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Review Article

Neurocognitive Impairment after Neonatal Sepsis

Effat H. Assar, Hesham A. El-Ghaiaty, Mohamed T. Ahmed

Department of pediatrics, Benha faculty of medicine, Benha University, Egypt

Correspondence to: Mohamed T. Ahmed, Department of pediatrics, Benha faculty of medicine, Benha University, Egypt.

Email:

mohamed.taha18@fmed.bu.edu.eg

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Abstract

Background: Brain development, during which neuronal connections are established and strengthened, is particularly crucial between the late gestational and early neonatal phases. **The aim of** this study was to evaluate the neurocognitive impairment after neonatal sepsis. **Methods:** This is a systematic review and meta-analysis of published papers from 2017 to 2021. We performed a search based on the following parameters: neonates and infants less than 90 days old diagnosed with sepsis who had reported neurocognitive outcomes or measures of developmental disability. **Results:** A total number of 2126 cases were included with a mean gestational age of 28.3 weeks. The commonest organism was Staphylococcus. Three studies with a total number of 610 patients showed cerebral palsy event with insignificant heterogeneity between studies p-value 0.0881, I2 (inconsistency) 58.84% and 95% CI for I2 was 0.00 – 88.28. Ten studies with a total number of 2094 patients showed survival with significant heterogeneity between the studies p-value <0.0001, I2 (inconsistency) 97.12% and 95% CI for I2 was 95.99–97.94. Five studies with a total number of 449 patients showed mechanical ventilation event with significant heterogeneity between the studies p-value <0.0001, I2 (inconsistency) 98.31% and 95% CI for I2 was 97.43– 98.89. **Conclusion:** This systematic review and meta-analysis will provide insight to the incidence and impact on long-term healthcare burden of neonatal sepsis among survivors. Ultimately, the knowledge gained will facilitate future research in the identification of high-risk groups and allow for resource planning in this vulnerable population.

Key words: Neurocognitive impairment; neonatal; sepsis

Introduction

Neonatal sepsis is a health problem because it causes high morbidity and mortality in neonatal intensive care units [(1).] The susceptibility of neonates to sepsis is due to immaturity of the immune response or due to maternal and environmental risk factors that can cause infection [(2).]

The World Health Organization (WHO) estimates 1 million deaths each year from neonatal sepsis; 42% of these deaths occur within the first week of life [(3).]

The cause of neonatal sepsis is multifactorial and could have a maternal, neonatal or environmental basis. In recent years, many studies have investigated the association of genetic variation to the incidence of neonatal sepsis [(4).]

Brain development, during which neuronal connections are established and strengthened, is particularly crucial between the late gestational and early neonatal phase. Insults to the developing brain during this period can negatively impact cerebral networking and control, leading to poor mental and psychomotor development, cerebral palsy, visual and/or auditory impairment, as well as intellectual disability later in life [(5).]

In the neonatal period, the insults include prematurity, low birth weight, seizures, respiratory distress syndrome, hyperbilirubinemia or kernicterus and sepsis. Among these, neurocognitive outcomes following neonatal sepsis are not well documented for the following reasons: lack of consensus in definition of neonatal sepsis, confounding due to the presence of other neonatal conditions with sepsis, wide variation in measures used to assess and document the neurocognitive outcomes, as well as the need for long-term follow-up [(6).]

The link between neonatal sepsis and adverse neurocognitive outcomes has been postulated to be a multifactorial process involving production of proinflammatory cytokines, hypoxic ischaemic encephalopathy due to hypotension and impaired autoregulation of cerebral blood flow, stimulation of microglia causing excitotoxicity, as well as free radical damage by reactive oxygen and nitrogen species. All these lead to injury in the cerebral white matter, particularly periventricular leukomalacia, and increase the vulnerability of the brain to subsequent injuries [(7).]

Common measurements of the neurocognitive outcomes include neurodevelopmental impairment and intellectual disability.

Neurodevelopmental impairment includes the following: cognitive delay based on standardized cognitive tests (e.g., Mental Development Index of Bayley Scales of Infant and Toddler Development), hearing deficits or loss requiring amplification, visual impairment and moderate to severe cerebral palsy defined as a score of two or more on the Gross Motor Function Classification System.

Intellectual disability is a commonly used measure and is defined as a disorder which begins before the age of 10 years, characterized by limitations in adaptive behavior which affects participation in everyday life and at least one of the three domains: conceptual, social and practical, as well as limitations in intellectual functioning which affect the general mental capacity and is indicated by an IQ that is 2 SDs below the mean [(8)]. This study aimed to evaluate the neurocognitive impairment after neonatal sepsis by a systematic review and meta-analysis of published papers from 2017 to 2021.

