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Neurocognitive outcomes at 10 years of age in extremely preterm newborns with late-onset bacteremia

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Abstract

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

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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 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. When 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 when adjusting for potential confounders. Adjustment for low IQ attenuated associations between bacteremia and all dysfunctions at 10 years. Children who had suspected bacteremia did not differ appreciably from children who did not have any 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 10 years of age.

Keywords

Academic function; Cognition; Extremely low gestational age newborn; Neurodevelopment; Executive function; School age; Sensorimotor impairment; Sepsis

Because of the immaturity of their immune responses (4) and their propensity to have indwelling catheters for extended periods of time, (5) preterm newborns are at increased risk of bacteremia. (1, 6, 7) Late-onset bacteremia is diagnosed in up to one quarter of infants born extremely preterm. Evidence from preclinical models suggests that perinatal infection and inflammation can disrupt brain development (8) and sensitize the brain to subsequent injurious factors. (9) In humans, bacteremia is associated with multiple indicators of brain damage evident at early ages. (10, 11)

In the Extremely Low Gestational Age Newborn (ELGAN) cohort, neonatal illnesses associated with systemic inflammation, as well as protein biomarkers of inflammation were associated with structural and functional neurological abnormalities. (3, 12, 13) Late-onset bacteremia was associated with a stronger inflammatory response than early bacteremia. (14) These observations prompted us to question whether late-onset bacteremia accounted for some of the apparent increased risk of neurocognitive impairments among children born preterm. (15, 16)

Little is known about the long-term implications of late-onset bacteremia among extremely preterm infants. In two small cohorts, school-age children with neonatal sepsis had lower intelligence quotients (IQ) than controls who had not acquired neonatal sepsis. (17, 18) The ELGAN study, with its large number of participants, high retention rate, and detailed neurocognitive assessments at 10 years of age, provides the opportunity to explore further the potential long-term impact of late-onset bacteremia among children born extremely preterm. Expanding on previous work, we hypothesized that late bacteremia, when compared with no or suspected bacteremia, is associated with adverse neurocognitive outcomes seen in former preterm infants at 10 years of age. (19)

METHODS

The ELGAN study is a multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants. (20) A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002–2004 and 1198 survived to 10 years. Of these 1198 children, 966 had neonatal blood specimens collected for assessment of systemic inflammation. Of the 966 eligible for recruitment at age 10 years, 889 children (92%) were enrolled. (Table I) 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 or more weeks (29%), LMP without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in referent samples not delivered for preeclampsia or fetal indications. (21) Documented late bacteremia was defined as recovery of an organism from blood drawn during weeks 2, 3 or 4. Specific organisms were not identified. Suspected infections were culture-negative, but the infant received antibiotics for more than 72 hours.

Neurocognitive assessments at 10 years of age

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

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales. (22) Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS). (23) Executive functions were assessed with both the DAS-II (22) and the NEPSY-II (A Developmental NEuroPSYchological Assessment-II). (24) The DAS 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 measured auditory attention, set switching and inhibition. The NEPSY-II Inhibition Inhibition and Inhibition Switching subtests measured simple inhibition and inhibition in the context of set shifting, respectively, and the NEPSY-II Animal Sorting subtest measured 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, while visual motor

function was measured with NEPSY-II Visuomotor Precision and Fingertip Tapping. The Wechsler Individual Achievement Test-III (WIAT-III [C]) provides standard scores in word recognition and decoding, spelling, and numerical operations. (25)

Gross motor function was assessed with Gross Motor Function Classification System. (26) A child was classified as level 3 or higher if s/he needed mobility assistance (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 (MACS). The classification 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 of quality and/or speed; Level III: handles objects with difficulty; Level IV: significant limitations; Level V: requires total assistance). (27)

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

Statistical Analyses

The null hypothesis was that documented bacteremia and suspected bacteremia during postnatal weeks two through four are not associated with limitations of cognition, executive function, academic achievement, or motor function at school age. A second null hypothesis was that each measure of function at 10 years of age was not differentially distributed among children with and without definite late bacteremia or suspected late bacteremia. Initially correlates of definite and suspected late bacteremia were assessed, 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 that are described by the authors of the assessments that were used. (22–24) Multinomial logistic regression models were created of the risk of a score ≥ 1 standard deviations below the normative mean of each assessment, or beyond the boundary of each assessment that the authors of that assessment considered within normal limits. Models included potential confounders [Black race, maternal education (≥ 12 years), public insurance, gestational age (23–24 and 25–26 weeks) and birth weight Z-score (< -2 and $-2, < -1$)]. Odds ratios (and 95% confidence intervals) were calculated for each 10-year characteristic associated with definite and suspected late bacteremia. Models take into account the correlation between children from the same pregnancy. Subjects with missing data were excluded from our analysis.

