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Socioemotional dysfunctions at age 10 years in extremely preterm newborns with late-onset bacteremia

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INTRODUCTION

Children born extremely preterm (EP)¹ are at a higher risk of social impairment than those born at term. These difficulties emerge early and persist throughout childhood.”(1) Among

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EP children, the “preterm behavioral phenotype,” a constellation of disorders and symptoms characterized by anxiety, inattention, and social and communication, problems has been described.(2) Some of these mental health disorders might account for the lower parent-reported health-related quality of life among extremely preterm infants than in their peers born at term.(3)

EP newborns are at increased risk of bacteremia,(4) which increases the risk of abnormal brain structure.(4) Some of this increased risk might reflect the propensity of bacteremia to promote systemic inflammation,(5) which is also associated with disturbed brain structure. (6-8) This, in turn, is associated with socio-emotional limitations.(9) We thus reasoned that very preterm newborns who experience bacteremia and its treatment might be at increased risk of social and related impairments.

The ELGAN study, with its relatively large extremely low gestational age cohort, detailed collection of information about bacteremia during the second through fourth postnatal weeks,(5) and about socio-emotional and communication competence 10 years later,(10) provided us with the opportunity to explore to what extent bacteremia might contribute to these social dysfunctions.

METHODS

Participants

The ELGAN study is a multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.(11) A total of 1506 infants born before the 28th week of gestation were enrolled from 2002-2004, and 1200 survived to 2 years. At age 2 years, 1102 had a developmental assessment.(11) For the current study, we targeted recruitment efforts at 966 of the 1102 children because we had collected neonatal blood specimens for assessment of systemic inflammation. Of the 966 eligible for recruitment at age 10 years, 889 children (89%) enrolled. Enrollment and consent procedures for this follow-up study are approved by the Institutional Review Boards of all participating institutions.

Demographic and pregnancy variables—After delivery, a trained research nurse interviewed each mother in her native language using a structured data collection form and following procedures defined in a manual. Shortly after the mother’s discharge, the research nurse reviewed the maternal chart using a second structured data collection form. The medical record was relied on for events following admission. The clinical circumstances that led to preterm delivery are operationally defined using data from the maternal interview and data abstracted from the medical record.(11) Each mother/infant pair was assigned to the category that described the primary reason for the preterm delivery.

¹ ADHD, Attention Deficit Hyperactivity Disorder; ADI-R, Autism Diagnostic Interview-Revised; ADOS-2, Autism Diagnostic Observation Schedule, 2nd Edition; ASD, Autism Spectrum Disorder; CCC-2, Children’s Communication Checklist, 2nd Edition; CHQ, Child Health Questionnaire; CSI-4, Child Symptom Inventory, 4th Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ELGAN, Extremely Low Gestational Age Newborn; EP, Extremely Preterm; NICU, Neonatal Intensive Care Unit; SCQ, Social Communication Questionnaire; SRS-2, Social Responsiveness Scale, 2nd Edition.

Newborn variables—The gestational age estimates are based on a hierarchy of the quality of available information. Most desirable are estimates based on the dates of embryo retrieval, intrauterine insemination, or fetal ultrasound before the 14th week (62%). When unavailable, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the neonatal intensive care unit log (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.(11) Because early onset sepsis can be a consequence of chorioamnionitis,(12) we made late-bacteremia our focus. Documented late-bacteremia was defined as recovery of an organism from blood drawn during weeks 2, 3 or 4. Specific organisms are not identified. Suspected infections are culture-negative, but the infant received antibiotics for more than 72 hours.

Procedures—All families who participated in the previous follow up are contacted by mail and then by phone to invite them to participate in the 10-year follow up. Lost to follow-up families are searched for on state vaccination registries, and other openly-available websites. Facebook was used where approved by the local institution's IRB.

Families willing to participate are scheduled for one visit during which all of the measures reported here are administered in 3 to 4 hours, including breaks. While the child was tested, the parent or caregiver completed questionnaires regarding the child's medical and neurological status and behavior. Children who met screening criteria for possible autism were brought back on a separate date to undergo in-depth testing for autism with the Autism Diagnostic Interview-Revised (ADI-R), and the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2).