Methods

This was a systematic review and meta-analysis of neonatal sepsis. We performed a search based on the following parameters: neonates and infants less than 90 days old diagnosed with sepsis that had neurocognitive outcomes or measures of developmental disability reported. Search on PubMed, Cochrane Central, Embase and Web of Science for articles in English language published between 2017 and 2021, was done.

Clinical trials and observational studies will be included. Two independent reviewers will screen studies for eligibility. Data extraction will then be performed using a standardized form. The quality of evidence and risk of bias will be assessed using Cochrane Collaboration's tool and Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I). The results will be synthesized qualitatively and pooled for meta-analysis.

Using the following keywords: Newborn, Infant, Low Birth Weight, Infant, Small for Gestational Age, Infant, Very Low Birth Weight, Infant, Postmature, Premature, Extremely Premature, Neonatal Sepsis, Sepsis, Bacteremia, Endotoxemia, Hemorrhagic Septicemia, Fungemia, Candidemia, Parasitemia, Shock, Septic Viremia, Hemorrhagic Septicemia, Cognitive Dysfunction, Chemotherapy-Related Cognitive Impairment, Postoperative Cognitive Complications. The initial literature search will identify

articles which will be assessed for possible inclusion. Figure 1

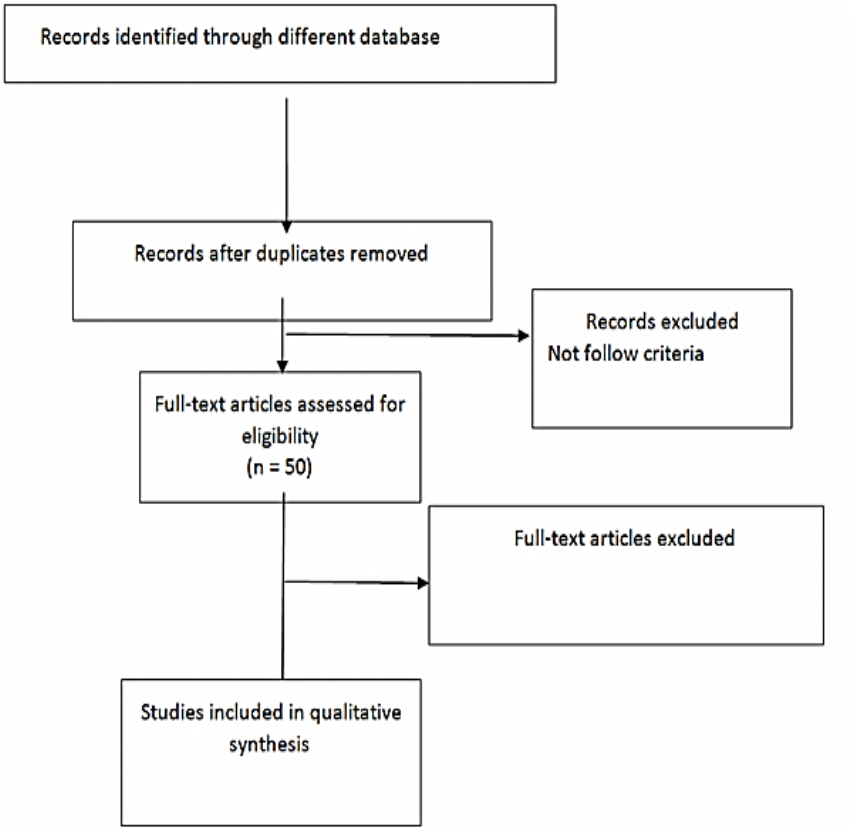

Fig 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram for study selection [(9)].

Inclusion criteria:

- Randomized controlled trials (RCTs) and observational studies
- All types of sepsis.
- All types of Neurocognitive impairments.
- The long-term survival of patients with or without impairment.
- Post-management complications.

Exclusion criteria:

- All articles that did not meet the inclusion criteria.
- Articles for which the full text is not available in English.
- Neonatal death.
- Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram for study selection.

Ethical considerations:

This study was approved by the ethical committee of the faculty of Medicine, Benha University Hospitals.

Statistical Analysis

Results were organized, tabulated and statistically analysed using the Statistical Package for Social Sciences (SPSS) software version 11. For quantitative data, the mean and standard deviation were calculated, the difference

between two means was statistically analysed using the student (t) test. For qualitative data the number and percent distribution were calculated. Chi square was used as a test of significance and when found inappropriate fisher exact test was used. Significance was adopted to $P \leq 0.05$ for interpretation of results of tests significance.

