Pediatric RESEARCH

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Assessment of neonatal EEG background and neurodevelopment in full-term small for their gestational age infants

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BACKGROUND: Delayed brain function development in small-gestational-age (SGA) infants has been reported. We aimed to quantify rates of immature neonatal EEG patterns and their association with neurodevelopment in SGA full-term neonates.
METHODS: Using a cohort design, 50 SGA (birthweight <10th percentile) and 44 appropriate-gestational-age (AGA) term neonates underwent continuous video-EEG recordings lasting >3 h. Seventy-three of them were assessed at 2-years-old using Bayley-III-Scales. For EEG analysis, several segments of discontinuous/alternating EEG tracings were selected. Main outcomes measured: (1) Visual analysis (patterns of EEG maturity); (2) Power spectrum in δ, θ, α and β frequency bands; and (3) scores in motor, cognitive and language development.
RESULTS: (1) SGA infants, compared to AGA, showed: (a) higher percentages of discontinuous EEG, both asynchrony and interhemispheric asymmetry, and bursts with delta-brushes, longer interburst-interval duration and more transients/hour; (b) lower relative power spectrum in δ and higher in α; and (c) lower scores on motor, language and cognitive neurodevelopment. (2) Asymmetry >5%, interburst-interval >5 s, discontinuity >11%, and bursts with delta-brushes >11% were associated with lower scores on Bayley-III.
CONCLUSIONS: In this prospective study, SGA full-term neonates showed high rates of immature EEG patterns. Low-birthweight and immaturity EEG were both correlated with low development scores.

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INTRODUCTION

Small for their gestational age (SGA) infants exhibit deficits in their neurodevelopmental outcomes at 6 years of age.[1] Disturbances in metabolism, microstructure, hemodynamics, morphology and brain connectivity have been found in late-onset intrauterine growth restriction (IUGR) children.[2,3]

At the acute moment of a cerebral injury, brain activity shows several degrees of electrophysiological depression. However, intrauterine unfavorable conditions can cause a slight but persistent brain insult that eventually causes irreversible chronic brain damage.[4] In this "chronic state", the neurophysiological abnormalities are replaced by dysmaturity and/or disorganization.[5]

The brain undergoes dramatic structural maturation during the last months of intrauterine life, allowing experienced clinicians to estimate the gestational age (GA) with differences of up to a week.[6] These maturational EEG changes continue in the postnatal life and are especially pronounced in the first 3 days of life as a result of adaptation to postnatal life.[7,8] The most recent studies in the development of brain activity have relied on quantitative analyses of EEG activity.[9–11]

Spectral EEG analysis and neonatal aEEG findings have found delayed maturation and less optimal scores on early EEG in preterm[12,13] and full-term SGA neonates.[14] But, specific patterns of maturity on the visual background EEG analysis regarding neonatal brain function development and its prognostic implications in IUGR children have never been analyzed.

Our hypothesis was that SGA term infants have high rates of immature patterns on the EEG background that could be associated to development deficits. Using the visual and spectral analysis, the objectives of the present study were: (1) to quantify rates of well-known patterns of EEG maturity in low-birth-weight term babies at 48–72 h after birth, and (2) to use the measurements obtained in these EEG variables as prognostic markers on the neurodevelopmental assessment in early childhood.

METHODS

Participants and design

Using a cohort design, between March 2014 and January 2016, 51 term SGA and 67 term appropriate-gestational-age (AGA) infants matched by GA were recruited. SGA babies were selected from IUGR fetuses diagnosed in the middle of the 2nd to the 3rd trimester by Doppler (middle cerebral artery and umbilical artery) and biometric measurements (abdominal and head circumference, and femur

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length) of the fetal ultrasound, and confirmed by presenting a birthweight <10th percentile according to tables of intrauterine growth customized in our population.[15] GA was calculated from the first day of the mother's last menstrual period and confirmed by prenatal ultrasound in the first trimester.

All SGA children of the present study were diagnosed prenatally and their etiology was evaluated following the guidelines of the Sociedad Española de Ginecología y Obstetricia (SEGO).[16] The postnatal etiological evaluation was conditioned by the clinical requirements of each baby. Inclusion criteria were GA >37 weeks, no neonatal resuscitation, 5-minute Apgar score >7 and umbilical cord pH >7.10. Exclusion criteria were maternal body mass index <20 or >30, chronic maternal disease (diabetes, epilepsy, moderate/severe asthma), obstetric pathology (hypertension, metrorrhagia), noxious habits (alcohol, drug use), multiple pregnancy, major congenital malformations or recognized/suspected genetic syndrome, congenital infections, birthweight >4 kg and admission to the neonatal special care unit.

All neonates underwent Amiel-Tison neurological assessment[17] at the third day of life. Only children with an optimal score were included.

Standard protocol approvals, registrations and patient consent. See in Statement of Ethics.

