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Brain disorders associated with corticotropin releasing hormone expression in the placenta among children born before the 28th week of gestation

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Abstract

Aim—To evaluate the relationship between placenta corticotropin releasing hormone (CRH) expression and brain structure and function abnormalities in extremely preterm newborns.

Methods—In a sample of 1243 infants born before the 28th week of gestation, we evaluated the relationship between CRH expression in the placenta and the risk of brain ultrasound scan abnormalities identified while these infants were in the intensive care nursery, low scores on the Bayley Scales of Infant Development-II of 900 of these children at age two years and head circumference measurements then more than one and two standard deviations below the mean.

Results—Infants who had a low placenta CRH messenger ribonucleic acid (mRNA) concentration were at increased risk of ventriculomegaly on an ultrasound scan. An elevated placenta CRH mRNA concentration was associated with increased risk of an inability to walk at age 2 years, and a Bayley Motor Scale 3 standard deviations below the mean.

Conclusion—Placenta CRH mRNA concentration appears to convey information about the risk of brain damage in the infant born at an extremely low gestational age.

Keywords

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

Cortisol is needed for normal brain development and very low levels are associated with diminished brain growth.(1) On the other hand, very high levels adversely affect brain development. For example, human infants whose mother had high plasma concentrations during gestation of cortisol or of corticotropin releasing hormone (CRH, also known as

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corticotropin-releasing factor) are more likely than others to have lower verbal scores on the Wechsler Intelligence Scale for Children at age 7 years.(2) Anxiety and depression, which are often associated with elevated cortisol concentrations in the blood, are also associated with a wide variety of developmental adversities in the offspring, including impaired cognitive performance during infancy, and decreased brain volume in areas associated with learning and memory in children.(3)

Elevated blood concentrations of endogenous corticoids in the preterm newborn are also associated with increased risks of brain structural alterations. Among ventilated infants who weighed less than 1000 grams at birth, those whose blood cortisol level was in the highest quartile during the first 48 hours were at increased risk of what the authors identified as "severe (grade 3 or 4) intraventricular hemorrhage," while those in the top decile were also at increased risk of periventricular leukomalacia.(4)

Exogenous corticosteroids also have the potential to result in developmental adversities.(1) High dose dexamethasone given to reduce the duration of ventilator dependency and the risk of bronchopulmonary dysplasia increases extremely preterm newborns' risks of cerebral palsy and cognitive limitations. Brain imaging studies have also documented the adverse effects of postnatal dexamethasone.(1)

Much of the increase in the gravida's free cortisol is attributed to elevated CRH activity in the placenta.(5) Placenta CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity.(6)

These observations raise the possibility that the extremely preterm brain might be especially sensitive to corticoids and that a measure of CRH activity in the placenta (CRH mRNA concentration) might provide information about the risk of early ultrasound indicators of cerebral white matter damage, and dysfunctions and microcephaly at older ages. Because CRH mRNA concentrations tended to be higher in placentas delivered for maternal and fetal indications, and lower in placentas delivered for spontaneous indications (including preterm labor, pre-labor ruptured membranes, placenta abruption, and cervical insufficiency),(7) we sought to separate the effect of CRH activity from the pregnancy disorders closely associated with it. Because the risk of brain damage appears to follow a U-shaped curve with increasing glucocorticoids dose/concentration,(1) we also evaluated the associations of both low and high placenta CRH mRNA with indicators of brain damage.

Methods

Details about the sample and the data collected are provided in the supplementary text

Data analysis

We evaluated the generalized null hypothesis that CRH mRNA concentration in the placenta is NOT associated with a) ultrasound lesions indicative of cerebral white matter damage (ventriculomegaly and a hypoechoic lesion) when the infant was in the intensive care nursery, b) cerebral palsy diagnosis, c) low Bayley Scales of Infant Development (MDI <55, MDI 55–69, PDI <55, PDI 55–69), d) screening positive on the M-CHAT (a screening test

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for autism spectrum disorders), and e) a head circumference Z-score < −2, or a Z-score ≥ −2 but < −1. This broad hypothesis was established *a priori* based on a review of the literature cited in the introduction.