Results:

A total number of 2126 patients with a mean gestational age of 28.3 weeks and m\f 772\ 754 were included in the study as shown in table 1. The mean birth weight was 1058.5 gm with 672 patients delivered by caesarian section (CS) and 240 delivered by normal delivery (ND). The causal organisms were mentioned in 5 studies and the most common organism was Staphylococcus as shown in table 1.

DASII scale Developmental quotient was mentioned in 1 study with a mean value of 77.41 ± 12.49. DASII scale Developmental age was 4.61 ± 0.77, DASII scale Mental age was 4.73 ± 0.79 and DASII scale Motor age was 4.48 ± 0.81. DASII scale Mental quotient and DASII scale Motor quotient were mentioned in 2 studies with mean values of 79.4 and 78.7 respectively as shown in table 2. The mean Composite cognitive and motor scores mentioned in 4 studies and was 101.5, 100.5 respectively as shows in table 3. Three studies with a total number of 610 patients showed cerebral palsy with insignificant heterogeneity between the studies; p-value 0.0881, **I^2 (inconsistency)** 58.84% and **95% CI for I^2** was 0.00 – 88.28, table 4.

Ten studies with a total number of 2094 patients showed **Survival** with significant heterogeneity between the studies; p-value <0.0001, **I^2 (inconsistency)** 97.12% and **95% CI for I^2** was 95.99 – 97.94, table 5. Three studies with a total number of 670 patients showed **periventricular leukomalacia** with significant heterogeneity between the studies p-value 0.0001, **I^2 (inconsistency)** 89.01% and **95% CI for I^2** was 69.95 – 95.98, table 6.

Table1: Delivery characteristics

Authors	Birth weight (g)	Mode of delivery	Causal microorganism
Shim SY et al.,2021	927.3	cs(338),ND(81)	Staphylococcus (204),coagulase-positive Staphylococcus aureus(61),
Ortgies T et al.,2021	1126	CS(151),ND (15)	
Pichler K et al.,2021	1250		
Mukhopadhyay S et al.,2020	713	cs(87),ND(66)	Viridans streptococci(1), Group B strep(28), Staph Viridans streptococci(3) Enterococcus(2), MRSA(2), Strep aureus(3) , E. pneumoniae(2), Alpha hemolytic strep(1), Acinetobacter(2), Capnocytophaga(2), Citrobacter(2), Morganella coli(65), Haemophilus(10), Klebsiella(4), Eikenella morganii(2), Bacteroides(1), Campylobacter(1), corrodens(1), Pseudomonas aeruginosa(1), Sphingomonas paucimobilis(1), Candida albicans(1), Saccharomyces(1)
Rallis D et al.,2019	1350		Coagulase-negative Staphylococcus(24), Enterobacter cloacae(4), Klebsiella pneumoniae(3), Enterococcus faecalis(3), Streptococcus species(3)
Zonnenberg IA et al.,2019	1078		Coagulase-negative staphylococci(70), Staphylococcus aureus(14), Escherichia coli(2), Klebsiella oxytoca(2), Enterococcus faecalis(1), Streptococcus agalactiae(1), Gram-positive rod, not further specified(1)
Singh L et al.,2018	1250	cs(15),ND(65)	Klebsiella pneumoniae (27), Escherichia coli(12), Candida species(11), coagulase-negative Staphylococci(6), Acinetobacter(5), Staphylococcus aureus(4), Enterococcus(4), Pseudomonas(3)
Pawar SJ et al.,2018		cs(81),ND(13)	
Bierstone D et al.,2018	1000		
Glass TJA et al.,2018	833		

Table2: Outcome scores

Authors	DASII scale Developmental quotient	DASII scale Developmental age	DASII scale Mental age	DASII scale Mental quotient	DASII scale Motor age	DASII scale Motor quotient
Pichler K et al.,2021				80 ± 21		83 ± 18
Singh L et al.,2018	77.41 ± 12.49	4.61 ± 0.77	4.73 ± 0.79	78.89 ± 13.13	4.48 ± 0.81	74.56 ± 13.43

Table3. Composite score

Authors	Composite cognitive score (BSID-II)	Composite motor score (BSID-II)
Rallis D et al.,2019	91(8)	93 (10)
Zonnenberg IA et al.,2019	100 (9.0)	100 (9.4)
Bierstone D et al.,2018	105	100
Glass TJA et al.,2018	110	109

