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Neonatal systemic inflammation and the risk of low scores on measures of reading and mathematics achievement at age 10 years among children born extremely preterm

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ABSTRACT

Background: Difficulties with reading and math occur more commonly among children born extremely preterm than among children born at term. Reasons for this are unclear.

Methods: We measured the concentrations of 27 inflammatory-related and neurotrophic/angiogenic proteins (angio-neurotrophic proteins) in multiple blood specimens collected a week apart during the first postnatal month from 660 children born before the 28th week of gestation who at age 10 years had an IQ ≥ 70 and a Wechsler Individual Achievement Test 3rd edition (WIAT-III) assessment. We identified four groups of children, those who had a Z-score ≤ −1 on the Word Reading assessment only, on the Numerical Operations assessment only, on both of these assessments, and on neither, which served as the referent group. We then modeled the risk of each learning limitation associated with a top quartile concentration of each protein, and with high and lower concentrations of multiple proteins.

Results: The protein profile of low reading scores was confined to the third and fourth postnatal weeks when increased risks were associated with high concentrations of IL-8 and ICAM-1 in the presence of low concentrations of angio-neurotrophic proteins. The profile of low math scores was very similar, except it did not include ICAM-1. In contrast, the profile of low scores on both assessments was present in each of the first four postnatal weeks. The increased risks associated with high concentrations of TNF-α in the first two weeks and of IL-8 and ICAM-1 in the next two weeks were modulated down by high concentrations of angio-neurotrophic proteins.

Conclusions: High concentrations of angio-neurotrophic proteins appear to reduce/moderate the risk of each learning limitation associated with systemic inflammation. The three categories of limitations have protein profiles with some similarities, and yet some differences, too.

1. Introduction

Compared to children born at term, those born very preterm are at increased risk of reading (Levandowski et al., 2016) and related limitations (Guarini et al., 2010), and math limitations (Simms et al., 2013; Simms et al., 2015; Tatsuoka et al., 2016; Taylor et al., 2009; Clark

Abbreviations: Ang-1, Angiopoietin1; Ang-2, Angiopoietin-2; BDNF, Brain-Derived Neurotrophic Factor; bFGF, basic Fibroblast Growth Factor; CRP, C-Reactive Protein; DAS-II, Differential Ability Scales–II; EPO, Erythropoietin; ICAM-1, Intercellular Adhesion Molecule −1; IGF-1, Insulin-like growth factor-1; IGFBP-1, Insulin-like growth factor binding protein-1; IL-1 β, Interleukin-1 β; IL-6, Interleukin-6; IL-6R, Interleukin-6 Receptor; IL-8, Interleukin-8; KBIT-2, Kaufman Brief Intelligence Test-2; LL, Learning limitation; MMP-9, Matrix Metalloproteinase-9; MPO, Myeloperoxidase; NT-4, Neurotrophin-4; PIGF, Placenta Growth Factor; RANTES, Regulated upon Activation Normal T-cell Expressed and Secreted; SAA, Serum Amyloid A; TNF-R1, Tumor Necrosis Factor-α Receptor-1; TNF-R2, Tumor Necrosis Factor-α Receptor-2; TNF-α, Tumor Necrosis Factor-α; TSH, Thyroid-Stimulating Hormone; VCAM-1, Vascular Cell Adhesion Molecule −1; VEGF, Vascular endothelial growth factor; VEGF-R1, Vascular endothelial growth factor Receptor-1; VEGF-R2, Vascular endothelial growth factor Receptor-2; WIAT-III, Wechsler Individual Achievement Test-III

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et al., 2014). These children are more likely than others to have structural and functional impairments of the brain (Scott et al., 2011; Ashkenazi et al., 2013; Feldman et al., 2012; Travis et al., 2015; Martin et al., 2015).

We reasoned that if very preterm children who had systemic inflammation during the first postnatal month are more likely than others to have structural and/or functional abnormalities of the brain (Mann and Kahana, 2015; Hartkopf et al., 2017; Korzeniewski et al., 2015; O'Shea et al., 2014), and children who have structural and/or functional abnormalities of the brain are more likely than others to have learning limitations (Scott et al., 2011; Ashkenazi et al., 2013; Feldman et al., 2012; Travis et al., 2015; Martin et al., 2015), then children who had systemic inflammation during the first postnatal month might be at increased risk of learning problems.

