Late Neonatal Sepsis in Very-low-birth-weight Premature Newborns Is Associated With Alterations in Neurodevelopment at Twenty-five Months of Age

Jose Uberos, MD, PhD,† Ana Nieto-Ruiz, PsD,‡ Francisco Contreras Chova, MD,* Marta Carrasco-Solis, PsD, Aida Ruiz-López, PhD,* Elisabeth Fernandez-Marín, PhD,* Carolina Laynez-Rubio, PsD,§, and Ana Campos-Martinez, PhD, MD**

Aim: To evaluate the impact of late-onset sepsis (LOS) on the neurodevelopment of very-low–birth-weight (VLBW) premature infants.

Methods: This is a retrospective cohort study of VLBW premature infants. The Mental Development Index (MDI) was determined for a population of 546 VLBW infants, at 14 and 25 months of age, and evaluated using the Bayley test. A history of meningitis or early neonatal sepsis was considered an exclusion criterion. The study parameters analyzed included perinatal variables, the development of neonatal comorbidities and a history of LOS. Multivariate linear regression and multinomial logistic regression analyses were performed.

Results: LOS was observed in 115 newborns, among whom microbiological testing showed that 65.0% presented Gram-positive bacteria, with *Staphylococcus epidermidis* being responsible for 55.4%. There was a significant association between the 25-month MDI and a history of LOS. This represents a decrease of 7.9 points in the MDI evaluation of newborns with a history of LOS. The latter history is also associated with the following neurodevelopmental alternations: mild motor disorders [odds ratio (OR): 2.75; 95% confidence intervals (CI): 1.07–7.05], moderate cognitive delay (OR: 3.07; 95% CI: 1.17–8.00) and cerebral palsy (OR: 2.41; 95% CI: 1.09–5.35).

Conclusions: In our study cohort, LOS was associated with alterations in neurodevelopment, including reduced MDI, together with motor and cognitive disorders and cerebral palsy. To improve neurodevelopmental outcomes in this group of newborns, neonatal intensive care unit personnel should focus attention on preventing hospital-acquired infections.

Key Words: late-onset sepsis, very-low-birth-weight infant, neurodevelopmental delay, cerebral palsy

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*From the Department of Pediatrics, Neonatal Intensive Care Unit, San Cecilio Clinical Hospital; †Department of Pediatrics, Medicine Faculty; ‡Department of Paediatrics, School of Medicine, University of Granada; and §Department of Pediatrics, Neuropaediatric Unit, San Cecilio Clinical Hospital, School of Medicine, University of Granada, Granada, Spain.

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Address for correspondence: Jose Uberos, MD, PhD, Neonatal Intensive Care Unit, San Cecilio Clinical Hospital, Granada University (Spain), Avda. Dr. Oloriz 16, 18012; Medicine Faculty, Avda. de la Investigación 11; 18016 Granada, Spain. E-mail: juberos@ugr.es.

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Neonatal sepsis is a clinical syndrome characterized by bacteremia with systemic inflammatory response syndrome.[1] It affects approximately 20% of very-low-birth-weight (VLBW) newborns and contributes to increased mortality and morbidity.[2] The prevalence of late-onset neonatal sepsis (LOS) is greater at lower gestational ages (GAs), reaching 40% in very immature newborns weighing less than 750 g.[3] Immune system immaturity, the use of central catheters during parenteral nutrition and delayed enteral nutrition with breast milk are known risk factors for LOS in the VLBW newborn.[4,5]

Some researchers suggest that the developing brain is vulnerable to an inflammatory environment and that the release of cytotoxic mediators during sepsis, together with ischemic lesions produced by hypotension and decreased cerebral flow, may alter brain development.[6] The brains of premature neonates often present impaired cerebrovascular autoregulation in response to changes in blood pressure, with minimal decreases provoking insufficient cerebral blood flow, which could provoke ischemia in vulnerable arterial areas.[7]

