Sleep-Wake Cycling on Amplitude-Integrated Electroencephalography in Term Newborns With Hypoxic-Ischemic Encephalopathy

Damjan Osredkar, MD*‡; Mona C. Toet, MD*; Linda G. M. van Rooij, MD*;
Alexander C. van Huffelen, MD, PhD§; Floris Groenendaal, MD, PhD*; and Linda S. de Vries, MD, PhD*

ABSTRACT. *Objective.* The objective of this amplitude-integrated electroencephalography (aEEG) study was to evaluate the influence of perinatal hypoxia-ischemia on sleep-wake cycling (SWC) in term newborns and assess whether characteristics of SWC are of predictive value for neurodevelopmental outcome.

Methods. From a consecutive series of newborns born during a 10-year period, the aEEG tracings of 171 term newborns with hypoxic-ischemic encephalopathy were assessed for the presence, time of onset, and quality of SWC. SWC patterns were categorized with regard to the background pattern on which they presented, as normal or abnormal SWC.

Results. SWC was seen in 95.4% of the surviving newborns and in 8.1% of those who died. The median time intervals from birth to onset of SWC were significantly different in newborns with hypoxic-ischemic encephalopathy grades I, II, and III (7, 33, and 62 hours, respectively). Newborns with seizure discharges developed SWC with a delay of 30.5 hours. Good outcome was associated with earlier onset of SWC and normal SWC pattern. The difference in the median Griffiths' developmental quotients in newborns who started SWC before/after 36 hours was 8.5 points. The good/poor neurodevelopmental outcome was predicted correctly by the onset of SWC before/after 36 hours in 82% of newborns.

Conclusions. The presence, time of onset, and quality of SWC reflected the severity of the hypoxic-ischemic insult to which newborns were exposed. The time of onset of SWC has a predictive value for neurodevelopmental outcome. *Pediatrics* 2005;115:327–332; *amplitude-integrated electroencephalography, cerebral function monitor, sleep-wake cycles, perinatal hypoxia-ischemia, asphyxia, neonate, prediction, neurodevelopmental outcome.*

ABBREVIATIONS. HIE, hypoxic-ischemic encephalopathy; EEG, electroencephalography; aEEG, amplitude-integrated electroencephalography; SWC, sleep-wake cycling; PPV, positive predictive value; NPV, negative predictive value; BS, burst suppression; CLV, continuous extremely low voltage; FT, flat trace; CNV, continuous normal voltage; DNV, discontinuous normal voltage.

Hypoxic-ischemic encephalopathy (HIE) is a major cause of morbidity and mortality in newborns. Monitoring of newborns with HIE with amplitude-integrated electroencephalography (aEEG) has been used for assessment of background pattern, detection of seizures, evaluation of the effects of anticonvulsive drugs, selection of patients for neuroprotective intervention, and prediction of neurodevelopmental outcome as early as in the first hours after birth.[1–6] Most of the aEEG studies relating to these issues have concentrated on the continuity of the background patterns and the presence of seizures.

Sleep characteristics have been used for prediction of neurodevelopmental outcome.[7,8] Sleep-wake cycling (SWC) is present in healthy term newborns and is a sign of brain integrity.[9,10] In newborns with HIE, sleep organization can be altered.[11] The presence of SWC pattern on aEEG is considered a good prognostic sign,[12–14] but this has not been thoroughly assessed yet. Most of the studies investigated exclusively the presence of SWC and did not take the time of onset or quality of SWC into account. Only 3 aEEG studies on term infants have addressed the relationship between SWC and outcome. In 2 of these studies, a relationship was noted between the presence of SWC and good outcome.[13,14]

The aim of this aEEG study was to evaluate the influence of perinatal hypoxia-ischemia and subsequent seizures on the presence, time of onset, and quality of SWC and identify SWC characteristics that may be of predictive value for neurodevelopmental outcome.

