The value of clinical examination in preterm newborns after neonatal sepsis: a case control study.

Marina Ortega Golin (maortegagolin@gmail.com)
Faculdade de Medicina do ABC
Fabíola Isabel Suano Souza
Faculdade de Medicina do ABC
Laércio da Silva Paiva
Faculdade de Medicina do ABC
Roseli Oselka Sacardo Sarni
Faculdade de Medicina do ABC

Research article

Keywords: Neonatal sepsis, Neurological examination, Infant premature

Posted Date: February 25th, 2020

DOI: https://doi.org/10.21203/rs.2.24423/v1

Abstract

Background

Neonatal sepsis is an important risk factor for lesions in the white matter of the brain of preterm newborns (PTNB) and the most effective strategies to minimize its deleterious effects are early detection and intervention. However, no studies were found to analyze the neurological behavior of PTNBs with neonatal sepsis. Thus, the objective of the present study was to investigate the presence of neurological abnormalities in PTNBs, after neonatal sepsis, by neonatal clinical evaluation.

Methods

This is a prospective cross-sectional study with 100 PTNBs selected at random, 50 of the study group (sepsis) and 50 of the control group (non-sepsis) of the university municipal hospital. PTNBs were evaluated at adjusted gestational age (37 to 42 weeks). The neurological evaluation protocol adopted was the Hammersmith Neonatal Neurological Examination (HNNE), which consists of 34 items grouped into six categories. Statistical analysis: Statistical analysis was performed using the Chi-square, Mann-Whitney and Binary Logistic Regression tests using the assumption of each statistical test. The statistical program used was Stata version 11.0.

Results

The PTNBs of the sepsis group had total HNNE scores lower than expected for normality in 86% of the cases, and the non-sepsis group in 26% ($p<0.001$). Higher prevalence levels of altered scores in tone category ($p<0.001$), tone patterns ($p=0.026$), reflexes ($p=0.002$), movements ($p<0.001$), abnormal signs ($p<0.001$) and behavior ($p<0.001$), were also found in the sepsis group, as well as in 26 of the 34 evaluation items.

Conclusion

The preterm neonatal sepsis showed significant frequency of neurological alterations. Thus, it is concluded that neurological dysfunctions in preterm newborns after neonatal sepsis can be identified by clinical neonatal neurological evaluation.

Introduction

Neonatal sepsis can be defined as a clinical syndrome resulting from the invasion of microorganisms in the bloodstream during the first month of life. Its incidence is high in preterm newborns (PTNB), with up to 30 per 1,000 live births.[1]

Scientific evidence suggests a notable contribution to the mechanism of neurological dysfunction in PTNBs[2, 3]. Since the systemic inflammatory response is a significant risk factor for white matter lesions that are characterized by cystic periventricular leukomalacia (PVL).[4, 5] Several clinical studies have

established through neuroimaging the association between neonatal infections and brain axonal lesions in PTNBs.[2, 6–9]

This neuronal damage may result in neurodevelopmental impairment in these children. Two meta-analyses have shown that children born prematurely with sepsis records have worse rates of intellectual and motor development, higher incidence of Cerebral Palsy (CP), visual and auditory dysfunctions.[10, 11]

However, it is a consensus in the literature that the earlier intervention in these cases, the higher the ability to minimize them, due to neuronal plasticity.[12] In this context, the importance of detecting neonates with neurological abnormalities is evident. Clinical evaluation remains the primary choice among several tools for this purpose.[13]

Among several methods of neonatal neurological evaluation, we highlight that of Dubowitz, later also known as the Hammersmith Neonatal Neurological Examination (HNNE).[14] This method was validated for PTNBs[14] and continues to be used in scientific research.[15]

The scientific literature emphasizes its predictive power of development in PTNBs, as in two Finnish studies, one with 216 children, in which the HNNE results were significantly associated with sensorimotor performance at the age of 2 years [12], and another with 98 participants, in which abnormalities in the early evaluation were predictors of neuromotor dysfunctions at the age of 11 years.[16]

Thus, the relationship between neonatal sepsis and lesions in the cerebral white matter of PTNBs, with resulting damages to neurodevelopment, has already been established, as well as the relevance of early identification of those who require follow-up and the validity of neonatal neurological evaluation for this purpose. However, no studies were found to analyze the neurological behavior of PTNBs with neonatal sepsis.

Thus, this study aimed to investigate the presence of neurological abnormalities in preterm infants after sepsis by the neonatal clinical evaluation.

Methods

This is a prospective cross-sectional study. The sample of 100 participants was obtained consecutively.

