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Antenatal and neonatal antecedents of learning limitations in 10-year old children born extremely preterm



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ABSTRACT

Background: Children born extremely preterm are at increased risk of learning limitations. Aim: To identify the antecedents of learning limitations of children born extremely preterm. Study design: Prospective observational study from birth to age 10 years. Variables entered into the multinomial logistic regression analyses were ordered temporally, with the earliest occurring predictors/covariates of each learning limitation risk entered first and not displaced by later occurring covariates. Subjects: 874 children who were born before the 28th week of gestation. Outcome measures: A reading limitation was defined as a score one or more standard deviations below the expected mean on the WIAT-III Word Reading and a mathematics limitation was defined as a similarly low score on the Numerical Operations component. Results: 56 children had a "reading ONLY" limitation, 132 children had a "math ONLY" limitation and 89 children had "reading AND math" limitations. All risk profiles included an indicator of socioeconomic disadvantage (e.g., mother's "racial" identity and eligibility for government-provided health care insurance), an indicator of newborn's immaturity/vulnerability (e.g., high illness severity score, receipt of hydrocortisone, and/ or ventilator-dependence at 36 weeks post-menstruation), and all but the math only limitation included an indicator of fetal growth restriction and inflammation (i.e., pregnancy urinary tract infection or late ventilatordependence). Conclusions: The themes of socioeconomic disadvantage and immaturity/vulnerability characterize all three risk

Conclusions: The themes of socioeconomic disadvantage and immaturity/vulnerability characterize all three risk profiles, while the themes of fetal growth restriction and inflammation are characteristic of a reading limitation only, and the reading and math limitations entity.

1. Introduction

Children born very preterm are at higher risk of reading and math limitations than children born at term [1]. Why should this be?

In the general pediatric population, the antecedents of mathematics limitations include low socioeconomic status (SES) [2], and its correlate African-American identification [2]. Among children born preterm, the antecedents of mathematics limitations include socioeconomic disadvantage [1], and its correlates cigarette smoking during pregnancy [3], as well as indicators of immaturity (low gestational age, and not receiving breast milk while in the neonatal unit) [1], and inflammation, including bronchopulmonary dysplasia/chronic lung disease of prematurity (BPD/CLD) [3], (need for) postnatal dexamethasone therapy

to reduce the risk of BPD/CLD [4], and necrotizing enterocolitis (NEC) requiring surgery or drainage [1].

The antecedents of reading limitations in the general population include socioeconomic disadvantage [2], and a correlate, African-American identification [2]. Low socioeconomic position is also an antecedent of reading limitations among children who had very low birth weight [5], and among children born before the 26th week of gestation [1]. Other antecedents of low reading scores in this very high risk group of former extremely low gestational age newborns (X-EL-GANs), included indicators of immaturity (low gestational age, no receipt of breast milk, neonatal illnesses, duration of stay in neonatal unit), and indicators of inflammation (NEC requiring surgery or drainage) [1].

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Abbreviations: BPD/CLD, bronchopulmonary dysplasia/chronic lung disease; NEC, necrotizing enterocolitis; SES, socioeconomic status; WIAT-III, Wechsler Individual Achievement Test-III; X-ELGANs, former extremely low gestational age newborns

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Among children born preterm or at a very low birth weight, a larger literature is devoted to the correlates of broad, often variously-defined learning limitations categorized as grade failure [6], special educational needs [7], use of special services [6], learning problems [8], placement in a special classroom [9], educational impairment [9], low teacher rating of academic achievement [9], and school difficulties [10], Almost all of these identified low gestational age and/or low birthweight as the prime risk factor. "Small-for-gestational-age" (lowest decile birth weight for gestational age) also placed the very preterm newborn at increased risk of school difficulties [10], and need for special education [11]. In the studies that evaluated socioeconomic status, socioeconomic disadvantage [6,9] was also associated with sub-optimal academic achievement.

We sought to identify the antecedents of reading and math limitations in X-ELGANs and to see in what ways the risk profiles of learning limitations among 10-year children born extremely preterm were similar to, or different from, the risk profiles of structural and functional indicators/correlates of brain damage. We were able to do this because the ELGAN Study evaluated 732 X-ELGANs at age 10 years who had an IQ \geq 70 and assessments of the Word Reading and Numerical Operations components of the WIAT-III. We limited the analyses reported here to those with an IQ \geq 70 because we wanted to identify the antecedents of reading and math limitations and not the antecedents of low IQ.

