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Behavioral dysfunctions of 10-year-old children born extremely preterm associated with CRH expression in the placenta

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Abstract

Aim—To evaluate the relationship between corticotropin-releasing hormone (CRH) expression in the placenta and the risk of school-related dysfunctions at age 10 years among children born extremely preterm (EP).

Methods—CRH expression was measured in the placenta of 761 EP children, who had the following assessments at age 10 years: Differential Ability Scales, Oral and Written Language Scales, the Wechsler Individual Achievement Test-III, NEPSY-II, and the Child Symptom Inventory-4. We evaluated if lowest and highest quartiles of CRH mRNA were associated with undesirable scores on these assessments. With 272 evaluations, we would expect 14 to be significant at $p < .05$.

Results—Only 16 associations were statistically significant. On the other hand, seven of these were social limitations among girls whose placenta CRH mRNA was in the top quartile. Adjusting for delivery indication or restricting the sample to one delivery indication group resulted in few differences.

Conclusion—Overall, placenta CRH mRNA concentrations in the top or bottom quartiles were not associated with increased risks of dysfunctions 10 years later. Girls whose placenta CRH expression was in the top quartile, however, were at increased risk of seven indicators/correlates of social limitations.

Keywords

Infant; premature; placenta; brain; development; corticotropin releasing hormone; corticosteroid

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Conflict of interest statement

None of the authors has any proprietary interests or conflicts of interest related to this submission. This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

Acknowledgements are in Appendix S1.

Introduction

Children born very preterm are at increased risk of anxiety, social limitations, and other behavioral and mood problems (1), as well as autism (2). Prenatal maternal stress has been invoked to explain some of these behavioral and mood difficulties (3), autism (4), and structural brain effects (5).

Cortisol is probably the main mediator of stress (6), and exogenous prenatal corticosteroids potentially have adverse effects on the developing brain (7). Recent studies, however, suggest that low dose exogenous corticosteroids (8) and high endogenous blood concentrations (9) might also enhance neurodevelopment.

Corticotropin-releasing hormone (CRH) can also mediate stress (10). The placenta synthesizes CRH that is identical in structure and activity to hypothalamic CRH (11). Placenta-derived CRH accounts for most of the CRH in the gravida's blood (12). Recent reports document the adverse effects of CRH on both brain structure (13) and function (14).

As the interface between the mother and the fetus, the placenta has the potential to convey maternal stress signals to the fetus (15), as well as modulate or exacerbate maternal influences on the fetus, and interfere with fetal brain development (16). However, we know of no study that assessed the relationship between maternal prenatal stress and placenta CRH mRNA concentration.

In the ELGAN Study, infants born before the 28th week whose placenta had a relatively low concentration of CRH messenger ribonucleic acid (mRNA) were at increased risk of ventriculomegaly on an ultrasound scan shortly after birth, while those whose placenta had a relatively high CRH mRNA concentration were at increased risk of an inability to walk, and a Bayley-II Motor Scale score more than 2 standard deviations below the normative mean at age 2 years (17). We sought to evaluate to what extent placenta CRH mRNA conveys information about school-related dysfunctions at age 10 years.

Methods

provided in Appendix S1

Results

Sample description (Tables S1–S3 in Appendix S1)

CRH expression was measured in the placenta of 378 girls and 383 boys. With the exception of teacher-completed Child Symptom Inventory-4 (CSI-4) assessments, which were available for 74% of girls (N=278), and 72% of boys (N=275), almost all children had each of the assessments (Table S1). Placenta CRH mRNA concentrations increased with gestational age, and were higher among children who were growth-restricted (i.e., birth weight more than one standard deviation below the external mean) and those delivered for maternal/fetal indications than among their peers (Table S2). Fully half of all growth restricted infants were delivered for maternal or fetal indications, while only 8% of their peers were delivered for these indications (Table S3). Because of these relationships, we

adjusted for gestational age and delivery indications (summarized in Table S4), and separately for growth-restriction and delivery indications (summarized in Table S5). The tables that Tables S4 and S4 summarize are available upon request to the corresponding author.

Risks of dysfunctions after adjustment for delivery indications and gestational age (Table S4)

After adjustment for delivery indications and gestational age, girls whose placenta CRH expression was in the top quartile were at increased risk of the inattentive form of ADHD as identified by a parent or caregiver, impaired social awareness on the SRS, and restricted interests and a pragmatic language disorder on the CCC-2. In contrast, girls whose placenta CRH expression was in the bottom quartile were at increased risk of a low score on the structural language component of the CCC-2. Structural language impairment is a frequent associated feature of autism spectrum disorder.(18)

Boys whose placenta CRH expression was in the top quartile were at reduced risk a parent-report of the combined form of ADHD, and at increased risk of a teacher-report of an autistic disorder, and teacher report of Asperger's disorder. Those whose placenta CRH expression was in the bottom quartile were at increased risk of a low score on the NEPSY-II visuoperceptual Arrows subtest, and social communication impairment on the SRS.