METHODS

Subjects Studied

A consecutive series of 191 term newborns, born between 1992 and 2002 in a hospital or at home and later admitted to the tertiary NICU of the Wilhelmina Children's Hospital (Utrecht, Netherlands), was studied. The inclusion criteria were HIE with/without convulsions, a time interval from birth to the start of the aEEG recording of ≤24 hours, and a known neurodevelopmental outcome at a minimum of 12 months after birth. HIE was defined by abnormal tone pattern, feeding difficulties, altered alertness, and at least 3 of the following criteria: (1) late decelerations on fetal monitoring or meconium staining; (2) delayed onset of respiration; (3) arterial cord blood pH <7.1; (4) Apgar scores <7 at 5 minutes; and (5) multiorgan failure. From the initial series of 191 newborns, 20 newborns were subsequently excluded because of focal infarction or parenchymal hemorrhage, neural tube defect, chromosomal abnormality, metabolic disorder, or infection of the central nervous system. Newborns treated with extracorporeal membrane oxygenation or surfactant were also excluded from the study

because of possible influence of the treatment on aEEG recording.[15] Thus, the final series consisted of 171 newborns.

After the newborns were admitted to the NICU, the aEEG recording was started by the attending neonatologist as part of routine care in patients who were deemed to be at risk of developing convulsions. Informed parental consent was obtained in all cases. When epileptiform activity was recognized by aEEG or standard EEG, anticonvulsive drugs were administered.

aEEG

The aEEG was recorded with the cerebral function monitor (CFM 4640, Lectromed, Devices Ltd, United Kingdom). Single-channel EEG was derived from bilateral needle electrodes (P_3 and P_4, ground F_z). The filtered signal was rectified, smoothed, and amplitude-integrated before it was written out on a semilogarithmic scale paper at slow speed (6 cm/hour) at the cot side. A second tracing continuously recorded the electrode impedance.

The aEEG tracings were reviewed by 2 clinicians who were blinded to the perinatal and follow-up data. The continuity of background patterns and epileptiform activity on aEEG tracings were assessed visually by using criteria published previously.[6]

SWC

SWC was recognized as periodic changes in bandwidth of the aEEG tracing.[16] During wakefulness/active sleep the bandwidth of the tracing was narrower, whereas during quiet sleep the bandwidth was broader.[9,10] Diagnosis of SWC was made when at least 3 consecutive cycles were seen on aEEG tracing during a period of 5 hours. If SWC was seen, the time interval from birth to the first of these SWCs was calculated. The background pattern and the presence of epileptiform activity at the onset of SWC were noted, as were the most abnormal background pattern and most severe epileptiform pattern before the onset of SWC. If seizure discharges were present before SWC, the time interval from the last seizure discharge to the onset of SWC was calculated. Administered anticonvulsive drugs were noted. The duration of 1 sleep-wake cycle and of the quiet sleep phase of the cycle were measured.

SWC patterns were qualitatively classified with regard to the background pattern on which they presented:

- Normal SWC: Presence of SWC on a continuous normal voltage (CNV) background pattern. The lower margin of the narrowest bandwidth was clearly >5 μV, and the lower margin of the

broadest bandwidth was either >5 μV (Fig 1A) or <5 μV (suboptimal variant of normal SWC; Fig 1B). At least 3 cycles had to be present on a CNV background pattern before the pattern was declared as normal SWC.
- Abnormal SWC: Presence of SWC on a discontinuous background pattern (Fig 1C). Lower margins of the narrowest and broadest bandwidth were continuously <5 μV.

In newborns who showed transition from abnormal to normal SWC, the time interval from SWC onset to the point of transition was calculated.

Follow-up and Outcome

The last follow-up examination of survivors was performed at a minimum age of 12 months up until 66 months of age. The follow-up consisted of Griffiths' Developmental Scale and items from Amiel-Tison and Grenier[17] and Touwen.[18] Cerebral palsy was classified according to the criteria of Hagberg et al[19] The data acquired at the last follow-up examination were used for analysis. Outcome of patients was categorized as:

- Good: absence of cerebral palsy, epilepsy, bilateral blindness, and hearing loss and a Griffiths' developmental quotient of ≥85.
- Poor: cerebral palsy (diagnosed at a minimum of 18 months), epilepsy, bilateral blindness, hearing loss requiring bilateral amplification, and/or a Griffiths' developmental quotient of <85.