2. Methods

2.1. Participants

The ELGAN study is a multi-center observational study designed to identify characteristics and exposures associated with increased risk of structural and functional neurologic disorders in extremely preterm infants [12]. During the years 2002–2004, women delivering before 28 weeks gestation at one of 14 participating institutions were asked to enroll in the study. A total of 1249 mothers of 1506 ELGANs consented to participate (Table 1). Enrollment and consent processes were approved by the individual institutional review boards.

Ten years later, we invited 966 children to return for an age-appropriate assessment of cognition, executive function, behaviors, and achievement. They were selected because the concentrations of inflammation-related proteins in their blood collected during the first postnatal month had been measured. Of these 966 children, 889 (92%) returned for follow up and 874 were administered the neurocognitive tests. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

2.2. Antecedents

Information about the characteristics and exposures considered potential antecedents is included in the appendix, as are tables that contain each of the candidates, and summary text describing the contents of the tables.

2.3. Procedures at age 10 years

The families of all children whose development was assessed at age 2 years 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 searched for on state vaccination registries, and other openly-available websites. Facebook was also used where approved by the local institution's institutional review board.

Families willing to participate were scheduled for one visit during which all of the measures reported here were administered in 3 to 4 h, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session.

2.4. General cognitive ability

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II Verbal and Nonverbal Reasoning scales [13]. We required that children have scores of 70 or higher on both scales to be included in our sample for these analyses.

2.5. Academic function

The Wechsler Individual Achievement Test-III (WIAT-III) provides grade- and age-adjusted standard scores for the Word Reading and Numeric Operations subtests [14]. As have others [15–17], we defined each learning limitation as a *Z*-score ≤ -1 (*i.e.*, below the 16th centile, which is equivalent to a score \leq 85) on a grade-based WIAT-III achievement test. Thus, we identified four mutually-exclusive groups, reading limitation only (Word Reading *Z*-scores ≤ -1 , Numerical Operations *Z*-scores > -1), math limitation only (Numerical Operations *Z*-scores ≤ -1 , Word Reading *Z*-scores > -1), both reading and math limitations (Word Reading *Z*-scores ≤ -1 , Numerical Operations *Z*scores ≤ -1), and neither limitation (Word Reading *Z*-scores > -1, Numerical Operations *Z*-scores > -1) (Table 1).

2.6. Data analyses

We evaluated the generalized form of the null hypotheses that each of the three learning limitations is not associated with any maternal, pregnancy, delivery, or postnatal characteristic or exposure in children who did not have a major impairment in cognitive function (DAS \geq 70). We began with univariate analyses (Appendix Tables 1–9), which identified candidate variables for the multivariate logistic regression analyses (Table 2). Because postnatal phenomena can be influenced by antepartum phenomena, the variables entered into the multinomial logistic regression analyses were ordered temporally, with the earliest occurring predictors/covariates of each learning limitation risk entered first and not displaced by later occurring covariates [18].

We used a step-down procedure seeking a parsimonious solution without interaction terms. The contributions of relevant variables are presented as risk ratios with 95% confidence intervals. The risk ratio for each variable expresses the increased or decreased risk of each learning limitation in one category of a characteristic or exposure relative to the other.

3. Results

3.1. Sample description (Table 1)

Of the 889 children who returned at age 10 years, 732 had an IQ of at least 70 and completed the WIAT-III assessment. Of these children, who comprise the sample for this report, 56 are identified as having a reading limitation only (defined as a Word Reading *Z*-score ≤ -1 and a Numerical Operations Z-score ≥ -1), 132 as having a math limitation only (*i.e.*, Numerical Operations Z-score $\leq -1 +$ Word Reading Z-score ≥ -1), and 89 as having both reading and math limitations (*i.e.*, Word Reading Z-score $\leq -1 +$ Numerical Operations ≤ -1).

3.2. Univariable analyses (Appendix Tables 1-9)

The Appendix tables display the prevalences of the three learning limitation entities among children classified by maternal, pregnancy, and newborn characteristics.

In this sample, 8% of children had a reading limitation, 18% had a math limitation, and 12% had both reading and math limitations. We identify higher prevalences as a prevalence that is 5 percentage points higher than these (*e.g.*, 13% for reading, 23% for math, and 17% for

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