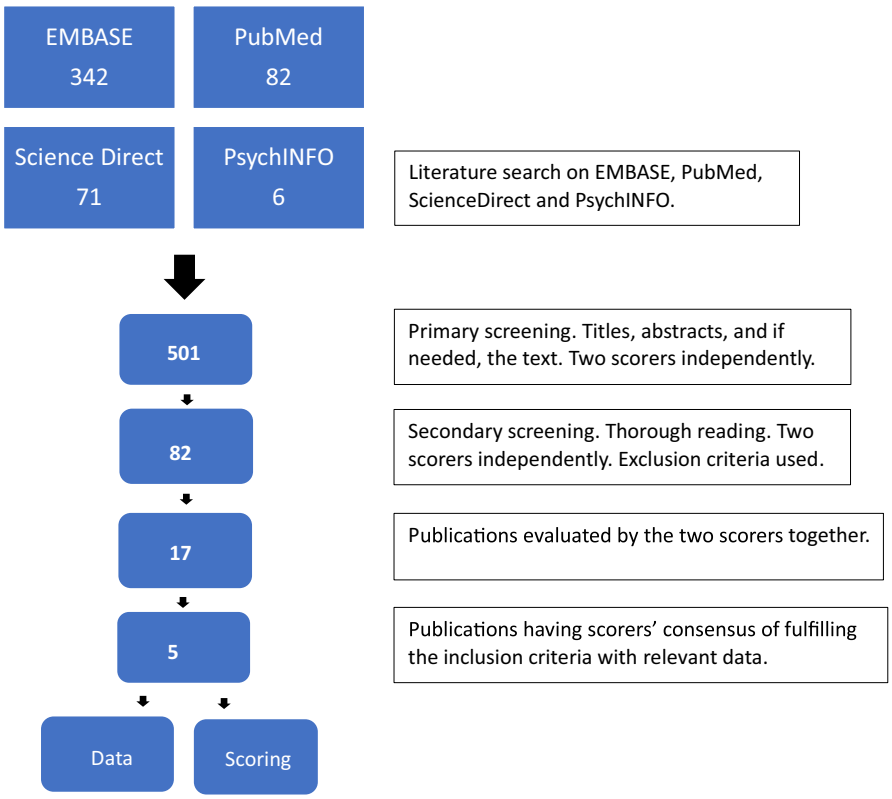

FIGURE 1 PRISMA Chart of the systematic literature review process.

to include sleep EEG. We were interested in EEG results recorded at the end of treatment, preferably in N2 stage and SWS, and therefore, we used the data of the last EEG performed on the patient, if available. We chose the outcome measures which were explicit and had DQ, IQ or related data on developmental and cognitive outcome. The methods to analyze cognitive development as well as the follow-up ages when the outcome was measured were variable. We included studies with a minimum of 6 months follow-up time after primary treatment.

A data extraction protocol was created, and the data were extracted and compared from the selected papers independently by two authors (JL and MMR). The Joanna Briggs Institute recommendation[24] (2014) was used for assigning a level of evidence for the selected publications according to the methodological quality. We judged the degree of evidence, giving 1–5 points, 1 being the best evidence and 5 the weakest.

The results are presented as the number of cases and percentages. Positive (PPV) and negative prognostic values (NPV), and sensitivity and specificity were calculated (Figure 2). Associations between spindles in sleep and the patient's cognitive development were tested with cross-tabulation using a chi-squared-test (SPSS Statistics 26.0; IBM, Armonk, NY, USA). P-values under 0.05 were considered statistically significant.

3 | RESULTS

The literature screening by two researchers ended up with five published studies that covered the three required aspects: IESS, sleep spindles and cognitive outcome[20,22,23,25,26] (Figure 1). The contents of the papers in order of publication year, their details and PPV of the lack of sleep spindles for the risk of poor cognitive outcome are listed in Table 1 and Appendix S1.

