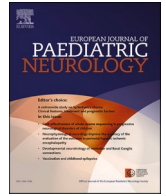


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# Sleep architecture in neonatal and infantile onset epilepsies in the first six months of life: A scoping review

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## ABSTRACT

**Aim:** Epilepsy occurs in approximately 80 per 100,000 infants in the first year of life, ranging in severity from self-limited and likely to spontaneously resolve, to severe developmental and epileptic encephalopathies. Sleep plays a key role in early brain development and the reciprocal relationship between sleep and seizures is not yet fully understood, particularly in young children. We conducted a Scoping Review to synthesise current knowledge of sleep architecture in neonates and infants with epilepsy.

**Method:** Peer-reviewed publications from 2005 to 2022 describing sleep architecture in infants up to six months of age with unprovoked seizures were included. The analysis set was derived from EMBASE, Web of Science and PubMed using key terms “sleep, epilepsy and infant” and related descriptors. Inclusion criteria were prospectively described in a Scoping Review protocol. Sleep architecture was assessed as macro- and micro-structural elements.

**Results:** 21 publications were included in the qualitative analysis. In self-limited familial and genetic epilepsy, sleep macrostructure was generally preserved. In DEEs and in epileptic encephalopathies of genetic or structural aetiology, sleep architecture was significantly disrupted.

**Interpretation:** Early identification of infants with epilepsy is important to ensure early and effective treatment. In the DEE spectrum, sleep architecture is significantly impacted, and abnormal sleep architecture may be associated with compromised developmental outcome. Further research is needed to identify the sequence of events in abnormal brain development, epilepsy and sleep disruption and potentially help to predict the course of epilepsy towards a self-limited epilepsy versus a DEE.

## 1. Introduction

### 1.1. The structure and importance of sleep

Sleep is a highly active process. The large amount of sleep during periods of rapid brain growth, connectivity and synaptic plasticity suggests an important role for sleep in early brain development [1–3]. Changes in sleep architecture from pre-term infant to childhood, reflect the ongoing development of brain networks and the emergence of different sleep states is one of the most significant aspects of early brain maturation in infancy [4].

Sleep occurs in cycles: in the first 3 months of life sleep cycles consist of active sleep, later developing to Rapid Eye Movement (REM) sleep, and quiet sleep, later NREM sleep [5]. Onset of sleep occurs during active sleep. At term, in an ultradian rhythm of 3 h, these sleep cycles are interrupted by a wakefulness phase with feeding [3]. After 3 months of age, babies fall asleep in NREM sleep and end their sleep cycle during a REM period. Ultradian rhythm is progressively replaced by circadian

rhythm [4,6]. NREM is composed of sleep stages N1, N2 and N3 with progressive sleep depth characterised by increasing amounts of slow wave activity. REM sleep is faster, desynchronised activity, like wakefulness [7]. Both NREM and REM are thought to play an important role in brain development [2,8].

Sleep architecture is composed of macro and microstructural elements, see [Table 1](#).

Slow wave activity is a marker of homeostatic regulation, synaptic strength and drive for sleep [11,23]. The morphology of slow waves provides information about nocturnal regeneration and cortical maturation [14,23,24] and slow wave sleep is suggested to be involved in nocturnal memory consolidation [13]. Decreased strength of cortical synapses during sleep due to pruning processes is represented by the declining slope of slow waves, and linked to neuronal recovery and learning capacity [25].

Cyclic alternating pattern (CAP) participates in the dynamic organisation of sleep. As a marker of sleep instability, build-up and maintenance of deep sleep, it is an important element of sleep microstructure

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**Table 1**  
Composition of sleep architecture.

Macrostructure [9–11].	Microstructure [12–14]
Total sleep time	Dynamics of slow wave activity
Proportion of REM and NREM sleep	Number and morphology of sleep spindles
Wake after sleep onset	Cyclic alternating pattern
Number of completed sleep cycles	
Sleep latency	
Sleep efficiency	

[26]. CAP is spontaneous periodic NREM sleep EEG activity, distinct from background EEG activity [27] which provides insights into the adaptive properties of the sleeping brain [13,27]. Age related changes in CAP reflect biological development through childhood and adolescence and CAP may be altered in epilepsy [26,28].

Studies have shown an alteration of slow wave activity and CAP in association with epilepsy, and a corresponding impairment of sleep quality [13,24,25,29].