Risks of dysfunctions after adjustment for birth weight Z-score ≤ −1 and gestational age (Table S5)

After adjustment for birth weight Z-score ≤ −1 and gestational age, girls whose placenta CRH expression was in the top quartile were at increased risk of parent-reported inattentive type of ADHD, parent-reported Asperger's disorder, diminished social motivation, social awareness, and social reciprocity on the SRS, and restricted interests and overall deficits in general communications on the CCC-2. Girls whose placenta CRH expression was in the bottom quartile were at increased risk of a low expressive language score on the OWLS and a low structural language score on the CCC-2.

Among boys, placenta CRH expression in the top quartile was associated with increased risk of teacher-reported generalized anxiety/social phobia, and autistic disorder on the CSI-4. Boys whose placenta CRH expression was in the bottom quartile were at increased risks of a low score on the Arrows visuoperceptual subtest of the NEPSY-II, and an SRS social communication score of 76 or higher.

Table 1 (Summarizes Tables S4 and Table S5)

This table compares what is found when adjustment was made for delivery indication to what is found when adjustment was made for growth restriction. A top or bottom quartile of CRH mRNA was associated with eight dysfunctions at age 10 years when adjustment was made for fetal/maternal indications for preterm delivery. Only one of these, teacher-identified Asperger's disorder, however, was not significant when adjustment was made for growth restriction. In contrast, six dysfunctions identified when adjustment was made for

growth restriction were not identified when adjustment was made for fetal/maternal indications for preterm delivery.

Girls, but not boys, whose placenta CRH mRNA was in the lowest quartile were at increased risk of an OWLS oral expression Z-score ≤ −1 and a CCC-2 speech Z-score ≤ −1. Girls, but not boys, whose placenta CRH mRNA was in the highest quartile were at increased risk of both the inattentive type of ADHD and of Asperger's disorder based on parent report. They were also at increased risk of a high total score on the SRS, as well as relatively high scores on two of the three main scales, social motivation and social awareness, a low Z-score on the CCC-2 Interests scale and a low score (< 64) on the CCC-2 Composite scale.

In contrast, boys, but not girls, whose placenta CRH mRNA was in the lowest quartile were at increased risk of an Arrows Z-score ≤ −1 of the NEPSY-II, and an SRS social communication T score ≥ 76. Boys, but not girls, whose placenta CRH mRNA was in the highest quartile were at reduced risk of the combined type of ADHD based on parent report, and at increased risk of generalized anxiety/social phobia, an autistic disorder, and Asperger's disorder, all based on teacher report.

Discussion

Perhaps our major finding is that we did not find much support for the hypothesis that placenta CRH expression conveys information about the risks of neurocognitive, language or behavioral dysfunction in 10-year-old children who were born extremely preterm. When we adjusted for maternal/fetal indications for preterm delivery 10 evaluations were statistically significant at the $p < .05$ level. Given 272 evaluations, we would expect 14 to be significant by chance alone. Consequently, we are reluctant to place any emphasis on the 14 assessments that were significant.

Importance of the lack of association of placenta CRH with 10-year dysfunctions

The main biomarkers of acute stress are blood cortisol and plasma cortisol (19). Maternal stress or anxiety during pregnancy has been only weakly associated with concentrations of maternal blood cortisol (20), salivary cortisol (21), and serum CRH (22). We know of no study that assessed the relationship between maternal prenatal stress and placenta CRH mRNA concentration. In addition, the link between maternal blood CRH and stress is tenuous (23).

Seven-year-old children whose mother had elevated blood cortisol concentrations during the pregnancy had lower memory and learning scores on the Test of Memory and Learning (ToMaL) (24), lower Wechsler Intelligence Scale for Children (WISC) IQ scores (25), and were more likely to be identified as anxious (26). Our failure to find any consistent relationship between placenta CRH mRNA and neurocognitive, behavior, and speech dysfunctions in 10-year old children born extremely preterm suggests that whatever information is conveyed by the abundance or paucity of placenta CRH mRNA does not appear to have long-lasting effects in this high-risk sample. Especially important is our reluctance to draw any inference about the relationship between maternal prenatal stress and the offspring's function at 10 years.

Increased risk of social dysfunctions among girls

We did not specifically include girl-boy differences among the hypotheses we wanted to evaluate. Nevertheless, our finding that girls whose placenta CRH expression was in the top quartile were at increased risk of seven indicators/correlates of social limitations is both prominent and a bit surprising.

Following prenatal exposure to high levels of maternal cortisol, girls are more likely than boys to have altered neural connectivity (27), and greater anxiety during childhood (28). Sex differences in fetal programming might account for some sex-differentials in behavior (29).

Adjusting for fetal growth restriction rather than delivery indication

In our cohort, the placentas of women who delivered prematurely for spontaneous indication had lower CRH expression than did the placentas of women who delivered for maternal or fetal indications. Common to both maternal and fetal indications for preterm delivery is the much higher percent of fetal growth restriction newborns than is seen among the babies born to women who delivered for “spontaneous” indications. Consequently, we felt compelled to adjust separately for delivery indication, and fetal growth restriction to avoid attributing to CRH expression what might better be attributed to the processes influencing delivery indication, and to adjust for processes related to fetal growth restriction.

