

Neurodevelopmental Evaluation of Very Low Birth Weight Infants with Sepsis at 18 to 24 Months' Corrected Age

DİLEK DİLLİ, ZEYNEP ERAS, *UGUR DİLMEN AND EVRİM DURGUT SAKRUCU

From the Department of Neurology and Developmental Pediatrics, Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey

Corresponding author:

Dilek Dilli, Zekai Tahir Burak Kadın
Sağlığı Eğitim ve Araştırma Hastanesi,
Neonatoloji Kliniği, Talatpaşa bulvarı,
Hamamönü/Ankara/Turkey.
dilekdilli2@yahoo.com

Received: April 03, 2012;

Initial review: April 23, 2012;

Accepted: June 28, 2012.

In this cohort study, neurodevelopmental outcome of 20 of 24 surviving very low birth weight infants with sepsis followed-up between 2008 and 2009 was compared with 20 control (uninfected infants). We found that plasma interleukin-6 and C-reactive protein values were negatively correlated with mental developmental index scores ($r = -0.33$, $P = 0.03$ and $r = -0.40$, $P = 0.01$, respectively) at 18 to 24 months' corrected age. The results of this study indicate that sepsis experienced in the neonatal period seems to be related to low mental developmental index scores at 18 to 24 months' corrected age.

Key words: Neurodevelopmental outcome, Preterm, Sepsis.

Published online: July 05, 2012. PII: S097475991200303-2

Despite recent advances in neonatal intensive care improving survival of very low birth weight (VLBW) infants, survival without major neonatal morbidity has not increased [1]. The risk factors for poor neurologic outcome include prematurity, male gender, bronchopulmonary dysplasia (BPD), intracranial hemorrhage (ICH) or periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP) [2]. To the best of our knowledge, to date three studies have demonstrated that neonatal infections were associated with an increased risk of poor neurodevelopmental outcomes [3-5].

METHODS

In our previous study [6], performed between April 2008 and May 2009, 35 infants with sepsis [proven sepsis (culture positive): 23, clinical sepsis: 12] were evaluated.

At the end of the first study, 7 of 35 (20.0%) infants with clinical or proven sepsis died. Surviving and weighed ≥ 1500 g ($n = 20$, 57.1%) infants were planned to be included for the current study at 18 to 24 months' corrected age. For each of the 20 VLBW sepsis survivors, 1 VLBW infant with the same gestational age, and the same year of admission were recruited as matched controls.

The subjects were evaluated for the relation between sepsis developed in the first weeks of life and

neurodevelopmental disabilities when the infants were 18 to 24 months' corrected age Bayley Scales of Infant Development-Second Edition (BSID-II) was administered for neurodevelopmental evaluation [7]. Cerebral palsy (CP) was defined as a nonprogressive central nervous system disorder. Neurodevelopmental impairment (NDI) was defined as any of the following: moderate-to-severe cerebral palsy; a mental developmental index (MDI) or psychomotor developmental index (PDI) of less than 70; bilateral deafness; or bilateral blindness. Profound impairment was defined as an MDI of less than 50 or a Gross Motor Function Classification System level of 4 or 5. Minimal impairment (MI) was defined as a MDI or PDI scores between 70-84 and not having moderate-to-severe cerebral palsy, bilateral severe hearing loss or blindness [7].

RESULTS

Perinatal data of the patients according to two groups are seen on **Table I**.

Correlation analyses showed that interleukin-6 (IL-6) and C reactive protein (CRP) values at the first weeks of life and MDI scores at 18 to 24 months' corrected age were negatively correlated ($r = -0.33$, $P = 0.03$ and $r = -0.40$, $P = 0.01$, respectively). IL6 and CRP values did not correlate with PDI scores. There was no correlation between neutrophil CD64 expression and MDI or PDI scores.

TABLE I PERINATAL DATA AND NEURODEVELOPMENTAL EVALUATION AT 18-24 MONTHS CORRECTED AGE OF STUDY SUBJECTS ACCORDING TO GROUPS.