The population of the study group (sepsis group) consisted of 50 PTNBs after sepsis diagnosis. The control group (non-sepsis group) consisted of 50 low-risk PTNBs assessed for neurological dysfunctions and with no records of sepsis in medical records.

The participants were hospitalized in the Neonatal Intensive Care Unit (ICU) and in the nursery or monitored at the preterm follow-up outpatient clinic at the University Municipal Hospital of São Bernardo do Campo, São Paulo, Brazil, a teaching hospital of the ABC Faculty of Medicine (FMABC). The project was approved by the Research Ethics Committee of the FMABC under opinion nº 1.357.613/2015. Those

responsible were approached personally, they agreed to participate in the survey and signed the Informed Consent Form before the evaluation.

Inclusion criteria for the non-sepsis group consisted of gestational age at birth up to 36 weeks, age equivalent to term birth at the time of assessment (between 37 and 42 weeks), absence of records of sepsis or neonatal asphyxia, Apgar score of the 5th minute ≥ 7 and normal cranial ultrasound or showing only minimal abnormalities. The same criteria were adopted for the composition of the sepsis group, except for the need for cranial ultrasound without significant abnormalities, and the clinical-laboratory diagnosis of neonatal sepsis recorded in the chart was determinant, since the sample was obtained by consulting medical records.[18, 19]

The exclusion criteria for both groups were the presence of congenital malformations, congenital infections of the Nervous System or genetic syndromes; use of mechanical ventilation, sedation or be in septic shock at the time of evaluation.

PTNBs' birth weight was classified as low weight (LW) (< 2500 g), very low weight (VLW) (< 1500 g) and extremely low weight (ELW) (< 1000 g). The expected weight for gestational age (GA) was classified by Intergrowth 21.[17] Gestational age at birth was classified by service neonatologists as per one of the criteria: date of last menstrual period (LMP) in three cases, gestational ultrasound in three cases, and objective evaluation calculated by the New Ballard method in 94 cases.

The diagnosis of sepsis was given by the medical staff of the hospital in question. Neonatal sepsis was considered in the presence of a positive blood culture and/or clinical and laboratory signs suggestive of infection. [18] Clinical signs included worsening of respiratory distress: tachypnea, sternal and/or subcostal retraction, groaning and cyanosis, apnea, body temperature instability, hyper- or hypoglycemia, poor peripheral perfusion, food intolerance, arterial hypotension, and underactive infants.[18]

Laboratory parameters included: complete blood count with three or more altered parameters according to Rodwell et al [19] and/or C-reactive protein > 0.5 mg/dL; negative or not performed blood culture; no evidence of infection at another site; and established and maintained antimicrobial therapy. Rodwell et al[19] considered the following hematological parameters: leukocytosis (white blood cells [WBC] ≥ 25,000 at birth, or ≥ 30,000 between 12 to 24 hours, or > 21,000 at over 48 hours of life), leukopenia (WBC ≤ 5,000); neutrophilia or neutropenia; increased number of immature neutrophils; increased neutrophilic index; ratio of immature over segmented neutrophils ≥ 0.3; neutrophils with toxic granulation and vacuolization; and thrombocytopenia Neonatal sepsis: risk factor for development 295 (< 150,000 platelets).

The classification of sepsis into early and late followed the national criteria for diagnosis in neonatology. Early sepsis was one recorded within the first 48 hours of life, and late, one recorded after that period.[18]

The neurological evaluation protocol adopted was HNNE[23], since it is validated for preterm infants, it does not require formal certification or training, is short of application and has a self-explanatory guide to

the achievement and scoring of each item.[13] Especially for its predictive power of neurodevelopment and its sensitivity in identifying clinical neurological abnormalities in preterm infants with brain lesions on imaging exams. [12, 16]

The HNNE consists of 34 items grouped into six categories: tone (ten items), tone patterns (five items), reflexes (six items), movements (three items), abnormal signs (three items) and behavior (seven items). It consists of a diagram with scores, and each item has three to five options that consider the expected responses to normality at the ages between 37 and 42 gestational weeks at the time of evaluation. The composition of the scores is calculated by adding all of the items within each category. The following scores are assigned as per the answer obtained in each item - normal, intermediate or altered: 1, 0.5 and 0, respectively. The range of normality of the total score varies from 30.5 to 34, scores below these levels are considered as modified. The normal scores for the categories are as follows: tone (9–10), tone patterns (5), reflexes (4–6), movements (3), abnormal signs (3) and behavior (6–7).

The neurological evaluations were performed on the PTNBs when they reached corrected gestational age, between 37 and 42 weeks, as validated by the same evaluator.