It has been suggested that the development of sepsis in VLBW newborns impairs neurodevelopment by altering the neuronal migration, gliogenesis and myelinogenesis, which occurs preferentially in the last weeks of gestation and the first weeks of postnatal life.[8,9] Systemic inflammatory response syndrome associated with LOS in the VLBW newborn can cause white matter lesions and diffuse lesions in premyelinating oligodendrocytes, heightening the risk of impaired cognitive and motor functions.[10] The disorders described are complex and can range from major impairments, such as cerebral palsy, to more subtle deficits, such as difficulties with memory and attention.[11] These alterations in neurodevelopment have been described and related to prematurity itself, but, to date, no detailed analysis has been performed to consider the contribution made by the multiple factors that affect prematurity and the extent to which they impact on the neurodevelopmental alterations described.[7,12] The term "encephalopathy of prematurity" has been used to define the set of neuronal abnormalities observed in premature newborns, especially those with cerebral white matter injury.[13] Other alterations that have been described include gray matter abnormalities, initially identified by volumetric magnetic resonance imaging studies, and defective growth of the cerebral medulla, cortex and deep nuclear structures.[14]

Follow-up of the VLBW newborn and assessment of neurodevelopment in preterm infants with a history of neonatal sepsis are crucial for the early identification of delay so that specific interventions can be prescribed to minimize long-term impairments. In view of these considerations, the aim of the present study is to evaluate the repercussions of LOS on the neurodevelopment of VLBW premature infants.

METHODS

Study Population

This retrospective longitudinal study was made of VLBW newborns with a GA of 23^{+0} to $32^{+}6$ weeks admitted to the Neonatal

Intensive Care Unit (NICU) of the San Cecilio University Hospital in Granada (Spain) between January 2008 and December 2021. A total of 570 VLBW newborns were admitted during this period. Newborns diagnosed with early neonatal sepsis or neonatal meningitis were excluded. Those with congenital infections or proven genetic alterations were also excluded. Figure 1 depicts the process applied for the recruitment and inclusion of participants in this study.

This study was carried out in accordance with the guidelines established in the Declaration of Helsinki. Informed consent was requested in every case from the children's parents/guardians. Perinatal data were recorded using the NEOSOFT program (Spanish Society of Neonatology, https://www.neosoft-sen.net/index.html), in accordance with the protocol established by the Provincial Bioethics Committee on January 14, 2020, as Code No. 80ed2fa1b452eca15f1715306dd309110af92a95. After hospital discharge, follow-up was carried out in the corresponding pulmonology, neonatology and neurology consultations, obtaining data related to the infant's comorbidity and neurodevelopment.

Neonatal Comorbidity

Late-onset sepsis (LOS) is defined as that which occurs beyond 72 hours of postpartum life and meets the criteria for infectious symptoms (fever, irritability, apathy, apnea, failure to thrive, refusal to feed, tachycardia or tachypnea) and the presence of acute phase reactants (elevated interleukin 6 or C-reactive protein), neutrophilia with left shift and/or leukopenia with positive blood culture.[15] Newborns with clinical manifestations of sepsis and an increase in acute phase reactants but with a negative blood culture are classified as presenting clinical sepsis "without microbiological confirmation."

The Clinical Risk Index for Babies (CRIB II) is derived from the following variables: sex, GA, birth weight and excess base in blood gases obtained in the first 12 hours. In the present study, the total CRIB II score (range: 0–27) was calculated.[16] The presence and degree of bronchopulmonary dysplasia (BPD) were recorded following the recommendations of National Institute of Child Health and Human Development[17] and Jobe and Bancalari.[18] BPD is defined as the need for supplemental oxygen >21% at 28 days of life and/or the need for