RESULTS

Sample characteristics

Children born to women who identified as Black, had no more than a high school education, or were eligible for government-provided health insurance were more likely than others to have had definite bacteremia. The lower the gestational age, the lower the birth weight, and the lower the birth weight Z-score, the higher the prevalence of definite bacteremia. The

prevalence of suspected late bacteremia varied much less with gestational age, birth weight, and birth weight Z-score (Table II) Intelligence, language, and achievement test scores (Definite bacteremia was associated with Z-scores ≤ -2 on assessments of verbal and non-verbal IQ, the Oral Expression subtest of the OWLS, and all four subtests of the WIAT-III (*i.e.*, Word Reading, Pseudoword Decoding, Spelling, and Numerical Operations) and with Z-scores > -2 and ≤ -1 for nonverbal IQ and spelling on the Spelling component of the WIAT-III. These associations were not observed with late suspected bacteremia (Table III)

Executive function and related assessments

Definite bacteremia was associated with Z-scores ≤ -2 on the DAS-II Working Memory assessment and Z-scores ≤ -2 on the following NEPSY-II subtests: Auditory Attention, Auditory Response Set, Inhibition Inhibition, Inhibition Switching, Animal Sorting, Arrows, and Geometric Puzzles. Children who had suspected bacteremia also had lower scores on the NEPSY-II Inhibition Switching, Animal Sorting, Arrows, and Geometric Puzzles assessments; however, their scores were intermediate between those seen for children who had definite bacteremia and those who did not have bacteremia. (Table III)

Sensorimotor impairment

Bacteremia, regardless whether definite or suspected, was not associated with low children's scores on either the Manual Ability Classification System or the Gross Motor Function Classification System. Children with either suspected or definite bacteremia were more likely than their peers without bacteremia to be legally blind in both eyes. Children with definite bacteremia were slightly more likely than other children to have a hearing impairment. (Table III)

Figure 1 shows the forest plots (28) of adjusted odds ratios and confidence intervals. When adjustment is made for Black race, maternal education, public insurance, gestational age, and birth weight Z-score categories, definite bacteremia was associated with increased risks of a Z-score ≤ -1 on both DAS-II Verbal and Nonverbal Reasoning, two NEPSY-II assessments (Arrows and Geometric Puzzles), and the Spelling component of the WIAT-III (top left panel). In contrast, suspected bacteremia was not associated with a low Z-score on any of the 18 DAS-II, NEPSY-II, and WIAT-III assessments subtests (top right panel).

After adjusting for DAS IQ ≤ -1 (in addition to the previously listed variables), many of these associations were lost, with definite bacteremia associated only with increased risk of a low score on the NEPSY-II Arrows assessment (bottom left panel). On the other hand, definite bacteremia was associated with decreased risk of a low score on the oral expression component of the OWLS, and of a low score on the DAS working memory component.

DISCUSSION

ELGANs who had documented bacteremia during the second to fourth postnatal week of life were at increased risk for intellectual impairment (low IQ) at 10 years of age. After adjustment for IQ, bacteremic children were no longer at increased risk of low academic achievement or low scores on executive function, consistent with the concept that lower intelligence is a mediator in the relationship between bacteremia early in life and such

impairments. Neither fine nor gross motor skills at school age were associated with neonatal bacteremia.

Late-onset bacteremia was not associated with executive or motor dysfunctions. This observation was an unexpected finding. Perhaps the effects of the inflammation associated with bacteremia do not act preferentially on the frontal lobes or their connections. (29) Alternatively, the complexity of cognition's components and the elaborate network connection involved (30) may explain why IQ is the most vulnerable function to exposure to inflammation.