Statistical Analysis

A statistical analysis was performed by using SPSS 11.5 for Windows (SPSS Inc, Chicago, IL). Univariate comparisons of clinical variables were made with Mann-Whitney U or Kruskal-Wallis tests for continuous variables and Fisher's exact or χ^2 tests for categorical variables. Logistic regression was used to develop a predictive model for good outcome by using the time interval from birth to onset of SWC. Area under receiver operator characteristic curve, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and efficiency (correct classification rate) of the test were calculated. Linear regression was used to develop a predictive model for Griffiths' developmental quotient by using the time interval from birth to emergence of SWC. The level of significance was set at .05.
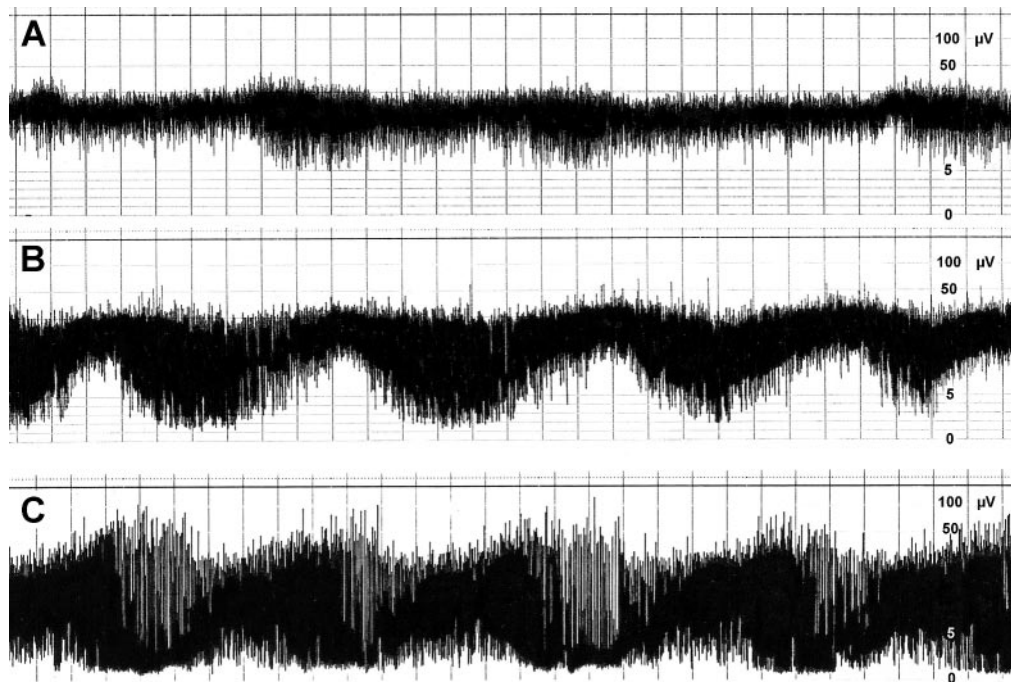

Fig 1. A, Normal SWC. SWC on a CNV background pattern, with the lower margin of the bandwidth >5 μV. Cycle period is unusually prolonged in this sample. B, Normal SWC (suboptimal variant). The lower margin of the bandwidth is <5 μV during quiet sleep. C, Abnormal SWC. SWC on a discontinuous background pattern, with the lower margin of the bandwidth <5 μV at all times.

RESULTS

The inclusion criteria were met for 171 newborns. The median gestational age was 40 weeks (range: 37–43 weeks), median birth weight was 3425 g (range: 1740–5300 g), and median Apgar scores at 1, 5, and 10 minutes were 1, 4, and 6, respectively. In 160 newborns, the grade of HIE according to Sarnat and Sarnat[20] was known; 37 (23.1%) newborns had grade I, 61 (38.1%) had grade II, and 62 (38.8%) had grade III. One hundred and nine (63.7%) newborns survived, and 62 (36.3%) died in the neonatal period. The median age of the surviving children at the last follow-up examination was 19.0 months (range: 12.0–66.0 months), of which 20 (18.3%) had a poor outcome. The median age at which poor outcome was first recognized was not different from the median age at last follow-up examination of newborns with good outcome (16.5 and 19.0 months, respectively; P = .29, Mann-Whitney test). Table 1 summarizes the outcome of newborns, grade of HIE, and the presence of SWC.

The median aEEG recording time was 69 hours (range: 14–312 hours) for the surviving newborns and 29 hours (range: 6–139 hours) for the newborns who died (P < .001, Mann-Whitney test). In the surviving newborns, those with poor outcome had longer aEEG recordings than those with good outcome (P = .035, Mann-Whitney test). The median start of aEEG recording was 3.0 hours after birth (range: 0.5–21.0 hours). SWC was found in 104 (95.4%) of the surviving newborns and in only 5 (8.1%) of those who died (P < .001, Fisher's exact test). Of the 5 surviving newborns who did not show SWC, 2 had a poor outcome (dyskinetic cerebral palsy) and 3 had a good outcome.