The five studies report results of 162 IESS patients, 16–49 IESS patients per study. All but one[23] were retrospective reports on hospital-based material. Of the patients 43% (69 of 162), were assigned to the unknown etiology group, earlier called "cryptogenic". PPV, that is, the proportion of cognitively affected persons among all those lacking spindles) in their EEG (the biomarker is the lack of spindles), was 82%, and NPV, that is, the proportion of cognitively normal persons among those who have spindles in their sleep EEG, was 45% ($p = .00048$). Sensitivity, that is, the proportion of cognitively disabled persons lacking spindles, was 60%, and specificity, that is, the proportion of cognitively normal persons having spindles in their sleep, EEG was 74%. It can be interpreted that having spindles does not serve as a reliable biomarker of normal cognitive development, whereas lacking spindles may indicate the possibility of cognitive deterioration and

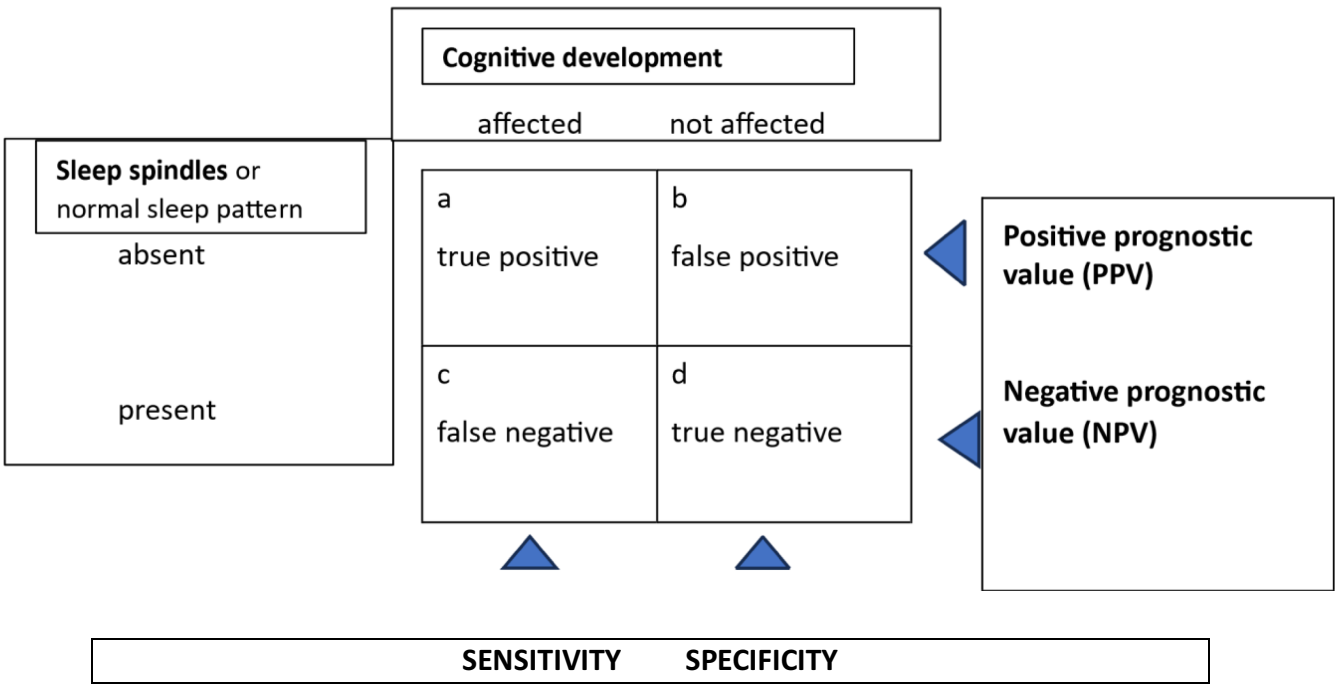

FIGURE 2 Principle of counting sensitivity, specificity, and positive (PPV) and negative prognostic value (NPV)s. (Adapted from Trevethan R. Sensitivity, specificity and predictive values: foundations, pliabilities and pitfalls in research and practice. Front Public Health 2017, 5:307. doi: 10.3389/fpubh.2017.00307). Sensitivity = [a/(a + c)] × 100. Specificity = [d/(b + d)] × 100. Positive prognostic value (PPV) = [a/(a + b)] × 100. Negative prognostic value (NPV) = [d/(c + d)] × 100.