**Table 2**  
Summarises epilepsies presenting in the first six months of life.

Epilepsy	Identified genes and other aetiologies that have been implicated include	Age of onset of seizures and responsiveness to treatment	Characteristic seizure type	Development
Self-limited (familial) neonatal epilepsy	Family history or de novo mutations in KCNQ2, KCNQ3	Days 2–7, rarely after first 4 weeks (within days of being at term by corrected age for pre-term infants)	Sequential seizures (focal clonic or tonic, often with apnoea and cyanosis)	Normal
Self-limited (familial) neonatal infantile epilepsy	Family history or de novo mutations SCN2A KCNQ2	Day 1–23 months of life (mean 11 weeks, median 13 weeks)	Initially focal tonic features with head and eye deviation, followed by other tonic and clonic features. Some have prominent apnea and staring. Seizures vary in duration from 20 s to 4 min. Seizures with fever are rare.	Normal
Self-limited (familial) infantile epilepsy	PRRT2 KCNQ2, KCNQ3 SCN2A	Infantile: 3–20 months of age, peak at 6 months	Brief focal seizures, often occurring in clusters	Normal
Early infantile developmental and epileptic encephalopathy (previously early myoclonic encephalopathy and Ohtahara syndrome)	PIGA, SETBP1, SIK1, SLC25A22, GLDC, AMT, Metabolic aetiologies, less often structural GNAO1, ARX, DOCK7, STXBP1, CDKL5, KCNQ2, KCNT1, NECAP1, PIGA, PIGQ, SCN2A, SCN8A, SIK1, SLC25A22, SCL35A2, STXBP1, UBA5, WWOX Structural aetiologies, less often metabolic	First 2 months of life (more than half of cases have onset of seizures by 10 days of life) First month of life (range 1–3 months)	Focal or multifocal myoclonus, focal seizures, spasms Tonic seizures, sequential seizures in neonates Tonic spasms and focal seizures	Profoundly impaired Delay, often severe
Genetic Epilepsy with febrile seizures + (GEFS+) spectrum	SCN1A and SCN1B pathogenic variants Other gene variants encoding voltage-gated sodium, calcium, and potassium channels, and ligand-gated ion channels including nicotinic cholinergic receptor subunits, the $\gamma$ -aminobutyric acid (GABA) A receptor subunits, and syntaxin 1B (STX1B) have also been linked to the syndrome	Febrile seizures in GEFS + families may begin prior to 6 months of age unlike typical febrile seizures and persist beyond 6 years of age. Other afebrile seizure types may develop at various ages.	Febrile seizures, which may be generalized or focal, are mandatory for diagnosis. In addition, a variety of other generalized or focal afebrile seizures may be seen	Usually normal
Infantile epileptic spasms syndrome (previously West Syndrome and Infantile Spasms)	CDKL5, STXBP1, ARX, ALG13, DOCK7, DNMI1, FOXG1, GABRA1, GABRB1, GABRB3, GNAO1, GRIN1, GRIN2A, GRIN2B, IQSEC2, KCNT1, SCA2, SCN1A, SCN2A, SCN8A, SETBP1, SIK1, SLC25A22, SLC35A2, SPTAN1, ST3Gal3, STXBP1, TBC1D24, TCF4, WWOX Metabolic and structural aetiologies	Between 3 and 12 months of age, although later onset may occur	Clusters of epileptic spasms at onset	Normal to severe delay at onset Over time, 70%–90% develop intellectual disability, often severe
Myoclonic epilepsy in infancy	Unknown	Between 4 months and 2 years of age, peak age of 6–18 months	Myoclonic seizures, often activated by startle, noise, or touch	Development is normal at onset A minority develop cognitive delays over time Severe delay
Epilepsy of infancy with migrating focal seizures	KCNT1; SCN2A; PLCB1, QARS, SCN1A, SCN8A, SLC25A22, TBC1D24, SLC12A5, TBC1D24, CHD2	First 6 months after birth (mean 3 months), later onset has been reported	Multifocal clonic or tonic seizures that are often subtle and associated with autonomic features	Severe delay

Terminology reflects updated 2022 ILAE Classification & Definition of Epilepsy Syndromes with Onset in Neonates and Infants [15].

Table 2 Epilepsies presenting in the first six months of life [15–22].

## 1.2. Seizures and epilepsy in infants

Epilepsy occurs in approximately 80 per 100,000 infants in the first year of life [30–33], ranging in severity from self-limited and likely to spontaneously resolve, to developmental and epileptic encephalopathies (DEE). DEE represent a group of severe heterogeneous disorders with developmental consequences arising directly from the effect of the genetic mutation in addition to the effect of the frequent epileptic activity on development [34].

Seizures occur relatively frequently at neonatal age, in approximately 3/1000 live births [35,36]. Most neonatal seizures are acute provoked seizures, secondary to hypoxic ischaemic encephalopathy (HIE), stroke, haemorrhage, or acute metabolic derangements, however 10–15% of seizures are unprovoked, reflecting the onset of neonatal epilepsies [31,36,37]. Only 15% of babies with neonatal seizures develop epilepsy [36], 68% of them appearing in the first year of life [38].

