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The risk of neurodevelopmental disorders at age 10 years associated with blood concentrations of interleukins 4 and 10 during the first postnatal month of children born extremely preterm

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ABSTRACT

Background: Interleukin (IL)-4 and IL-10 are viewed mainly as anti-inflammatory cytokines. Yet, high concentrations have also been associated with inflammation-related diseases in newborns.

Methods: We measured the concentrations of IL-4 and IL-10, as well as IL-8 and ICAM-1 in blood specimens collected on postnatal day 21 (N = 555), day 28 (N = 521), and both days 21 and 28 (N = 449) from children born extremely preterm (EP) (< 28 weeks gestation) who at age 10 years had a DAS-II IQ Z-score > −2 (which approximates a score of > 70) and the following assessments, CCC-2, and CSI-4, DAS-II, NEPSY-II, OWLS-II, SCQ, and WIAT-III. Selected children also were assessed with the ADI-R and the ADOS-2. We modeled the risk of low scores or dysfunctions associated with top quartile concentrations of IL-4 and IL-10 on each day and on both days.

Results: The risks of low scores on the Animal Sorting and Arrows components of the NEPSY-II, both components of the OWLS-II, and the PseudoWord and Spelling components of the WIAT-III were heightened among children who had top quartile concentrations of IL-4 on postnatal days 21 and 28. Children who had high concentrations of IL-10 on days 21 and 28, individually and collectively, were at increased risk of low scores on the WIAT-III Spelling component. High concentrations of IL-4 on day 28 were associated with autism spectrum disorder (ASD). High concentrations of IL-10 on day 28 were also associated with a doubling of ASD risk, but this did not achieve statistical significance. Top quartile concentrations of IL-4 and IL10 on both days were not associated with increased risk of social, language, or behavioral dysfunctions.

Conclusion: Among children born EP, those who had top quartile concentrations of IL-4 and/or IL-10 on postnatal days 21 and/or 28 were more likely than their peers to have low scores on components of the NEPSY-II, OWLS-II, and WIAT-III assessments, as well as identification as having an ASD.

What is known:

- IL-4 and IL-10 are viewed as predominantly anti-inflammatory proteins.
- Less commonly, high concentrations of IL-4 and IL-10 have been associated with adverse health outcomes.

What is not known:

- We do not know to what extent elevated concentrations of IL-4 and IL-10 during the third and fourth postnatal weeks are associated with increased risk of neurocognitive, behavioral, language, and social dysfunctions among children born very preterm.

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS-2, Autism Diagnostic Observation Schedule, Second edition; ASD, Autism Spectrum Disorder; CCC-2, Children's Communication Checklist-2 (CCC-2); CSI-4, Child Symptom Inventory-4; DAS-II, Differential Ability Scales, Second Edition; ELGAN, Extremely Low Gestational Age Newborn; ICAM-1, Intercellular Adhesion Molecule-1 (CD54); IL-4, Interleukin-4; IL-8, Interleukin-8 (CXCL-8); IL-10, Interleukin-10; NEPSY-II, A Developmental NEuroPSYchological Assessment, Second Edition; OWLS, Oral and Written Language Scales, Second Edition; SCQ, Social Communication Questionnaire; SRS-2, Social Responsiveness Scale, Second Edition; WIAT-III, Wechsler Individual Achievement Test, Third Edition; WM, Working memory

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What this study adds:

- Children born very preterm who have elevated concentrations of IL-4, but not IL-10, on both postnatal days 21 and/or 28 are at increased risk of low scores on assessments of processing speed, visuospatial skills, listening comprehension, oral expression, and reading and spelling achievement.

1. Introduction

Sustained systemic inflammation appears to contribute to brain damage in extremely low gestational age newborns (ELGANs) [1]. We do not yet know why the inflammation once initiated continues [2]. One possibility is the limited ability of ELGANs to resolve inflammation [3].

Interleukin-4 (IL-4) and interleukin-10 (IL-10) are viewed as anti-inflammatory [4], and capable of resolving inflammation [5,6]. Indeed, one group of authors wrote, "Interleukin-10 (IL-10) is arguably the most potent anti-inflammatory cytokine." [7] Others express hope that increasing IL-10 availability might be therapeutic for a number of neuroimmune disorders [8]. The possibility that this hope might apply to the developing brain comes from a report that the neuroprotective effects of early administration of umbilical cord blood cells to fetal sheep are attributable, in part, to the subsequent elevation of IL-10 blood concentrations [9].

We found only one study that assessed the risk of brain damage among preterm newborns associated with IL-4 and IL10 concentrations [10]. In a sample of 74 infants whose mean gestational age was 27 weeks, area-under-the-curve assessments of IL-4 and IL-10 concentrations were not associated with sonographically-defined brain damage (hyperechoic or hypoechoic lesions for ≥7 days).

We are not aware of any assessment of the risk of indicators of brain dysfunction at older ages associated with IL-4 and IL-10 concentrations during the first postnatal month. The ELGAN Study [11] provided us the opportunity to evaluate to what extent elevated concentrations of these proteins were associated with reduced risk of neurocognitive, language, social, and academic dysfunctions at school age among children born extremely preterm (i.e., < 28 weeks gestation) [12].