EEG procedure

All infants underwent continuous video-EEG recordings at 48–72 h after birth in the nursery within a single postnatal ward. The duration of each EEG recording was >3 h. Several montages were used with electrodes placed according to the international 10–20 system adapted for neonates. The control of environmental variables, the polygraph and the technical adjustments of EEG recording complied with previous recommendations.[18]

Visual analysis

The visual analysis included at least 1 h of sleep recording. Sleep states regarding behavioral and EEG parameters were classified as quiet sleep (QS), active sleep (AS) or indeterminate sleep (IS), in accordance with previous recommendations.[19] We calculated the percentages of time of both discontinuous pattern and tracé alternant in relation to the sum of IS and QS of the entire EEG recording. We defined discontinuous pattern as bursts of EEG activity with amplitude >50 μV separated by low-voltage activity <30 μV (if ≥ 30 μV = alternating tracing) for >1 s. The following specific EEG patterns of GA maturity were analyzed exclusively during discontinuity or alternating tracing: (1) maximum duration in seconds of interburst interval (IBI), (2) percentage of bursts with delta brushes, (3) percentage of bursts with both interhemispheric asynchrony and asymmetry, and (4) transients/hours (Fig. 1).

The definitions of these variables were strictly adjusted to those used previously to analyze the EEG in healthy term neonates:[8]

Interburst intervals of inactivity or hypoactivity (IBI). Epochs with an EEG activity <30 μV on all channels for >1 s.

Delta brushes. Delta waves of 500–1500 ms duration with amplitude of 50–250 μV, with rapid activity (8–20 Hz) of amplitude >15 μV superimposed on the ascending slope of the first slow wave of the burst.

Inter-hemispheric asynchrony. Burst onset between hemispheres separated by ≥1.5 s.

Inter-hemispheric asymmetry. Bursts with a difference of amplitude ≥50% between the two hemispheres and/or with superimposed rapid activity in only one hemisphere.

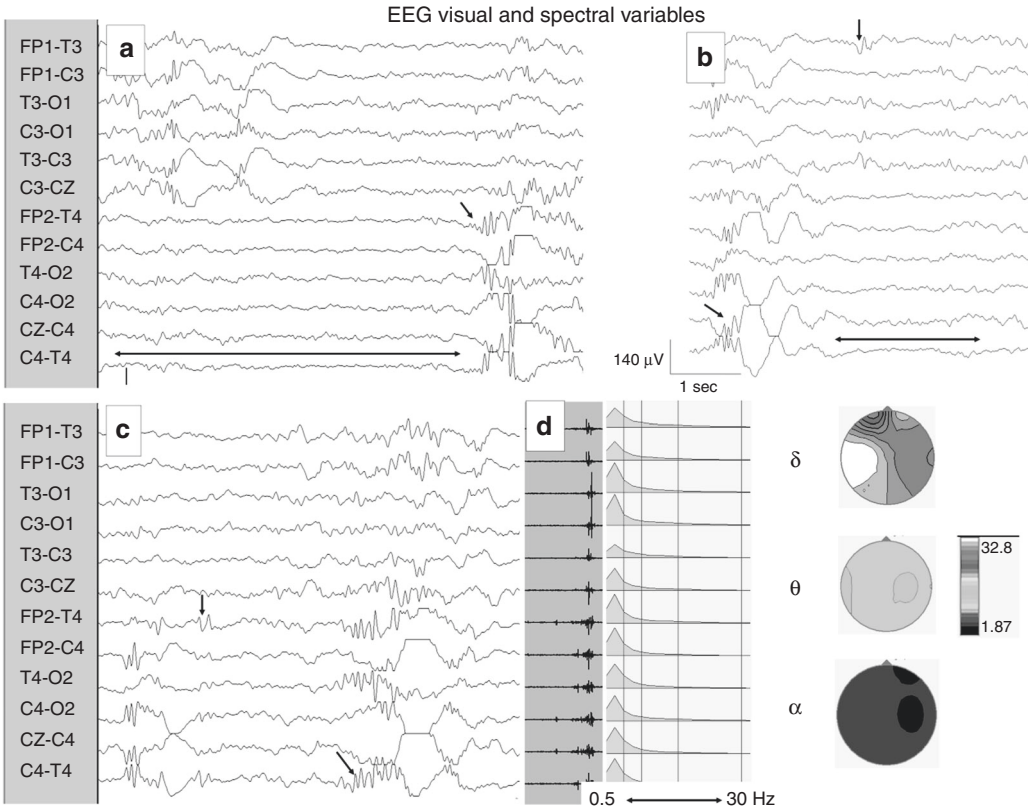

Fig. 1 Examples the EEG variables studied in the visual and spectral analysis in an SGA term infant. a and **b** Discontinuous EEG tracings showing interhemispheric asynchrony and asymmetry, respectively, with transient rolandic sharp waves (vertical arrow), interburst interval (two-headed arrow) and delta brushes in the bursts (Inclined arrows). **c** Interhemispheric asymmetry of the bursts on the EEG background with tracé alternant and transient temporal sharp waves (vertical arrow). **d** Graphs and topographic maps of absolute power spectrum in the *δ*, *θ* and *α* frequency bands; the values in the color scale represent absolute power spectrum in μV^2.

Table 1. Results obtained from the EEG parameters evaluated in the visual analysis, expressed as mean, standard deviation, statistical significance, and cut-off points of maximum likelihood to discriminate both study groups.

