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

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1. Introduction

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

2. Methods

2.1. 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 to 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.

Abbreviations: 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

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2.1.1. 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.

2.1.2. 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 pre-eclampsia 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 > 72 h.

2.1.3. 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 h, 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).

2.2. Socioemotional and behavioral assessments at age 10 years

2.2.1. 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.

2.2.1.1. 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.

2.2.1.2. 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.

2.2.1.3. 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].

2.2.1.4. 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].

2.3. 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.

3. 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.