TABLE 1 Summary of results in five studies in the systematic literature review listed in order of publication.

Reference	IESS patients	Patients with unknown IESS etiology	Last sleep EEG	Follow-up time	Measures for cognitive development	Absence of sleep spindles predictive of poor outcome (PPV)	Presence of sleep spindles predictive of good outcome (NPV)	Level of evidence	Bias
Dulac et al. 1986[25] R ID no	32	32[a]	At 15–48 months, mean 24.5 months	46–63 months, mean 49 months	WPPSI[b], Brunet-Lezine Developmental Quotient	86%	81%	4	Individual data missing
Kramer et al. 1997[22] R ID no	49	13[c]	Posttreatment, not specified, HPI[d]	12–64 months, mean 33 months	Denver Developmental Scale -based score	74%	29%	4	Normal sleep = spindles or K complexes present
Guzzetta et al. 2008[23] P ID yes	21	4	At 24 months posttreatment	2 years	Modified Griffith's scale	91%	44%	4	Normal sleep = spindles present and sleep stages identified
Altunel et al. 2015[20] R ID Yes	16	7	30–45 days posttreatment, HPI[d]	2–6 years	Clinical evaluation or academic ability at 5 years	100%	75%	4	Lack of control group Small study
Spenner et al. 2019[26] R ID no	44	13	At the end of treatment, median 16.3 months	24–34 years	FIM = Functional Independence Measurement Score	82%	26%	4	Outcome measure different from other studies

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development; FIM, Functional Independence Measurement; Griffith, Griffith's Scales of Child Development; HINE, Hammersmith Infant Neurological Examination; ID, individual data available; P, prospective; R, retrospective.

[a]32 "cryptogenetic". MRI not performed but computerized tomography (CT) and diazepam i.v.-test for focal etiology. Two subgroups: prognosis unfavorable 10, favorable 22.

[b]WPPSI = Wechsler Preschool & Primary Scale of Intelligence™.

[c]6 pure "cryptogenic" + 7 symptomatic unknown.

[d]HPI = Hypsarrhythmia Paroxysm Index which includes presence or absence of sleep spindles (Kramer et al. 1997).

of intellectual disability. Since the result is based on only five low-evidence studies (Table 1), the total outcome of this literature review is not conclusive.