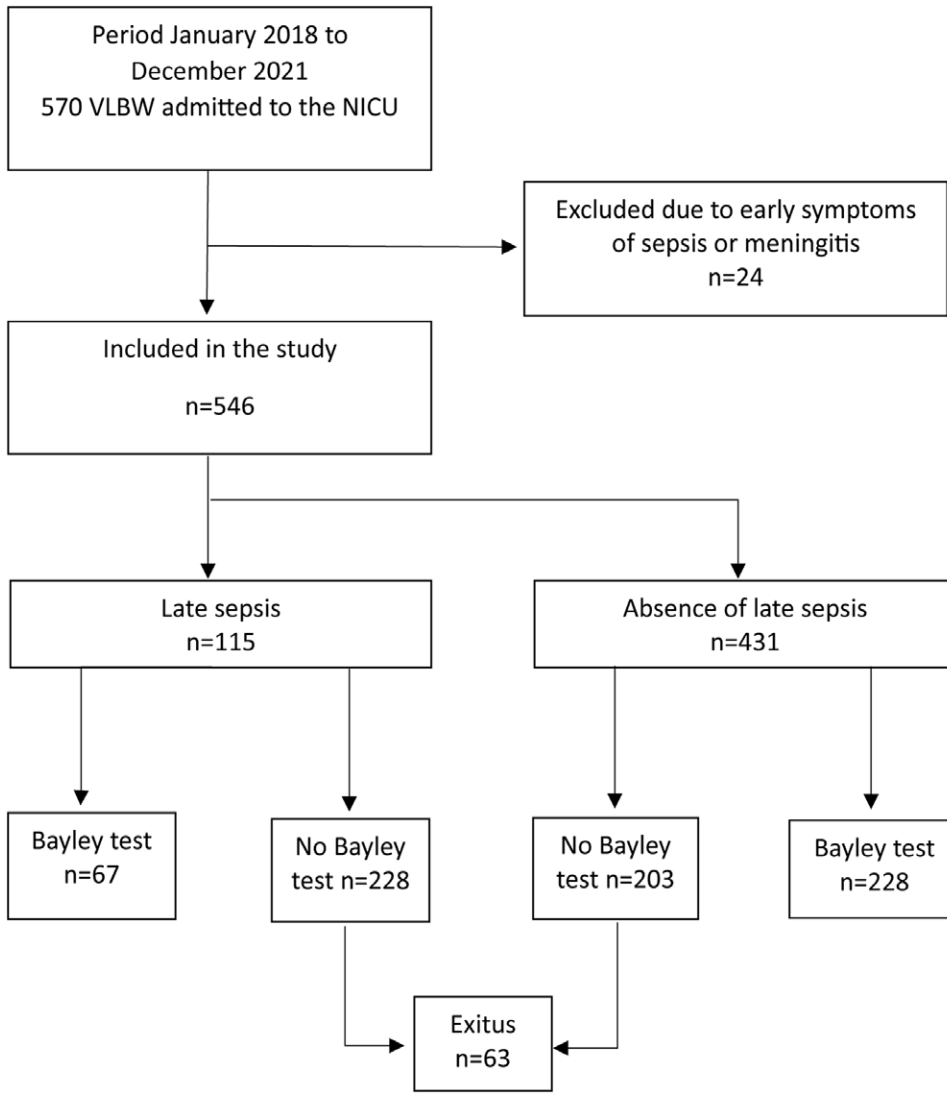

FIGURE 1. Patient flow chart.

supplemental oxygen >21% or positive airway pressure at 36 weeks of corrected GA. BPD is classified as mild, moderate or severe. Patent ductus arteriosus (PDA) is diagnosed by Doppler ultrasound and treatment is indicated when there are clinical repercussions or when the diameter is greater than 2 mm. The diagnosis and staging of intraventricular hemorrhage (IVH) are based on the Papile classification.[19] To obtain this diagnosis, all newborns are given a brain ultrasound scan on the third day of life and every week thereafter. The diagnosis and staging of necrotizing enterocolitis (NEC) are performed using Bell's criteria.[20]

Psychomotor and Sensory Development

In our hospital, this parameter is evaluated in the neuropediatric consultation. For each child included in our study, 2 reviews of this type were performed, as follows: review 1 at 14 months [95% confidence interval (CI): 13.1–14.5] and review 2 at 25 months (95% CI: 20.7–28.7). Motor alterations are classified as: (1) mild motor disorder, which includes motor coordination disorders that are not a consequence of cognitive or neurological alterations evidenced by imaging tests; this category includes fine and gross motor skills that are significantly below the expected level; (2) monoparesis, that is, a motor alteration that affects a single limb, muscle or group of muscles; (3) hemiparesis, that is, a motor alteration that affects an arm and a leg on the same side of the body; (4) tetraparesis, that is, a motor alteration that affects all 4 limbs. Visual and auditory sensory abilities were determined by evoked potential tests. Motor development, coordination, language, social and cognitive developments were all evaluated, and the Mental Development Index (MDI) was scored using the Brunet-Lezine and Bayley III scales. The level of cognitive delay was determined according to the mental age derived from the MDI and the resulting intelligence quotient (IQ), as follows: mild delay (IQ: 50–70), moderate delay (IQ: 35–50) or severe delay (IQ: 20–35).

When 2 or more motor or sensory deficiencies were detected, this was considered a multiple deficiency. Behavioral disorders were evaluated using the CUMANIN questionnaire and the Wechsler Intelligence Scale. Cerebral palsy is a group of developmental disorders that affect movement and posture, thereby limiting activity. The condition is attributed to a nonprogressive insult to the developing brain, during the fetal period or the first years of life, and is frequently associated with sensory disturbances.[21] When detected, the presence of epilepsy, defined as repeated seizures with alterations in electrical activity in the electroencephalogram, was also recorded.