Table 2 summarizes background patterns and the presence of epileptiform activity at the onset of SWC and the most abnormal background pattern and most severe epileptiform pattern before the onset of SWC.

Relationship Between HIE and SWC

The median time interval from birth to onset of SWC in newborns with HIE grade I was 7 hours, in grade II 33 hours, and in grade III 62 hours (P < .001, Kruskal-Wallis test). The differences were also significant in pairs of HIE I–II newborns and HIE II–III newborns (P < .001 and P = .013, respectively; Mann-Whitney test). The HIE grade II newborns were of particular interest, because their outcome was more difficult to predict than of those with HIE grade I or III (Table 1). In newborns with HIE grade II who had a good outcome, the median time interval from birth to onset of SWC was 29 hours, whereas it

TABLE 1. The Outcome, Grade of HIE, and Presence of SWC

Outcome	HIE Grade				SWC	
	I	II	III	NA	Present	Absent
Survived						
Good (n = 89)	35	43	0	11	86 (96.6%)	3
Poor (n = 20)	2	16	2	0	18 (90%)	2
Died (n = 62)	0	2	60	0	5 (8.1%)	57

NA indicates that the grade of HIE was not available.

TABLE 2. Background Patterns (BP) and Patterns of Epileptiform Activity (EA) in Patients With SWC (N = 109)

	At Onset of SWC		Before Onset of SWC	
	BP	EA	Worst BP	Worst EA
CNV	57 (52.3%)		37 (33.9%)	
DNV	51 (46.8%)		51 (46.8%)	
BS	1 (0.9%)		17 (15.6%)	
CLV	None		3 (2.8%)	
FT	None		1 (0.9%)	
No EA		105 (96.4%)		58 (53.2%)
Single seizures		1 (0.9%)		7 (6.4%)
Repetitive seizures		3 (2.7%)		33 (30.3%)
Status epilepticus		None		11 (10.1%)

was 48 hours in those who had a poor outcome or died (P = .011, Mann-Whitney test; Fig 2A). The quality of SWC was also related to the grade of HIE (P < .001, χ^2 test). SWC more often emerged as normal SWC in newborns with HIE grade I than in those with HIE grade II (P < .001, Fisher's exact test) but never in newborns with HIE grade III (Fig 2B).

Quality of SWC

At the onset of SWC, 57 (51.8%) newborns showed normal SWC. Abnormal SWC emerged and persisted throughout the recording in 15 (13.6%) newborns. Transition from abnormal to normal SWC was seen in 37 newborns (34.6%), and an earlier transition did not correlate with a better outcome (P = .59, Mann-Whitney test). Normal SWC at onset was significantly related to good outcome (P = .018, Fisher's exact test; Fig 3).

In newborns with normal SWC, the suboptimal variant (Fig 1B) was seen in 43 (75.4%) newborns. The outcome of newborns who showed a suboptimal variant of normal SWC was not significantly different from the rest of newborns with normal SWC (P = .59, Fisher's exact test).

In newborns with normal SWC, the median cycle period was 52 minutes (range: 30–110 minutes) and the median duration of the quiet sleep phase was 30 minutes (range: 18–43 minutes). In newborns with persistently abnormal SWC, the median cycle period was 53 minutes (range: 40–100 minutes) and the median duration of the quiet sleep phase was 35 minutes (range: 23–55 minutes). These 2 subgroups of newborns did not have significantly different cycle periods, but the quiet sleep phase of SWC was prolonged in newborns who showed persistently abnormal SWC (P = .30 and .024, respectively; Mann-Whitney test).