3.1 | Summaries of the main characteristics of selected articles

1. The first study published by Dulac et al. (1986)[25] is a retrospective analysis of "benign" infantile spasms, a subgroup of West syndrome. The initial number of IESS patients was 100, but the results concern 32 cases here called "cryptogenetic". Patients were randomized to treatment with hydrocortisone for either 1 or 3 months followed by valproate. Etiological investigations included computerized tomography (CT) of the skull with contrast compound. EEG was recorded several times, first at eight and 30 days after treatment initiation, and later at control visits up to an average age of 4 years. Each time among other observations, sleep spindles were identified and their symmetry analyzed. Neuropsychological testing was carried out by standardized methods including the Wechsler Scale Test reinforced by items from a few other tests. Twenty-one patients had a favorable development, whereas ten had an unfavorable development, and one patient was not reached for follow-up. Ten children in the favorable group showed normal intelligence (IQ 71–128, mean 102). Only one had IQ under 90. Among ten unfavorable patients, one could not be examined, three of nine showed spindles in the Rolandic area. The developmental quotient at 2–5 years of age showed six cases of IQ less than 40 and four others with DQ 55–67. Two of the four had mainly speech and language disability, and two others had deficits in visual perception and visuomotor functions.
2. Kramer et al.[22] analyzed retrospectively the records of 53 IESS patients to estimate the severity of their disorder. The absence of normal sleep patterns was included as an element in a score created for prognostic purposes and consisting of electrophysiological abnormalities, typical patterns and variants. Absence of normal sleep activity was equal to absence of sleep spindles or unequivocal K complexes in the sleep EEG. The other points came from asymmetry, hypsarrhythmia, burst-suppression or synchronization of the EEG. A favorable outcome was associated with a lower score. Absence of normal sleep activity was seen in 69% of the records. Higher hypsarrhythmia scores correlated with higher outcome scores (worse prognosis) on longer than 1 year follow-up. The cognitive outcome was evaluated 12–64 months after treatment, mean 33 ± 14 months, by a modified Denver Developmental Scale. Of 49 patients, 36 had poor developmental outcome and 13 had good outcome. The range was from normal development (three patients) to profound delay (in five cases). Patients with "cryptogenic" IESS tended to do better on follow-up than patients with symptomatic IESS, but the difference was not statistically significant.[22] Without showing individual data, the authors state that they "did not find any correlation between the presence of sleep spindles and outcome". The hypsarrhythmia severity score, instead, had a significant positive correlation to poor outcome, albeit with a wide scatter. Calculated on the bases of data presented in their article, "absence of normal sleep patterns" had a PPV of 74% (Table 1) for poor outcome.
3. The only prospective study is by Guzzetta et al.[21] Twenty-one infants were followed for 2 years. Abnormalities of sleep organization were measured by the presence or absence of sleep spindles, hypsarrhythmia, and other EEG abnormalities. Neurosensory effects of IESS were analyzed by special methods, a battery of visual function tests or auditory brainstem responses. Patients were treated with vigabatrin or ACTH or both. In addition to thorough clinical examination, developmental measurements such as the Hammersmith Infant Neurological Examination (HINE) and Griffiths Mental Scale were used at an evaluation 24 months after treatment initiation. After etiological work-up, four patients had "cryptogenic" IESS. Seven children including the four "cryptogenic" cases, two with tuberous sclerosis, and one with early vascular brain injury showed normal development and the 14 others abnormal development. In EEG, sleep abnormalities, equivalent here to lack of sleep spindles, yielded lower scores of cognitive tests and neurological examination.[23] The time span of the follow-up was considered too short to assess later cognitive deficits.
4. Altunel et al.[20] used in their retrospective study the Hypsarrhythmia Paroxysm Index[22] and sleep spindles to study 16 IESS patients treated with ACTH and to prevent relapses with small doses of ACTH when necessary. Cognitive development was measured at the median age of 5 years. Sleep spindles were present in patients considered to have "cryptogenic" IESS. No spindles were seen before or after treatment in those patients with a lag-time to treatment over 1 year or that were cognitively severely deteriorated. In three patients, spindles disappeared, and in two, they reappeared during treatment. The cognitive development of those two was affected less than that of patients in the severe group.[20] Long persistence of

hypsarrhythmia was thought to block the generation of sleep spindles. The PPV in this study is 100%, and the authors state that "if sleep spindles are not observed despite the disappearance of hypsarrhythmia, one can expect a poor developmental outcome". They suggest evaluating sleep spindles concurrently with hypsarrhythmia.

5. The prognostic value of sleep spindles as a biomarker of developmental outcome in IESS was studied by Spenner et al.[26] The patients having had IESS or their parents were interviewed, and data were extracted from medical records of 44 children. The Functional Independence Measure (FIM) scale, which contains a subtest on cognition, was applied. They reanalyzed, on average, 11 sleep EEGs per person. Of 44 patients, 11 never developed sleep spindles. Eight patients showed sleep spindles from IESS onset throughout the follow-up. In 25 patients, anticonvulsive treatment normalized the sleep architecture and sleep spindles. Among them there was no correlation to cognitive outcome. In the group of 13 patients with "cryptogenic" IESS, 11 developed sleep spindles within the primary follow-up of 90 days. This is in accordance with the fact that recurrence of sleep spindles at follow-up was more common in patients having a good or intermediate cognitive outcome than in those with poor outcome, as well as with the findings of Lee et al.,[27] who studied just seizure outcome in "cryptogenic" cases relative to the recurrence of sleep spindles.

