ORIGINAL RESEARCH

Amplitude-Integrated EEG and Brain Sparing in Preterm Small-for-Gestational-Age Infants

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Purpose: Preterm small-for-gestational-age (SGA) infants are at risk for a high mortality rate and impaired cognitive development. Only a few studies have focused on amplitude-integrated EEG (aEEG) in preterm SGA infants. They have been shown to have a slower rate of brain maturation, but these findings have not consistently been related to neurodevelopmental outcomes. The aim of our study was to evaluate early aEEG monitoring in SGA compared with adequate-for-gestational-age preterms.

Methods: This prospective cohort study enrolled infants with very low birth weight who were admitted to the neonatal intensive care unit at Hospital Puerta del Mar, Cádiz, Spain, from June 2009 to September 2012. This study was a subanalysis of SGA from the global cohort previously described by our group. Adverse outcome included severe intraventricular hemorrhage and/or death. Cerebral function was monitored using aEEG recordings during the first 72 hours of life.

Results: Preterm SGA infants (18 SGA in the global cohort of 92 patients) had lower 1- and 5-minute Apgar scores, higher score for neonatal acute physiology perinatal extension II scores, and higher proportion of adverse outcomes. When comparing preterm adequate-for-gestational-age infants with SGA infants with good prognosis, those with SGA had more mature and continuous aEEG patterns. Low margin amplitude depression was not as severe in these patients, and a higher proportion of these patients developed sleep–wake cycles.

Conclusions: The results of our study suggest that SGA infants with a good prognosis have a more mature aEEG pattern than preterm adequate-for-gestational-age patients with the same outcome. These findings support the brain sparing theory in SGA infants.

Key Words: aEEG, Preterm infants, Small for gestational age, Brain.

(J Clin Neurophysiol 2017;34: 456–460)

Advances in perinatal care have been associated with a substantial increase in the survival of preterm infants, thus raising questions about their neurological outcomes. Preterm small-for-gestational-age (SGA) infants are a population of particular interest, because they exhibit immaturity secondary to low gestational age combined with the consequences of growth restriction.[1]

Previous studies have demonstrated that being SGA at birth is associated with a high mortality rate and impaired cognitive development.[2–5] It is thought that growth-restricted fetuses attempt to compensate for the substrate limitation associated with placental insufficiency by preferentially perfusing the central nervous system.[1,6–8]

Although the need to follow this high-risk group is well accepted, it is not clear which risk factors contribute to the cognitive deficits in SGA infants, including whether any early markers exist that may predict high risk.[9]

Neurophysiological studies using video-EEGs and amplitude-integrated EEGs (aEEGs) allow real-time monitoring of cerebral activity. The aEEG has demonstrated its usefulness in the prognosis of newborns with hypoxic ischemic encephalopathy.[10–12] aEEG recordings in premature newborns are still not considered as a routine practice, even though multiple studies regarding normal and pathological aEEG tracings in this population have been conducted and published in recent years.[13–19] Some evaluation scores for the aEEG recording in premature newborns have previously been described.[16,20–22]

Only a few studies have focused on the aEEG populations of preterm SGA infants and with varying methodologies used for aEEG interpretation. Preterm SGA infants have been shown to have a slower rate of brain maturation,[9,23,24] although these findings have not been consistently related to their neurodevelopmental outcome.

To increase the knowledge of the vulnerability of this preterm population of infants, our study intended to explore the different aEEG patterns, this population might show in the first 72 hours of live and its relation to the short-term outcome.

METHODOLOGY

We designed a prospective cohort study through the consecutive inclusion of very low birth weight infants (VLBWIs) admitted to our neonatal intensive care unit (NICU) at Hospital Puerta del Mar, Cádiz, Spain, from June 2009 to September 2012. Our group has previously reported the study methodology and results for the global cohort.[19] This study was intended to be a subanalysis of the global cohort to ascertain the aEEG patterns in VLBWI who were SGA and to compare them with those of preterm adequate-for-gestational-age (AGA) infants. SGA infants

The authors have no funding or conflicts of interest to disclose.

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ISSN: 0736-0258/17/3405-0456
DOI 10.1097/WNP.0000000000000399

were defined on the basis of a birth weight below the tenth percentile for gestational age on the appropriate population growth curve. Very low birth weight infants were defined on the basis of birth weights less than 1,500 g and/or 32 GW. We excluded preterm infants with major congenital defects, cerebral malformations, infections involving the central nervous system, lack of informed consent, or death within the first 24 hours after birth.