The aetiology of epilepsy is primarily genetic (42%), structural (41%) due to congenital malformations, overlapping structural and genetic (9%), or rarely due to inborn errors of metabolism [31,36,16].

Approximately one-third of newborns with brain malformations as their primary seizure aetiology also have co-existing precipitators of symptomatic seizures, eg HIE and infection [31].

### 1.3. The complex and reciprocal relationship between sleep and epilepsy

Frequent seizures and high intensity of epileptic activity can disrupt sleep regulation and circadian rhythms and fragment sleep [39]. Sleep disruption, in turn, may interfere with seizure control [9]. Antiepileptic therapy can also contribute to sleep architecture disturbance [40].

Seizures are associated with adverse neurodevelopmental outcomes [41], however, it has yet to be established whether abnormal sleep reflects abnormal brain development, or whether abnormal sleep exacerbates pre-existing abnormal neurodevelopment [42].

We conducted a scoping review to systematically map research in this sensitive period of development and to help identify potential knowledge gaps and topics for further research. The more we understand about this complex interplay between sleep and epilepsy, the more precisely we can intervene to improve the lives of young children.

## 2. Material and methods

This paper adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews [43]. A scoping review protocol was created a priori (Appendix 1).

To identify relevant publications we searched MEDLINE, EMBASE and Web of Science databases with a search strategy of keywords. The main search concept combined the terms “epilepsy” AND “infant” AND “sleep” with related descriptors for each of these elements. “Epilepsy” included epilepsy, epilepsies, epileptic seizure and encephalopathy, “infant” included infant, baby, babies, child\*, neonate, newborn, month-old, months-old and “sleep” included sleep, wakefulness, bed, cyclic alternating pattern and polysomnography. Additional searches included the combination of “epilepsy” OR “seizure” AND “sleep” AND individual aetiologies “metabolic”, “genetic”, “infectious”, “structural”, “immune”, “porencephalic”, “tumour”, “DNET”, “ganglioma” (Appendix 2).

The original database searches were conducted on 11/5/20 and re-run on 19/12/21 to identify more recent sources.

We included case reports, case-control studies, other types of studies and reviews published from 2005 to date, meeting the following eligibility criteria: 1) Original research published in peer-reviewed journals; 2) Population with unprovoked seizures and onset of epilepsy in the first six months of life; 3) Publications providing data on sleep architecture if they gave information for at least one data variable on microstructure/microstructure of sleep as described in Table 2, even if the primary intent of the study was not focused on sleep architecture.

We excluded studies if 1) no full text study was published; 2) the publication language was not English; 3) the publication only described seizure semiology or sleep quality; 4) the primary focus was Dravet Syndrome.

The rationale for selecting the 6 month cut-off is pathophysiological and sleep related, based on the expected peak impact of the underlying condition on sleep architecture.

Epilepsies within the first six months of life were defined according to the ILAE 2017 classification [34]. We excluded papers exclusively describing seizure semiology and also those focused on Dravet Syndrome, because the highest seizure burden and its impact on sleep and development of patients with Dravet syndrome is after the first 6 months of life [16,17].

Title, abstract and full-text searches were screened against the inclusion criteria by one reviewer. We also hand searched grey literature and scanned relevant review articles and journal tables of content for additional references.

Final search results were exported into EndNote and duplicates manually removed. To increase consistency, two reviewers (SJ and AD) discussed the final list of publications to agree on study selection and

amended the screening and data extraction plan. Disagreements were resolved through discussion.

We grouped publications by aetiology and epilepsy type. Two reviewers (SJ and AD) agreed the fields for data charting. One reviewer (SJ) extracted the data, which was then cross-checked by a second reviewer (DK), see Supplementary Information.

In line with accepted scoping review methodology [43], a formal risk of bias and methodological quality of data was not conducted, however, a level of evidence from 1 to 5 (1 being the highest) was assigned to each manuscript, according to the Joanna Briggs Institute recommendation [44] (Table 3).

During the conduct of the review, we noted that the protocol was not specific enough. A post-hoc modification was made specifying that infants with provoked seizures were excluded.

## 3. Results

We reviewed 7237 abstracts and 561 full-text articles, duplicates were manually removed and 540 publications were excluded (Fig. 1). 21 publications were included in the final analysis (Table 4).

### 3.1. Results: summary of findings

We identified 21 publications providing data relating to sleep architecture in our target population. We found no data relating to sleep architecture in non-familial self-limited neonatal epilepsy or in structural epilepsies due to paediatric tumours.