4 | DISCUSSION

Poor cognitive outcome is common in patients with IESS. New options for treatment are lacking. The main aim should be to reduce intellectual disability caused by IESS.

A biomarker related to the outcome of IESS has been searched for during the last 30 years among special EEG features, such as hypsarrhythmia and its variations, slope of slow waves, high-frequency oscillations, etc. This systematic review, which tried to show that absence of sleep spindles after treatment might have predictive value for poor cognitive outcome, resulted in only five research articles fulfilling the search criteria, and not yielding sufficient data to prove the hypothesis. Poor cognitive outcome may naturally be expected regardless of the derangements of sleep spindles in, for example, developmental epileptic encephalopathies with genetic etiology, such as Down syndrome or Miller-Dieker syndrome.

There were several methodological aspects in the papers retrieved from the literature that made it difficult to compare the results of the different studies, in particular because of the retrospective design in 4/5 studies, such as small cohort size in some studies, heterogeneity of the population investigated, heterogeneity of the assessment of sleep spindles and heterogeneity of the cognitive assessments.

The PPV of the absence of sleep spindles being 82%, however, suggests that further studies on this question are warranted. If confirmed by larger studies, sleep spindles or their absence might serve as biomarkers and may become a tool in the clinic for physicians discussing the prognosis with parents of an infant with IESS.

There are several possible sources of bias. In general, the data are scarce. The five studies selected[20,22,23,25,26] were conducted at different temporal occasions, originally targeting variable clinical aspects of IESS, concerning sick children without controls, using different EEG follow-up protocols, and diverse tests of cognitive development (Table 1). In the present study, the risk of bias in the literature search was avoided by two readers working independently. Individual data were also inferred independently from the text of the publication. The effect measures used were PPV and NPV. They are epidemiological tools especially of screening methods in health care,[28] applied to prognostic purposes.

Sleep is important for memory consolidation and learning. In IESS, abnormal sleep plays an important role as a mediator of brain dysfunction. Similarly, abnormal sleep may mediate deleterious effects on cognitive development by Lennox–Gastaut syndrome, prolonged status epilepticus, FIRES and ESES or CSWS in older children.[29] Different aspects of epilepsy, sleep, and learning have been elucidated by a great number of published studies. Some that we think are in line with the present results are summarized in Appendix S2.

Sleep spindles are a vital part of the brain functions that constitute the basis of human cognitive abilities.[10] In the future, it will be interesting to broaden the analysis of spindles to their location, frequency distribution, duration, and spindle groups. The technology applied by Auno et al.[30] is an example of how these and other parameters of brain connectivity can be added to the panel of outcome measures. Automated systems based on artificial intelligence may help in reducing inter- and intrarater variation and increasing the amount of data per patient in sleep spindle detection.[31,32] Due to the rarity of IESS, there should be international collaboration for a prospective study on this subject as suggested by Spenner et al.[26]

5 | SUMMARY

We asked the simple question of whether in IESS the presence of sleep spindles – which is representative of normal sleep patterns – is a feasible prognostic marker for later favorable cognitive development, and whether their absence is an appropriate marker of poor cognitive development. Given the small amount of data, the retrospective quality of most studies, and the differences in many of the outcome parameters reported, it is prudent to say that currently available data do not allow us to conclude whether spindles have a specific and independent role in the cognitive prognosis of these children.

To definitively determine the role that spindles play, it would be necessary to have:

1. An etiologically well-defined group of infants with IESS, and a group of matched typically developing children.
2. Methodologically well-described sleep EEG registrations with SWS after IESS treatment.
3. A more detailed spindle analysis, possibly by automatic systems, may eventually give more information. Spindle duration, density (spindles per time unit) and total number of spindles per sleep period can be analyzed.[33] Data on slower and faster spindles, spindles relative to their oscillation frequencies, and spindle groups could be gathered and analyzed[30] with improved accuracy.[31,32]
4. A longer follow-up time to retrieve more data of cognitive outcome and intellectual disability before 16 years of age.
5. Standardized methods for cognitive testing are needed since the Wechsler Scales or Bayley Scales are difficult or impossible to use in severely disabled children.