Variables

The following perinatal variables were collected: sex; birth weight; gestational age at birth; type of birth; Apgar scores at 1, 5, and 10 minutes; systolic and diastolic blood pressure, respectively, at the time of admission to the NICU; score for neonatal acute physiology perinatal extension (SNAPPE); clinical risk index for babies score; respiratory support; and the use of inotropic, sedative, or antiepileptic drugs during the first 4 days of life.

A cranial ultrasound was performed within the first 3 days of life and at weekly intervals. Short-term outcome was considered adverse if the patient developed severe neurological lesion (defined as the presence of grade III intraventricular hemorrhage (IVH) and/or intraparenchymatous hyperechogenicity) or died. Favorable short-term outcome was considered if the patient survived with no IVH or IVH grade I-II.[25]

aEEG

Cerebral function was monitored using aEEG recordings during the first 72 hours of life. Recordings were started after the clinical stability of the patient was assessed after admission to the NICU.

Electrodes were placed in the standard locations: C3, P3, C4, and P4 (in such a way that two biparietal channels were monitored). The monitoring equipment used was a Brainz BRM3 (Brainz Instrument Ltd., New Zealand). The processing of the standard EEG signal used to obtain the aEEG tracing has been described in previous publications (21).

The aEEG tracings were evaluated independently by two researchers (S.P.L.-L. and I.B.-F.), who were masked to patient identity and prognosis in addition to each other's assessments.

The patients were assessed during the following three 2-hour time periods: 12 to 14 hours of life, 46 to 48 hours of life, and 70 to 72 hours of life.

The tracings were evaluated according to the previously published criteria (9, 13, 14, and 22) based on the four main components of the aEEG tracing: continuity, sleep–wake cycles (SWCs), amplitude of the inferior margin, and bandwidth. A full description of the methodology can be found in our previous report.[19]

Data Analysis

The data are presented in a descriptive manner using the average SD (±) or the median (min.-max.) according to the variable's distribution.

The statistical analysis was conducted using STATA 13.0.

Pearson χ^2 test was used to compare two dichotomous variables, Fisher exact test was used for variables when the expected frequency was less than 5, and Student *t* test was used to compare two averages.

The study was approved by the ethical committee of our institution (Hospital Puerta del Mar Investigation Subcommittee), in accordance with the international ethical conduct recommendations (Helsinki Declaration) and the current Spanish legislation (Oviedo Apostille Convention). Written informed parental consent was obtained in each case.

TABLE 1. Gestational Age at Birth of the Total Cohort of VLBWI Included and Those Who Were Defined as SGA or AGA as Grouped by Gestational Age

	SGA, *n* (%)	AGA, *n* (%)	Total, *n* (%)
23–26 WG	4 (22.22)	23 (31.08)	27 (29.35)
27–30 WG	7 (38.89)	30 (40.54)	37 (40.22)
>30 WG	7 (38.89)	21 (28.38)	28 (30.43)
Total	18 (100)	74 (100)	92 (100)

AGA, adequate for gestational age; SGA, small for gestational age; VLBWI, very low birth weight infants; WG, weeks of gestation.

RESULTS

Three hundred eligible preterm infants were admitted to the NICU during the study period. The main limitation to patient recruitment in this study was aEEG monitor availability. There were 208 patients who were excluded and 92 who were included; 18 in the latter group were SGA infants.

There were no differences in perinatal characteristics between included and excluded VLBWIs, except for higher clinical risk index for babies scores in the inclusionary group ($P = 0.027$). After patients were admitted to the NICU and were considered stable in terms of cardiorespiratory support, we prioritized the monitoring of patients who were more critical (i.e., in multiple pregnancies), thus potentially explaining the observed differences.