At the time of the evaluation, among the sepsis group PTNB, 47 remained hospitalized and three under follow-up at the preterm follow-up outpatient clinic. While in the group no sepsis, only four remained hospitalized. The hospitalized preterm infants were clinically stable, did not use respiratory support, participated in the Kangaroo Method and were in the preparation phase for hospital discharge.

Statistical Analysis

In the analysis of the results, the qualitative variables were shown by absolute and relative frequency and the quantitative ones by the median, 25th and 75th percentile values and respective 95% confidence intervals, according to the Shapiro-Wilk normality test, with $p < 0.05$.

The chi-square test was used to compare and associate the classifications of the total scores, and in each category of the assessment obtained by the sepsis and non-sepsis groups, as well as to compare the scores classifications obtained by PTNBs with early and late sepsis, clinical and verified sepsis and those developing septic shock or not. The Bonferroni correction was performed to verify the applicability conditions. The Mann-Whitney test was used to compare the values of the scores in the categories and totals.

The Chi-square test (qualitative variables) and the Mann-Whitney test (quantitative variables) were used to identify the association between the other factors and the total score in the sepsis group.

The Enter method logistic binary regression was used to evaluate the effect of neonatal sepsis on the clinical neurological alterations of PTNBs. All analyses were performed in the statistical software Data Analysis and Statistical Software for Professionals (Stata) version 11.0® and p-values below 0,05 were considered as statistically significant.

A convenience study sample was used with 100 preterm infants, and the effect size was calculated later. For this, the Cohen's d test was used, with a value of 1.74 (95% CI: 1.28; 2.20). The power of the test was 1.00.

Results

Table 1 shows the maternal characteristics and the studied PTNBs.

Table 1
Comparison of maternal characteristics and stratified PTNB by presence or absence of neonatal sepsis.

Characteristics	**Sepsis (n = 50)**	**Non-sepsis (n = 50)**	**p***
	n(%)		
MATERNAL			
Habits			
Smoking	7 (14)	11 (22)	0.298
Alcoholism	4 (8)	2 (4)	0.400
Illicit drugs	2 (4)	0 (0)	0.153
Schooling			0.007
≤ 8 years	5 (10)	4 (8)	
8–12 years	15 (30)	15 (30)	
= 12 years	14 (28)	27 (54)	
> 12 years	7 (14)	4 (8)	
Not informed	9 (18)	0 (0)	
Use of medication	27 (54)	20 (40)	0.161
Corticosteroid	18 (36)	6 (12)	0.005
Anti-hypertensive	10 (20)	9 (18)	0.799
Antibiotic	16 (32)	12 (24)	0.373
Gestational diseases			
Maternal infection	27 (54)	19 (38)	0.108
Maternal hypertension	19 (38)	13 (26)	0.198
Other	2 (4)	12 (24)	0.004
Type of delivery			0.523
Normal	21 (42)	18 (36)	
Cesarean	29 (58)	31 (62)	
Captions: PIVH (peri-intraventricular hemorrhage). PL (periventricular leukomalacia).			
* Chi-square test level of significance. ** Mann-Whitney test level of significance			

Characteristics	Sepsis (n = 50)	Non-sepsis (n = 50)	p*
Forceps	0 (0)	1 (2)	
PTNB Median (IR) p**			
Gestational age at birth	31.22 (24–36)	34.76 (30–36)	< 0.001
Birth weight	1419 (550–2300)	2007(1250–2470)	< 0.001
Gestational age at assessment	38.90 (37-42.57)	38.8 (37–42)	0.004
Twinning	n (%)		p*
Yes	12 (24)	11 (22)	0.500
Weight classification			< 0.001
Low weight	26 (52)	43 (86)	
Very low weight	14 (28)	7 (14)	
Extremely low weight	10 (20)	0 (0)	
Weight / Gestational Age Classification			0.517
Adequate	33 (66)	36 (72)	
Small	17 (34)	14 (28)	
Large	0 (0)	0 (0)	
Neonatal intercurrences	50 (100)	35 (70)	
Jaundice	24 (48)	26 (52)	0.532
Respiratory	45 (90)	26 (52)	
Respiratory distress syndrome	23 (46)	6 (12)	< 0.001
Respiratory distress	21 (42)	20 (40)	0.839
Pulmonary hypertension	4 (8)	0 (0)	0.041
Pneumomediastinum	0 (0)	1 (2)	0.315
Pneumothorax	4 (8)	0 (0)	0.041
Laryngomalacia	0 (0)	1 (2)	0.315

Captions: PIVH (peri-intraventricular hemorrhage). PL (periventricular leukomalacia).