EEG variables	Interrater agreement ICC (95% CI)[b]	Group of study		Sig.	Cut-off points[c]
		SGA ($n = 45$) Mean ± SD	AGA ($n = 44$)		
Artifact-free tracing (minutes)[a]	0.89 (0.85–0.97)	35 ± 8.70	28 ± 14.70	0.097	–
% Tracé alternant	0.93 (0.90–0.96)	26.37 ± 20.72	51.94 ± 21.18	**<0.001**	**<30%**
% Discontinuous tracing	0.97 (0.96–0.98)	37.62 ± 26.79	5.53 ± 13.032	**<0.001**	**>11%**
% Asynchony	0.76 (0.60–0.89)	10.87 ± 8.36	4.72 ± 5.38	**<0.001**	**>7%**
% Asymmetry	0.87 (0.81–0.95)	11.68 ± 8.58	2.65 ± 4.20	**<0.001**	**>5%**
% Bursts with Delta Brushes	0.83 (0.68–0.92)	23.78 ± 18.04	6.45 ± 6.13	**<0.001**	**>11%**
Maximum IBI duration (s)	0.77 (0.66–0.85)	6.84 ± 2.60	2.82 ± 2.67	**<0.001**	**>5 s**.
No. transients/hour	0.73 (0.61–0.89)	17.68 ± 13.02	8.20 ± 6.48	**<0.001**	**>11**

ICC intraclass correlation coefficient
[a]Time (minutes) of artifact-free EEG tracing only including trace alternant and discontinuous pattern
[b]The significance of interrater reliability for all EEG variables was $P < 0.001$
[c]Cut-off points obtained from of the ROC curve analysis with a positive predictive value >80% and P value < 0.001 belonging to the group of SGA infants

Transients. Positive or negative waves with amplitude >50 μV and duration between 100 and 400 ms clearly present only in the interburst epochs.

Examples of some of these EEG variables are shown in Fig. 1a–c. Each EEG parameter of the visual analysis, including artifact rejection, was measured individually and independently by two neuropediatricians experienced in neonatal brain monitoring who were unaware of the baby's birth weight. We accepted an EEG feature only when both observers agreed. Since all variables of the visual EEG analysis were continuous, the interrater reliability analysis was performed using intraclass correlation coefficient.[20] The interrater agreement rate (mean and 95% CI) for all these variables is shown in Table 1.

Spectral analysis

In the valid EEG recording of each neonate, both neuropediatricians independently selected all segments of the total EEG recording exclusively with tracé alternant and/or discontinuous pattern regardless of the sleep state and without any evident artifacts. All EEG segments with full concordance between the two observers, lasting ≥1 min each (time considered to define a behavior state), were included in the analysis. The cumulative recording time of the selected EEG segments ranged between 15 and 21 min. The analysis was performed using Persyst Insight II EEG analysis software (version 6.0.0/Build 632-XLDB; Persyst Development Corporation, Prescott, AZ). The software settings complied with previous studies.[8,21]

Spectral analysis included relative power spectrum in the frequency bands: δ (0.5–4 Hz); θ (4–8 Hz); α (8–13 Hz); and β (13–30 Hz). Relative power spectrum was defined as the absolute power spectrum for each frequency band divided by the sum of absolute power spectrum of all frequencies, expressed as a percentage. The EEG channels used for the measurements of the power spectrum were: Fp1-T3, Fp1-C3, C3-Cz C3-T3; O1-C3, O1-T3, Fp2-T4, Fp2-C4, C4-Cz C4-T4; O2-C4, and O2-T4 (Fig. 1d). We computed the total relative power spectrum (averaging all EEG channels) in each frequency band as well as the δ/θ, δ/α and δ/β ratios.

Neurodevelopment

A total of 73 (41 SGA and 32 AGA) 2-year-old (range 24–26 months) children were examined (Flow chart in Fig. 2). Using the Bayley Scales of Infant Development Third Edition (Bayley-III), neurodevelopmental data were collected and analyzed by two psychometricians who were unaware of the children's birthweight.

Statistical analysis

We carried out a pre-hoc exploratory analysis with 30 children in each group and we observed that the mean difference in the discontinuity percentage was 18.74% (24.55% ± 21.24% vs 5.10% ± 8.27% in SGA and AGA, respectively). For a confidence level of 95% and a power of more than 99%, at least 40 children per group are required to demonstrate that the percentages of discontinuous patterns are higher in the SGA group.

ROC curves analyses, including Youden index, were used to obtain the cut-off point of each visual EEG variable with the maximum likelihood to discriminate between SGA and AGA neonates. Regardless of birthweight, we used these cut-off points as neonatal specific markers of maturity EEG, establishing two groups: (1) children with higher values, and (2) children with values equal to or lower than the cut-off point. Those whose EEG backgrounds showed ≤2 variables with values above the cut-off point were classified as mature and those with >3 as immature.

For comparisons between birthweight (SGA vs AGA), sex (males vs females), EEG maturity (mature vs immature), and children in the follow-up (lost vs non-lost) groups for EEG visual and spectral variables, we used Mann–Whitney U test. The correlations between the continuous variables of the visual analysis with those of the power spectrum and between the variables of the spectral analysis with the development scores were estimated using the Spearman correlation coefficient (two-sided) and using the Bonferroni correction to correct multiple comparisons.