TABLE 2. Perinatal Characteristics of the Study Population

	SGA ($n = 18$)	AGA ($n = 74$)	*P*
Birth weight, g	550 (400–1,250)	990 (550–1710)	0.0001
Gestational age, w	28.2 (2.7)	27.9 (2.2)	NS
Apgar 1 minute	4 (1–8)	6 (0–9)	0.0136
Apgar 5 minute	6 (4–9)	8 (1–10)	0.0181
Systolic blood pressure	42 (23–84)	47.5 (31–96)	NS
Diastolic blood pressure	30 (10–55)	28 (15–59)	NS
CRIB	4 (1–15)	2 (0–15)	NS
SNAPPE II	40 (11–77)	19 (0–102)	0.0026
Death	7 (38.89%)	14 (18.92%)	0.0018
Severe IVH	5 (27.78%)	10 (13.51%)	0.0127
Death and/or severe IVH	8 (44.4%)	18 (24.32%)	0.0028

Quantitative variables are expressed as the median (range) or qualitative as the frequency (percentage).

AGA, adequate for gestational age; CRIB, clinical risk index for babies; IVH, intraventricular hemorrhage; SGA, small for gestational age; SNAPPE, score for neonatal acute physiology perinatal extension.

TABLE 3. aEEG Parameters in Those Preterm Infants Who Developed Favorable Outcomes

Subgroup of Patients With Favorable Outcomes	SGA ($n = 10$)	AGA ($n = 56$)	*P*
Maturation score*	5.5 (2–8)	3 (0–10)	0.017
Continuity 12 hours: DHV/C	8 (80%)	28 (50%)	<0.0001
Continuity 24–48 hours: DHV/C	5 (71.43%)	24 (51.07%)	0.0031
Continuity 72 hours: DHV/C	5 (83.33%)	16 (69.56%)	0.0218
LMA 12 hours (<3 μV)	1 (10%)	17 (30.36%)	0.0003
LMA 24–48 hours (>3 μV)	1 (14.29%)	10 (21.28%)	NS
SWC developed at 12 hours	5 (50%)	8 (14.29%)	<0.0001

*Maturation score described by Burdjalov et al.[21] in the first 12 hours of life.
AGA, adequate for gestational age; DHV/C, discontinuous high voltage/continuous; LMA, low margin amplitude; SGA, small for gestational age; SWC, sleep–wake cycle.

Preterm infants who were defined as SGA had lower 1- and 5-minute Apgar scores ($P < 0.05$) and higher illness scores, and there were statistically significant differences in the score for neonatal acute physiology perinatal extension II scores when compared with AGA infants (Table 1). A higher proportion of SGA infants had adverse outcomes (Table 2). When compared both groups in terms of favorable outcome, we only found differences in score for neonatal acute physiology perinatal extension (median score 15(0–57) in AGA versus 34 (20–77) in SGA; $P = 0.0120$). The preterm infants defined as SGA with favorable outcomes (10/18) when compared with those AGA with favorable outcomes (56/74) had more mature and continuous aEEG patterns, as indicated by a higher proportion of discontinuous high voltage and continuous traces in every studied period. Low margin amplitude depression was not as severe in these patients, and a higher proportion of these patients developed SWCs (Table 3).

A total of 23 preterms of the whole cohort were found to have very depressed bandwidths (bandwidth <15 μV with low margin amplitude <5 μV) in the first 12 hours of life. The SGA infants who developed severe IVH or died (3/18 [37.5%]) showed very depressed bandwidths, whereas none of the SGA infants with good outcomes (10/18) had very depressed bandwidths ($P < 0.0001$).

DISCUSSION

Although other studies have reviewed the differences in early aEEG tracing in SGA VLBWI compared with AGA, our study is the first to analyze the aEEG pattern in SGA infants in different categories, including severe IVH or death. Our study shows that even though SGA VLBWI have a higher risk of morbidity and mortality, infants who do not develop severe IVH or death have a more mature aEEG tracing than AGA infants at the same gestational age (Table 4).

This finding may be interpreted as a successful mechanism of brain sparing initiated during fetal life in this population. Brain sparing is the consequence of the fetal response to hypoxia as cardiac output redistribution favors vital organs, including the brain.[8] Asymmetric types of intrauterine growth restriction reflect the "brain sparing" effect and result in a high brain/body ratio.[26,27] Preterm or term SGA neonates with relative head sparing have neurodevelopmental outcomes that are significantly better than those of infants whose head circumference percentiles are the same as or lower than their birth weight percentiles.[1,9,28]

Brain sparing has been intensively studied from a hemodynamic point of view, but this study indicates how brain maturation, with more advanced and continuous aEEG tracing with a more mature SWCs, may be considered a feature of brain sparing.[1,6–9,28]

