HHS Public Access

Author manuscript

Pediatr Res. Author manuscript; available in PMC 2020 November 12.

Published in final edited form as:

Pediatr Res. 2020 August ; 88(2): 155–156. doi:10.1038/s41390-020-0954-y.

Application of metabolomics to neonatal meningitis

James L. Wynn[1,2]

[1]Department of Pediatrics, University of Florida, Gainesville, Florida

[2]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida

The risk of infant meningitis has been dramatically reduced by successful vaccination programs over the last several decades(1). A study of 931 infants ≤28 days old (nearly all 36 weeks or greater at birth) with a history of fever presenting for evaluation to the emergency room between 2006 and 2017 found just 5 cases (0.54% *of febrile infants*) of bacterial meningitis(2). Compared to the risk in term infants, bacterial meningitis is only slightly more common among preterm infants cared for in the neonatal intensive care unit (NICU). Over a 7-year period among 28144 neonates <33 weeks completed gestation cared for in Canadian Neonatal Network NICUs, there were 215 cases (0.76% *of all infants*) of meningitis (all pathogen causes)(3). This result is similar to work published nearly two decades ago among 11028 very low birth weight infants (<1500 grams) cared for in the *Eunice Kennedy Shriver* National Institute of Child Health and Development Neonatal Research Network over a 3-year period (1998-2001). They found bacterial meningitis in 1.1% of all infants and in 4% of infants evaluated with a CSF culture after day 3 (excluded 187 infants with shunts)(4). Bacterial meningitis is strongly associated with mortality, as well as with poor mental and neurodevelopmental outcome among preterm survivors(4-7). Preterm infants with post-hemorrhagic hydrocephalus may require placement of a shunt that significantly increases the risk of bacterial meningitis. A study of 1036 children with CSF shunts placed, for which 22% were preterm infants with post-hemorrhagic hydrocephalus as the indication, revealed bacterial infection occurred in 11%(8). Taken together, bacterial meningitis remains a severe but infrequent diagnosis among neonates that is much more likely in the setting of a shunt.

Gordon and Colleagues performed a nested cohort analysis on prospectively enrolled infants aged 0–12 months cared for in the Neonatal Intensive Care Units (NICUs) at Children's Hospital of Philadelphia who underwent LP or withdrawal of CSF from indwelling neurosurgical hardware (ventriculo-peritoneal [VP] shunt or *Ommaya* reservoir) for

Correspondence to: James L. Wynn, MD Professor of Pediatrics, Department of Pediatrics, Division of Neonatology, University of Florida, 1600 SW Archer Road, PO Box 100296, Office: (352) 273-8980, Fax: (352) 273-9054S, james.wynn@peds.ufl.edu.

Author contributorship statement

Dr. Wynn wrote the commentary

Conflict of interest statement:

The author declares no competing financial interests.

Patient consent was not required

evaluation of possible meningitis(9). Patients for whom the CSF culture result was positive for a bacterial pathogen and that received prolonged antibacterial treatment were considered to have bacterial meningitis (n=19). An uninfected group (n=19) of matched patients (by gestational age, postnatal age, sex, and race) was selected for comparison with both negative CSF culture results as well as no laboratory evidence of meningitis in samples obtained *prior to* the initiation of antibacterial treatment. The CSF metabolome was determined via mass spectroscopy on all samples. Using a machine learning approach, a metabolomic signature of bacterial meningitis was developed on a small number of patients in the cohort and validated on the remaining patients. The number of metabolites in the model were then systematically reduced with the aim to reach the smallest number of predictive analytes with the greatest accuracy for the diagnosis of bacterial meningitis. The derived metabolic signature predicted bacterial meningitis equally well in preterm and term infants of varying post-natal ages. Importantly, the authors found no metabolites significantly differed between infants with shunt- or reservoir-associated bacterial meningitis and infants with bacterial meningitis without indwelling neurosurgical hardware. This finding is particularly important because CNS hardware was present in nine infants with bacterial meningitis versus only one infant among the uninfected group. Pathways that were over-represented in CSF from patients with bacterial meningitis included alanine, aspartate, and glutamate metabolism. Taken together, these data strongly suggest glutamate dysregulation may play a key role in diagnosis and pathophysiology of BM in infants. Use of the top 6 metabolites found altered in the training set of patients, resulted in an AUC for bacterial meningitis of 0.97.