The "paucity of protectors" hypothesis offers one explanation for why extremely preterm newborns are at increased risk of limitations of brain development, and of brain damage. According to this hypothesis the mother and/or placenta provide the fetus with proteins needed for brain maturation, and birth before the newborn can synthesize adequate amounts of these proteins deprives the brain of needed brain-maturation enhancers (Reuss et al., 1994). These proteins with neurotrophic properties, which are often growth factors, are now recognized as having angiogenic properties (Su et al., 2018; Kermani et al., 2005; Usui et al., 2014), and capable of reducing the risk of brain damage and/or promoting repair (Larpthaveesarp et al., 2015; Wagenaar et al., 2017) Some of these proteins are viewed as mainly neurotrophic, while others are primarily considered angiogenic (Jin et al., 2002; Sun et al., 2003). Regardless, these proteins almost invariably have both neurotrophic and angiogenic properties (Sun et al., 2003; Madri, 2009; Meng et al., 2014; Rosa et al., 2010; Marteau et al., 2011; Liu et al., 2009; Wang et al., 2015; Hansen et al., 2008; Kosacka et al., 2006). prompting the names "angioneurins" (Zacchigna et al., 2008; Giampietro et al., 2015; Shin et al., 2010; Finkelstein et al., 2010; Nag, 2011; Saito et al., 2011; Liu et al., 2014) and "angioglioneurins." (Lafuente et al., 2012). To emphasize the trophic properties of these proteins, we prefer the name "angio-neurotrophic protein."

Data from the ELGAN (Extremely Low Gestational Age Newborn) Study provided an opportunity to explore this possibility because of the availability of the concentrations of 27 proteins with inflammation-related and/or neurotrophic/angiogenic properties in blood specimens obtained during the first postnatal month from children born before the 28th week of gestation and assessments of their educational achievements at age 10 years with the Wechsler Individual Achievement Test, Third Edition (WIAT-III).

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 (O'Shea et al., 2009). A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002–2004 and 1198 survived to age 10 years. At age 10 years, 966 of these were recruited for an age-appropriate assessment of cognition, executive function, behaviors, and achievement, 889 (92%) returned for follow up, and 874 were administered the neurocognitive tests (Table 1). Because children who had early systemic inflammation are at heightened risk of cognitive impairment (Kuban et al., 2017), and children who are cognitively impaired do not do well on academic achievement tests, we wanted to restrict our search for any relationship between early systemic inflammation and learning limitations not attributed to global limitation to children who were not cognitively impaired. Thus, the sample for the analyses presented here is restricted to the 666 children who had a DAS-II verbal IQ ≥ 70 and non-verbal IQ ≥ 70. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

Table 1
Sample description.

	Yes
Enrolled	1506
Survived to age 10 years	1198
Recruited for assessment at age 10 years	966
Returned for an assessment at age 10 years	889
Proteins measured in blood collected on 2 separate days	857
DAS-II verbal IQ ≥ 70 and non-verbal IQ ≥ 70	666
Word Reading and Numberical Operations Z-scores available	660
Word Reading Z-score ≤ −1 + Numerical Operations Z-score > −1	48
Numerical Operations Z-score ≤ −1 + Word Reading Z-score > −1	113
Word Reading Z-score ≤ −1 + Numerical Operations ≤ −1	69
Word Reading Z-score > −1 + Numerical Operations > −1	430

2.2. Procedures

All families who participated in the previous follow up 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 IRB.

Families willing to participate were scheduled for one visit during which all of the tests reported here were administered in 3–4 h, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session. While the child was tested, the parent or primary caregiver completed questionnaires regarding the child's educational, medical, and neurological status and behavior, and completed the Kaufman Brief Intelligence Test − 2 (KBIT-2) nonverbal subscale (Ritterband et al., 2009).

2.2.1. General cognitive ability

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales (Hansen-Pupp et al., 2013). We required that children have scores of 70 or higher on both scales to be included in our sample for these analyses.

2.2.2. 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 (Fiks et al., 2014). We defined each learning limitation as a Z-score ≤ −1 (i.e., below the 16th centile, which is equivalent to a score ≤ 85) on a grade-based WIAT-III achievement test (Costa et al., 2017). Thus, we identified four mutually-exclusive groups, reading limitation only (Word Reading Z-score ≤ −1, Numerical Operations Z-score > −1), math limitation only

(Numerical Operations Z-score ≤ −1, Word Reading Z-score > −1), both reading and math limitations (Word Reading Z-score ≤ −1, Numerical Operations Z-score ≤ −1), and neither limitation (Word Reading Z-score > −1, Numerical Operations Z-score > −1) (Table 1).

Because the reading and math limitations occur more commonly than would be expected if they were independent of each other (Ashkenazi et al., 2013; Tannock, 2013; Landerl and Moll, 2010; Willcutt et al., 2013; Slot et al., 2016; Lopes-Silva et al., 2016) we considered it prudent to view children with the combination as possibly having protein profiles that differed from those of children with either isolated limitation. Thus, we have three outcomes of interest, isolated reading limitation (i.e., not accompanied by a math limitation), isolated math limitation (i.e., not accompanied by a reading limitation), and the combination of reading and math limitations. Children with these entities were compared to children who had no reading or math

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