In self-limited familial and genetic epilepsy, sleep macrostructure was generally preserved. In DEEs and in epileptic encephalopathies of genetic or structural aetiology, sleep architecture was significantly disrupted.

## 4. Discussion

In self-limited familial and genetic epilepsy, sleep macrostructure was generally preserved. In DEEs and in epileptic encephalopathies of genetic or structural aetiology, sleep architecture was significantly disrupted. More macrostructural than microstructural elements were reported in the articles included (Table 5).

The early identification of infants with epilepsy, is important, to ensure early and effective treatment, however the evolution from seizures to a non-reversible encephalopathy cannot be predicted [35]. Development of children with self-limited epilepsies is usually normal (Table 2), while developmental outcomes are impaired in other forms of epilepsy. The following questions need to be addressed: Is disturbed sleep architecture a marker of abnormal brain development, or does

**Table 3**  
Level of evidence framework.

Level of evidence	
1	Inception cohort studies
1a	Systematic review of inception cohort studies
1b	Inception cohort study
2	Studies of all or none
2a	Systematic review of all or none studies
2b	All or none studies
3	Cohort studies
3a	Systematic review of cohort studies (or control arm of Randomised Controlled Trial (RCT))
3b	Cohort study (or control arm of RCT)
4	Case series/Case Controlled/Historically Controlled studies
4a	Systematic review of Case series/Case Controlled/Historically Controlled studies
4b	Individual Case series/Case Controlled/Historically Controlled study
5	Expert Opinion and Bench Research
5a	Systematic review of expert opinion
5b	Expert consensus
5c	Bench research/single expert opinion

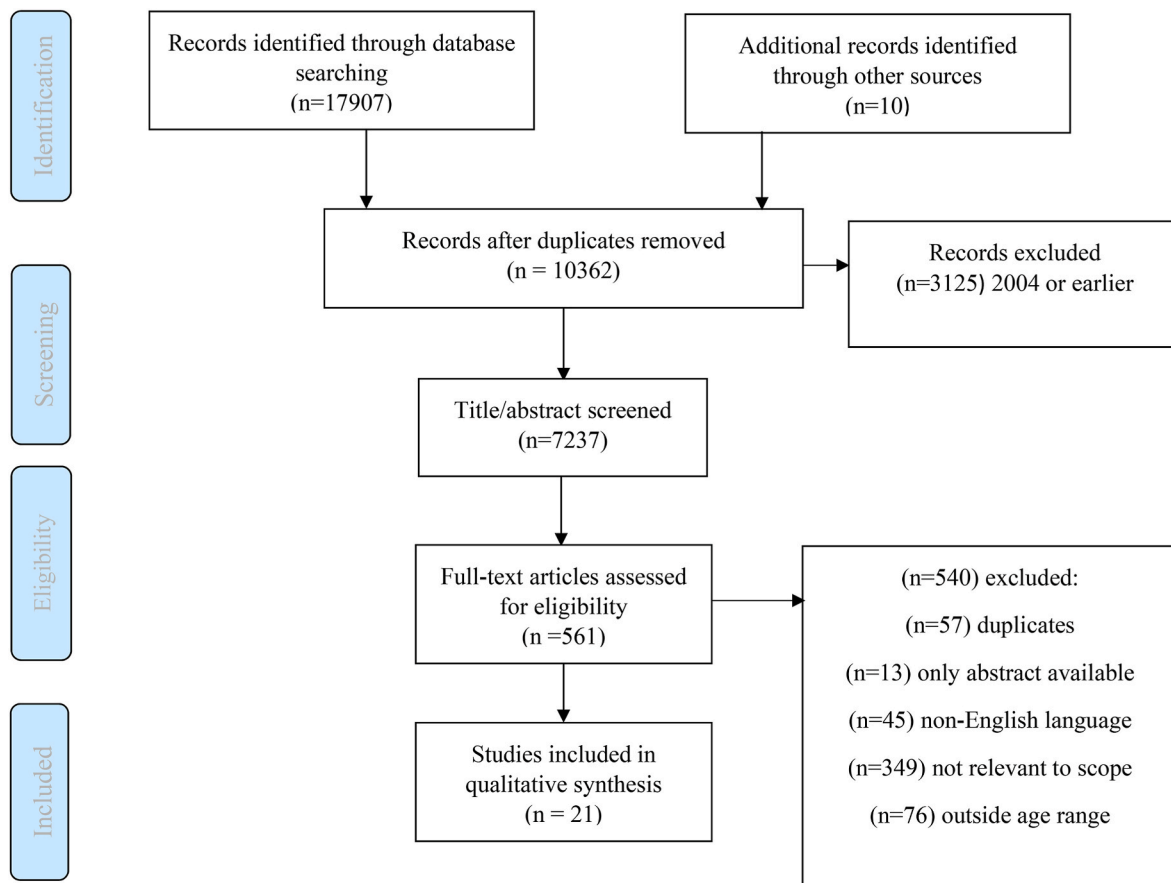


Fig. 1. PRISMA diagram.

abnormal sleep contribute to pre-existing abnormal neurodevelopment? If sleep architecture is conserved in self-limited epilepsy, how could the study of sleep play a role in helping to predict the evolution of epilepsy early in the disease process?