The potential ability to identify the metabolic milieu consistent with meningitis in neonates brings with it the exciting possibility of precision medicine-based interventions in this population. The diagnosis of bacterial meningitis requires the isolation of a bacterial pathogen from cerebral spinal fluid (CSF); most often performed using classic culture methods. A lumbar puncture (LP) performed is not universally performed at the time of a sepsis evaluation and in some cases may only be performed after a diagnosis of bacteremia has been made(4). A delay in the timing of LP relative to when a blood culture and initiation of antibacterial treatment are performed, decreases the likelihood of isolating a pathogen in CSF, and increases the dependence upon CSF studies (chemistry, cell count) to make the diagnosis of meningitis. The interpretation of CSF culture results, chemistry, and cell counts is often challenging due to a high frequency of contaminating blood. Patients with equivocal CSF studies may receive prolonged, and perhaps unnecessary, antibacterial treatment. These important clinical conundrums and diagnostic test limitations might be successfully mitigated by the presence or absence of a CSF metabolic signature that has strong diagnostic utility.

A diagnosis of meningitis remains only a simple yes/no decision followed by prolonged treatment with anti-bacterials and supportive care because at present we lack the understanding and sophistication to modify the pathologic process based on *when* the infant is in the disease process. The potential to address this critical deficiency is particularly fascinating when one considers the pathogen-specific responses that the authors touched on by presenting the signature associated with Group B *Streptococcus*. By determining and incorporating the overlap between mechanistic preclinical animal modeling and human ‘omic’ observational results such as these, we begin to construct a detailed molecular

landscape of the dynamic process for which we now have only a mere snapshot. The work from *Gordon and Colleagues* takes us one step closer to a time when the question "*Will this test change my management*?" actually could prompt an affirmative response.

Acknowledgments

Grant support:

The authors did not receive support specific to this work. Dr. Wynn receives support from the National Institutes of Health (NIH)/National institutes of General Medical Science (R01GM128452) and the *NIH/Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (R01HD089939, R01HD097081).

References

1. Agrawal S, Nadel S 2011 Acute bacterial meningitis in infants and children: epidemiology and management. Paediatr Drugs 13:385–400. [PubMed: 21999651]
2. Ramgopal S, Walker LW, Tavarez MM, Nowalk AJ, Vitale MA 2019 Serious Bacterial Infections in Neonates Presenting Afebrile With History of Fever. Pediatrics 144.
3. Zipursky AR, Yoon EW, Emberley J, et al. 2019 Central Line-Associated Blood Stream Infections and Non-Central Line-Associated Blood Stream Infections Surveillance in Canadian Tertiary Care Neonatal Intensive Care Units. J Pediatr 208:176–182 e176. [PubMed: 30853200]
4. Stoll BJ, Hansen N, Fanaroff AA, et al. 2004 To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics 113:1181–1186. [PubMed: 15121927]
5. Stoll BJ, Hansen NI, Adams-Chapman I, et al. 2004 Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 292:2357–2365. [PubMed: 15547163]
6. van Vliet EO, de Kieviet JF, Oosterlaan J, van Elburg RM 2013 Perinatal infections and neurodevelopmental outcome in very preterm and very low-birth-weight infants: a meta-analysis. JAMA Pediatr 167:662–668. [PubMed: 23689313]
7. Pappas A, Adams-Chapman I, Shankaran S, et al. 2018 Neurodevelopmental and Behavioral Outcomes in Extremely Premature Neonates With Ventriculomegaly in the Absence of Periventricular-Intraventricular Hemorrhage. JAMA Pediatr 172:32–42. [PubMed: 29181530]
8. Simon TD, Butler J, Whitlock KB, et al. 2014 Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort study. J Pediatr 164:1462–1468 e1462. [PubMed: 24661340]
9. Gordon SM, Srinivasan L, Taylor DM, et al. 2020 Derivation of a metabolic signature associated with bacterial meningitis in infants. Pediatr Res.