* Chi-square test level of significance. ** Mann-Whitney test level of significance

Characteristics	Sepsis (n = 50)	Non-sepsis (n = 50)	p*
Chronic lung disease	14 (28)	0 (0)	< 0.001
Heart-related	30 (60)	5 (10)	
Persistent oval foramen	28 (56)	3 (6)	< 0.001
Interventricular communication	2 (4)	0 (0)	0.153
Neurological	6 (12)	0 (0)	
Seizure	5 (10)	0 (0)	0.022
Meningitis	1 (2)	0 (0)	0.315
Ultrasound Scanner	50 (100)	14 (28)	< 0.001
Normal	9 (18)	42 (84)	< 0.001
PIVH I	13 (26)	5 (10)	
PIVH II	20 (40)	3 (6)	
PIVH III	5 (10)	0 (0)	
PL	3 (6)	0 (0)	
Respiratory support	45 (90)	14 (28)	< 0.001
Invasive Ventilation	37 (74)	1 (2)	< 0.001
Non-invasive	41 (82)	5 (10)	< 0.001
Oxygen therapy	31 (62)	10 (20)	< 0.001
Captions: PIVH (peri-intraventricular hemorrhage). PL (periventricular leukomalacia).			
* Chi-square test level of significance. ** Mann-Whitney test level of significance			

The prenatal examination was performed in 48 mothers (96%) of the sepsis group and 49 (98%) of the non-sepsis group (p = 0.812). Premature rupture of membranes was found in 40% of the mothers in the sepsis group and 28% in the non-sepsis group (p = 0.445). The median of its duration was 57.94 hours (0-576) in the former and 4.42 (0–99) in the latter (p = 0.002).

Regarding the characteristics of PTNBs, the proportion of females in the sepsis group was 50% and 56% (p = 0.548) in the non-sepsis group. Surfactants were administered to 62% and 38% of PTNBs in the sepsis and non-sepsis group, respectively (p < 0.001). All participants in the sepsis group underwent antibiotic therapy, with a median duration of 18.6 days (7–84) and only one in the non-sepsis group followed this course for 13 days, due to respiratory infection (p < 0.001).

Regarding the diagnosis of sepsis, 41 had clinical sepsis and 9 had proven sepsis. And regarding the classification, 27 developed early sepsis, 6 developed late sepsis and 17 developed early and late sepsis.

The hemoculture examination was performed in 84%, and was positive only 9%. The infectious agents detected were Gram-positive in 1, Streptococcus b in 1, Bacillus gram negative + Klebsiella pneumoniae in 1, Escherichia coli in 3, Escherichia coli + Enterococcus faecalis in 1 and Escherichia coli + Bacillus gram-negative in 1.

In the HNNE neurological evaluation, the sepsis group had a higher percentage of inadequacy for all the categories evaluated (Table 2). Table 3 shows that the sepsis group had significantly altered scores in 26 of the 34 evaluation items. The median total score was 22 (20–24) in the sepsis group and 32 (31.26-33) in the non-sepsis group ($p < 0.001$).

Table 2. Ratio of modified scores in HNNE neurological assessment and total in PTNBs.

	Sepsis (n = 50)	**Non-sepsis (n = 50)**	**p***
	n (%)		
Categories			
Tone	39 (78)	10 (20)	< 0.001
Tone patterns	34 (68)	23 (46)	0.026
Reflexes	13 (26)	2 (4)	0.002
Movements	43 (86)	16 (32)	< 0.001
Abnormal signs	19 (38)	3 (6)	< 0.001
Behavior	27 (54)	4 (8)	< 0.001
Total Score	43 (86)	13 (26)	< 0.001
* Chi-square test level of significance			

Table 3. Ratio of modified scores on items of the HNNE neurological assessment in PTNBs.