From the data analysed, it is not possible to infer whether sleep architecture disruption precedes epilepsy in this population, or vice versa. One could hypothesise that alterations in sleep arise rather secondary to encephalopathy, but this assumption requires additional exploration.

As a disorder of cortical network organisation [68] epilepsy affects brain structures involved in sleep plastic functions, such as the cortico-thalamic and hippocampal systems [69]. Seizures or high intensity of epileptiform discharges occurring early in life do so during a critical period of activity-dependent synaptogenesis (blooming) and its regulation by elimination of extra synapses (pruning), a sign of plasticity [25,70]. Early alterations of sleep could have a lasting impact on the maturation of neural networks, resulting in functional disorders [3,71]. The disappearance of physiological sleep elements may reflect dysfunctional networks, particularly in structures such as the thalamus, hypothalamus and brain stem. One could envisage a ‘tipping point’ of pathophysiologic events and remodelling, beyond which the developing brain is unable to compensate. These manifest either simultaneously, or sequentially, as disruption of sleep architecture and an epilepsy that cannot spontaneously resolve.

Genetics may also influence the magnitude and appearance of sleep disruption. A genetic epilepsy either directly or through seizure activity or neurodevelopmental impact, could also impact genes involved in regulation of sleep, such as clock genes [72].

Sleep homeostasis and circadian regulation interact on a molecular/genetic level [72]. A high seizure or epileptic activity burden would also disrupt circadian regulation [40]. In the population we analysed, it would be interesting to explore how the underlying pathophysiology of

epilepsy impacts the evolution of ultradian to circadian rhythm, further confounding sleep changes. In infants with DEE, even with good seizure control, there is an underlying development delay due to the genetic component, which may also lead to further changes.

Cellular mechanisms that underlie the vicious cycle of sleep disturbance and seizures are yet to be fully elucidated [73] and the aetiology of disrupted sleep architecture is likely to be multifactorial. Epilepsy per se, through seizure activity, interictal discharges and ASM may play a role [40,42,74]. Specific seizure characteristics, in terms of frequency, type and diurnal distribution have been described in association with sleep disturbance in older children and mostly adult patients [75,76], however this information was not readily available from the publications included in the qualitative analysis.

Change of the slope of slow waves and alteration of cyclic alternating pattern, an important element of microstructure, represent biomarkers of physiological sleep and sleep protection, although we found no data relating to CAP in our population. The physiological decrease of the slope of slow waves across the night during NREM sleep was reduced in infants with West Syndrome compared to controls [24]. This reflects hypersarrhythmia, a loss of organised brain activity, which impairs brain development. If brain activity is disorganised, then sleep is also disorganised and nocturnal regenerative processes will be impacted. Together with sleep spindle frequency, these elements allow a quantification of the integrity of sleep. In our analysis, sleep spindles were disturbed, reduced, asynchronous or absent in infants with DEE.

Anti-seizure medication (ASM) can affect REM and NREM sleep, in particular slow wave sleep, NREM N3, both beneficially and detrimentally [77]. Very few drugs are licensed for use in neonates and most data relating to ASM and sleep originate from adult studies [35]. ASMs affect sleep architecture, some positively. Valproate may increase daytime sleepiness and slow wave sleep and decrease REM [77]. Levetiracetam