Using multivariate linear regression, we tested the independent effects of the birthweight group on EEG variables and development scores, controlling the confounding effects of perinatal factors (maternal smoking, sex and cesarean delivery).

Otherwise all P values < 0.05 were considered statistically significant. Statistical analysis were performed with SPSS v. 21.0 (Chicago, IL), Statistica v. 5.0 (StatSoft, OK) and MedCalc Statistical Software version 13.0.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org).

RESULTS

Perinatal data

The main perinatal data are shown in Table 2. There were 38 SGA infants who had birthweight < 3rd percentile and the remaining

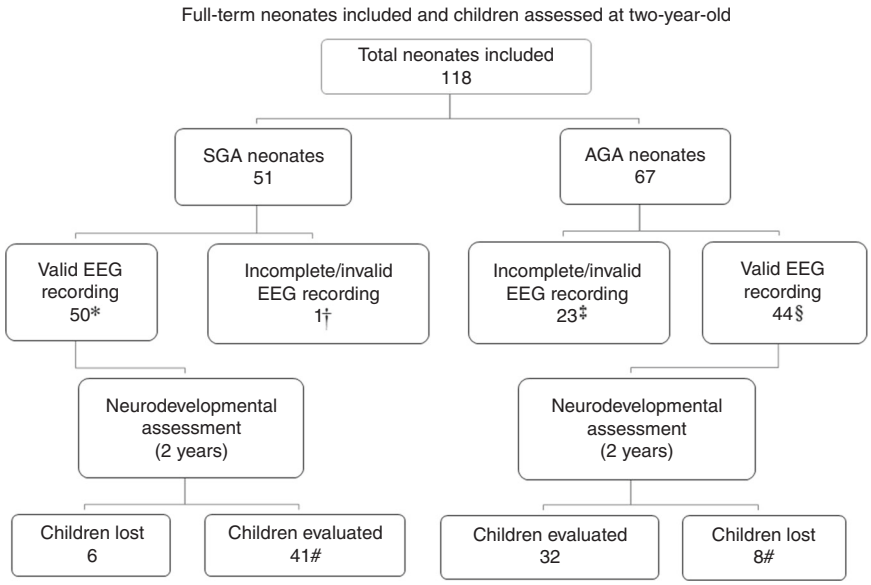

Fig. 2 Flow chart of children included in the study sample. *It was necessary to practice more than one EEG recording of different days in 17 newborns. † His parents refused a new EEG recording. ‡ In none of them could a new EEG recording be repeated. § The EEG recording was repeated in four of them. # There were three SGA children and four other AGA children who did not collaborate.

Table 2. Perinatal data of all infants included in the present work.

Perinatal data	SGA ($n = 50$)	AGA ($n = 44$)	Significance P value
Birthweight (g)	2140.14 ± 330.09	2987.16 ± 522.32	<0.001
Body length (cm)	44.11 ± 3.23	49.47 ± 2.40	0.009
Male sex	27/50 (54 %)	21/44 (47.7%)	0.44
Head circumference	32.20 ± 1.50	34.06 ± 1.59	<0.001
Birthweight percentile	1.87 ± 2.05	47.98 ± 27.45	<0.001
Gestational age	37.73 ± 1.73	38.10 ± 2.00	0.69
Maternal age	33.14 ± 5.22	33.75 ± 5.20	0.58
Maternal smoking	(11/50) 22 %	(3/44) 6.8%	0.046
Cesarean delivery	(18/50) 36 %	(8/44) 18.2%	0.07
Apgar (1 min)	8.44 ± 1.36	8.59 ± 1.07	0.56
Apgar (5 min)	8.89 ± .451	8.92 ± 0.363	0.79
Umbilical cord PH	7.239 ± .069	7.256 ± 0.068	0.34
Cerebroplacental ratio[a]	1.215 ± .557	1.694 ± 1.281	0.08
Maternal educational level			
Primary school	(7/50) 14 %	(5/44) 11.4%	0.77
High school	(22/50) 44 %	(26/44) 59.1%	0.23
College/university education	(21/50) 42 %	(13/44) 39.5%	0.60

[a]Only nine AGA neonates had registered their CPR after 31th week of gestation

12 babies SGA ≥ 3rd and <10th percentile. Fetal brain and umbilical Doppler ultrasound was performed in all SGA infants. The cerebral/placenta ratio (CPR) calculated by the pulsatility index, was (1) <3rd percentile in 15 SGA; and (2) between ≥3rd and <10th percentile in another 13 SGA fetuses. No emergent cesarean delivery, delivery room resuscitation or respiratory support was necessary in any infant.

The invalid or incomplete EEG recordings were due to the prolonged duration of the monitoring video-EEG without obtaining one full sleep–wake cycle and/or discomfort of the baby. It was possible to practice ≥one new EEG recording until getting a valid one in 17 SGA and four AGA infants. Parents refused another new video-EEG recording in one SGA, and in 23 AGA. A valid EEG recording was obtained in 50 SGA and in 44 AGA neonates, who were the babies included for the study.