Seizure Discharges and SWC

Seizure discharges were seen on aEEG tracings before the onset of SWC in 51 (46.8%) newborns. The median time interval from birth to onset of SWC was 8.5 hours in newborns without seizure discharges and 39.0 hours in newborns with seizure discharges (P < .001, Mann-Whitney test). The median time interval from the last seizure discharge to the onset of SWC was 15.0 hours (range: 0–129.0 hours), and a shorter time interval was not related to a better outcome in surviving patients (P = .50, Mann-Whitney test). In the surviving newborns, the presence of
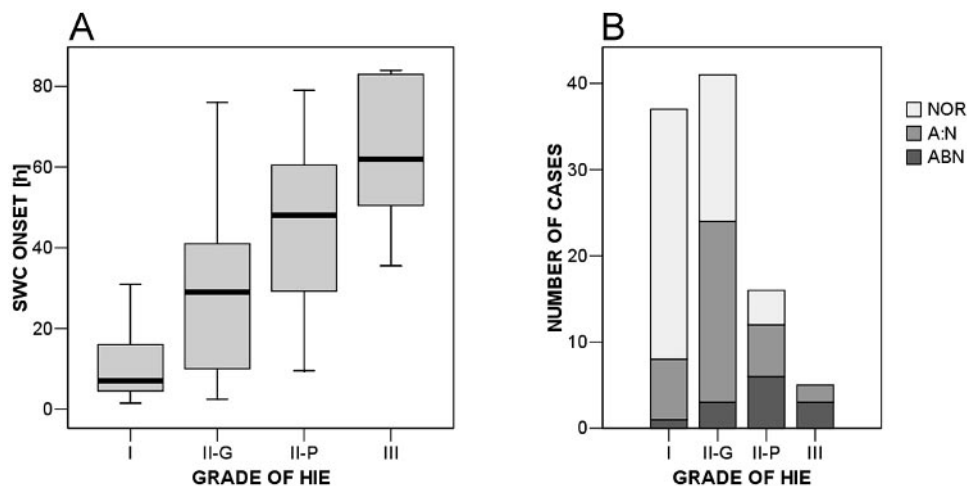
Fig 2. A, Box plot of time intervals from birth to onset of SWC with regard to the grades of HIE. The horizontal line indicates the median; box, 25th and 75th percentiles; limit lines, the range. B, Relationship between the quality of SWC and the grade of HIE. II-G indicates newborns with HIE grade II and good outcome; II-P, newborns with HIE grade II and poor outcome; NOR, normal SWC; ABN, abnormal SWC; A:N, transition from abnormal to normal SWC.
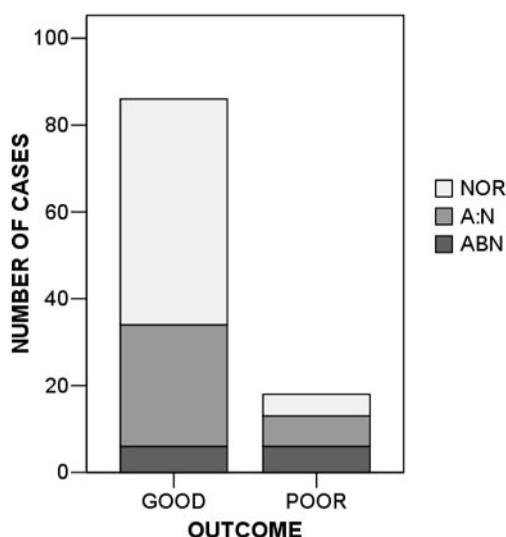

Fig 3. Relationship between the quality of SWC and the outcome of newborns. NOR, normal SWC; ABN, abnormal SWC; A:N, transition from abnormal to normal SWC.

seizure discharges did not preclude the development of SWC ($P = .18$, Fisher's exact test). Although seizure discharges can disrupt SWC, SWC with simultaneous seizure discharges was seen in 4 patients. Newborns without seizure discharges showed normal SWC significantly more often than those with seizure discharges ($P < .001$, Fisher's exact test).

The following anticonvulsive drugs were used (the numbers in parentheses represent the percentage of newborns treated with the respective drug): phenobarbital (94.1%), lidocaine (58.8%), midazolam (43.1%), clonazepam (39.2%), phenytoin (35.3%), and pyridoxine (2.0%). Many newborns were treated with >1 drug simultaneously or in succession. In the newborns with good outcome, there were no significant differences in the time intervals from birth to onset of SWC between newborns who were not treated with anticonvulsive drugs and those who were treated with 1 or 2 anticonvulsive drugs ($P = .9$ and .3, respectively; Mann Whitney test). There was

a significant delay in SWC onset in newborns treated with ≥3 anticonvulsive drugs, compared with newborns not treated with anticonvulsive drugs ($P < .001$, Mann-Whitney test; Fig 4).

