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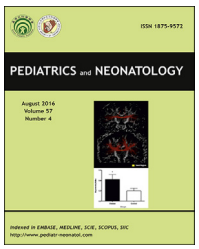

Original Article

Timing of sepsis is an important risk factor for white matter abnormality in extremely premature infants with sepsis

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Key Words
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white matter

Background: Systemic infection is a major upstream mechanism for white matter abnormality (WMA). Our aim was to evaluate the risk factors for moderate-to-severe WMA in extremely premature infants (gestational age < 28 weeks) with neonatal sepsis.
Methods: Extremely premature infants with culture-proven sepsis between 2006 and 2015 in a tertiary neonatal intensive care unit were classified as having none-to-mild or moderate-to-severe WMA based on WM scores of brain magnetic resonance imaging at the term-equivalent age. Various risk factors for WMA were analyzed.
Results: Sixty-three infants (87.5%) had none-to-mild WMA, and nine infants (12.5%) had moderate-to-severe WMA. Multivariate logistic regression analysis revealed that postmenstrual age (PMA) at sepsis diagnosis (OR: 0.640, 95% CI: 0.435–0.941, $p = 0.023$) and PMA at sepsis diagnosis <28 weeks (OR: 9.232, 95% CI: 1.020–83.590, $p = 0.048$) were independently associated with moderate-to-severe WMA. PMA at sepsis diagnosis had a significant negative correlation with WM scores ($r = -0.243$, $p = 0.039$).
Conclusion: PMA at sepsis diagnosis might be an important risk factor for moderate-to-severe WMA in extremely premature infants with postnatal sepsis, especially before PMA 28 weeks. Infants who suffer from sepsis before PMA 28 weeks might need additional therapy for neuroprotection.

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1. Introduction

Although the survival of premature newborns has improved over past decades, it has been accompanied by an increase in the number of infants affected by long-term neurodevelopmental morbidities.[1–3] The neuropathologies underlying these morbidities are diverse, although the primary type of lesion appears to be white matter abnormality (WMA),[4] which is characterized by deep focal areas of cystic necrosis and more diffuse cell-specific WM injury.[5–7] Importantly, the severity of WMA is strongly correlated with the degree of neurodevelopmental impairment.[8]

One of the major upstream mechanisms of WMA is systemic infection/inflammation,[5,7,9] and the majority of preterm infants develop at least one neonatal infection during their hospital stay.[10] In particular, early- or late-onset sepsis, meningitis and necrotizing enterocolitis (NEC) cause overwhelming systemic inflammation, often resulting in brain injury.[11] Multiple clinical studies have demonstrated an association between WMA and postnatal sepsis.[12–17] Few reports, however, have described the risk factors for WMA in the context of neonatal sepsis.

In this study, we analyzed data from extremely premature infants diagnosed with neonatal sepsis who underwent brain magnetic resonance imaging (MRI) prior to discharge to identify clinical risk factors for moderate-to-severe WMA in septic neonates. Identifying the cause of WMA in infants with sepsis will be important for predicting neurodevelopmental outcomes and may lead to more advanced therapies for intervention and prevention.

2. Methods

2.1. Study design and population

The study subjects were extremely premature infants born before 28 weeks of gestation who were admitted to the neonatal intensive care unit of the Seoul National University Children's Hospital between January 1, 2006 and December 31, 2015. The medical records of all neonates with a positive blood culture who underwent brain MRI before discharge were retrospectively reviewed.

A total of 335 infants were born before 28 weeks of gestation during the study period (Fig. 1). One hundred-four infants (31.0%) were diagnosed with postnatal sepsis during their hospital stay, and 74 infants (71.1%) underwent brain MRI before discharge. Among the 30 infants who did not undergo brain MRI, four had intraventricular hemorrhage (IVH) $\geq$ grade 3 (classified by Papile et al.,[18]) and three had significantly increased echogenicity of WM according to cranial sonography. Among the 74 infants who underwent brain MRI, two were excluded from the study due to the presence of IVH grade 4 not concurrent with sepsis. These two cases had IVH grade 4 before the septic event. In total, the medical records of 72 infants, including clinical investigations and treatment, were reviewed in this study.

2.2. Ethics statement

The study protocol was approved by the institutional review board (IRB) of the Seoul National University Hospital (IRB No. 1508-137-697) with a waiver of informed consent. Patient records/information were anonymized and de-identified prior to data analysis.

2.3. Clinical data collection

A trained neonatologist collected data from maternal and infant medical charts. The data collected included variables that could be associated with WMA. The diagnosis of neonatal sepsis required the isolation of a microorganism from a blood culture and at least one of the following clinical signs or symptoms: apnea, bradycardia, hypothermia (core temperature of $<$36.5 °C), fever (core

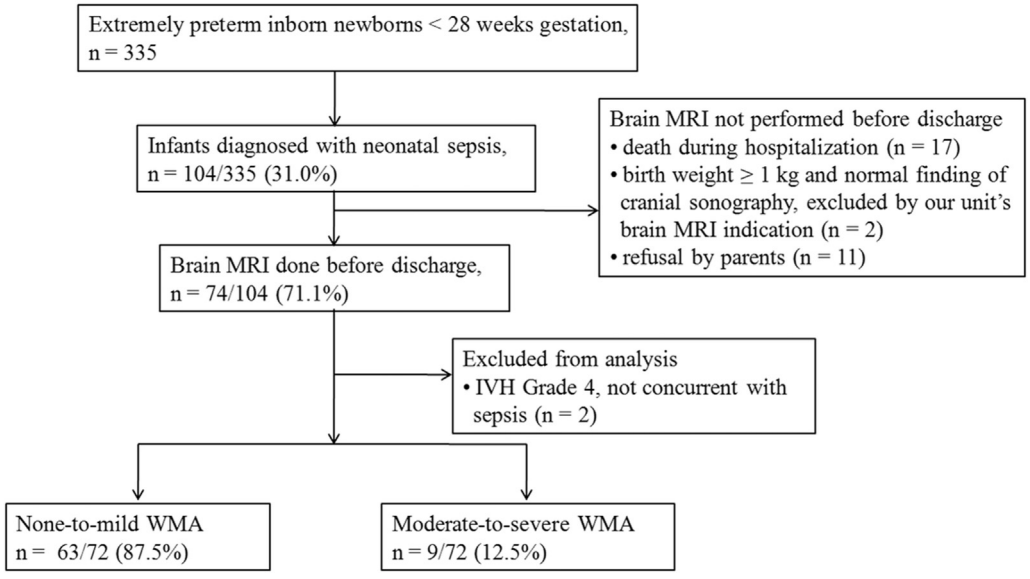

Figure 1 Cohort flow diagram depicting study population selection. IVH, Intraventricular hemorrhage; MRI, Magnetic resonance imaging; WMA, White matter abnormality.

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