Abstract Information

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Title :	Cytokine-mediated inflammatory responses in neonatal Group B Streptococcus disease and their role in neurodevelopmental impairment

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Abstract :

Background and Objectives

Streptococcus agalactiae, known as Group B Streptococcus (GBS), a Gram-positive bacterium, causes invasive GBS (iGBS) disease in neonates, often resulting in neurodevelopmental impairment (NDI). Clinical presentations include pneumonia, meningitis, and sepsis, with sepsis being most common. While meningitis is strongly associated with NDI, ~18% of neonates with iGBS-related sepsis also develop NDI. We proposed that cytokines may be one of the role players involved in iGBS-induced NDI. Therefore, this study investigated cytokine responses using a neonatal rat model of iGBS disease and human neonates presenting with iGBS disease. Neurodevelopmental assessments were also performed on human iGBS survivors.

Methods

Neonatal rats were injected intraperitoneally with GBS or saline. Plasma and hippocampal samples were analyzed for cytokine levels using RT-PCR and Luminex protein assays. Plasma concentrations and hippocampal mRNA levels of tumour necrosis factor-alpha (TNF-?), interleukin-1 beta (IL-1?), and interleukin-6 (IL-6) were measured. Protein levels of IL-6, and interleukin-10 (IL-10) in the hippocampus were assessed. Human serum TNF-?, IL-6, and IL-10 levels were measured in neonates without iGBS disease (non-iGBS) (n=152) and

neonates who survived iGBS disease (iGBS) (n=54) within 24-72 hours of onset. Neurodevelopmental outcomes in iGBS survivors were assessed using the Griffiths Mental Development Scales-Extended Revised (GMDS-ER).

Results

Compared to neonatal saline rats, infected pups showed elevated plasma levels and increased hippocampal mRNA expression of TNF-?, IL-1?, IL-6 and IL-10 (all $p<0.05$). Hippocampal protein levels of IL-1? were increased in infected pups ($p<0.05$). Human neonates with iGBS-meningitis and iGBS-sepsis had increased levels of serum IL-6 versus non-iGBS neonates ($p<0.001$). IL-10 levels were higher in iGBS-meningitis neonates versus iGBS-sepsis neonates ($p=0.003$) and non-iGBS neonates ($p<0.001$). Neurodevelopmental outcomes showed that iGBS survivors had impairments versus non-iGBS children, with meningitis survivors more notably affected than sepsis survivors..

Discussion

GBS infection induces systemic and central inflammatory responses characterized by elevated pro-and anti-inflammatory cytokines. These responses likely contribute to neuronal damage and subsequent NDI. Children surviving iGBS disease, particularly meningitis, are more likely to have increased cytokine concentrations and NDI compared to non-iGBS children. This study highlights the need for further research to elucidate how specific cytokine responses drive neurodevelopmental impairments in survivors of iGBS disease.