Visual EEG analysis

EEG immaturity was found in 39 SGA and only in four AGA neonates ($P < 0.001$). Table 1 shows the results obtained in all different variables of background EEG visual analysis, including cut-off points obtained from of the ROC curve analysis with a positive predictive value >80 % and P value < 0.001 belonging to the group of SGA infants. The main results in visual EEG analysis comparing both birthweight groups are shown in Fig. 3a. No epileptiform EEG discharges were recorded in any neonate. No significant differences were found between sex (males vs females) and children in the follow-up (lost vs non-lost) groups for visual and spectral EEG variables. No contribution of confounding factors (cesarean delivery and smoking) were found on any EEG variable.

No significant differences were found in any EEG variable between SGA babies with birthweight <3rd percentile and those with birthewight ≥3rd and <10th percentile. The results obtained when comparing three birthweight groups (SGA <3rd percentile, SGA ≥3rd and <10th percentile, and AGA babies) are graphically shown in Supplemental Fig. S1 (online).

Quantitative analysis

Compared with the AGA, the neonates SGA group showed lower total relative power spectrum in δ and higher faster frequency bands. (Fig. 3b). The results of the total relative power spectrum for each frequency band and the ratios, expressed as mean, 95% confidence interval and statistical significance, are shown in Supplemental Table S1 (online).

After Bonferroni correction, we found a significant correlation between relative power spectrum in: (1) δ, α and β frequency bands with percentage of discontinuous pattern ($r = -0.39$, $P < 0.001$; $r = 0.41$, $P < 0.001$; $r = 0.44$, $P < 0.001$, respectively), (2) α with percentage of bursts with delta brushes ($r = 0.30$, $P = 0.004$), and (3) β with percentage of asymmetry ($r = 0.29$, $P = 0.007$). No other statistically significant correlations were found between visual and spectral EEG variables.

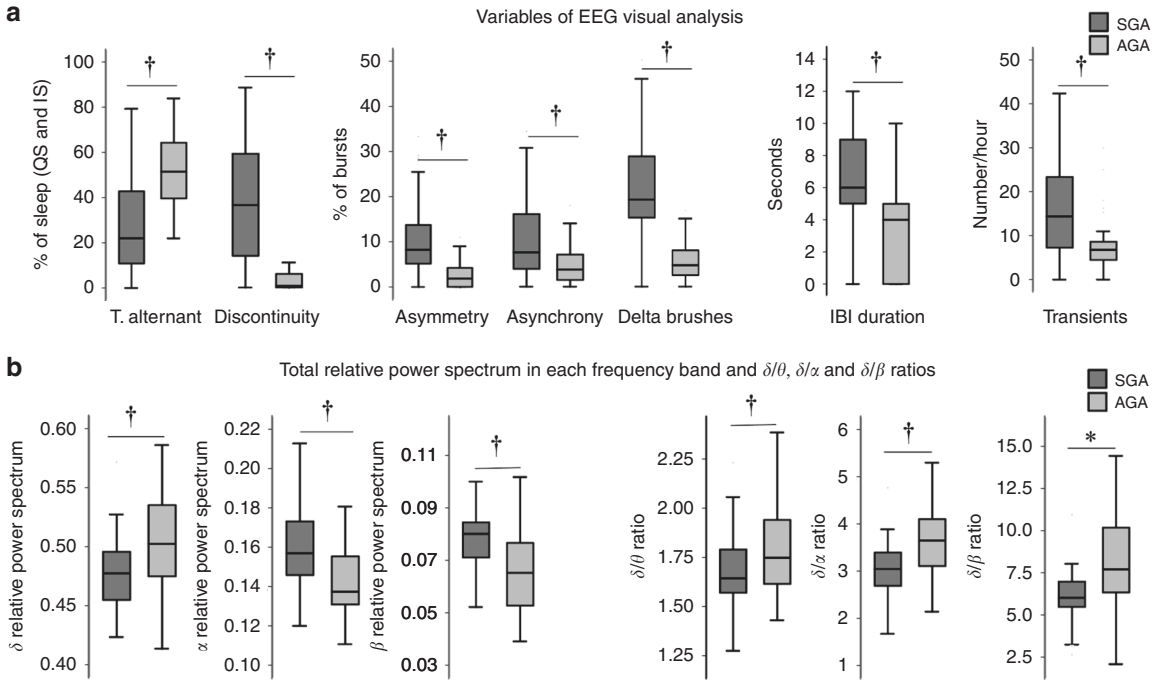

Fig. 3 Main results of visual and spectral analysis. Box plots represent medians, interquartile ranges (P25 to P75), and min-max (whiskers) of the main results of the visual EEG analysis (**a**) and of the relative power spectrum (**b**). *$P < 0.05$; †$P < 0.01$.