Socioemotional and behavioral assessments at age 10 years Assessment instruments

We used four questionnaires to obtain information about the preterm behavioral phenotype and/or the presence of autism spectrum disorder. The Child Symptom Inventory-4 (CSI-4) provides the parent's and the teacher's perception of whether or not the child had features of emotional disorders, ADHD and autism. The Social Responsiveness Scale (SRS) provides information about the severity of social deficits (social awareness, social cognition, social communication, and social motivation), while the Children's Communication Checklist-2 (CCC-2) provides information about social language skills (initiation, discourse, stereotyped language, use of context, non-verbal communication, and social relations).(11) The ADOS-2 provides diagnostic information regarding autism spectrum disorder. Together, these questionnaires offer a broad and relatively complete picture of each child's behavior, "emotional intelligence," and social communication abilities.

Child Symptom Inventory-4—While the child was being evaluated during 10-year follow-up, the parent or caregiver completed questionnaires regarding the child's medical and neurological status and behavior, including the Child Symptom Inventory-4 (CSI-4) Parent Checklist.(11, 13) The child's current teacher was also asked to complete CSI-4

Teacher Checklist. Cut-offs in the CSI-4 manual were used to assign CSI-4 diagnostic classifications.

Social Responsiveness Scale, Second Edition (SRS-2)—The SRS-2 identifies autism-related social impairment and quantifies its severity.(14) This 65-item instrument provides a total score reflecting severity of social deficits, as well as five subscale scores: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior.

Children's Communication Checklist-2 (CCC-2)—The Children's Communication Checklist-2 (CCC-2) has 70 items that assess speech, vocabulary, sentence structure, and social language skills.(15) The 10 subscales are discourse, syntax, semantics, coherence, inadequate initiation, stereotyped language, use of context, non-verbal communication, social relations, and interests. We calculated Z-scores using normative data.(11)

Autism Spectrum Disorder (ASD) assessment—All children are screened by parent report for risk of ASD with the Social Communication Questionnaire (SCQ).(11) Children determined to be at risk of ASD based on the SCQ or because of clinical suspicion are further assessed with the ADI-R, an in-depth parent interview.(11) Children meeting ADI-R modified criteria for ASD(11) are administered the ADOS-2 by experienced child psychologists who did not have knowledge of the child's SCQ results, ADI results, or prior clinical history.(11) All children meeting standardized research criteria for ASD on both the ADI-R and ADOS-2 are classified as having ASD.(16) Additional details regarding the diagnostic process are available elsewhere.(16)

Data Analyses

We sought to determine if children who had documented or suspected bacteremia during postnatal weeks 2 through 4 are at higher risk than their non-bacteremic peers of socioemotional, communication difficulties, and autism spectrum disorder at age 10 years. We also sought to determine if any increased social impairment we noted was independent of autism spectrum disorder. We began by searching for potential confounders, including the maternal demographic characteristics and the child's characteristics at birth (Table 1).

We used Z-scores to allow for the differences in age at the time of the 10-year assessment, and to facilitate a comparison of our findings to those reported for children presumably born very near term. The Z-scores are based on distributions of values reported for the historical normative samples described by the authors of the assessments utilized.(11) We created logistic regression models of the risk of a score one or more standard deviations below the normative mean of each assessment. These models, which included potential confounders (including sex, birth weight Z-score < -1, and mother's eligibility for government-provided medical insurance as a proxy for socio-economic status), allowed us to calculate the odds ratios (and 95% confidence intervals) for each 10-year characteristic associated with definite and suspected late bacteremia.

RESULTS

The tables below can be read in two related ways. One approach is to compare children who had definite bacteremia to children who did not have bacteremia. The other is to see whether children who had suspected bacteremia are more similar to those who had confirmed bacteremia, or to those with no bacteremia at all.