Statistical Analysis

The descriptive data obtained are summarized using medians (P50) and the interquartile range (P25–P75) for the continuous values and frequency distribution (%) for the categorical ones. Univariate comparisons were made using the Mann-Whitney test for the continuous variables and the χ^2 test for the categorical ones. The association analysis was performed first by univariate and then by multivariate logistic regression. Collinearity in the linear regression analyses was assessed by the variance inflation factor (VIF). We adjusted for the variables that did not present multicollinearity with the remaining predictor variables when the VIF was less than 5.[22] All statistical analyses were performed with IBM SPSS 28.0 for Windows (IBM, Armonk, NY).

RESULTS

Of the 570 VLBW newborns included in the initial study cohort, 24 were excluded due to early meningitis or sepsis, 115 developed late sepsis and 63 died. Moreover, of 257 premature newborns, the results of the neurodevelopment evaluation using the Bayley test were unknown; in 63 cases, this circumstance was due to their death. This pattern of events led us to investigate the comparability between the newborns with and without this neurodevelopment evaluation, with respect to the LOS variables and the other variables recognized as risk factors for sepsis (Table 1). Since no significant differences were observed in the distribution of LOS or GA among the newborns, and although other factors related to a higher risk of late sepsis (duration of parenteral nutrition and of central catheter insertion) were significantly higher among the infants with Bayley evaluation, we assume that the group of 295 newborns for whom a neurodevelopment evaluation was performed are representative of the entire cohort.

In our study population, LOS was significantly more common among the newborns of lower GA (Table 2). Among those who developed LOS, the average stay in the NICU was significantly longer, as was the duration of central catheter insertion and that of parenteral nutrition, compared with the newborns without LOS. We also observed greater ventilatory assistance, in the form of mechanical ventilation and oxygen therapy. Comorbidities such as PDA, BPD and NEC ≥ stage II were also more prevalent among the VLBW newborns who developed LOS.

About 27.8% of the infants in our sample with LOS did not obtain microbiological confirmation; consequently, according to our protocol, they were classified as "clinical sepsis" (Table 3). Moreover, 65.0% of those with microbiologically confirmed LOS were Gram positive, with *Staphylococcus epidermidis* being responsible for 55.4%. Among those found to be Gram negative, *Klebsiella pneumoniae* was the most frequent, which was observed (as were yeasts) in 10.8% of the cases.

Table 4 shows the linear regression model obtained for the LOS variable and the MDI at 14 months. This model is adjusted for the significant variables with a VIF of less than 5 to avoid effects of overfitting. No significant association between the variables was observed. Table 5 describes the linear regression model obtained for LOS and MDI at 25 months. MDI at 25 months and a history of LOS were significantly associated. This effect represents a decrease of 7.9 points in the evaluation of the MDI in VLBW newborns with a history of LOS.

A history of LOS is also associated with neurodevelopmental disorders such as mild motor disorders [odds ratio (OR): 2.75; 95% CI: 1.07–7.05], moderate cognitive delay (OR: 3.07; 95% CI: 1.17–8.00) and cerebral palsy (OR: 2.41; 95% CI: 1.09–5.35) (Table 6). The prevalence of neurodevelopmental alterations is not significantly different in LOS caused by Gram-positive or Gram-negative bacteria. The prevalence that a LOS caused by fungi/yeast is associated with any neurodevelopmental disorder is 66.6% (Table 7). The overall mortality rate due to infection was 10.8%, considering pathogens, mortality was 5.5% for Gram-positive bacteria, 15.0% for Gram-negative bacteria and 33.3% for yeasts/fungi.

TABLE 1. Baseline Clinical Variables for Newborns With and Without Bayley Test

Maternal Variables	Total (n = 546)	Bayley Test Result Known (n = 295)	Bayley Test Result Unknown (n = 251)	*P*
Weeks gestation (*)	30 (28–31)	30 (28–31)	29 (28–31)	0.351
Days parenteral nutrition (*)	10 (6–19)	12 (7–20)	8 (5–16)	0.006
Days central catheter (*)	0 (0–13)	1 (0–14)	0 (0–10)	0.001
Days assisted ventilation (*)	1 (0–5)	1 (0–5)	1 (0–5)	0.898
NEC ≥ stage II, n (%)	50 (9.0)	24 (8.1)	26 (10.1)	0.363
Late-onset sepsis, n (%)	103 (18.6)	66 (22.3)	37 (14.3)	0.330

*Interquartile range.