Neurodevelopment

Low birthweight and high rates of some immature EEG patterns both correlated with each other and, independent of other variables, were associated with significantly lower scores in one or more development domains. Table 3 shows these findings in detail. Taking into account only the group of SGA babies, we found: (1) no differences in the development scores between the mature and immature EEG, (2) using cut-off point, only interhemispheric asymmetry > 5% presented significantly lower scores in the language domain (95.76 ± 12.03) compared to SGA with asymmetry ≤5% (104.55 ± 13.71) ($P = 0.049$), and (3) using Spearman correlation coefficient, a significant negative correlation between asymmetry and motor development ($r = -0.310$; $P = 0.02$) and borderline not significant in the language domain ($r = -0.236$, $P = 0.061$). When considering exclusively the AGA group, we also found a significant negative correlation between interhemispheric asymmetry and motor development ($r = -0.328$; $P = 0.031$).

In the quantitative analysis, we found: (1) a significant negative correlation between relative power spectrum in *a* with the scores in the language development domain ($r = -0.316$, $P = 0.005$), and (2) a significant positive correlation between *δ/a* ratio with the scores in language and motor domains ($r = 0.305$, $P = 0.007$; $r = 0.247$, $P = 0.017$, respectively). No other significant correlations were found between the remaining quantitative EEGs variables and neurodevelopment scores.

DISCUSSION/CONCLUSIONS

Perinatal data

When birth weight <10th percentile is used as the only selection criterion, "normal SGA children" may be included. In the present study, we also use maternal pregnancy information, doppler and biometrics measurements of fetal ultrasound, in addition to other neonatal measures such as head circumference or body length. According to a recent consensus,[22] where these measures were considered, all our term infants SGA meet the criteria for IUGR definition. This consensus concluded that this definition (three of the following: birthweight <10th percentile; head circumference <10th percentile; length <10th percentile; prenatal diagnosis of IUGR; and maternal pregnancy information) "could be adopted in clinical practice and in clinical trials to better focus on newborns at risk".

Visual analysis

No neonate included in this study had acute pathology or was critically ill. Thus, the purpose of the present study was to analyze specific parameters of EEG maturity and not to classify the severity of a perinatal encephalopathy. We classified the EEG background in two degrees of maturity and found that most SGA babies were in the immature group. There is a wide and rich bibliography referring to specific patterns of intra and extra-uterine EEG maturation in preterm and term "healthy" and "sick" neonates.[23,24] However, to date, neither in IUGR preterm nor in SGA term babies, there are no publications on maturity parameters by visual EEG analysis of the conventional video-EEG recording. The coexistence of dysmature EEG patterns and excessive number of transients has been associated with chronic and persistent brain lesion;[4,5] described in premature infants when reaching term GA,[18] with chronic lung disease[25] and with postnatal malnutrition;[26] and in term neonates with other pathological intrauterine conditions.[27]

Asymmetry and asynchrony, together with flattening of the background EEG, most frequently unilateral, followed by a more discontinuous tracing, have been referred to as a benign variant of a more immature morphology in neonates >35 weeks GA.[28] To date, except in the acute period of the ischemic perinatal stroke,[21] asynchrony and asymmetry in term neonates have not been reported in the literature associated with other specific pathology.

Some aEEG studies conducted in neonates with IUGR have been associated with brain function immaturity.[7,8,29] Our results provide new data, until now unreported, that contribute to a better knowledge on brain function maturation in these children. The analysis of the well-recognized EEG patterns of maturity in the clinical setting such as discontinuity, delta brushes, IBI duration, asymmetry, asynchrony or transients may have clinical relevance on the evaluation of SGA neonates.

Table 3. Scores, expressed as means with their 95% CI, obtained in each development domain for birthweight and for optimal cut-off points in the EEG variables of the visual analysis using Bayley-III.

Birthweight goup	Motor		Language		Cognitive	
SGA ($n = 41$)	99.33	(‡)	95.30	(‡)	100.50	(‡)
	94.40–104.27		88.91–101.69		94.49–106.51	
AGA ($n = 32$)	109.22		108.61		111.61	
	104.10–114.34		100.72–116.50		105.26–117.96	
Cut-off (SGA/AGA)[a]						
>11% (31/7)	99.96	(†)	96.38	(*)	102.39	(*)
% Discontinuity	93.27–106.64		90.14–113.62		93.89–110.89	
≤11% (10 /27)	108.00		105.37		108.73	
	102.83–113.17		97.11–113.62		103.75–113.70	
>5% (28/7)	98.61	(†)	95.60	(†)	101.61	(*)
% Asymmetry	93.18–104.04		88.18–103.04		94.60–108.62	
	109.41		106.49		109.55	
≤5 % (13/27)	103.24–115.58		99.46–113.72		102.64–116.45	
>7% (21/11)	101.33	(*)	100.59	(*)	105.63	(*)
% Asynchrony	94.13–108.53		91.93–111.18		99.74–111.52	
	105.59		101.56		105.28	
≤7 % (20/23)	100.06–111.12		94.14–107.04		96.07–114.48	
>5 s. (25/5)	98.00	(†)	93.26	(†)	97.37	(‡)
Max. IBI Duration	92.04–103–96		85.81–100.72		88.97–105.77	
	108.52		105.48		111.08	
≤5s. (16/29)	102.63–114.41		98.86–112.11		105.83–116.33	
	99.31	(†)	95.91	(†)	99.77	(‡)
>11% (26/5) %	92.89–105.74		88.78–103.03		91.75–107.79	
Delta brushes	108.26		105.83		110.96	
≤11% (15/29)	102.78–113.74		98.24–113.41		105.65–116.26	
Immature (38/73)[b]	100.33	(†)	97.06	(*)	99.70	(†)
EEG maturity	96.34–104.33		92.66–101.46		94.09–105.30	
	109.08		107.73		111.65	
Mature (35/73)	104.91–113.25		102.77–112.68		107.16–116.14	