The current study adds to accumulating evidence indicating that prevention of perinatal infection could be an effective strategy for improving the neurocognitive outcomes of individuals born extremely prematurely. Therapies that modulate inflammation, such as erythropoietin (31, 32) and melatonin, (31, 33) show promise as strategies to improve brain-related outcomes in newborns. The results of our study support antibiotic stewardship with a goal of improving morbidity and mortality, (34, 35) as the associations reported here apply only to confirmed bacteremia, rather than suspected bacteremia.

It is not clear why children who had definite bacteremia were at reduced risk of low scores on the OWLS oral expression component and the DAS working memory component. In comparing the risks evident before and after adjustment for IQ, it is apparent that OWLS oral expression and DAS working memory are closely associated with IQ. That association would be expected to account for a null relationship with definite bacteremia after IQ adjustment, and not a possibly protective effect. Until this finding is replicated, however, we prefer to just call attention to it and not yet invoke inflammatory preconditioning (36) or other possible explanations.

One strength of this study is that participants were enrolled based on their gestational age, rather than on their birth weight. This reduces the number of children with older gestational ages who would be included due to fetal growth restriction, which introduces bias (37). With a large sample of 889 participants, it is unlikely that important associations were missed. The high enrollment rate (92% of children eligible to participate at 10 years were enrolled) reduces the likelihood of "lost to follow-up" bias. Furthermore, examiners at 10 years were blinded to clinical histories, which reduces information bias.

The limitations of this study include the potential for residual confounding because what leads to definite and suspected bacteremia might also impact long-term outcomes. (38, 39) This might occur if gestational age does not capture all of the information about the immaturity-associated risk of bacteremia and brain damage. Our definition of late bacteremia differs from the traditional one.

In conclusion, the results of this study support of the hypothesis that late onset neonatal bacteremia is associated with low IQ at school age. This association was not present for suspected bacteremia. The low incidence of motor dysfunctions in our cohort and the lack of significant association between motor dysfunction and bacteremia are worthy of note to clinicians in counseling families of extremely preterm infants.

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ABBREVIATIONS

DAS-II	Differential Ability Scales, 2nd Edition
ELGAN	Extremely Low Gestational Age Newborn
GMFCS	Gross Motor Function Classification System
IQ	Intelligence Quotient

MACS	Manual Ability Classification System
NEPSY-II	NEuroPSYchological Assessment, 2nd Edition
NICU	Neonatal Intensive Care Unit
OWLS	Oral and Written Language Scales
WIAT-III	Wechsler Individual Achievement Test, 3rd Edition

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Figure 1.

Forest plots of odds ratios (ORs) and 95% confidence intervals of a Z-score -1 on each DAS-II and NEPSY-II neurocognitive assessment at age 10 associated with definite bacteremia and suspected bacteremia. Odds ratios in the top panel are adjusted for Black race, maternal education (< 12 years), public insurance, gestational age (23–24 and 25–26 weeks) and birth weight Z-score (< -2 and $-2, < -1$). Odds ratios in the bottom panel are also adjusted for DAS IQ -1 . DAS Verbal and Nonverbal Reasoning do not appear in the bottom panel since DAS IQ is the average of the two. Models in both panels take into account the correlation between children from the same pregnancy.

Table 1

Sample description among children classified by none, suspected, or definite late onset bacteremia.

	Late Onset Bacteremia			Total N
	None	Presumed	Confirmed	
Enrolled				1506
Survived to postnatal day 7				1387
Information about late bacteremia available	801	201	362	1364
Survived to postnatal day 28	770	189	331	1290
Survived to discharge/transfer home	728	183	304	1215
Survived to 2 years	718	179	296	1193
Survived to 10 years	717	178	296	1191
Recruited for 10-year follow-up	575	142	244	961
Enrolled for 10 year follow-up	532	139	223	884
Differential Ability Scales-II (DAS-II)	521	128	219	868
Oral and Written Language Scales (OWLS)	510	123	215	848
Wechsler Individual Achievement Test-III (WIAT-III)	520	127	217	864
Neuropsychological Assessment-II (NEPSY-II)	523	128	218	869

Table 2

Sample characteristics among children classified by none, suspected, or definite late onset bacteremia. These are **row** percents.