**Table 4**  
Overview of publications included in qualitative analysis.

Data sources		Type of epilepsy described								
Manuscript	Description	Level of evidence	Self-limited	Early infantile developmental and epileptic Encephalopathy				Aetiology specific		
				West Syndrome and infantile spasms	Early infantile epileptic encephalopathy	Early myoclonic epilepsy	Epilepsy of infancy with migrating focal seizures	Structural	Genetic	Metabolic
Nunes, 2010 [45]	Review article of sleep and epilepsy in neonates. Literature review with search of PubMed database using key words “neonatal seizures” and “sleep”	4	+		+		+			
Caraballo, 2013 [46]	Retrospective chart review of 38 patients with myoclonic epilepsy in infancy	4	+							
Koutromanidis, 2017 [21]	Review article by the ILAE Neurophysiology Task Force on the role of EEG in diagnosis and classification of the main neonatal and paediatric epilepsy syndromes	5	+	+	+		+	+		
Lee, 2015 [47]	Retrospective review of 66 children with non-lesional West Syndrome, comparing those with and without seizure free outcomes	4		+						
Fois, 2010 [48]	Literature review and personal experience of infantile spasms	5		+						
Guzzetta, 2008 [49]	2 year prospective study of 21 infants with West Syndrome	3		+						
Fattinger, 2015 [24]	Retrospective case-controlled study in 14 infants diagnosed with West syndrome, assessing slow wave sleep	4		+						
Muzykewicz, 2009 [50]	Retrospective chart review of 45 children with tuberous sclerosis and a history of Infantile Spasms	4		+						
Spenner, 2019 [51]	Retrospective single observer review of 448 sleep EEGs recorded during first two years of life in 44 patients with West syndrome	4		+						
Fusco, 2020 [52]	Review article summarising three different scenarios in which epileptic spasms (ES) may occur	5		+	+					
Heinrich, 2021 [53]	Retrospective case-controlled analysis of 61 infants with onset of West Syndrome between 2 and 24 months of age, treated with vigabatrin (VGB) or hormones, or both.	4		+						
Gofschteyn, 2021 [54]	Retrospective single-centre cohort study including 35 children with epileptic encephalopathy (excluding infantile spasms). Age range at onset of epilepsy ranged from 0 to 3years	3			+					
Liu, 2017 [55]	128 term neonates with neonatal seizures followed up until 1 year old. 66 neonates evolved into EOEE (Early onset epileptic	3						+		+

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Table 4 (continued)

Data sources	Type of epilepsy described
	encephalopathy) the other 62 served as the non-EOEE (nEOEE = control) group. Primary causes of seizures were severe perinatal cerebral injury, congenital encephalodysplasia, and congenital metabolic diseases. Aetiology unclear in 72.4% of infants.
Khan, 2008 [56]	Retrospective analysis of 58 pairs of sequential EEGs from newborns with seizures belonging to 2 historical cohorts of infants admitted to NICU. Mix of provoked and unprovoked seizures.
Carvalho, 2017 [57]	Case series including sleep EEG patterns in 37 infants aged <6 months with microcephaly diagnosed with congenital Zika virus infection
Kanda, 2018 [58]	Retrospective review of sleep EEGs in 10 patients with microcephaly associated with Zika virus infection
Aravindhana, 2018 [59]	Case report of a 10-month-old with early-onset epileptic encephalopathy due to hemizygous deletion 9q33.3q34.11 involving STXBP1 and SPTAN1 genes
Serino, 2013 [60]	Case report of an infant with genetic variant of KCNQ2 gene and review of 15 cases from literature
Alsaleem, 2019 [61]	Case report of a term infant with genetic variant of KCN, multiple seizures refractory to anti-seizure medication
Bozarth, 2018 [62]	Case report of one infant who presented with neonatal onset epileptic encephalopathy with de novo missense variant in CACNA1C (c.4087G > A (p.V1363 M))
Olson, 2012 [63]	Case report and review of the literature (29 publications) of CDKL5 mutations in early onset epilepsy
Olischar, 2012 [64]	aEEG tracings of 30 neonates with metabolic disorders from an international registry
Guerrero, 2017 [65]	Case series of 6 infants from one centre with PNPO deficiency, neonatal-onset epileptic encephalopathy with developmental delay and seizures
Schmitt, 2010 [66]	Retrospective case review of four patients with PDE and one patient with PNPO
Melikishvili, 2020 [67]	Retrospective case review of three patients with de novo SCN2A mutations

**Table 5**

Summarises the key findings from our data analysis.