Sample characteristics (Table 1)

Children born to Black women, those who had no more than a high school education, and those eligible for government-provided health insurance (i.e., Medicaid) are more likely than others to have definite late-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 late-bacteremia. The prevalence of suspected late-bacteremia varied much less with gestational age, birth weight, and birth weight Z-score.

Parent-completed Child Symptom Inventory-4 (CSI-4) (Supplement Table 1)

Compared to their peers without bacteremia, girls with suspected or definite bacteremia had similarly elevated prevalence of symptoms of the inattentive form of ADHD, oppositional-defiant disorder, and specific phobia. Boys with definite bacteremia had higher rates of symptoms of the inattentive form of ADHD, oppositional-defiant disorder, motor and vocal tics, as well as encopresis.

Teacher-completed Child Symptom Inventory-4 (CSI-4) (Supplement Table 2)

Girls and boys with definite bacteremia did not have a higher prevalence of any teacher-identified behavioral disorder than their peers. Compared to their peers without bacteremia, girls with suspected bacteremia had higher rates of symptoms of inattentive ADHD, specific phobia, motion tics, and social phobia. Boys with suspected bacteremia had higher prevalence of symptoms of specific phobia, obsessions, motion tics, and vocal tics.

Social Responsiveness Scale (SRS) and ASD Assessment (Supplement Table 3)

Children with suspected or definite bacteremia are more likely than their peers to have high SRS total scores, indicative of social impairment, and to have high scores on several SRS subscales, including Social Awareness, Social Communication, and Autistic Mannerisms. Children with suspected or definite bacteremia are about twice as likely as those without bacteremia to be diagnosed with ASD on the ADOS-2. Even after excluding children with a diagnosis of ASD based on the ADOS-2, children with suspected or definite bacteremia have higher SRS scores than their peers.

Children's Communication Checklist (CCC-2) (Supplement Table 4)

Two separate patterns of elevated prevalence of low (impaired) scores on the CCC-2 are evident. One pattern was of progressively higher prevalence in moving from no bacteremia, to suspected bacteremia, and on to definite bacteremia. This was seen for low scores on structural language components of speech, syntax, and semantics, as well as the scripted language component of pragmatic language. A pattern of similarly high prevalence among

children with suspected or definite bacteremia was seen for low scores on the structural language component of coherence, the pragmatic language components of context and nonverbal communication, social relations, and interests. Children with suspected or documented bacteremia are also more likely than others to have a score in the lowest quartile for structural language, as well as a moderately low general composite score.

Odds ratios of Socioemotional and Communication Outcomes (Figures 1–3)

In the figures, we present odds ratios and confidence intervals in forest plots.⁽¹⁷⁾ The black circle near the middle of each horizontal line represents the point estimate of the odds ratio, while the vertical tips of the line represent the 95% boundaries of the confidence interval. Statistical significance of an increased risk is indicated by a left boundary of a confidence interval that is to the right of the vertical line (representing an odds ratio of 1.0), while statistical significance of a decreased risk is indicated by a right boundary of a confidence interval that is to the left of the vertical line.

Odds ratios of disorders identified with the Child Symptom Inventory-4 (CSI-4) (Figure 1)

Based on the findings in Supplement Table 1 and on characteristics of the preterm behavioral phenotype, we assessed the risk for symptoms of inattentive ADHD, oppositional-defiant disorder, generalized anxiety, specific phobias, and motor and vocal tics associated with culture-proven and suspected bacteremia. After adjustment for low gestational age, fetal growth restriction, maternal eligibility for government-provided insurance, and $IQ < 70$, no statistically increased or decreased risks for parent-reported entities are present for either form of bacteremia. The risks for teacher-reported inattention, specific phobias, and both motor and vocal tics are significantly reduced among children who had documented bacteremia, while the risks for specific phobias and motor tics are increased among children with suspected bacteremia.

Odds ratios of high Social Responsiveness Scale (SRS) scores and ASD Assessment (Figure 2)

After adjustment for potential confounders, definite bacteremia was associated with increased risk for a high total SRS score, as well as high scores on all the SRS subscales except Autistic Mannerisms (left lower panel). Suspected bacteremia was associated with increased risk for high scores on two SRS components: Social Cognition and Social Communication (right lower panel). The increased risk of autism (based on the ADOS-2) associated with definite bacteremia was not statistically significant.