[a]Number of SGA and AGA children for each EEG variable
[b]Number of children with immature or mature EEG/total children assessed
*Not significant; †$P < 0.05$; ‡$P < 0.01$

Spectral analysis

When the sleep state has been defined by EEG and other polygraph channels, previous studies in term infants have found proportions of QS significantly reduced and increased in IS with great difficulty in exactly distinguishing sleep states in the first hours of life.[8,19,27] For this, in the present work, for spectral analysis we selected EEG segments with discontinuous and/or alternating tracings regardless of behavioral state. Given the existence of asymmetry, asynchrony and transients, long epochs-analysis that included all bursts during a stable period of sleep would allow to obtain spectral values more objective than those obtained from short periods of tracing EEG arbitrarily selected.

Currently most studies aiming at analyzing neonatal brain function are performed using the quantitative analysis of EEG background. There are multiple articles on brain maturation in premature and term "healthy" and critically ill infants.[7–11,30,31] However, contributions in SGA babies are more limited. In premature infants with IUGR, it has been described: (1) greater relative power in δ, and lower in θ, α and β frequency bands in relation to those non-IUGR, and (2) the relative power in the δ decreases with the increase of GA.[12,13,29] In term infants, SGA neonates have been reported to have a maturational delay, defined as power spectrum increased in δ.[14]

In the present work, SGA infants, compared to AGA controls, showed higher values in the power spectrum of frequencies faster (α and β) and lower in the δ. Therefore, our findings do not agree with the maturational delay patterns described in these previous studies. This discordance could be explained by major methodological differences in the procedure and selection of the EEG recording segments for spectral analysis. In previous works in late preterm infants[12] and term neonates with 38–42 weeks of GA,[14] the EEG recordings were obtained in the first 24–48 h and in the 3–6 days of postnatal life, respectively; both studies selected short EEG segments of QS (4–10 s) that included both continuous and alternating tracings. However, the present work included term neonates a week younger that those studied by Özdemir.[14] Our EEG recordings were performed between 48 and 72 h of life, and the EEG segments selected for the spectral analysis, exclusively with tracé alternant or discontinuous pattern, were much longer than in both previous studies.

In agreement with our results, a recent study on power spectrum analysis, conducted in the first month of postnatal life, found that those preterm infants (24–35 weeks GA) with IUGR had significantly increased relative power in θ, α and β and reduced in δ compared to AGA peers.[32] These authors, supported by published neuroimaging findings in fetuses with IUGR,[33]

suggested that SGA brain is relatively mature compared to AGA brain. However, our findings in the quantitative analysis correlate with immature patterns in visual analysis, suggesting that the reduction of relative power spectrum in δ and the increase in α and β indicate true delay in the maturation of brain function development in SGA babies.

Neurodevelopment

We found lower neurodevelopmental scores in SGA children compared to the AGA peers. Recent systematic reviews concluded that IUGR infants often display neurodevelopmental delays in early childhood[34] and that late-onset IUGR babies have an increased risk of low cognitive scores.[35]

Our results also suggest that some patterns of EEG immaturity, such as interhemispheric asymmetry, in term SGA neonates may be warning features for development risks, as already suggested for preterm infants with IUGR.[12] Due to the limited number of SGA neonates with mature EEG, we were unable to correlate neurodevelopmental scores with most of the maturity variables in this group of children. We only found a tenuous but significant association between high rates of interhemispheric asymmetry with decreased language and motor development scores. Only with this finding, where multiple variables were analyzed, a definitive conclusion cannot be obtained. However, our results, at least, invite further studies in order to assess whether the implementation of the video-EEG screening and early neurodevelopmental intervention in SGA children at risk could improve their outcome. The implementation of a video-EEG recording for all term SGA infants would have a significant increase in healthcare costs. However, any intervention capable of improving development scores even in a small quantity could have a high impact on public health.[36]

Although we found statistical differences in the development scores between SGA and AGA, all the children in our study, including those with EEG immature, obtained developmental scores within limits considered normal. Therefore, any neurodevelopmental intervention would be questionable. However, smallness at birth is a frequent problem. Some trials have been carried out to assess the influence of early elective delivery on neurodevelopment.[37,38] None of these trials managed to find outcomes benefits in the short or long term. A systematic review concluded that "a trial designed to assess the impact of intervention in term SGA in order to improve the outcome is urgently needed" and that "an intervention capable of improving the neurodevelopmental scores from 0.3 SD to 0.15 SD would be clinically significant.[36] Although, video-EEG monitoring, in itself, is not an intervention that will improve the development scores, immature EEG patterns at birth (particularly asymmetry) could potentially help identify SGA neonates at higher risk.