Type of epilepsy		Summary of evidence	Macrostructure	Microstructure	Other
Self-limited epilepsy		Level 4 and 5 evidence from 2 review articles describing self-limited familial neonatal seizures, self-limited infantile epilepsy, myoclonic epilepsy of infancy [21,45] and 1 retrospective chart review of myoclonic epilepsy of infancy [46].	Self-limited familial neonatal seizures: sleep features do not seem to be disrupted [45]. Self-limited infantile epilepsy and myoclonic epilepsy of infancy: preserved sleep architecture [21,46].		
<b>Early infantile development and epileptic encephalopathy (EIDEE)</b>	<b>West Syndrome</b>	9 publications, primarily level 4 and 5 evidence [24,21,47,48,50–53], with one level 3 evidence source, a prospective cohort study [49].	Normal sleep patterns are absent, background is abnormal [24,48–50,52]. One study demonstrated comparable total sleep time and sleep quality in overnight recordings [24] compared with healthy controls. Reduced REM sleep reported, although no significant difference was observed in REM amount in nap recordings [24]. Sleep latency is comparable between control and treated infants [53].	Physiological graphoelements of sleep (vertex waves, spindles, and K-complexes) are usually absent [21,52]. Emergence of sleep spindles may be disturbed, although retention of sleep spindles from disease onset has been described, as well as recurrence of sleep spindles after initiation of anti-convulsive treatment [51]. Normal to borderline features of the sleep-spindle were reported to be more significantly and commonly maintained in seizure-free infants [47]. The physiological decrease of the slope of slow waves across the night during NREM sleep was reduced in infants with West Syndrome compared to controls [24]. Lack of sleep spindles which may reappear transiently with treatment [54].	Among the sleep activities, the normal to borderline features of the sleep-spindle were more significantly and commonly maintained in the SF group [47]. More typical hypsarrhythmia and loss of sleep-spindles may suggest a more severe phenotype with more affected normal cortical functions [47]. Disorganisation of slow wave sleep (NREM N3) was an unfavourable prognostic factor for neurosensory and developmental outcome [24,49,51] and associated with lower follow-up Intelligent Quotient (or equivalent measure) [50]. Significant but disparate effects of treatment on sleep slow waves [54].
	Early infantile epileptic encephalopathy		Sleep stages are unclassified and REM sleep is not detectable [45]. Suppression burst is associated with impaired sleep quality and lack of physiological sleep elements including sleep cycles [21].		Suppression burst pattern occurs in both wakefulness and sleep, in contrast to early myoclonic encephalopathy, where it can be present only during sleep or enhanced by sleep [21].
	Early myoclonic epilepsy		May have preserved sleep background rhythms at complete presentation [21].	–	Consistent suppression-burst pattern during sleep has been described in early myoclonic encephalopathy [45].
	Epilepsy of infancy with migrating focal seizures			During seizure-free periods, sleep and wakefulness are clearly differentiated [21].	Sleep spindles are rare, asynchronous, and asymmetric [21].
<b>Genetic (overlaps with EIDEE)</b>		Level 4 evidence from six case reports, often including associated literature reviews [59–63,67] of CDKL5 deficiency disorder [63] pathogenic variants of KCNT1 [61] and KCNQ2 [60], STXBP1 and SPTAN1 deletion [59], SCN2A [67] and CACNA1C pathogenic variant [62].	Poor wake-sleep transitions in KCNT1 [61] and general disturbance of the sleep/wake cycle with CACNA1C mutation [62]. In CDKL5 deficiency disorder, EEG at onset can be normal with background slowing and preserved sleep features [63]. One infant who presented with neonatal onset epileptic encephalopathy and CACNA1C variant had a severe disturbance of sleep/wake cycle, however, normal sleep architecture at 5 months of age on polysomnography [62]. Severely abnormal background pattern and absence of sleep wake cycling	STXBP1 and SPTAN1 variant: Interictal EEG showed a lack of normal organisation and complexity, and multifocal polyspike-wave during wakefulness and sleep [59]. Following seizure cessation, improvement of sleep activity organisation and normalisation of architecture with improved continuity of background and resolution of suppression-burst pattern was reported in KCNQ2 and CACNA1C variant [60,62].	A very discontinuous pattern during sleep evolves towards a defined burst-suppression pattern in KCNQ2 [60]. A very discontinuous pattern during sleep remains distinct from burst-suppression in SCN2A [67].
<b>Structural</b>		Level 3 evidence from two cohort studies		–	A correlation with probable HIE and neurodevelopmental delay was also observed [56].

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Table 5 (continued)

Type of epilepsy	Summary of evidence	Macrostructure	Microstructure	Other
Self-limited epilepsy	Level 4 and 5 evidence from 2 review articles describing self-limited familial neonatal seizures, self-limited infantile epilepsy, myoclonic epilepsy of infancy [21,45] and 1 retrospective chart review of myoclonic epilepsy of infancy [46].	Self-limited familial neonatal seizures: sleep features do not seem to be disrupted [45]. Self-limited infantile epilepsy and myoclonic epilepsy of infancy: preserved sleep architecture [21,46].		
<b>Structural: Congenital Zika Virus</b>	Level 4 evidence from two case series	in the encephalopathic group of infants [55] Abnormal background activity and abnormal sleep architecture, even in infants who had not yet developed epilepsy [57]	Lack of sleep spindles [57, 58]	Modified hypsarrhythmia with or without burst suppression [57,58]
<b>Inborn errors of metabolism</b>	Level 3 and 4 evidence, composed of the following: 1. Review of aEEG tracings of 30 neonates from an International Registry of metabolic disorders and congenital malformations [64]. Specific metabolic disorders include inborn errors of energy metabolism, hyperammonaemia, amino and organic amino acid acidaemias, peroxisomal disorders or non-ketotic hyperglycinaemia [64]. 2. A case series of six neonates, including five pre-term, with Pyridox(am)ine 5'-Phosphate Oxidase Deficiency (PNPO) deficiency, neonatal-onset epileptic encephalopathy, developmental delay and seizures [65]. 3. A case series of five infants, four of whom have pyridoxine dependent epilepsy and one with PNPO [66].	More infants with inborn errors of energy metabolism and peroxisomal disorders retained SWC compared with other groups [64,65].	In one infant with pyridoxine dependent epilepsy, interictal EEG demonstrated trace alternant in sleep and a few sharp waves in the neonatal period.	'Sleep disturbance' without specification was also reported [66].