ACKNOWLEDGMENTS

We thank professor Raili Riikonen for valuable comments on the manuscript.

FUNDING INFORMATION

Funding by Aivosäätiö, Finnish Brain Foundation, Finland, to J.L.

CONFLICT OF INTEREST STATEMENT

No one of the authors.

DATA AVAILABILITY STATEMENT

All data extracted from the studies is presented in this manuscript and its appendixes (supplementary data) and in the original papers.

ORCID

Jaana Lähdetie https://orcid.org/0000-0002-4962-248X

REFERENCES

1. Czochańska J, Langner-Tyszka B, Losiowski Z, Schmidt-Sidor B. Children who develop epilepsy in the first year of life: a prospective study. Dev Med Child Neurol. 1994;36:345–50.
2. Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;63:1349–97.
3. Riikonen R. Infantile spasms: outcome in clinical studies. Pediatr Neurol. 2020;108:54–64.
4. Lagae L, Verhelst H, Ceulemans B, De Meirleir L, Nassogne MC, De Borchgrave V, et al. Treatment and long term outcome in west syndrome: the clinical reality. A multicentre follow up study. Seizure. 2010;19:159–64.
5. Widjaja E, Go C, Mccoy B, Snead OC. Neurodevelopmental outcome of infantile spasms: a systematic review and meta-analysis. Epilepsy Res. 2015;109:155–62. https://doi.org/10.1016/j.eplepsyres.2014.11.012
6. Gaily E, Appelqvist K, Kantola-Sorsa E, Liukkonen E, Kyyrönen P, Sarpola M, et al. Cognitive deficits after cryptogenic infantile spasms with benign seizure evolution. Dev Med Child Neurol. 1999;41:660–4.
7. Plihal W, Born J. Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology. 1999;36: 571–82.
8. Mason GM, Lokhandwala S, Riggins T, Spencer RMC. Sleep and human cognitive development. Sleep Med Rev. 2021;57:101472. https://doi.org/10.1016/j.smrv.2021.101472
9. Lokhandwala S, Spencer RMC. Relations between sleep patterns early in life and brain development: a review. Dev Cogn Neurosci. 2022;56:101130. https://doi.org/10.1016/j.dcn.2022.101130
10. Fogel SM, Smith CT. The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev. 2011;35(5):1154–65. https://doi.org/10.1016/j.neubiorev.2010.12.003
11. Gorgoni M, D'Atri A, Scarpelli S, Reda F, De Gennaro L. Sleep electroencephalography and brain maturation: developmental trajectories and the relation with cognitive functioning. Sleep Med. 2020;66:33–50. https://doi.org/10.1016/j.sleep.2019.06.025
12. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93:681–766.
13. Gruber R, Wise MS. Sleep spindle characteristics in children with neurodevelopmental disorders and their relation to cognition. Neural Plast. 2016;2016:4724792. https://doi.org/10.1155/2016/4724792
14. Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsáki G. Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature. 2004;432:758–61.
15. Surtees ADR, Oliver C, Jones CA, Evans DL, Richards C. Sleep duration and sleep quality in people with and without intellectual disability: a meta-analysis. Sleep Med Rev. 2018;40:135–50. https://doi.org/10.1016/j.smrv.2017.11.003
16. Shibagaki M, Kiyono S, Watanabe K. Spindle evolution in normal and mentally retarded children: a review. Sleep. 1982;5(1):47–57.