Table (4): Meta-analysis for Cerebral Palsy

Study	Total number	Event	Event rate (%) (Proportion)	95% CI of rate (%)
Ortgies T et al.,2021	166	4	2.410	0.660 – 6.054
Pawar SJ et al.,2018	94	7	7.447	3.046 – 14.743
Bierstone D et al.,2018	350	22	6.286	3.981 – 9.362
Total (fixed effects)	**610**		5.446	3.787 – 7.549
Total (random effects)	**610**		5.335	2.741 – 8.724
Test for heterogeneity				
Q	4.8592			
DF	2			
Significance level	0.0881			
I^2 (inconsistency)	58.84%			
95% CI for I^2	0.00–88.28			

Q: Total variance for heterogeneity
I2: Observed variance for heterogeneity
CI: Confidence interval (LL: Lower limit–UL: Upper Limit)

Table (5): Meta-analysis for Survival

Study	Total number	Event	Event rate (%) (Proportion)	95% CI of rate (%)
Shim SY et al.,2021	419	419	100.0	99.123 – 100.0
Ortgies T et al.,2021	166	166	100.0	97.802 – 100.0
Pichler K et al.,2021	600	600	100.0	99.387 – 100.0
Mukhopadhyay S et al.,2020	153	90	58.824	50.591 – 66.708
Rallis D et al.,2019	37	37	100.0	90.511 – 100.0
Zonnenberg IA et al.,2019	85	76	89.412	80.850 – 95.043
Singh L et al.,2018	80	66	82.500	72.385 – 90.089
Pawar SJ et al.,2018	94	94	100.0	96.152 – 100.0
Bierstone D et al.,2018	350	350	100.0	98.952 – 100.0
Glass TJA et al.,2018	110	110	100.0	96.702 – 100.0
Total (fixed effects)	**2094**		98.876	98.327 – 99.281
Total (random effects)	**2094**		96.958	90.826 – 99.816
Test for heterogeneity				
Q	312.8369			
DF	9			
Significance level	<0.0001			
I^2 (inconsistency)	97.12%			
95% CI for I^2	95.99–97.94			

Q: Total variance for heterogeneity
I^2: Observed variance for heterogeneity
CI: Confidence interval (LL: Lower limit–UL: Upper Limit)

Table (6): Meta-analysis for periventricular leukomalacia

Study	Total number	Event	Event rate (%) (Proportion)	95% CI of rate (%)
Shim SY et al.,2021	419	40	9.547	6.908 – 12.773
Ortgies T et al.,2021	166	2	1.205	0.146 – 4.284
Zonnenberg IA et al.,2019	85	4	4.706	1.297 – 11.613
Total (fixed effects)	**670**		6.450	4.714 – 8.579
Total (random effects)	**670**		4.971	0.925 – 11.977
Test for heterogeneity				
Q	18.2062			
DF	2			
Significance level	0.0001*			
I^2 (inconsistency)	89.01%			
95% CI for I^2	69.95–95.98			

Q: Total variance for heterogeneity
I^2: Observed variance for heterogeneity
CI: Confidence interval (LL: Lower limit–UL: Upper Limit)

Discussion

The mean birth weight was 1058.5 gm with 672 of the patients delivered by CS and 240

delivered by ND. The causal organism was mentioned in 5 studies and the most common organism was Staphylococcus.

In accordance with our results was the study of Shim et al., [10] as they reported that a mean gestational age of 28±2 weeks and the majority of them were males. The mean birth weight was 1,052.3 ± 262.0 gm with 78% of the patients delivered by CS. The most frequently detected organisms were coagulase-negative Staphylococcus (48.8%) and coagulase-positive *Staphylococcus aureus* (14.6%) in 1.170 very low birth weight infants (VLBWIs) with late-onset sepsis (LOS). Gram negative and gram-positive bacteria accounted for 19.0% and 79.5% of them, respectively.

It was revealed [11] that infants with sepsis were of 30.6 ± 3 weeks' gestational age and 1350 ± 429 gm of birth weight, compared to 31.5 ± 3 weeks' gestational age and 1435 ± 324 gm of birth weight for controls. There were no significant differences between the two groups regarding the perinatal characteristics. Early onset sepsis was diagnosed in 24%, while late onset sepsis in 76% of the infants of the sepsis group. Coagulase-negative Staphylococcus (CoNS) was predominantly isolated in the blood culture of the septic infants (65%), followed by *Enterobacter cloacae* (11%), *Klebsiella pneumonia* (8%), *Enterococcus faecalis* (8%), and other Streptococcus species (8%).

Furthermore, in another research [12] it was revealed that the mean gestational age was 27 4/7 weeks and the majority of the patients were males. The mean birth weight was 1029 gm. During the study period, 32 infants (14 boys and 18 girls) were included. CoNS (n = 23) were the causal agents in 72% in cases with proven late-onset sepsis. *Staphylococcus aureus* (n = 3) and *Escherichia coli* (n = 1) counted for the other proven late-onset sepsis episodes.