All odds ratios and confidence intervals were calculated from logistic regression models, comparing children whose CRH mRNA concentration was in the lowest or highest quartiles to children whose CRH mRNA concentration was in the middle two quartiles. We adjusted for gestational age in groups of weeks (23–24, 25–26, 27). For entities that had mutually exclusive subtypes (i.e., cerebral palsy diagnoses, as well as groups classified by Bayley Mental and Motor Scales and head circumference Z-scores), we created multinomial logistic regression models.

Because gestational age, pregnancy disorder, and CRH mRNA concentration are highly interrelated in this sample, we conducted additional analyses in two subgroups, those delivered for maternal or fetal indications, and those delivered for spontaneous indications. Infants delivered for maternal-fetal indications (severe preeclampsia, failure to grow) are more likely than others to be severely growth restricted. Consequently, these analyses also allowed us to examine if correlates of fetal growth restriction influenced the relationship between CRH and neurodevelopmental disorders.

Results

A total of 1243 infants had their placenta CRH mRNA concentration measured and had a consensus reading of a protocol ultrasound scan. Of the 1020 who survived until age 2 years, 940 also had various components of the developmental assessment (Supplement Table 1).

In both the ultrasound sample and the follow-up sample, children in the highest quartile of the distribution of CRH mRNA concentrations were least likely to have been born before the 25^{th} week and much more likely than others to be growth restricted (Supplement Table 2). Those whose CRH mRNA concentration was in the lowest quartile were least likely to be a product of a multi-fetal gestation.

The increased risk of ventriculomegaly associated with a CRH mRNA concentration in the **lowest** quartile was evident regardless of whether data analysis adjustment was made for maternal and/or fetal indications, or whether the sample was divided into spontaneous indications and maternal/fetal indications [OR: 1.5 (1.01, 2.2)] (Table 1). The increased risk of a hypoechoic lesion associated with a low CRH mRNA concentration was confined to the sample of children delivered for maternal or fetal indications. Although the odds ratio is very large, so is the width of the confidence interval. The prominently increased odds of a GMFCS score of 2 or higher (indicating the child could not walk even with assistance) associated with a low CRH mRNA concentration was not statistically significant at $p < .05$.

The prominently increased odds of such a high GMFCS category associated with a **high** CRH mRNA concentration was statistically significant in all three of the analyses in the entire sample [OR: 2.3 (1.04, 5.0)], and in the sub-sample of spontaneous deliveries [OR: 2.7 (1.2, 6.3)] (Table 2). A diagnosis of quadriparetic cerebral palsy was associated with a high CRH mRNA concentration only in the sub-sample of births for spontaneous indications

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[OR: 2.4 (1.1, 5.2)]. An increased risk of a Bayley Motor Scale less than 55 was associated with a high CRH mRNA concentration when the analyses adjusted for both maternal and fetal indications for preterm birth [OR: 1.7 (1.03, 2.8)], and in the sub-sample of children delivered for spontaneous indications [OR: 1.9 (1.1, 3.4)].

Discussion

Our main findings are that infants whose placenta had low CRH mRNA concentration were at increased risk of ventriculomegaly, and of a hypoechoic lesion in the maternal and fetal indications sub-sample, while elevated expression of placenta CRH was associated with an increased risk of an inability to walk, a Bayley Motor Scale more than 3 standard deviations below the mean, and of quadriparetic cerebral palsy in the spontaneous indications sub-sample.

Glucocorticoids needed for normal brain develpment

We made the assumption that extremes of CRH expression (lowest and highest quartiles) convey much more risk information than measures of central tendency (median and mean). This assumption is especially appropriate in light of the relationships between glucocorticoids in the brain and neurogenesis (*v.i.*).(1) Although cortisol is needed for normal brain development, both cortisol and corticosterone levels tend to have a typical inverted U-shape dose–response relationship with brain growth and synaptic plasticity, showing diminished brain growth at very low and very high levels.