17. Kiyono S, Shibagaki M. Duration of spindle bursts during nocturnal sleep in mentally retarded children. Electroencephalogr Clin Neurophysiol. 1983;55:645–51.
18. Bower BD, Jeavons PM. Infantile spasms and hypsarrhythmia. Lancet. 1959;273:605–9.
19. Muzykewicz DA, Costello DJ, Halpern EF, Thiele EA. Infantile spasms in tuberous sclerosis complex: prognostic utility of EEG. Epilepsia. 2009;50:290–6.
20. Altunel A, Altunel E, Sever A. The utility of the hypsarrhythmia paroxysm index and sleep spindles in EEG for predicting cognitive outcomes in a case series of infantile spasms. J Neurol Neurophysiol. 2015;6:1000319.
21. Zhang Y, Yu L, Zhou Y, Zhang L, Wang Y, Zhou S. Prognostic utility of hypsarrhythmia scoring in children with West syndrome after ketogenic diet. Clin Neurol Neurosurg. 2019;184:105402. https://doi.org/10.1016/j.clineuro.2019.105402
22. Kramer U, Sue WC, Mikati MA. Hypsarrhythmia: frequency of variant patterns and correlation with etiology and outcome. Neurology. 1997;48:197–203.
23. Guzzetta F, Cioni G, Mercuri E, Fazzi E, Biagioni E, Veggiotti P, et al. Neurodevelopmental evolution of West syndrome: a 2-year prospective study. Eur J Paediatr Neurol. 2008;12:387–97.
24. The Joanna Briggs institute (JBI). Critical appraisal tools. JBI levels of evidence. [cited 2023 June 20]. Available from: https://jbi.global/critical-appraisal-tools
25. Dulac O, Plouin P, Jambaque I, Motte J. Spasmes infantiles épileptiques bénins. Rev Electroencephalogr Neurophysiol Clin. 1986;16:371–82.
26. Spenner B, Krois-Neudenberger J, Kurlemann G, Althaus J, Schwartz O, Fiedler B. The prognostic value of sleep spindles in long-term outcome of west syndrome. Eur J Paediatr Neurol. 2019;23:827–31.
27. Lee Y, Min G, Mi Y, Ook S. Relationship between initial electroencephalographic characteristics and seizure outcomes in children with non-lesional west syndrome. Epilepsy Res. 2015;110:49–54. https://doi.org/10.1016/j.eplepsyres.2014.11.019
28. Trevethan R. Sensitivity, specificity, and predictive values: foundations, pliabilities, and pitfalls in research and practice. Front Public Heal. 2017;5:1–7.
29. Parisi P, Bruni O, Pia Villa M, Verrotti A, Miano S, Luchetti A, et al. The relationship between sleep and epilepsy: the effect on cognitive functioning in children. Dev Med Child Neurol. 2010;52:805–10.
30. Auno S, Jonsson H, Linnankivi T, Tokariev A, Vanhatalo S. Networks of cortical activity in infants with epilepsy. Brain Commun. 2022;4:1–12. https://doi.org/10.1093/braincomms/fcac295
31. Kaulen L, Schwabedal JTC, Schneider J, Ritter P, Bialonski S. Advanced sleep spindle identification with neural networks. Sci Rep. 2022;12:1–10. https://doi.org/10.1038/s41598-022-11210-y
32. Tveit J, Aurlien H, Plis S, Calhoun VD, Tatum WO, Schomer DL, et al. Automated interpretation of clinical electroencephalograms using artificial intelligence. JAMA Neurol. 2023;80:805–12.
33. Reynolds CM, Short MA, Gradisar M. Sleep spindles and cognitive performance across adolescence: a meta-analytic review. J Adolesc. 2018;66:55–70. https://doi.org/10.1016/j.adolescence.2018.04.003

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lähdetie J, Muñoz-Ruiz M, Kokki H. Does the absence or presence of sleep spindles on EEG have prognostic value for cognitive outcome in children with infantile epileptic spasms syndrome? A systematic literature review. Epileptic Disord. 2024;00:1–9. https://doi.org/10.1002/epd2.20192

Test yourself

1. Slow-wave sleep (deep sleep) is
   A. needed for memory consolidation
   B. needed mainly for declarative memory
   C. needed mainly for procedural memory
2. Sleep spindles have a frequency distribution of about
   A. 5–10 Hz
   B. 10–15 Hz
   C. 15–25 Hz
3. The cognitive outcome in IESS according to this systematic review
   A. is generally poor if etiology is unknown
   B. is generally poor (positive prognostic value >80%) if sleep spindles are absent
   C. is generally good (negative prognostic value >80%) if sleep spindles are present

Answers may be found in the Supporting information.