Items of the assessment	Sepsis (n = 50)	Non-sepsis (n = 50)	p*
	n (%)		
Posture	9 (18)	6 (12)	0.401
Arm recoil	20 (60)	3 (6)	< 0.001
Arm traction	27 (54)	9 (18)	< 0.001
Leg recoil	22 (44)	9 (18)	0.005
Leg traction	20 (40)	4 (8)	< 0.001
Popliteal angle	17 (34)	4 (8)	0.001
Head control 1	22 (44)	3 (6)	< 0.001
Head control 2	16 (32)	1 (2)	< 0.001
Head lag	21 (42)	3 (6)	< 0.001
Ventral suspension	22 (44)	6 (12)	< 0.001
Flexor tone 1	3 (6)	0 (0)	0.079
Flexor tone 2	2 (4)	1 (2)	0.558
Leg extensor tone	10 (20)	14 (28)	0.349
Neck extensor tone	22 (44)	6 (12)	< 0.001
Increased extensor tone	19 (38)	8 (16)	0.013
Tendon reflex	25 (50)	1 (2)	< 0.001
Suck / gag	15 (30)	2 (4)	0.001
Palmar grasp	15 (30)	0 (0)	< 0.001
Plantar grasp	17 (34)	7 (14)	0.019
Moro reflex	12 (24)	7 (14)	0.202
Placing	5 (10)	7 (14)	0.538
Spontaneous movements 1	19 (38)	3 (6)	< 0.001
Spontaneous movements 2	38 (76)	6 (12)	< 0.001
Head raising prone	31 (62)	13 (26)	< 0.001
Abnormal hand or toe postures	8 (16)	2 (4)	0.046

*Chi-square test level of significance.

Items of the assessment	Sepsis (n = 50)	Non-sepsis (n = 50)	p*
Tremor	12 (24)	2 (4)	0.004
Startle	5 (10)	1 (2)	0.092
Eye movements	9 (18)	2 (4)	0.025
Auditory orientation	9 (18)	0 (0)	0.002
Visual orientation	30 (60)	12 (24)	< 0.001
Alertness	20 (40)	1 (2)	< 0.001
Irritability	19 (38)	3 (6)	< 0.001
Cry	18 (36)	6 (12)	0.005
Consolability	4 (8)	2 (4)	0.400
*Chi-square test level of significance.			

Logistic binary regression was performed to evaluate the effect of sepsis, adjusted for maternal variables (schooling and antenatal corticosteroid use) and variables of PTNBs (birth weight, gestational age, neonatal respiratory diseases and neurological diseases), on the probability of inadequate total neurological evaluation score. PTNBs were 7.08 (95% CI 2.13–23.53, p = 0.001) times more likely to have an inadequate neurological evaluation score, compared to those without this condition (Table 4).

Table 4. Logistic binary regression evaluating the effect of neonatal sepsis on clinical neurological alterations of PTNBs.

Variables	B	S.E.	Wald	Df	p	Odds ratio	(IC 95%)
Sepsis	1.96	0.61	10.2	1	0.001	7.08	(2.13; 23.53)
Schooling	-0.37	0.56	0.44	1	0.507	0.68	(0.22; 2.07)
Corticosteroid	-0.53	0.75	0.50	1	0.477	0.58	(0.13; 2.54)
Birth weight	-0.07	0.79	0.00	1	0.927	0.92	(0.19; 4.44)
Gestational age	1.17	0.78	2.20	1	0.137	3.23	(0.68; 15.16)
Respiratory disease	0.53	0.59	0.80	1	0.369	1.70	(0.53; 5.45)
Neurological disease	0.53	0.84	0.40	1	0.523	1.71	(0.33; 8.87)
* Dependent variable: inadequacy of total neurological score							
* Independent variables: sepsis (yes), schooling (< 12 years), use of antenatal corticosteroids (yes), birth weight (< 1500 grams), gestational age (< 32 weeks), neonatal respiratory diseases (yes), neurological diseases (yes: meningitis, seizure or periventricular/intraventricular hemorrhage (PIVH) grade III, IV and V) β: inclination, S.E: standard error, DF: degree of freedom, IC95%: Intervalo de confiança de 95%.							

When comparing the HNNE categories' score, taking into account the proven sepsis and clinical groups, there was no statistically significant difference for tone (p = 0.384), tone patterns (p = 0487), reflexes (p = 0.580), movements (p = 0.181), abnormal signs (p = 0.066) and behavior (p = 0.400) and neither for the total scores (p = 0.783). Between groups early and late sepsis, a more significant percentage of inadequacy for "movements" (p = 0.031) and "behavior" (p = 0.011) was found in the late sepsis group. For the other variables, no significant differences were observed: tone (p = 0.093), tone patterns (p = 0.062), reflexes (p = 0.089), abnormal signs (p = 0.113) and totals (p = 0.181).

No significant differences were found when comparing the performance in the evaluation of PTNBs with sepsis that progressed to septic shock or not. The following p-values were found in the following categories: tone (p = 0.242), tone patterns (p = 0.725), reflexes (p = 0.503), movements (p = 0.595), abnormal signs (p = 0.899) and behavior (p = 0.967) and in the total scores (p = 0.595).