CRH also appears to be needed for normal brain development

CRH has been identified in neurons in multiple areas of the brain.(1) Indeed, CRH can stimulate dendritic outgrowth of hippocampal neurons, but does not seem required for normal brain structure and function. Thus, it appears that cortisol and CRH might have separate effects on the developing brain.

Exogenous corticosteroid exposure can, but need not, adversely affect the developing brain

High dose dexamethasone, given to reduce the duration of ventilator dependency and the risk of bronchopulmonary dysplasia, increases the risk of cerebral palsy and/or cognitive limitations.(8) Lower doses of dexamethasone, however, appear to pose no obvious neuro-developmental hazard, nor does the postnatal administration of hydrocortisone.(9) These findings lead to the inference that dose, type of corticosteroid, and endogenous vulnerability are probably each important.

Placenta 11β-hydroxysteroid dehydrogenase type2 (11β-HSD2)

Among infants born before the 33rd week of gestation, those who are small for gestational age tend to have lower placental 11β-HSD2 function than those whose birthweight is appropriate for gestational age.(10) Placental 11β-HSD2 promotes the degradation of cortisol to the less brain-damaging cortisone. Consequently, infants delivered for maternal or fetal indications, who already tend to have a higher placenta CRH mRNA concentration than

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infants delivered for spontaneous indications, might have the highest cortisol blood levels, and therefore the highest cortisol exposure to the developing brain.

Inferences prompted by our findings

a. Antenatal contribution—One of the more important inferences we draw from our placenta CRH findings is that antenatal phenomena contribute to the associations we see. We base this inference on the recognition that the placenta conveys information about what happened *in utero*.

b. Low CRH mRNA concentrations predict ventriculomegaly—In our sample, low placenta CRH mRNA concentrations are associated with placenta inflammation.(7) Placenta and neonatal indicators of inflammation are also associated with ventriculomegaly.(11, 12) Thus, our finding that ventriculomegaly is associated with low CRH expression should not be surprising. In some ways, however, it is surprising because we found the association among infants at low risk for placenta and day-1 neonatal systemic inflammation (*i.e.*, those delivered for fetal or maternal indications). It remains to be determined if the association between ventriculomegaly and low placenta CRH mRNA concentration reflects residual confounding associated with the correlates of placenta inflammation and the recovery of bacteria from the placenta parenchyma, or the contribution of correlates of CRH mRNA concentration that can protect developing brain from adversity.

c. High CRH mRNA concentrations predict motor dysfunctions—In our sample, cerebral palsy diagnoses and other motor dysfunctions are associated with indicators of perinatal inflammation,(11, 13) which are inversely related to placenta CRH expression.(7) A likely explanation for our finding that motor dysfunctions are associated with high CRH expression is that inflammation and CRH expression each convey relatively independent information about the risk of risk of brain damage.

d. Biphasic nature of cortisol-brain relationships—One lesion (ventriculomegaly) was associated with low placenta CRH mRNA concentrations, while motor dysfunctions were associated with high CRH mRNA concentrations. These findings are compatible with the biphasic nature of cortisol-brain relationships.(1) Our finding that ventriculomegaly is associated with low concentrations and motor dysfunctions are associated with high concentrations is all the more impressive in light of the ability of ventriculomegaly to predict motor dysfunctions.

e. Sub-group analyses—We are cautious about drawing inferences about relationships found in only one stratum of our sample. In part, this reflects awareness that findings restricted to one sub-set are not readily generalized to the entire population, and are prone to inferential errors (14).

We found that a low placenta CRH mRNA concentration places an infant at increased risk of a hypoechoic lesion, but only in the sub-sample of those delivered for maternal or fetal indications (which tend to have high CRH mRNA concentrations). We also found that the increased risk of quadriparetic cerebral palsy associated with high CRH mRNA

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concentrations was limited to the sub-set of infants delivered for spontaneous indications, which tend to have a low placenta CRH mRNA concentration.