TABLE 2. Comparison of Clinical Variables Between VLBW Premature Newborns With and Without LOS

	Total (n = 546)	Late-onset Sepsis (n = 115)	No Late-onset Sepsis (n = 431)	*P*
Maternal variables				
GH, n (%)	59 (10.6)	14 (12.1)	45 (10.2)	0.578
Chorioamnionitis, n (%)	80 (14.5)	19 (16.5)	61 (13.9)	0.505
Antibiotics, n (%)	196 (35.5)	44 (38.2)	151 (34.5)	0.500
Glucocorticoids, n (%)	474 (85.8)	99 (86.0)	375 (85.8)	0.796
PROM, n (%)	127 (23.0)	29 (25.2)	98 (22.4)	0.551
Weeks gestation (*)	30 (27–31)	28 (26–30)	30 (28–31)	0.000
Gestation ≤ 27 weeks, n (%)	140 (25.3)	50 (43.4)	90 (20.5)	0.000
Multiple gestation, n (%)	224 (40.5)	38 (33.0)	186 (42.5)	0.055
Cesarean delivery, n (%)	418 (75.7)	92 (80.0)	326 (74.5)	0.275
Neonatal period				
Days in ICU (*)	24 (13–38)	45 (27–64)	21 (11–32)	0.000
Days parenteral nutrition (*)	10 (6–19)	22 (12–32)	9 (5–15)	0.000
Days central catheter (*)	8 (1–17)	18 (7–28)	6 (0–14)	0.000
CRIB score (*)	3 (1–6)	3 (1–6)	3 (1–6)	0.728
Male sex, n (%)	260 (47.1)	50 (43.4)	210 (48.0)	0.382
Apgar <5.5, n (%)	66 (11.9)	18 (15.6)	48 (10.9)	0.214
SGA, n (%)	107 (19.3)	26 (22.6)	81 (18.5)	0.361
Days assisted ventilation (*)	1 (0–5)	5 (1–17)	0 (0–3)	0.000
Days CPAP (*)	3 (1–6)	5 (2–16)	2 (1–5)	0.000
Days oxygen (*)	19 (5–44)	40 (14–63)	14 (4–38)	0.000
BPD, n (%)	194 (35.1)	70 (60.8)	124 (28.3)	0.000
PDA, n (%)	94 (17.0)	41 (35.6)	53 (12.1)	0.000
NEC ≥ stage II, n (%)	80 (14.4)	23 (20.0)	57 (13.0)	0.000
IVH (stage I–II), n (%)	64 (11.5)	19 (16.5)	45 (10.2)	0.058
IVH (stage III–IV), n (%)	37 (6.7)	12 (10.4)	22 (5.0)	0.027
Exitus, n (%)	63 (11.4)	12 (10.4)	51 (11.6)	0.710

*Interquartile range.

CPAP indicates continuous positive airway pressure; GH, gestational hypertension; ICU, intensive care unit; PROM, premature rupture of membranes; SGA, small for gestational age.

TABLE 3. Microbiology Results in Late Neonatal Infection

	LOS With Microbiologic Confirmation, n = 83	LOS No Microbiologic Confirmation
Gram-positive		
Staphylococcus epidermidis	46 (55.4%)	n = 32 (27.8%)
Staphylococcus aureus	3 (3.6%)	
Enterococcus faecalis	2 (2.4%)	
Staphylococcus hominis	1 (1.2%)	
Staphylococcus haemolyticus	1 (1.2%)	
Staphylococcus warneri	1 (1.2%)	
Gram-negative		
Klebsiella pneumoniae	9 (10.8%)	
Serratia marcescens	5 (6.0%)	
Pseudomonas aeruginosa	3 (3.6%)	
Escherichia coli	2 (2.4%)	
Enterobacter cloacae	1 (1.2%)	
Yeasts		
Candida albicans	7 (8.4%)	
Candida parapsilosis	1 (1.2%)	
Candida glabrata	1 (1.2%)	

TABLE 4. Linear Regression Model for the Dependent Variable MDI at 14 Months and LOS Adjusted for the Significant Predictor Variables

	Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
	Beta	SE	Beta	*t*	*P*	Tolerance	VIF
Constant	77.9	16.3		4.75	0.000		
LOS	0.413	2.513	0.12	0.164	0.870	0.808	1.238
Gestational age	0.429	0.519	−0.068	0.827	0.409	0.651	1.537
Parenteral nutrition	−0.384	0.161	−0.297	−2.380	0.018	0.280	3.573
Central catheter	0.026	0.158	0.019	0.164	0.870	0.332	3.015
NEC ≥ stage II	0.086	3.569	0.002	0.024	0.981	0.797	1.254

Dependent variable: Mental Development Index (MDI).