Discussion

In this study, PTNBs who developed sepsis in the neonatal period had a higher prevalence of abnormalities in neurological behavior detected by HNNE. Among the 50 participants in the sepsis group, 43 (86%) underperformed for normality. This group showed significant proportions of changes in all categories of the evaluation, as well as in most of its items.

To date no studies describing the neurological performance of PTNBs with neonatal sepsis to enable comparative analysis are available. However, two national studies investigating possible risk factors for neurological lesions in the neonatal period found an association between the presence of sepsis and

abnormalities in the HNNE assessment [20, 21] In the first one, consisting of 30 PTNBs, the only factor associated with abnormalities in the evaluation was the presence of sepsis.[20] In the second study, with 20 PTNBs, 83.3% of PTNBs with neonatal infections had below-normal scores.[21]

The frequent neurological abnormalities found in PTNBs after a septic episode are due to the systemic inflammatory response associated with the extreme vulnerability of the developing brain in the neonatal period.[5] The lesion mechanism begins with increased pro-inflammatory cytokines, which easily cross the blood-brain barrier, striking the glial cells, causing hypomyelination and possible cerebral white matter lesions, besides inducing neuronal apoptosis and impairing differentiation of neurons and cerebral blood flow, favoring the occurrence of ischemic and hemorrhagic events.[2, 4]

Clinical studies with neuroimaging evidence brain lesions in these PTNBs. One British study with 117 participants[22] and another Australian study, with 192[6] individuals found a significant association of white matter lesions detected by Neuromagnetic Resonance Imaging (NMRI) and neonatal sepsis. Also, a multicenter study with 32 centers from several countries and a sample of 910 PTNBs reaffirms these findings, since it found an association between neonatal infections and brain lesions seen in the cranial ultrasound exam.[7]

Similar to the motivation of this study, many investigations in the last decades have been devoted to evaluating the presence of neurological abnormalities resulting from neonatal sepsis. Neurodevelopmental disorders were noted in these children with a history of sepsis had significant proportions of neuromotor, cognitive, attention deficit and hyperactivity disorders.[23–24]

Here, no differences were found in the neurological performance of PTNBs with sepsis identified by clinical parameters and confirmed by positive hemoculture. In both cases, the losses were evident. This is in agreement with other publications using neuroimaging, which found lesions in the cerebral white matter in both sepsis conditions[22], and these were also identified as the main isolated risk factors for minor neurological dysfunctions, between four and six years of age.[25] This is because axonal tracts are more affected by the systemic inflammatory process rather than infectious agents itself.[5]

However, the PTNBs with late sepsis had worse performances in the HNNE movements and behavior categories, with significant results and with a tendency to the significance of tone, tone patterns and reflexes. The prominent role of this type of sepsis in neurological dysfunctions was evidenced by a French developmental follow-up study, consisting of 139 PTNBs, which compared the frequency of CP at five years of age among those with early and late sepsis. The latter had a greater significant association with this type of motor dysfunction. Possibly, its contribution to worse outcomes is related to the fact that this type increases the presence of associated morbidities (hypotension, disseminated intravascular coagulation, chronic lung disease, and severe PIVH).[26]

Studies have shown that changes in the categories movements (assesses the quantity and quality of spontaneous movements and the ability to raise head in prone) and behavior (assesses auditory and

visual orientation, alertness, irritability, cry and consolability) are associated with abnormalities on magnetic resonance imaging at term and neuromotor outcome at the age of 11 years. [27, 16] In the study by Brown et al (2009), changes in the movements and behavior categories showed greater associations with white matter abnormalities at term, respectively. [27] And in the one performed by Setänen et al (2016), the category that best predicted neurological status at 11 years of age was behavior. [16]

In this study, gestational ages and birth weight were significantly lower in the sepsis group, possibly because they were risk factors for the development of sepsis in the neonatal period.[3, 28] This fact could constitute a bias, influencing the results. However, gestational ages at birth were not associated with the presence of neurological lesions in our study, since 26 out of 50 preterm newborns in the sepsis group had gestational ages greater than 31 weeks. This data that is in agreement with the results of studies showing that neurological sequelae are not present only in extreme but also in moderate and late PTNBs. [3, 29]

The clinical evaluation of HNNE was effective in the detection of neurological alterations. Its predictive power for neurodevelopmental dysfunctions has been emphasized since the publication of its first version in 1981, even in more recent papers.[12, 16]

All HNNE categories had a higher frequency of abnormalities in the sepsis group, but the categories of tone, movements, abnormal signs and behavior were even more significant compared to the non-sepsis group. In a developmental follow-up study, abnormalities in the tone patterns, tone and behavior categories correlated with sensorineural dysfunctions at the age of two years.[12] Another study also found an association of changes in the behavior categorie with the presence of CP at 11 years of age. These data reinforce the long-term neurological impairment of neonatal sepsis.[16]