One inference we draw from these disparities is that the CRH mRNA concentration is not extreme for the entire sample, but rather, extreme only in relationship to other children who were delivered for the same indications. The neurologically-impaired children might have responded differently from their peers. Perhaps their brain damage before delivery, and their placenta CRH mRNA concentrations reflect a dysfunctional hypothalamic-pituitary-adrenal axis (15) Another possible interpretation invokes early inflammation, which "impacts the developmental trajectory of CNS stress neurocircuitry" (16), as well as potentially damaging the fetal brain (17).

Methodological issues

Details are in the supplementary text.

Limitations and strengths

Details are in the supplementary text.

Conclusions

In a large sample of extremely low gestational age newborns, those whose placenta CRH mRNA concentration was low were at increased risk of ventriculomegaly when in the intensive care nursery, while those whose placenta had high concentrations of placenta CRH mRNA were at increased risk of motor limitations at age 2 years (including an inability to walk). These findings are compatible with the hypothesis that processes associated with steroid metabolism are associated with processes leading to perinatal brain damage, and with the hypothesis that some of these originate *in utero*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgements are listed in the supplement

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Abbreviations

CRH	Corticotropin Releasing Hormone
GMFCS	Gross Motor Function Classification System
M-CHAT	Modified-Checklist for Autism in Toddlers
MDI	Mental Development Index of the Bayley Scales of Infant Development-II

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mRNA	messenger ribonucleic acid
PDI	Psychomotor Development Index of the Bayley Scales of Infant Development-II

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Key Notes

- Children whose placenta CRH expression was relatively low were at increased risk of cranial ultrasound abnormalities, but only in the subsample of those delivered for maternal or fetal indications.
- Children whose placenta CRH expression was relatively high were at increased risk of motor-impairment, but only in the subsample delivered for spontaneous indications.
- These findings appear to document that endogenous antenatal phenomena influence the risk of brain damage in preterm newborns

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Table 1

Odds ratios (and 95% confidence interval) of each outcome listed on the left associated with the **lowest** placenta CRH mRNA concentration quartile. The referent group for all analyses is composed of all infants whose placenta CRH mRNA concentration was in the middle two quartiles. All analyses adjust gestational age.

		Total sample with additional adjustments for:			**Sample restricted to indications:**	
Outcome	**Classification**	**Nothing else**	**Maternal[A]**	**Maternal[A] or fetal[B]**	**Maternal[A] and fetal[B]**	**Spontaneous[C]**
Ultrasound	Ventriculomegaly	**1.5 (1.01, 2.2)**	1.5 (0.98, 2.2)	**1.5 (1.01, 2.2)**	3.3 (0.7, 17)	1.4 (0.9, 2.2)
Lesion	Hypoechoic	1.4 (0.9, 2.2)	1.1 (0.9, 2.2)	1.4 (0.9, 2.2)	**13 (1.4, 120)**	1.2 (0.7, 1.9)
Cerebral palsy	Quadriparesis	1.5 (0.7, 2.8)	1.4 (0.7, 2.9)	1,5 (0.7, 2.9)	1.8 (0.2, 15)	1.4 (0.7, 2.9)
	Diparesis	0.8 (0.3, 1.9)	0.8 (0.3, 1.9)	0.8 (0.3, 1.9)	----	0.7 (0.3, 1.8)
	Hemiparesis	1.9 (0.6, 5.7)	1.8 (0.6, 5.6)	1.9 (0.6, 5.8)	----	1.9 (0.6, 5.7)
GMFCS[D]	≥ 2	1.6 (0.8, 3.5)	1.6 (0.8, 3.5)	1.6 (0.9, 3.5)	5.7 (0.5, 61)	1.3 (0.6, 3.0)
Bayley MDI	< 55	1.4 (0.9, 2.2)	1.4 (0.9, 2.2)	1.4 (0.8, 2.2)	1.2 (0.3, 4.6)	1.3 (0.8, 2.2)
	55–69	1.3 (0.8, 2.2)	1.3 (0.8, 2.2)	1.3 (0.8, 2.1)	0.5 (0.1, 3.3)	1.4 (0.8, 2.4)
Bayley PDI	< 55	1.3 (0.8, 2.1)	1.3 (0.8, 2.1)	1.3 (0.8, 2.1)	0.6 (0.1, 3.3)	1.4 (0.9, 2.4)
	55–69	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	3.9 (0.7, 20)	1.0 (0.6, 1.7)
Autism screen	Positive	0.8 (0.6, 1.2)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	1.1 (0.3, 4.2)	0.8 (0.5, 1.2)
	Positive[E]	0.9 (0.5, 1.5)	0.9 (0.5, 1.4)	0.9 (0.5, 1.4)	2.3 (0.4, 13)	0.8 (0.5, 1.4)
Head circum	< −2	1.3 (0.7, 2.2)	1.2 (0.7, 2.2)	1.2 (0.7, 2.2)	1.6 (0.2, 10)	1.2 (0.7, 2.2)
Z-score (24 mn)	≥ −2, < −1	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	1.4 (0.4, 5.2)	0.6 (0.4, 1.03)