Prediction of Outcome in the Surviving Newborns

An earlier onset of SWC was related to a better outcome. Each increase in time interval from birth to onset of SWC for 1 hour was associated with a 0.96-fold decrease in the odds of a good outcome (95% confidence interval: 0.938–0.981; $P < .001$, logistic regression). Area under receiver operator characteristic curve for prediction of outcome by the time of onset of SWC was 0.79. Likewise, an inverse-linear relationship was found between the time interval from birth to emergence of SWC and the Griffiths' developmental quotient only ($P = .012$, linear regression). When the cutoff point of the SWC onset was
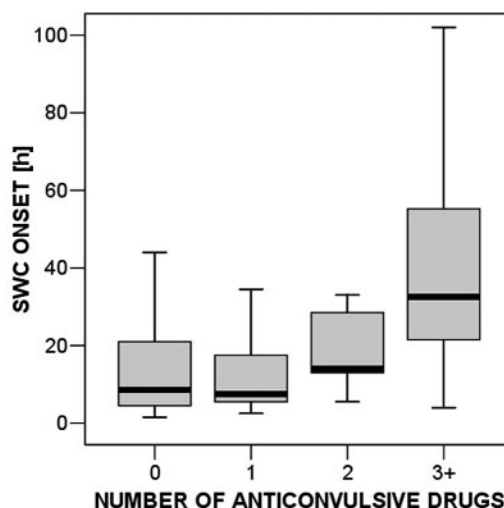

Fig 4. The differences in time intervals from birth to onset of SWC in newborns with good outcome, with regard to the number of anticonvulsive drugs administered. Newborns who were treated with ≥3 anticonvulsive drugs developed SWC with a significant delay.

set at 36 hours, the difference in the median Griffiths' developmental quotients between the so-formed groups was highest and was statistically most significant. The newborns who developed SWC within 36 hours after birth had a higher median Griffiths' developmental quotient than those who showed SWC at a later stage (103.0 and 94.5, respectively; $P = .003$, Mann-Whitney test). Prediction of good neurodevelopmental outcome by onset of SWC within 36 hours after birth gave a sensitivity of 84.9%, specificity of 66.7%, PPV of 92.1%, NPV of 48.0%, and efficiency of 82%.

Prediction of good neurodevelopmental outcome by time of onset of SWC was not improved when combined with the quality of SWC. However, 96.1% of newborns who showed normal SWC before 36 hours had good neurodevelopmental outcome, whereas only 20% of those who developed persistently abnormal SWC after 36 hours had a good outcome.

DISCUSSION

The present aEEG study confirmed that the presence of normal SWC early after birth is a valuable predictor for good neurodevelopmental outcome in term infants with HIE. In our cohort of newborns, SWC was present significantly more often in the surviving infants than in those who died in the neonatal period. In some of the newborns who died the treatment was discontinued on the basis of persistently abnormal background pattern (burst suppression [BS], continuous extremely low voltage [CLV], flat trace [FT]) associated with abnormalities on neuroimaging. One cannot exclude that SWC could have emerged in some of these newborns if they had been monitored for a longer period. SWC is considered to reflect brain integrity, and it is not surprising, therefore, that newborns with severe HIE showed SWC less often.

Our data clearly demonstrated that an earlier onset of SWC was related to a better neurodevelopmental outcome. This was also true for HIE grade II newborns only, who were of particular interest because of their variability in outcome. When predicting outcome of newborns by the time of onset of SWC, 36 hours after birth was found to be the most valuable cutoff point. The good/poor neurodevelopmental outcome, assessed at a median age of 19 months, was predicted correctly by the onset of SWC before/after 36 hours in 82% of newborns. Follow-up into school age is needed to especially appreciate whether this prediction is also valid for perceptual-motor and cognitive problems, which can not be recognized yet at this early stage.[21]

A small number of infants had an abnormal outcome despite early onset of SWC. This may have been caused by antenatal onset of HIE in some of these infants. In most infants, however, an acute adverse event occurred around the time of birth. Because most of the infants had neuroimaging performed during the first week after birth, the type of injury could be categorized in the majority as either "acute near-total asphyxia" or "subacute partial asphyxia."[22] These 2 types of brain injury involve both hemispheres and will invariably affect the aEEG background.

SWC in newborns with HIE often had a more discontinuous character, compared with SWC in healthy newborns.[9,10] As suggested by our data, the distinction between normal and abnormal SWC is important. It reflected the grade of HIE, was influenced by the presence of seizure discharges (and anticonvulsive drugs), and was related to outcome. Normal SWC at onset was associated with good neurodevelopmental outcome. On the other hand, the distinction between the 2 variants of normal SWC (Fig 1 A and B) in newborns with HIE was less important, because it was not related to significant differences in outcome.