The present study showed that DASII scale Developmental quotient was mentioned in 1 study with a mean value of 77.41 ± 12.49. DASII scale Developmental age was 4.61 ± 0.77, DASII scale Mental age was 4.73 ± 0.79 and DASII scale Motor age was 4.48 ± 0.81. DASII scale Mental quotient and DASII scale Motor quotient were mentioned in 2 studies with mean values of 79.4 and 78.7 respectively.

Our results were in agreement with the study done previously [13] as it was reported that the mean DASII scale Developmental quotient was 77.41 ± 12.49, the mean DASII scale Developmental age was 4.61 ± 0.77, the mean DASII scale Mental age was 4.73 ± 0.79 and the mean DASII scale Motor age was 4.48 ± 0.81. Also, it was reported [14] that the mean DASII scale Mental quotient was 80 ± 21 and the mean DASII scale Motor quotient was 83 ± 18.

The current study showed that the mean Composite cognitive and motor scores were

mentioned in 4 studies and was 101.5 and 100.5 respectively.

Our results were in line with the study of Rallis et al., [11] as they reported that the mean Composite cognitive score (BSID-II) was 91 and the mean Composite motor score (BSID-II) was 93.

Similarly, it was declared [12] that the mean Composite cognitive score (BSID-II) was 100 and the mean Composite motor score (BSID-II) was 100. Moreover, it was proved in another study [15], the mean Composite cognitive score (BSID-II) was 105 and the mean Composite motor score (BSID-II) was 100.

Common impairments affecting the central nervous system (CNS) are intellectual disability, cerebral palsy, and sensory impairments. Several mechanisms have been proposed as to how systemic inflammation and subsequently elevated cytokine levels in the mother and child in the perinatal period may damage brain parenchyma. Other well established risk factors for adverse long-term neurological outcomes are low gestational age, low birth weight, male gender, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP) [16].

In the study in our hands, 3 studies with a total number of 610 patients show cerebral palsy event with insignificant heterogeneity between the studies, p-value 0.0881 , I2 (inconsistency) 58.84% and 95% CI for I2 was 0.00 – 88.28. Our results were supported by the study [17] which reported that the occurrence of cerebral palsy was significantly higher in the early onset sepsis (EOS) group than in the control group.

It was [18] was declared that comparing the outcomes between the two groups the outcome of abnormal neurological examination was significantly more in the sepsis group than in the controls. The incidence of cerebral palsy was more in sepsis group but did not reach statistical significance. Incidences of tone abnormality not qualifying for cerebral palsy, squint, and osteopenia were similar between the two groups. In a previously done study [15], 22 cases (6.3%) of their studied group had cerebral palsy.

The present study showed that 10 studies with a total number of 2094 patients showed survival events with significant heterogeneity between the studies; p-value <0.0001, I2 (inconsistency) 97.12% and 95% CI for I2 was 95.99 – 97.94.

In accordance with our results, others [10, 11 & 17], revealed that their entire studied group survived. I was demonstrated that [19] 58.8% of their studied group survived. Also, in a similar study [13], 82.5% of their studied group survived.

Our results showed that 3 studies with a total number of 670 patients showed

periventricular leukomalacia event with significant heterogeneity between the studies; p-value 0.0001, I2 (inconsistency) 89.01% and 95% CI for I2 was 69.95 – 95.98.

Our results were in line with the recent study done in 2021 where it was reported [(10)] that the prevalence of comorbidities, such as periventricular leukomalacia (PVL) was higher in very low birth weight infants (VLBWIs) with late onset sepsis (LOS). In the study performed 2019 [(12)], 4.7% of the studied cases had periventricular leukomalacia. Furthermore, the recent study 2021 [(17)] revealed that 1.2% of the studied cases had periventricular leukomalacia.

With decreasing over time mortality rates from neonatal sepsis, focus has shifted to caring for the survivors. Sepsis causes significant disruption to cerebral networking in the neonatal period and is detrimental to brain development. Consequentially, neurocognitive impairment of motor, cognitive, language, learning and behavioral skills can occur and will negatively impact a child's performance and integration into school, and eventually into society as an adult [(21).]

Conclusion

This systematic review and meta-analysis of neonatal sepsis and its outcomes of neurocognitive impairment will provide insight to the incidence and impact on long-term healthcare burden of neonatal sepsis among survivors. Ultimately, the knowledge gained will facilitate future research in the identification of high-risk groups and allow for resource planning in this vulnerable population.

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