	Group 1 (Sepsis)(n= 20)	Group 2 (Without sepsis)(n = 20)	P value*
Gestational age, median (IQR), wk	28.5 (28-32)	29 (28-32)	0.60
Age at study, median (IQR), d	11.5 (9.2-16.7)	13.5 (11-18)	0.23
Birth weight, median (IQR), g	1150 (932-1295)	1390 (1172-1470)	0.007
Male gender, n (%)	10 (50)	10 (50.0)	1.0
Premature rupture of membranes, n(%)	6 (30)	4 (20.0)	0.71
Antenatal steroid, n (%)	10 (50)	11 (55.1)	1.0
Cesarean delivery, n (%)	16 (80)	17 (85.0)	1.0
5-min Apgar score, median (IQR)	7 (7-8)	8 (7-9)	0.10
RDS, n (%)	12 (60)	8 (40.0)	0.34
PDA, n (%)	5 (25)	2 (10.0)	0.40
Mechanical ventilation, n (%)	16 (80)	14 (70.0)	0.71
IL-6, median (IQR), pg/mL	185 (77-727)	12 (2-62.7)	0.001
CRP, median (IQR), mg/L	22 (10-34)	2 (1-6.8)	0.001
CD64 _{MFI} , median (IQR)	98 (59-238)	34 (32-76)	0.001
NEC, n (%)	1 (5.0)	0	1.0
BPD, n (%)	4 (20)	2 (10.0)	0.66
ICH, n (%)	9 (45)	0	0.001
PVL, n (%)	2 (25)	0	0.13
ROP, n (%)	2 (10)	1 (14.3)	0.48
Length of hospital stay, median (IQR)	44.5 (33.5-67)	22 (17-38)	0.001
Corrected age, median (IQR), mo	19 (18-21)	20 (18-21)	0.62
Body weight, median (IQR), g	10 (10-11.2)	11(10-11.4)	0.22
Body length, median (IQR), cm	81(75.5-85)	81 (81-84)	0.54
Head circumference, median (IQR), d	45 (41-49)	46 (45-48)	0.52
MDI, point, median (IQR),	70 (62-76)	93 (71-100)	0.001
PDI, point, median (IQR)	86.5 (70.5-94)	96 (85-110)	0.001
Minimal impairment, n %	8 (40.0)	3 (15.0)	0.15
Neurodevelopmental Impairment, n %	9 (45.0)	4 (20.0)	0.17

*P values of Mann Whitney-U or Fisher's exact test comparing infants with proven or clinical sepsis versus without sepsis.

Table I shows growth and neurodevelopmental evaluation at 18 to 24 months' corrected age and its relation to sepsis at the first weeks of life. CP was defined in 2 (15.4%) infants with proven sepsis. NDI occurred in 8 (61.5%) infants with proven sepsis and 1 (14.3%) infant with clinical sepsis compared to 4 (20.0%) infants without sepsis ($P=0.02$). MI occurred in 5 (71.4%) infants with proven sepsis and 3 (23.1%) infants with clinical sepsis compared to 3 (15.0%) infants without sepsis ($P=0.01$). NEC (grade 3) was defined in one patient with proven sepsis and PVL was detected in two patients from each sepsis group. NDI was observed in these patients at neurodevelopmental evaluation. Profound impairment was not defined in any of the infants.

MDI and the PDI scores according to the groups are shown in **Fig. 1**.

Clinical characteristics of the subjects with and without NDI are shown in **Table II**. It was noticed that birthweight was significantly lower among the subjects with NDI. There were no significant differences in other clinical variables including sepsis between the two groups.

Median MDI and PDI scores were significantly lower among infants with NDI than those of infants without NDI.

DISCUSSION

In this cohort study on VLBW infants, MDI and PDI

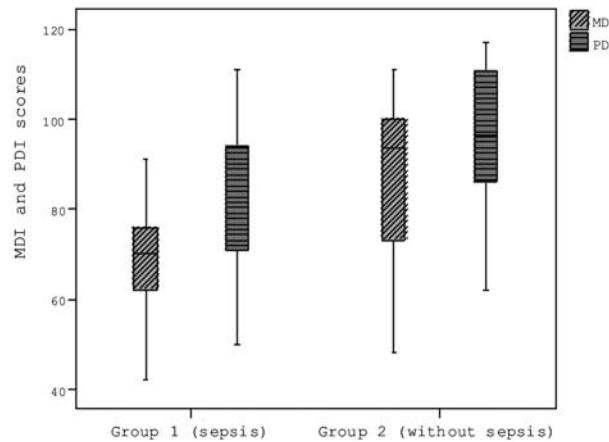


FIG. 1 MDI and PDI scores according to groups are shown; Group 1: proven or clinical sepsis, Group 2: without sepsis.