To apply HNNE, the PTNBs should reach corrected gestational age, that is, 37 weeks. During the data collection period of this study, most individuals in the non-sepsis group had already been discharged from the hospital and performed longitudinal follow-up at the outpatient clinic at the time of the evaluation, while most of the members of the sepsis group were still hospitalized in the ICU or medium-risk unit. This may be one of the limitations of this study since the literature indicates that the hospitalization environment may contribute to worse rates in the neurological evaluation.[15]

The other limitations of the present study are the differences found between the characteristics of the groups, especially regarding weight and gestational ages at birth, presence of respiratory complications, transfontanel ultrasound abnormalities and low rate of positive bacterial cultures in the group with sepsis.

It was evidenced that children born prematurely and who developed a septic condition in the neonatal period require longitudinal monitoring of neurodevelopment since the probability of dysfunction is high, and only early intervention can minimize its deleterious effects.[29]

Finally, it can be inferred that it is possible to detect neurological abnormalities due to sepsis from the neonatal period. Even if such occurrences are transient and the milder manifestations can progress to resolution by the second year of life[13], follow-up studies showed that children with long-term dysfunctions already had alterations in HNNE.[30, 31, 12]

Conclusion

PTNBs with neonatal sepsis evidenced unfavorable clinical changes in neurological evaluations by HNNE. As no factors associated with these abnormalities were detected, the clinical neurological evaluation can suggest that the presence of sepsis in PTNBs may played a prominent role in the etiology of neurological dysfunctions.

Thus, we can conclude that neurological dysfunctions in preterm newborns after neonatal sepsis can be identified by clinical neonatal neurological evaluation.

Abbreviations

CP: Cerebral Palsy

ELW: extremely low weight

FMABC: The ABC Faculty of Medicine

GA: gestational age

HNNE: Hammersmith Neonatal Neurological Examination

LM: last menstrual period

LW: low weight

NMRI: neuromagnetic resonance imaging

PIVH: periventricular/intraventricular hemorrhage

PTNB: preterm newborns

PVL: periventricular leukomalacia

VLW: very low weight

WBC: white blood cells

Declarations

Ethics approval and consent to participate: The project was approved by the Research Ethics Committee of the ABC Faculty of Medicine (FMABC), Santo André / SP, Brazil, under opinion nº 1.357.613/2015. The parents were approached personally, they agreed to participate in the survey and signed the Informed Consent Form before the evaluation.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: There was no funding.

Authors' contributions:

1. Golin MO:Their participation was present at all stages of the study, including data collection. 2. Souza FIS: Co-coordinator of the research. She assisted in all stages of the study. 3. Paiva LS: He assisted in the stages of data writing and analysis. 4. Sarni ROS: Research coordinator. She assisted in all stages of the study.

Acknowledgements: Special acknowledgements to all staff at University Municipal Hospital of São Bernardo do Campo, São Paulo, Brazil.

Authors' information (optional): The information can be found on the cover page.

References

[1] Carvalho JK, Moore DB, Luz RA, Xavier-Elsas PP, Gaspar-Elsas MIC. Prediction of sepsis-related outcomes in neonates through systematic genotyping of polymorphisms in genes for innate immunity and inflammation: a narrative review and critical perspective. Sao Paulo Med J 2013;131(5):338-50.

[2] Chau V, Brant R, Poskitt KJ, Tam EW, Synnes A, Miller SP. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. Pediatr Res 2012;71:274-279.

[3] Strunk T, Inder T, Wang X, Burgner D, Mallard C, Levy O. Infection-induced inflammation and cerebral injury in preterm infants. The Lancet infect Dis 2014;14:751-762.

[4] Kuypers E, Ophelders D, Jellema RK, Kunzmann S, Gavilanes AW, Kramer BW. White matter injury following fetal inflammatory response syndrome induced by chorioamnionitis and fetal sepsis: Lessons from experimental ovine models Early Hum Dev 2012;88:931-936.

[5] Patra A, Huang H, Bauer JA, Giannoneet PJ. Neurological consequences of systemic inflammation in the premature neonate. Neural Regen Res J 2017;12(6):890-896.

[6] Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr 2008;153(2): 170 –175.

[7] Bassler D, Stoll BJ, Schmidt B, Asztalos EV, Roberts RS, Robertson CM, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. Pediatrics 2009;123:313-318.