Limitations

IUGR is a heterogeneous condition that may have a variety of etiologic causes. Despite the prenatal and postnatal diagnostic assessment in all our SGA babies, and rigorous exclusion criteria, it is possible that some of them suffered an undiagnosed underlying etiology as genetic syndromes that influenced the results of the study.

There is a great variability in the definition of neonatal EEG variables. Except in discontinuity, the EEG variables analyzed in our study conform to the endorsed by the American Clinical Neurophysiology Society (ACNS). To consider abnormal discontinuity in an EEG tracing, most authors, including ACNS,[23] accept IBI duration >2 s with amplitude as low as 25 μV in the tracé alternant pattern. However, when normality ranges are evaluated in the EEG maturity framework, this definition is too restrictive. Subsequently, other investigators have used an IBI amplitude of ≤30 μV to define discontinuous pattern.[8,11,39]

In the present study and according with a recent guideline,[20] the interrater reliability was good or excellent in the interpretation of all EEG variables of visual analysis. However, Wusthoff et al.,[40] using the ACNS standardized scoring system, evaluated the interrater agreement in the interpretation of neonatal EEG in hypoxic ischemic encephalopathy. The authors found very good interrater for identification of seizures and classification of EEG background, but other specific EEG features (voltage, symmetry, variability or abnormal sharp waves) showed lower interrater agreement, suggesting limited reproducibility. There are methodological differences with the present work. Wusthoff analyzed the first 3 h of each EEG recording performed in the first 24 h after birth in asphyxiated infants under hypothermia. In our work, we measured these specific EEG patterns only in the discontinuous and alternating tracings at three days of life, and some graph-elements such as transients were only counted in the interburst periods.

In the present study, there was a high percentage of children born to smoking mothers and cesarean sections. Both factors could have led to EEG modifications. However, in the multiple analysis, we did not find any level of significance between these factors with the EEG variables nor with the scores obtained in the neurodevelopment. Yerushalmy-Feler et al.[12] found a significant correlation between cesarean delivery and EEG immaturity. However, apart from the methodological differences in the EEG analysis procedure, these children were premature, many of them receiving prenatal corticosteroids and the EEG recording was performed very early (<48 h of life). Prenatal steroids and EEG recordings carried out before adaptation to extrauterine life can be associated with immaturity in visual and spectral EEG analysis.[8,9,12]

Another potential limitation could be the high number (higher in the AGA group) of invalid video-EEG recordings and of children lost in the follow-up and/or without collaboration in their neurodevelopment assessment. However, it is easy to understand that there were important practical barriers for the recruitment of healthy neonates (AGA group) for intensive video-EEG monitoring (>3 h), and undergo another new EEG recording when there was a previous invalid EEG tracing. Following the recommendations of the Spanish Society of Neonatology, from birth, SGA babies are periodically monitored at neonatal follow-up hospital visits. This would explain that most parents of SGA children were aware of the possible postnatal and developmental risks of their children, and of their greater compliance with this research project.

Using the ROC curves and the Youden Index, we obtained cut-off points as markers of EEG maturity to discriminate between SGA and AGA neonates. These cut-off points were also used later to evaluate their involvement in neurodevelopment. Compared with AGA, SGA babies had both: (1) higher values than these cut-off points, and (2) lower developmental scores. Therefore, there may be some bias when lower neurological development outcomes are obtained in children in whom only higher rates of EEG immaturity are considered. However, taking into account only the group of SGA infants, we found a significant correlation between interhemispheric asymmetry with lower scores in motor and language development.

Conclusions

Using conventional video-EEG recordings in the third day of extrauterine life, the present prospective study provides specific findings of EEG immaturity in SGA children so far not reported: (1) In the visual analysis of the EEG background, it is common to find high rates of specific EEG patterns of immaturity and excessive transients per hour, and (2) in the quantitative analysis of alternating or discontinuous EEG tracings, higher values in the relative power spectrum to faster frequencies (α and β) and lower in delta can be found.

In the neurodevelopmental assessment, compared to AGA, SGA children can obtain lower scores in motor, language and cognitive development. We also provide relevant findings in the clinical setting, to date not referenced in the literature. Term neonates (AGA and SGA) with excessive IBI duration and high rates of immature EEG patterns, such as discontinuity, interhemispheric asymmetry of the bursts or percentage of bursts with delta brushes in their video-EEG recordings at third day after birth, may have unfavorable prognostic implications resulting in decreased scores in the neurodevelopmental assessment in early childhood. However, further studies including a greater number of SGA infants are needed in order to determine what rates of immaturity EEG could predict outcomes in low-birth-weight term neonates.

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AUTHOR CONTRIBUTIONS

Dr. Castro Conde conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs. González Campo, Quintero Fuentes and Jiménez Sosa designed the data collection instruments, coordinated and supervised data collection, and reviewed and revised the manuscript. Drs. González González, González Barrios and Reyes Millán carried out the initial analyses, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

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Statement of ethics: The study was approved by the Research Ethics Committee of our Hospital. Written informed parental consent was obtained after delivery.

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