Beta indicates regression coefficient; SE, standard error.

TABLE 5. Linear Regression Model for the Dependent Variable MDI at 25 Months and LOS Adjusted for the Significant Predictor Variables

	Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
	Beta	SE	Beta	*t*	*P*	Tolerance	VIF
Constant	84.7	22.7		7.733	0.000		
LOS	−7.371	3.614	−0.179	−2.040	0.043	0.794	1.260
Gestational age	0.325	0.723	0.043	0.450	0.653	0.661	1.514
Parenteral nutrition	0.021	0.214	0.015	0.099	0.921	0.282	3.547
Central catheter	−0.246	0.197	−0.167	−1.252	0.213	0.344	2.909
NEC ≥ stage II	−3.475	4.738	−0.067	−0.733	0.464	0.736	1.358

Dependent variable: Mental Development Index (MDI).
Beta indicates regression coefficient; SE, standard error.

TABLE 6. Regression Analysis for Neurologic Disorders in VLBW Premature Children (Dependent Variable) and History of LOS

Neurologic Disorders	OR (95% CI) Nonadjusted	OR (95% CI) Adjusted*
Motor system disorder		
Mild	3.16 (1.34–7.44)†	3.17 (1.19–8.45)‡
Diparesia	1.20 (0.32–4.45)	0.46 (0.09–2.37)
Hemiparesia	4.42 (0.27–71.7)	3.31 (0.17–64.4)
Tetraparesia	7.38 (1.71–31.6)†	2.93 (0.55–15.4)
Visual disorder	2.49 (1.39–4.46)†	1.63 (0.83–3.22)
Auditory disorder	0.75 (0.30–1.84)	0.45 (0.13–1.49)
Cognitive delay		
Mild	1.58 (0.92–2.73)	1.25 (0.69–2.24)
Moderate	3.60 (1.49–8.69)†	3.07 (1.17–8.00)‡
Severe	5.05 (1.21–21.0)‡	2.92 (0.62–13.7)
Behavioral disorder	1.67 (0.91–3.05)	1.56 (0.82–2.99)
Multiple deficiency	1.81 (0.71–4.61)	1.08 (0.38–3.03)
Cerebral palsy	3.40 (1.67–6.92)§	2.41 (1.09–5.35)‡
Epilepsy	2.44 (0.97–6.11)	1.67 (0.61–4.57)

Follow-up at 25 months of age.
*Adjusted for gestational age and NEC ≥ stage II.
†$P \leq 0.01$.
‡$P < 0.05$.
§$P < 0.001$.

DISCUSSION

According to our study results, LOS is associated with alterations in neurodevelopment, with a decrease in MDI at the age of 20–28 months, moderate cognitive delay and cerebral palsy. A history of early or late neonatal sepsis has been associated with neurodevelopmental alterations.[10,23] In our study, after excluding cases of early neonatal sepsis, LOS was found to be associated with twice as much cerebral palsy and 3 times more cases of moderate cognitive delay. A systematic review of 17 studies of VLBW neonates with neonatal sepsis concluded that these neonates have twice the risk of neurodevelopmental impairment compared with their counterparts without sepsis.[24] As reported by Hentges et al[25] in our study lower GA and duration of hospital stay were the main risk factors for LOS.

Corroborating our findings, Shim et al[10] observed cognitive delay at 24 months in VLBW premature infants with a history of LOS. LOS was most frequently associated with severe IVH or periventricular leukomalacia. Similarly, our study shows a higher prevalence of IVH stage III–IV among VLBW newborns with a history of LOS, among whom the MDI at 24 months is significantly lower. The association of a history of LOS and alterations in neurodevelopment has been reported by various authors who relate it to the systemic inflammatory response produced.[3] In line with Shim et al,[10] we observed a significantly longer stay in the NICU and duration of mechanical ventilation among the newborns with sepsis. The frequencies of comorbidities such as IVH ≥ stage III, BPD and NEC ≥ stage II were also higher in the group with late sepsis. Prenatal characteristics related to the frequency of vertically transmitted early sepsis, such as chorioamnionitis or antibiotic therapy before delivery, did not vary significantly between children with or without LOS. Although some authors[26,27] report that a history of chorioamnionitis may have a protective effect against the development of LOS, this was not confirmed in our study.