[8] Helderman JB, Welch CD, Leng X, O'Shea MT. Sepsis-associated electroencephalographic changes in extremely low gestational age age neonates. Early Hum Dev 2010;86:509-513.

[9] Martin CR, Dammann O, Allred EN, Patel S, O'Shea TM, Kuban KC, et al. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. J Pediatr 2010; 157:751-756.

[10] Alshaikh B, Yusuf K, Sauve R. Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: systematic review and meta-analysis J Perinatol 2013;33:558-564.

[11] Bakhuizen SE, Haan TR, Teune MJ, Van Wassenaer-Leemhuis AG, Van der Heyden JL, Van der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. Acta Paediatr 2014;103:1211-1218.

[12] Setänen S, Lahti K, Lehtonen L, Parkkola R, Maunu J, Saarinen K, et al. Neurological examination combined with brain MRI or cranial US improves prediction of neurological outcome in preterm infants. Early Hum Dev 2014;90:851-856.

[13] Wusthoff CJ. How to use: neonatal neurological examination. Arch Dis Child Educ Pract Ed 2013;98:148-153.

[14] Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. J Pediatr 1998;133(3):406-416.

[15] Brown N, Spittle A. Neurbehavioral evaluation in the preterm and term infant. Curr Pediatr Ver 2014;10(1):65-72.

[16] Setänen S, Lehtonen L, Parkkola R, Aho K, Haataja L. Predicition of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations. Dev Med Child Neurol 2016;58:721-727.

[17] Vilar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH, et al. INTERGROWTH-21st very preterm size at birth reference charts. Lancet 2016;387(10021):844-845.

[18] Brasil, Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Neonatologia: Critérios Diagnósticos de Infecção Associada à Assistência à Saúde. 2ª ed 2017:39-53.

[19] Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neoantal sepsis using a hematologic scoring system. J Pediatr 1988;112:761-7.

[20] Golin MO, Souza FIS, Sarni ROS. Avaliação neurológica pelo método Dubowitz em recém-nascidos prematuros com idade corrigida de termo comparada a de nascidos a termo. Rev Paul Pediatr 2009;27(4):402-409.

[21] Grinaboldi A, Hinnig P, Moura SPS, Golin MO, et al. Avaliação neurológica de recém-nascidos pré-termo: correlação com fatores de risco neonatais. Rev Neurocienc 2015;23(2):267-274.

[22] Vann C, Brant R, Poskitt KJ, Tam EW, Synnes A, Miller SP, et al. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. Pediatr Res 2012;71(3):274-279.

[23] Jenster M, Bonifacio SL, Ruel T, Rogers EE, Tam EW, Partridge JC et al. Maternal or neonatal infection: association with neonatal encephalopathy outcomes**.** Pediatr Res 2014:76(1):93-99.

[24] Rand KM, Austin NC, Inder TE, Bora S, Woodward LJ. Neonatal infection and later neurodevelopmental risk in the very preterm infant. J Pediatr 2016;170:97-104.

[25] Kavas N, Arısoy AE, Bayhan A, Kara B, Günlemez A, Türker G, et al. Neonatal sepsis and simple minor neurological dysfunction. Pediatr Infect Dis J 2017;59:564-569.

[26] Mitha A, Foix-L'Hélias L, Arnaud C, Marret S, Vieux R, Aujard Y, et al. Neonatal Infection and 5-year Neurodevelopmental Outcome of Very Preterm Infants. Pediatrics 2013;132:372-380.

[27] Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at Term and White and Gray Matter Abnormalities in Very Preterm Infants. J Pedriatr 2009;155:32-8.

[28] Chenouard A, Gascoin G, Gras-Le Guen C, Montcho Y, Rozé JC, Flamant C. Neurodevelopmental impairment in preterm infants with late-onset infection: not only in extremely preterm infants. Eur J Pediatr 2014;173:1017-1023.

[29] Chu SM, Hsu JF, Lee CW, Lien R, Huang HR, Chiang MC, et al. Neurological complications after neonatal bacteremia: The clinical characteristics, risk factors and outcomes. PLoS One 2014;9(11): 1-3. Disponível em: <https://doi.org/10.1371/journal.pone.0105294>, Acesso em: 20 de Julho de 2018.

[30] Romeo DM, Cioni M, Palermo F, Cilauro S, Romeo MG. Neurological assessment in infants discharged from a neonatal intensive care unit. Eur J Paediatr Neurol 2013;17:192-198.

[31] Amess P, McFerran C, Khan Y, Rabe H. Early prediction of neurological outcome by term neurological examination and cranial ultrasound in very preterm infants. Acta Paediatr 2009;98:448-453.