can also enhance daytime sleepiness, but decreases slow wave sleep and REM [78]. Phenobarbitone also reduces REM sleep. Carbamazepine increases slow wave sleep and decreases REM sleep [78]. These effects appear independent of their anticonvulsant actions [77]. Data from adult studies with perampanel suggest an decrease in wake after sleep onset (WASO), increase of total sleep time, sleep maintenance index, duration of N3, a decrease of wake time, sleep latency and WASO, but no effect on micro-awakenings [79,80].

In our analysis, there were insufficient data to provide meaningful observations related to the impact of ASM on sleep architecture.

#### 4.1. Limitations

Our scoping review was conducted according to accepted scoping review methodology, however there are some inherent limitations.

To maximise feasibility of the review, we limited publications to the last fifteen years, accepting the possibility of excluding older publications that might yield informative data.

We assigned a level of evidence to each publication, however, in line with accepted scoping review methodology, we did not conduct a formal quality and risk of bias analysis of individual manuscripts. The level of evidence ranged from 3 to 5, reflecting the absence of randomised or even longitudinal controlled trials in this area. This may impact the robustness of conclusions from the data.

Many of the studies were not designed or focused to study sleep architecture and there is variability in the parameters used to assess sleep

architecture. In some publications only aEEG was used and no polysomnography was conducted. In others only sleep wake cycling is mentioned, with few additional elements of sleep architecture (Table 1) considered.

Categorising publications by epilepsy type and aetiology allowed us to manage the data, although it is well recognised that aetiology of epilepsy may be multi-factorial [34].

We noted that our protocol was not specific enough at the outset. One post-hoc modification was to specify that infants with provoked seizures were excluded.

#### 5. Conclusions

Sleep macrostructure is generally preserved in self-limited genetic epilepsy in the first 6 months of age. In infants with epilepsies in the DEE spectrum, sleep architecture is significantly impacted. Infants with abnormal sleep architecture may also experience compromised developmental outcomes, however a direct association is hypothetical and more likely to be multi-factorial, reflecting underlying aetiology, evolution of the disease and seizure burden. The relative contribution of each factor is difficult to tease out.

More longitudinal and well-controlled studies are needed to assess and quantify the changes in sleep architecture in this population and to characterise the individual contribution of sleep, epilepsy and ASM in this vicious cycle of disruption. Additional insights may also provide opportunities for biomarkers, enabling earlier interventions and



therapeutic progress for this patient population.

Further research could also help in elucidating the sequence of events of abnormal brain development, epilepsy and sleep disruption and potentially contribute to understanding the likelihood of epilepsy evolution towards a self-limited condition, or a DEE.

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#### Author contributions

Dr Jethwa designed the scoping review protocol, conducted literature searches, reviewed publications, extracted data, prepared the qualitative analysis and drafted the initial manuscript.

Dr Datta conceptualised and designed the scoping review, reviewed the final list of publications for analysis and reviewed and revised the manuscript.

Didem Kaya cross-checked the extracted data.

Dr Pressler reviewed and revised the manuscript and provided helpful input to the concept and data analysis.

#### Declaration of competing interest

R.P. is an investigator for studies with UCB and Johnson & Johnson. She served as a consultant, speaker and on Advisory Boards for Natus, Persyst, GW and UCB. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital and Cambridge University Hospital, NIHR and Evelina Charity. She is on the editorial board of Journal of Clinical Neurophysiology, Neurophysiologie Clinique and European Journal of Paediatric Neurology as well as an Associated editor for Epilepsia Open.

A.D. is an investigator for studies with Neurocrine and Idorsia. He serves as a consultant, speaker and on Advisory Boards for Neurocrine, Idorsia, Epilog, Eisai, Jazz Pharmaceuticals.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2022.11.004>.

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