		Late onset bacteremia			Row N
		None	Suspecte	Definite	
Maternal characteristics					
Racial identity	White	65	14	21	552
	Black	50	14	36	224
	Other	58	17	24	95
Hispanic	Yes	58	14	28	86
	No	61	15	25	795
Age, years	< 21	56	19	25	115
	21–35	60	14	27	591
	> 35	65	15	21	178
Education, years	12	56	12	32	354
	> 12, < 16	62	14	24	199
	16	64	17	19	305
Single marital status	Yes	57	15	28	351
	No	62	14	24	533
Public insurance	Yes	53	15	32	304
	No	64	14	22	566
Perinatal characteristics					
Any antenatal corticosteroids	Yes	61	14	25	784
	No	54	16	30	99
Delivery complication	PE/PI	52	20	28	150
	Spontaneous	62	13	25	734
Newborn characteristics					
Sex	Male	59	15	25	453
	Female	61	14	25	431
Gestational age, weeks	23–24	47	19	35	187
	25–26	59	14	27	399

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			Late onset bacteremia			Row N
			None	Suspecte	Definite	
	27		70	12	17	298
Birth weight, grams	750		50	18	32	331
	751–1000		63	14	23	382
	> 1000		75	9	16	171
Birth weight Z-score	< -2		47	19	34	53
	-2, < -1		54	17	29	119
	-1		62	14	24	712
Maximum column N			532	129	223	884

Table 3

Distribution of intelligence, language, executive function, achievement subtest scores and sensorimotor impairment by bacteremia category in each category of late onset bacteremia. These are column percentages.

<i>IQ</i>	<i>Z-score</i>	<i>Late onset bacteremia</i>			<i>Row N</i>
		<i>None</i>	<i>Suspected</i>	<i>Definite</i>	
DAS-II Verbal	-2	13	16	28	150
	> -2, -1	18	17	22	162
DAS-II Nonverbal reasoning	-2	13	14	20	130
	> -2, -1	21	25	32	212
<i>Language</i>					
OWLS Listening Comprehension	-2	17	20	24	161
	> -2, -1	27	26	28	231
OWLS Oral Expression	-2	17	16	29	165
	> -2, -1	23	25	20	189
<i>Executive Function</i>					
DAS-II Working memory	-2	15	16	25	155
	> -2, -1	18	17	16	152
NEPSY-II Auditory Attention	-2	20	26	26	189
	> -2, -1	22	21	19	176
NEPSY-II Auditory Response Set	-2	17	23	25	169
	> -2, -1	27	29	27	232
NEPSY-II Inhibition Inhibition	-2	29	37	41	285
	> -2, -1	24	24	22	199
NEPSY-II Inhibition Switching	-2	23	30	37	229
	> -2, -1	29	33	27	242
NEPSY-II Animal Sorting	-2	24	29	39	246
	> -2, -1	30	33	28	260
<i>Processing Speed</i>					
NEPSY-II Inhibition Naming	-2	29	33	35	266
	> -2, -1	20	21	19	169

IQ	Z-score	Late onset bacteremia			Row N
		None	Suspected	Definite	
Visual Perception					
NEPSY-II Arrows	-2	22	28	35	225
	> -2, -1	21	20	27	194
NEPSY-II Geometric Puzzles	-2	13	20	24	143
	> -2, -1	21	21	27	190
Fine Motor Function					
NEPSY-II Visuomotor Precision	-2	20	22	22	177
	> -2, -1	35	33	35	299
Academic Achievement					
WIAT-III Word reading	-2	9	13	19	106
	> -2, -1	16	18	20	149
WIAT-III Pseudoword decoding	-2	12	14	20	126
	> -2, -1	15	20	19	145
WIAT-III Spelling	-2	8	12	18	95
	> -2, -1	15	14	20	136
WIAT-III Numerical operations	-2	14	14	24	141
	> -2, -1	22	25	24	199
Sensorimotor function					
Manual ability classification system	3	8	12	12	85
Gross motor function classification system	3	5	5	6	44
Visual Impairment	Yes	2	6	7	34
Hearing impairment	Yes	3	3	7	32
Maximum column N		532	129	223	884