Kiechl-Kohlendorfer et al[28] reported that children who developed neonatal sepsis were 3 times more likely to have alterations in neuromotor and cognitive development (MDI < 85) at 12 months of corrected age. Schlapbach et al[29] evaluated a cohort of premature newborns at 24 months of corrected age. This cohort included 136 infants with confirmed sepsis, 169 with sepsis but without microbiological confirmation and 236 without infection. The children with confirmed sepsis were found to be 3 times more likely to present cerebral palsy than those without sepsis. This observation is in line with our own findings.

With respect to a cohort of 2665 VLBW premature newborns, Mitha et al[30] performed a neuropsychological evaluation of 2277 children at 5 years of age. The authors observed that

TABLE 7. Neurologic Alterations Observed Depending on Whether the LOS Is Caused by Gram-positive, Gram-negative or Fungi/Yeast

	Gram Positive (n = 54)	Gram Negative (n = 20)	Fungi/Yeast (n = 9)	*P*
Motor system disorder, n (%)	12 (22.2)	4 (20.0)	2 (22.2)	0.978
Cerebral palsy, n (%)	10 (18.5)	3 (15.0)	3 (33.3)	0.497
Visual disorder, n (%)	14 (25.9)	4 (20.0)	3 (33.3)	0.723
Auditory disorder, n (%)	3 (5.5)	2 (10.0)	0 (0)	0.498
Cognitive delay, n (%)	24 (44.4)	6 (30.0)	6 (66.6)	0.176
Behavioral disorder, n (%)	7 (12.9)	5 (25.5)	2 (22.2)	0.424
Multiple deficiency, n (%)	4 (7.4)	1 (5.0)	2 (22.2)	0.273
Epilepsy, n (%)	3 (5.5)	2 (10.0)	2 (22.2)	0.239
Any neurologic alteration, n (%)	26 (48.1)	9 (45.0)	6 (66.6)	0.532

neonatal infections were associated with an increased risk of cerebral palsy at 5 years of age, particularly when both early and late neonatal sepsis were present. Although our study evaluated only newborns with LOS, our findings are in line with those reported by Mitha et al. However, the latter authors did not observe an association between neonatal infection and cognitive impairment, in contrast to our findings in the neuropsychological evaluation at 24 months.

O'Shea et al[31] studied the impact of proinflammatory proteins on neurodevelopment, finding that elevated levels of inflammation-related proteins were associated with attention problems at the age of 2 years.

S. epidermidis is the most frequently observed etiology in late neonatal sepsis. Hentges et al[25] reported that the presence of Gram-positive infection generated a 6-fold increased risk of motor deficit in this population of VLBW newborns, perhaps (at least partly) because this infection is observed in more than half of the cases of LOS. In the present study, LOS was observed in 20.8% of the VLBW premature newborns, a proportion similar to that reported in previous studies,[29] and with a predominance of Gram-positive organisms (65.0%). These findings align very closely with those obtained in a large study conducted by the Neonatal Research Network of the National Institute of Child Health and Human Development, according to which 70% of infections were caused by Gram-positive bacteria.[32] Unlike those reported by Hentges et al,[25] in our study, we did not observe a higher prevalence of alterations in neurodevelopment in newborns with LOS due to Gram-positive bacteria.

The main limitation of our study is that of its retrospective nature, together with the relatively high number of children whose neuropsychological evaluation could not be recovered. We are aware that this circumstance poses a certain risk of bias in the selection of patients. Nevertheless, the comparative analysis performed of known risk factors for LOS indicates that the 2 groups of children are comparable and consequently that the sample studied is representative of the whole cohort of VLBW children.

In view of the above considerations, we conclude that LOS is associated with alterations in neurodevelopment, decreased MDI, motor and cognitive disorders and cerebral palsy. Particular attention in the NICU aimed at preventing hospital-acquired infections will improve neurodevelopmental outcomes in this group of newborns.

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