TABLE 4. Recent Studies on SGA Infant aEEG Patterns

Author	Year	*n* (SGA)	Main Observations in SGA	Main Differences
Natalucci[29]	2014	14	Higher margin amplitude	Studied SGA as a pool and did not search for differences depending on encountered outcomes.
Griesmaier[30]	2015	50	Higher bursts per hour in the first day of life. No differences in the base pattern or maturation score.	
Schwindt[23]	2015	47	Lower maturation score and fewer SWC.	Median aEEG tracing at 8.5 days of life and a median duration of 225 minutes.
Yerushalmy-Feler[31]	2014	14	Reduced aEEG continuity, with a lower aEEG margin and a wider aEEG trace.	Mean gestational age: 34 weeks
Benavente-Fernández	(current study)	18	Without severe IVH and/or death: more mature aEEG pattern Those who developed severe IVH or died: severe bandwidth depression	aEEG in the first 72 hours, with a mean duration of 56 hours. Studied aEEG features separately after prognosis.

aEEG, amplitude-integrated EEG; IVH, intraventricular hemorrhage; SGA, small for gestational age; SWC, sleep–wake cycle.

The SGA VLBWI included in our study had lower 1- and 5-minute Apgar scores and higher score for neonatal acute physiology perinatal extension II scores and were therefore at an increased risk of severe IVH and/or death. A higher mortality rate and impaired cognitive development in SGA VLBWI have previously been reported.[2–5]

SGA infants who develop severe IVH or death show, as the main aEEG feature, very depressed bandwidths, thus accounting for 40% of the preterm infants, whereas SGA infants with good prognoses have immature (but not depressed) tracings (40% vs. 0%).

Natalucci et al.[29] have reported an increased higher margin amplitude in 14 SGA VLBWI, which they suggest as a sign of possible dysmature brain activity. There were no findings that supported differences in the maturation scores during the first 4 days of life. Griesmaier et al.[30] have studied a larger sample size, comprising 50 SGA VLBWI, and did not find differences in the maturation score in either group. None of these studies evaluated SGA infants with an adverse prognosis separately from infants with good prognoses. Instead, these studies examined all SGA infants as a single group. This approach may be an important limitation in interpreting results in the population of SGA infants. Recently, Schwindt et al.[23] have evaluated aEEG base patterns, SWCs, seizures, and outcomes at 2 years in a global cohort of 136 VLBWI, 47 of whom were SGA. These researchers found that SGA infants had lower maturation scores, a lower proportion SWCs, and higher adverse outcomes. It should be considered that a high proportion of sedation was used in these patients and that the median of the aEEG tracing occurred at 8.5 days and included a median duration of 225 minutes. These methodological aspects make this study incomparable to ours because we considered "early monitoring" as being within the first 3 days of life with a 72-hour duration versus the 3-hour of aEEG tracing in this study. Yerushalmy-Feler[31] have shown a reduction in aEEG continuity during the first 2 days of life, with a lower aEEG margin and a wider aEEG tracing width in SGA infants compared with AGA infant controls; these results were considered to indicate delayed-EEG maturation in this population. Nevertheless, their study included a median gestational age of 34 weeks, an important difference from our study cohort, which had a median age of 28 weeks (range, 23–32 weeks).

The reported studies on SGA VLBWI aEEG tracings differ in both the methodology and results, as reported. This finding, coupled with small sample sizes, is common in all the reported studies and makes it difficult to draw definitive conclusions in this population. Our study offers interesting data because SGA infants were not only studied as a general pool but also dichotomized on the basis of outcome. Our study is the first to consider this methodology, which may provide a different paradigm of studying brain activity in this population in the future. The results of our study support the brain sparing theory in SGA infants and are related to early outcomes. Examination of the previously known global data suggests that SGA VLBWI shows a more immature aEEG pattern. Nevertheless, our findings suggest that SGA with good prognoses have more mature aEEG patterns. These results may be considered a success of intrauterine compensation mechanisms wherein growth-restricted fetuses preferentially perfuse the central nervous system.[1,6–8] Further research on this high-risk population, including larger sample sizes, is needed to confirm this hypothesis.

Early monitoring of brain function in this population through aEEG is of great interest as a potential predictor of increased biological vulnerability.

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