When we adjusted for fetal growth restriction instead of maternal/fetal indications for preterm delivery, 13 evaluations were statistically significant at the $p < .05$ level, still not beyond what might be expected by chance. On the other hand, girls whose placenta CRH mRNA was in the top quartile were at increased risks of parent-reported ADHD inattentive type and Asperger’s disorder, as well as characteristics of social impairment identified with the SRS and CCC-2. These seven dysfunctions/characteristics associated with only one of the four exposure groups represent more than half of all associations that were statistically significant. Their thematic cohesion is what is most impressive.

Why associations at age 2 years, but not at 10 years?

Exposures and experiences between ages 2 and 10 years could very readily alter the trajectory that would have been expected based only on the prenatal exposure (30). Then again, what was measured at age 2 years differs very much from what was measured at age 10 years.

Strengths and limitations

The ELGAN study is large and collected high-quality information in a rigorous manner. Despite the large number of children evaluated, our study has limited power. For example, 37% of 378 girls had an OWLS oral expression score more than one standard deviation below the normative mean, and yet the odds ratio of 1.7 associated with a lowest quartile of placenta CRH expression did not quite achieve statistical significance (95% CI: 0.98, 2.9). Adjusting for potential confounders, including three levels of gestational age (23–24, 25–26, and 27 weeks) and two levels of indication for preterm delivery variable (spontaneous vs maternal/fetal), or two levels of birth weight Z-score (≤ -1 vs > -1) severely limited the power of our multinomial logistic regression models.

Conclusion

By and large, placenta CRH mRNA concentration does not appear to convey information about the risk of brain dysfunctions in school-age children born at an extremely low gestational age. On the other hand our finding that girls whose placenta CRH mRNA concentration was in the top quartile were at increased risk of multiple indicators of the social limitations deserves additional study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview – Revised
ADOS-2	Autism Diagnostic Observation Schedule-2 (ADOS-2
ASD	Autism spectrum disorder
CCC-2	The Children’s Communication Checklist–2
CRH	Corticotropin-releasing hormone
CSI-4	The Child Symptom Inventory-4
DAS-II	Differential Ability Scales–II
mRNA	messenger ribonucleic acid
NEPSY-II	Developmental NEuroPSYchological Assessment
OWLS	Oral and Written Language Scales
SCQ	Social Communication Questionnaire
SRS	Social Responsiveness Scale
ToMaL	Test of Memory and Learning
WIAT-III	The Wechsler Individual Achievement Test-III
WISC	Wechsler Intelligence Scale for Children

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Key notes

- By and large, placenta corticotropin-releasing hormone (CRH) mRNA concentrations are not associated with increased risks of school-related dysfunctions at age 10 years.
- Among girls, however, those whose placenta had high concentrations of placenta CRH mRNA appear to be at increased risk of social dysfunctions at age 10 years.
- The association of high concentrations of placenta CRH mRNA with increased risk of social dysfunctions among girls deserves assessment in other samples.

Table 1

This table summarizes Summary of Supplement Tables S4 and S5

"**Mat-Fetal**" (for maternal or fetal indications for preterm delivery) in this table indicates that the association was seen in supplement B, which includes analyses that adjusted for maternal and fetal indications for delivery, while "**BWZ**" " (for birthweight Z-score < −1) indicates that the association was seen in supplement C, which includes analyses that adjusted for birthweight Z-score <−1. The two italicized and underlined ***"Mat-Fetal"*** indicate reduced risk. All analyses adjusted for gestational age.

		Placenta CRH mRNA quartile			
		Girls		Boys	
Assessment	**Classification**	**Lowest**	**Highest**	**Lowest**	**Highest**
OWLS	Oral expression Z-score ≤ −1	**BWZ**			
NEPSY-II	Arrows Z-score ≤ −1			**Mat-Fetal, BWZ**	
Parent CSI-4	ADHD inattentive type		**Mat-Fetal, BWZ**		
	ADHD combined type				***Mat-Fetal***
	Asperger's disorder		**BWZ**		
Teacher CSI-4	Generalized anxiety/Social phobia				**BWZ**
	Autistic disorder				**Mat-Fetal, BWZ**
	Asperger's disorder				**Mat-Fetal**
SRS	Total T score ≥ 76		**BWZ**		
	Social communication T score ≥ 76			**Mat-Fetal, BWZ**	
	Social motivation T score ≥ 76		**BWZ**		
	Social awareness T score 60–75		**Mat-Fetal, BWZ**		
CCC-2	Speech Z-score ≤ −1	**Mat-Fetal, BWZ**			
	Interests Z-score ≤ −1		**Mat-Fetal, BWZ**		
	Composite score < 64		**BWZ**		
	SIDI [a] < 0		***Mat-Fetal***		

[a]SIDI= Social Interaction Difference Index (SIDI)