Low scores on the Children's Communication Checklist-2 (CCC-2) (Figure 3)

After adjustment for potential confounders, definite bacteremia was associated with increased risk for low scores on the following CCC-2 subscales: Semantics, Coherence, Scripted language, and Context (left lower panel). Low scores on the Syntax and Interests subscales did not reach statistical significance. In contrast, suspected bacteremia was associated with an increased risk for a low score on the Coherence and Context subscales (right lower panel).

DISCUSSION

Our main finding is that ELGANs who had suspected bacteremia and those who had documented bacteremia during some of the first postnatal weeks were at increased risk for indicators of socioemotional and communication impairments 10 years later, independent of an autism diagnosis. Children who experienced documented bacteremia were at reduced risk for teacher-reported inattentive symptoms of ADHD, specific phobia, as well as motor and vocal tics.

Reduced risk of teacher-reported behaviors

The risks for teacher-reported inattention, specific phobias, and motor and vocal tics are significantly reduced among children who had documented bacteremia. We cannot invoke over-adjustment(18) as an explanation because even before adjustment, documented bacteremia was associated with reduced risks. Because these inverse relationships are not reduced by adjustment, we are left with our provocative findings. Given that our questionnaires (CSI-4, SRS, CCC-2) are screening tests, it is possible that parents are over-reporting or teachers are underreporting. Discrepancies in reporting between parents and teachers have been previously noted, particularly when behaviors are subtle or internalized. (19) Considering we are not aware of any biological explanation for these findings, we are left with the possibility of a chance finding.

Bacteremia associated with social limitations, but not with ASD

High scores on the SRS(20) and the CCC-2(21) are associated with ASD characteristics. We found a small but non-statistically significant increased risk of autism on the ADOS-2. Perhaps this is because children with pragmatic, social, and communication difficulties do not completely overlap (as a group) those displayed by children who have most of the characteristics of autism.(22) Thus, the social limitations we found associated with bacteremia do not support a strong association between bacteremia and ASD. This may be due to a limited sample size and a type II error.

After excluding all children given a diagnosis of ASD based on the ADOS-2, the social impairment associated with late bacteremia remain, suggesting the social impairment cannot be solely attributed to children who have ASD.

Neonatal infection/inflammation and the risk of the components of the Preterm Behavioral Phenotype

For both the fetus and the newborn, neuro-immune stimulation and/or dysfunction can have adverse effects on children's behavior.(23) Thus, we are not surprised by our finding of a relationship between a very potent inflammatory stimulus, represented by suspected or definite bacteremia, and some components of the preterm behavioral phenotype among 10-year olds.

How might neonatal bacteremia contribute to the occurrence of social-communication impairments?

We do not yet have documentation that neonatal bacteremia in children born extremely preterm specifically diminishes the connectivity of pathways involved in social and related capabilities at school age. In animal models, however, bacteremia-related phenomena promote cytokine and chemokine synthesis, impaired oligodendrocyte maturation, microglial activation, and diminished connectivity of brain pathways.(4, 24-26) It is possible that bacteremia contributes to the occurrence of numerous dysfunctions of the perinatal behavioral phenotype as a consequence of an inflammatory response that damages cerebral white matter rather diffusely, resulting in diminished connectivity among pathways. The treatment of bacteremia itself could play a role. Although antibiotics are capable of interfering in myelination,(27) when administered to newborn rodents exposed to intense inflammatory stimuli (i.e., lipopolysaccharide or E. coli sepsis), they can minimize myelination delay(28) and late neurobehavioral limitations.(29) Antibiotics administered shortly after birth alter the gut microbiome, and their use in early life has been associated with behavioral difficulties and symptoms of depression later in childhood.(30, 31) Given the increased brain immaturity at birth in those born extremely preterm, antibiotic use might have lasting neurocognitive effects.

