Neurocognitive Outcomes at 10 Years of Age in Extremely Preterm Newborns with Late-Onset Bacteremia

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Objective To evaluate the difference in 10-year neurocognitive outcomes between extremely low gestational age newborns without bacteremia and those with suspected or confirmed late-onset bacteremia.

Study design Neurocognitive function was evaluated at 10 years of age in 889 children born at <28 weeks of gestation and followed from birth. Definite (culture-positive) late-onset bacteremia during postnatal weeks 2-4 was identified in 223 children, and 129 children had suspected bacteremia.

Results Infants with the lowest gestational age and birth weight *z*-score had the highest prevalence of definite and suspected late-onset bacteremia. Compared with peers with no or suspected bacteremia, infants with definite bacteremia performed worse on tests of general cognitive ability, language, academic achievement, and executive function, even after adjustment for potential confounders. Adjustment for low IQ attenuated the associations between bacteremia and all dysfunctions at age 10 years. Children with suspected bacteremia did not differ appreciably from those with no evidence of bacteremia. The motor domain was unaffected.

Conclusions Extremely low gestational age newborns who had definite late bacteremia during postnatal weeks 2-4 are at heightened risk of neurocognitive limitations at age 10 years. *(J Pediatr 2017;187:43-9).*

O wing to their immature immune responses[1] and propensity for use of indwelling catheters for extended periods,[2] preterm newborns are at increased risk of bacteremia.[3-5] Late-onset bacteremia is diagnosed in up to one-quarter of infants born extremely preterm.[3] Evidence from preclinical models suggests that perinatal infection and inflammation can disrupt brain development[6] and sensitize the brain to subsequent injurious factors.[7] In humans, bacteremia is associated with multiple indicators of brain damage evident at an early age.[8,9]

In the extremely low gestational age newborn (ELGAN) cohort, neonatal illnesses associated with systemic inflammation, as well as protein biomarkers of inflammation, are associated with structural and functional neurologic abnormalities.[10-12] Late-onset bacteremia is associated with a stronger inflammatory response than early bacteremia.[13] These observations prompted us to question whether late-onset bacteremia accounts for some of the apparent increased risk of neurocognitive impairments in children born preterm.[14,15]

Little is known about the long-term implications of late-onset bacteremia in extremely preterm infants. In 2 small cohorts, school-age children with neonatal sepsis had lower IQ than controls without neonatal sepsis.[16,17] The ELGAN Research Study, with its large number of participants, high retention rate, and detailed neurocognitive assessments at 10 years of age, provides an opportunity to further explore the potential long-term impact of late-onset bacteremia in children born extremely preterm. Expanding on previous work, we hypothesized that compared with no or suspected bacteremia, late bacteremia is associated with adverse neurocognitive outcomes seen in former preterm infants at age 10 years.[18]

Methods

The ELGAN Research Study is a multicenter prospective observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.[19] A total of 1506 infants born before 28 weeks of gestation were enrolled

DAS-II	Differential Ability Scales, Second Edition
ELGAN	Extremely low gestational age newborn
NEPSY-II	NEuroPSYchological Assessment, Second Edition
OWLS	Oral and Written Language Scales
WIAT-III	Wechsler Individual Achievement Test, Third Edition

Table I. Sample description among children classified as none, suspected, or definite late-onset bacteremia

| Characteristics | Late-onset bacteremia | | | |
	None	Suspected	Definite	Total
Enrolled, n				1506
Survived to postnatal day 7, n				1387
Information about late bacteremia available, n	801	201	362	1364
Survived to postnatal day 28, n	770	189	331	1290
Survived to discharge/transfer home, n	728	183	304	1215
Survived to 2 y, n	718	179	296	1193
Survived to 10 y, n	717	178	296	1191
Recruited for 10-y follow-up, n	575	142	244	961
Enrolled for 10-y follow-up, n	532	139	223	884
DAS-II, n	521	128	219	868
OWLS, n	510	123	215	848
WIAT-III, n	520	127	217	864
NEPSY-II, n	523	128	218	869

between 2002 and 2004, of whom 1198 survived to age 10 years. Of these 1198 children, 966 had neonatal blood specimens collected for assessment of systemic inflammation. Of the 966 children eligible for recruitment at age 10 years, 889 (92%) were enrolled in the study (Table I). The enrollment and consent procedures for this follow-up study were approved by the Institutional Review Boards of all participating institutions.