scores were lower in infants with sepsis compared to ones without sepsis at 18 to 24 months' corrected age. In a multicenter Swiss cohort study, Schlapbach, *et al.* [5] performed neurodevelopmental evaluation on 541 extremely low birth weight infants. Their results indicated that sepsis was among the four main risk

factors influencing long-term outcomes in their population, together with BPD, brain injury, and ROP, all of which had a greater impact on outcome than gestational age, birth weight, and gender. Benjamin, *et al.* [3] and Stoll, *et al.*'s [4] studies have also supported the relationship between sepsis and poor neurodevelopmental outcomes.

Several mechanisms may play role in neurodevelopmental impairment associated with sepsis. First, bacterial products and the cytokine storm in the course of the systemic inflammatory response syndrome may directly damage the highly vulnerable premature brain and other organs, such as the lung and retina [8,9]. Martin, *et al.* [10] also reported a higher risk of neurodevelopmental dysfunction and microcephaly in NEC infants with late bacteremia.

Recently, Silveira RC and Procianoy RS [11] studied on 62 very preterm infants to evaluate association between severity of early inflammatory response and neurodevelopment outcome. They did not find any association of high cytokines plasma levels with poor neurodevelopment outcome at 22 to 24 months'

TABLE II CLINICAL CHARACTERISTICS OF THE SUBJECTS WITH AND WITHOUT NEURODEVELOPMENTAL IMPAIRMENT

	Subjects with neuro-developmental impairment (n= 13)	Subjects without neuro-developmental impairment (n= 27)	P value*
Gestational age, median (IQR), wk	28 (26-32)	29 (28-32)	0.33
Birth weight, median (IQR), g	1160 (925-1290)	1350 (1100-1470)	0.02
Male gender, n (%)	6 (46.2)	14 (51.9)	1.0
5-min Apgar score, median (IQR)	7 (7-8)	8 (7-9)	0.22
Respiratory distress score, n (%)	8 (61.5)	12 (44.4)	0.50
Patent ductus arteriosus, n (%)	4 (30.8)	3 (11.1)	0.18
Mechanical ventilation, n (%)	1 (7.7)	9 (33.3)	0.12
IL-6, median (IQR), pg/mL	165 (10-675)	25.8 (12-110)	0.17
CRP, median (IQR), mg/L	12 (2.3-31.5)	6 (2-24)	0.20
CD64 _{MFI} , median (IQR)	88 (34-168)	69.7-207)	0.75
Sepsis (proven or clinical), n(%)	9 (69.2)	11 (40.7)	0.17
Necrotising enterocolitis, n(%)	1 (7.7)	0	0.32
Bronchopulmonary dysplasia, n (%)	2 (15.4)	4 (14.8)	1.0
Intracranial bleed, n (%)	4 (30.8)	5 (18.5)	0.43
Periventricular leucomalacia, n(%)	1 (16.7)	1 (6.7)	0.50
Retinopathy of prematurity, n (%)	1 (7.7)	1 (3.7)	1.0
Length of hospital stay, median (IQR)	47 (24-73)	32 (22-42)	0.24
MDI, point, median (IQR),	62 (45-63)	87 (76-99)	<0.001
PDI, point, median (IQR)	65 (53-77)	96 (87-110)	<0.001

**P values of Mann Whitney-U or Fisher's exact test comparing infants with and without neurodevelopmental impairment.

corrected age. In the current study, we found that inflammatory markers obtained at the first weeks of life were negatively correlated with MDI but not PDI scores at 18 to 24 months' corrected age.

The sample size is too small to make any meaningful conclusions for a study of this nature. As this was a cohort study we could include in the study only available patients 18 to 24 months' corrected age. On the other hand, assessing neurodevelopment at two years of age may underestimate the full spectrum of cognitive and neuromotor outcomes, such as specific learning difficulties or milder motor dysfunctions [12]. Additionally, a higher risk of poor neurodevelopment has been reported in infants with NEC and with meningitis [13]. Because there was only one case of grade 3 NEC among infants with proven sepsis, we did not analyze its effect separately.

The results of this study indicate that sepsis experienced in the neonatal period seems to be related to low MDI scores at 18 to 24 months' corrected age.

Conflict of interest: There is no conflict of interest; *Funding:* None.

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