Seizure discharges that were eventually controlled did not preclude the development of SWC in surviving newborns, but their presence significantly prolonged the time interval from birth to onset of SWC. It was not possible to assign this delay specifically to seizure discharges or anticonvulsive drugs, because all newborns with seizures were treated with anticonvulsive drugs. The onset of SWC in newborns with good outcome who were treated with ≥3 anticonvulsive drugs was delayed, which was not the case in those treated with only 1 or 2 anticonvulsive drugs. Anticonvulsive drugs can also depress EEG background activity depending on the severity of HIE.[4,23] In such cases, SWC may become temporarily unrecognizable, which was seen most often after administration of midazolam.[24] Nevertheless, controlling seizures with anticonvulsive drugs usually promoted the development of SWC regardless of the drug used.

Our data are in agreement with those of others. Ter Horst et al[14] studied 30 term newborns with HIE. They found SWC in 10 of 13 newborns with a normal outcome, in 3 of 6 with a mildly abnormal outcome, and in none of 11 newborns who had an abnormal outcome or died. In the study of Thorngren-Jerneck et al,[13] comparing aEEG and positron emission tomography findings in 19 term newborns with HIE, early SWC correlated with a good outcome. However, in the study of Thornberg and Ekström-Jodal,[25] none of the 38 newborns with HIE showed SWC within the first 3 days after birth, although 17 newborns had a normal outcome. This discrepancy could be partly due to the shorter duration of their recordings and seizure activity in 9 of the infants with normal outcome.

In our cohort of newborns, SWC always emerged on a CNV or discontinuous normal voltage (DNV) background pattern, except in 1 child in whom it emerged on a BS pattern. This is in agreement with the data of Watanabe et al,[26] who reported maintained gross SWC organization in newborns with HIE who showed normal or minimally depressed EEG, whereas the organization was considerably disrupted or absent in newborns who showed severely depressed EEG. The presence of a normal background pattern or improvement of the background pattern on aEEG within 12 to 24 hours after birth is a favorable prognostic sign by itself, obtainable in the first hours after birth.[6] Although the emergence of SWC, compared with the observation of background pattern trends, is an event that is also easy to recognize, it often presents later in life. The presence of

SWC is therefore of limited value for selection of newborns for therapeutic intervention, which can potentially reduce brain damage after perinatal hypoxia-ischemia if initiated in the first hours after birth.[27] The aEEG background patterns should be used instead, and prediction of an adverse neurodevelopmental outcome is already reliable within the first 6 hours after birth.[1,3] A poor background pattern (BS, CLV, FT) seen within the first 6 hours after birth predicted a poor outcome, with a PPV of 86%, and the onset of SWC after 36 hours after birth predicted a poor outcome, with an NPV of 48.0%.

In healthy newborns, the SWC period is 50 to 60 minutes, with a quiet sleep phase of ~20 minutes.[8,10,28] In our cohort of newborns with HIE, the duration of 1 sleep-wake cycle (52–53 minutes) was similar to those found in healthy newborns, but the quiet sleep phase was somewhat prolonged (30–35 minutes). An increased proportion of quiet sleep in newborns with HIE was reported previously.[11] SWC usually presented with distinctive and relatively stable cycles of broader bandwidth spindles of quiet sleep, followed by narrower bandwidth of active sleep/wakefulness. However, the appearance of SWC or the cycle length can change in time without any obvious cause. SWC can sometimes be very subtle, which was most often the case when SWC emerged very early after birth or in patients on high-frequency oscillation.

No attempt was made in this study to assess SWC in preterm newborns, although patterns similar to SWC were reported in infants with gestational ages of <30 weeks.[12,29] Hellström-Westas et al[12] demonstrated predictive value of the presence of SWC in extremely small, low birth weight newborns (gestational age: 23–33 weeks).

CONCLUSIONS

The presence, time of onset, and quality of SWC were influenced by the hypoxic-ischemic insult to which the newborns were exposed. Good neurodevelopmental outcome was associated with early onset and normal SWC and could be predicted by the time of onset of SWC. When aEEG is used, it is recommended to allow sufficient time for the development of SWC.

ACKNOWLEDGMENTS

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