Limitations and strengths

Because what contributes to definite and suspected bacteremia might also influence long-term socioemotional outcomes,(32) the main limitation of this study is the potential for residual confounding. Second, we did not have any information about family history of ADHD or about other disorders and dysfunctions, and so could not assess familial contributions or gene-environment interactions. Third, we had limited power for infrequently-reported disorders/dysfunctions, such as oppositional-defiant disorder and generalized anxiety in boys, as acknowledged by the parent. Fourth, because our outcomes are subjective and based on screening instruments, the quality might be limited.

Strengths of this study include both its size and the criteria for enrollment. The high enrollment rate (89% of children eligible to participate at 10 years enrolled) and modest attrition reduces the likelihood of follow-up bias and of missing important associations. Furthermore, the large number of infants allows for the identification of statistically significantly elevated risk ratios of less than 2.0. In addition, enrollment was based gestational age, rather than on birth weight, thereby minimizing confounding associated with fetal growth restriction. Finally, all antecedent data were collected years before identification of each child's social limitations.

In conclusion, infants born before 28 weeks' gestational age who had late-bacteremia in the first post-natal month appear to be at increased risk of numerous indicators of social impairment at 10 years of age. This paper broadens the developmental outcomes that have been associated with neonatal sepsis in very preterm infants, and can direct future research efforts to inform prevention of such outcomes. There also are implications for the clinicians who assume responsibility for developmental surveillance and monitoring of very preterm children who survive neonatal sepsis and similar perinatal conditions, such as necrotizing

enterocolitis. Great emphasis should be placed on vigilance, as the predominating outcomes we have found are subtle and easily overlooked.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Extremely preterm newborns are at increased risk for the “preterm behavioral phenotype.”
- We examined the communication and socioemotional characteristics associated with late-bacteremia in 10-year-olds born extremely preterm
- This prospective cohort study looked at definite late-bacteremia, suspected late-bacteremia, and no bacteremia.
- Definite late-bacteremia was associated with a small, non-statistically significant increased risk of autism.
- Extremely preterm infants with suspected or definite late-bacteremia were at increased risk of social and communication impairments at 10 years of age.

Figure 1. Forest plots of odds ratios (ORs) and 95% confidence intervals of a positive screen on Child Symptom Inventory (CSI-4) disorders

ORs in the top panel are for parent report and ORs in the bottom panel are for teacher report. The ORs are adjusted for public insurance, sex, gestational age 23-24 weeks, birth weight Z-score < -1, and DAS IQ < 70. The upper bound of the confidence interval marked with * is truncated for this display.

Figure 2. Forest plots of odds ratios (ORs) and 95% confidence intervals of a T score ≥ 60 on the Social Responsiveness Scale (SRS) subtests, and of documented characteristics of ASD based on the Autism Diagnostic Observation Schedule-2 (ADOS-2) at age 10 associated with definite bacteremia and suspected bacteremia

Odds ratios are adjusted for Black race, maternal education (≥ 12 years), public insurance, gestational age (23-24 and 25-26 weeks) birth weight Z-score (< -2 and $-2, < -1$), and DAS IQ ≥ 1 .

Figure 3. Forest plots of odds ratios (ORs) and 95% confidence intervals of a Z-score ≤ -1 on the Children's Communication Checklist-2 (CCC-2) subtests at age 10 associated with definite bacteremia and suspected bacteremia

Odds ratios are adjusted for Black race, maternal education (≥ 12 years), public insurance, gestational age (23-24 and 25-26 weeks) birth weight Z-score (< -2 and $-2, < -1$), and DAS IQ ≤ -1 .

Table 1

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

Characteristics	Late onset bacteremia			Row	
	None	Suspected	Definite	N	
Maternal					
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					
Any antenatal corticosteroids	Yes	61	14	25	784
	No	54	16	30	99
Delivery Indication	Maternal/fetal	52	20	28	150
	Spontaneous	62	13	25	734
Newborn					
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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Characteristics	Late onset bacteremia				Row N
	None	Suspected	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
Max column N		532	129	223	884