Gestational age estimates were based on a hierarchy of the quality of available information. Optimally, estimates were based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%), followed sequentially by fetal ultrasound at 14 weeks or later (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

An infant's birth weight z-score is defined as the number of SDs above or below the median weight of infants of the same gestational age in referent samples not delivered for preeclampsia or fetal indications.[20] Documented late bacteremia was defined as recovery of an organism from blood drawn during week 2, 3, or 4. Specific organisms were not identified. Suspected infections were culture-negative, but the infants received antibiotics for more than 72 hours.

Neurocognitive Assessments at Age 10 Years

The 966 eligible families were contacted by mail and then by phone to invite them to participate in the 10-year follow-up. Families lost to follow-up were located using state vaccination registries and other openly available websites. Facebook was also used where approved by the local Institutional Review Board. Families willing to participate were scheduled for a 3- to 4-hour evaluation. Specific assessments were selected to provide the most comprehensive information about each child's neurocognitive, academic, and neurosensory function in a single testing session.

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales, Second Edition (DAS-II) Verbal and Nonverbal Reasoning scales.[21] Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS).[22] Executive functions were assessed with both the DAS-II[21] and the NEPSY-II (A Developmental NEuroPSYchological Assessment, Second Edition).[23] The DAS-II Recall of Digits Backward and Recall of Sequential Order subtests were used to measure verbal working memory. The NEPSY-II Auditory Attention and Response Set subtest was used to measure auditory attention, set switching, and inhibition. The NEPSY-II Inhibition and Inhibition Switching subtests were applied to measure simple inhibition and inhibition in the context of set shifting, respectively, and the NEPSY-II Animal Sorting subtest was used to measure visual concept formation and set shifting. Processing speed was assessed with NEPSY-II Inhibition Naming, which provides a baseline measure of processing speed and has no inhibitory component. Visual perception was assessed with NEPSY-II Arrows and Geometric Puzzles, and visual motor function was measured with NEPSY-II Visuomotor Precision and Fingertip Tapping. The Wechsler Individual Achievement Test, Third Edition (WIAT-III) was used to provide standard scores in word recognition and decoding, spelling, and numerical operations.[24]

Gross motor function was assessed using the Gross Motor Function Classification System.[25] A child was classified as level III or higher if he or she needed assistance with mobility (level III, walks using a hand-held mobility device; level IV, self-mobility with limitations, may use powered mobility; level V, transported in a manual wheelchair).

Manual abilities were assessed using the Manual Ability Classification System. This classification scheme assigns a single level for the collaborative use of both hands when handling objects in daily life (level I, handles objects easily and successfully; level II, some reduction in quality and/or speed; level III, handles objects with difficulty; level IV, significant limitations; level V, requires total assistance).[26]

Severe visual impairment was defined as a parent report that the child is legally blind in both eyes. Severe auditory impairment was defined as a parent report that the child has hearing aids or a cochlear implant and/or receives special services for the hearing-impaired.

Statistical Analyses

Our null hypothesis was that documented bacteremia and suspected bacteremia during postnatal weeks 2-4 are not associated with limitations in cognition, executive function, academic achievement, or motor function at school age. A second null hypothesis was that each measure of function at age 10 years is not differentially distributed among children with and without definite late bacteremia or suspected late bacteremia. Initially, we assessed correlates of definite and suspected late bacteremia, including characteristics of the mother, the pregnancy, and the newborn.

For the 10-year assessments, test scores were converted to z-scores based on distributions of values reported for the historical normative samples described by the authors of the assessments used.[21-23] Multinomial logistic regression models were created of the risk of a score >1 SD below the normative mean