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 during the years 2002–2004 and 1200 survived to 2 years. For the assessment at age 10 years, we enrolled 889

Table 1
Odds ratios (95% confidence intervals) for low IQs and for Z-scores ≤ −1 on the assessments listed on the left associated with top quartile concentrations of IL-4 and IL-10 on the days at the top of each column. All assessments listed beneath the DAS IQ listings are limited to children whose IQ Z-score was above −2. Adjustment has been made for gestational age category (23–24, 25–26, and 27 weeks), birth weight Z-score < −1, and for IL-8 concentrations in the top quartile on the relevant days.

	IL-4			IL-10		
	Day 21	Day 28	Both days[b]	Day 21	Day 28	Both days[b]
DAS-IQ						
≤ −2	1.6 (0.98, 2.6)	**1.7 (1.02, 2.8)**	1.5 (0.8, 2.6)	**1.7 (1.1, 2.8)**	**2.0 (1.2, 3.3)**	1.7 (0.9, 3.0)
> −2, ≤ −1	1.4 (0.9, 2.2)	0.8 (0.5, 1.3)	1.0 (0.6, 1.7)	1.3 (0.8, 2.0)	0.8 (0.5, 1.4)	0.9 (0.5, 1.7)
Maximum N	661	616	539	661	616	539
DAS-WM[a]						
	1.4 (0.9, 2.2)	1.1 (0.7, 1.7)	1.3 (0.8, 2.2)	1.3 (0.8, 2.0)	1.0 (0.6, 1.6)	1.0 (0.6, 1.9)
Maximum N	557	523	330	557	523	330
NEPSY-II						
Aud Attntn[c]	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	0.8 (0.5, 1.4)	0.8 (0.5, 1.2)	1.1 (0.7, 1.7)	0.9 (0.5, 1.6)
Aud Rspns	1.0 (0.7, 1.5)	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.2 (0.8, 1.9)	0.9 (0.6, 1.4)	1.1 (0.6, 1.8)
Inhib Inhibtn	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.9 (0.5, 1.5)
Inhib Switch	1.2 (0.8, 1.8)	1.3 (0.8, 1.9)	1.4 (0.8, 2.3)	1.5 (0.96, 2.2)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
Animal Sort	**1.6 (1.03, 2.3)**	1.5 (0.98, 2.3)	**1.7 (1.1, 2.9)**	**1.6 (1.1, 2.5)**	1.3 (0.8, 1.9)	1.5 (0.9, 2.5)
Inhib Naming	1.3 (0.9, 1.9)	1.2 (0.8, 1.8)	1.3 (0.8, 2.2)	**1.5 (1.01, 2.2)**	0.9 (0.6, 1.4)	1.4 (0.8, 2.3)
Arrows	**1.7 (1.1, 2.5)**	1.3 (0.8, 1.9)	**1.8 (1.1, 3.1)**	**1.6 (1.1, 2.5)**	1.0 (0.6, 1.5)	1.2 (0.8, 2.2)
Geo Puzzle	1.3 (0.8, 2.0)	1.2 (0.8, 1.8)	1.2 (0.7, 2.0)	1.1 (0.7, 1.7)	1.0 (0.7, 1.6)	1.1 (0.7, 1.9)
VisMot Precs'n	1.3 (0.9, 1.9)	1.1 (0.7, 1.7)	1.3 (0.8, 2.2)	1.4 (0.9, 2.1)	1.2 (0.8, 1.8)	1.7 (0.97, 2.8)
Maximum N	558	524	453	558	524	453
OWLS						
Listen Comp	**1.7 (1.1, 2.6)**	1.5 (0.98, 2.3)	**1.8 (1.1, 2.9)**	**1.7 (1.2, 2.6)**	1.4 (0.9, 2.1)	1.6 (0.95, 2.7)
Oral Exprsn	**1.9 (1.2, 2.9)**	1.5 (0.97, 2.3)	**2.1 (1.3, 3.6)**	**1.6 (1.1, 2.5)**	1.1 (0.7, 1.7)	1.6 (0.9, 2.7)
Maximum N	548	513	446	548	513	446
WIAT-III						
Word Read	**1.6 (1.03, 2.6)**	1.3 (0.8, 2.1)	1.6 (0.9, 2.6)	**1.8 (1.1, 2.8)**	1.2 (0.7, 2.0)	1.3 (0.7, 2.4)
PseudoWord	**1.7 (1.1, 2.7)**	1.4 (0.9, 2.2)	**1.8 (1.1, 3.0)**	1.4 (0.9, 2.1)	1.2 (0.7, 1.9)	1.7 (0.97, 2.9)
Spelling	**2.0 (1.2, 3.2)**	1.4 (0.8, 2.3)	**2.0 (1.1, 3.6)**	**2.3 (1.4, 3.7)**	**1.8 (1.1, 3.0)**	**2.8 (1.6, 5.0)**
Numerical	1.2 (0.8, 1.9)	1.3 (0.9, 2.1)	1.5 (0.9, 2.5)	1.2 (0.8, 1.8)	1.5 (0.96, 2.3)	1.3 (0.8, 2.3)
Maximum N	555	521	449	555	521	449

Bolded odds ratios are statistically significantly increased at the p < .05 level.

[a] Working memory.

[b] Protein in the highest quartile on both days 21 and 28.

[c] The full names of the assessments can be found in Supplemental Table 2.