[A] preeclampsia

[B] severe intrauterine growth restriction based on antepartum ultrasound examination, non-reassuring fetal testing, oligohydramnious, and Doppler abnormalities of umbilical cord blood flow

[C] preterm labor, pre-labor membrane rupture, abruption, cervical insufficiency

[D] Gross Motor Function Classification System

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$E_{\text{among those with GMFCS} < 1 \text{ (able to walk) and no vision or hearing abnormality}}$

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Table 2

Odds ratios (and 95% confidence interval) of each outcome listed on the left associated with the **highest** placenta CRH mRNA concentration quartile. The referent group for all analyses is composed of all infants whose placenta CRH mRNA concentration was in the middle two quartiles. All analyses adjust gestational age.

		Total sample with additional adjustments for:			**Sample restricted to indications:**	
Outcome	**Classification**	**Nothing else**	**Maternal[A]**	**Maternal[A] or fetal[B]**	**Maternal[A] and fetal[B]**	**Spontaneous[C]**
Ultrasound	Ventriculomegaly	1.1 (0.7, 1.7)	1.4 (0.9, 2.2)	1.4 (0.9, 2.3)	1.1 (0.3, 4.2)	1.6 (0.97, 2.6)
Lesion	Hypoechoic	0.8 (0.4, 1.3)	0.9 (0.5, 1.7)	0.8 (0.4, 1.5)	2.8 (0.2, 23)	0.8 (0.4, 1.6)
Cerebral palsy	Quadriparesis	1.9 (0.96, 3.7)	2.0 (0.96, 4.1)	2.0 (0.96, 4.1)	0.9 (0.2, 5.0)	**2.4 (1.1, 5.2)**
	Diparesis	0.8 (0.3, 2.0)	0.9 (0.3, 2.5)	1.0 (0.4, 2.7)	----	1.0 (0.4, 2.9)
	Hemiparesis	1.3 (0.4, 4.6)	2.0 (0.6, 7.2)	2.1 (0.6, 7.5)	----	2.2 (0.6, 7.7)
GMFCS[D]	≥ 2	**2.6 (1.3, 5.4)**	**2.3 (1.06, 5.1)**	**2.3 (1.04, 5.0)**	2.3 (0.3, 20)	**2.7 (1.2, 6.3)**
Bayley MDI	< 55	**1.6 (1.04, 2.6)**	1.4 (0.8, 2.3)	1.2 (0.7, 2.0)	0.8 (0.3, 2.0)	1.5 (0.9, 2.7)
	55–69	0.9 (0.5, 1.6)	0.8 (0.4, 1.4)	0.7 (0.4, 1.3)	0.8 (0.2, 2.2)	0.6 (0.3, 1.3)
Bayley PDI	< 55	**2.0 (1.3, 3.1)**	1.6 (0.98, 2.7)	**1.7 (1.03, 2.8)**	1.0 (0.4, 2.5)	**1.9 (1.1, 3.4)**
	55–69	1.0 (06, 3.1)	1.2 (0.7, 2.0)	1.1 (0.7, 1.9)	0.7 (0.2, 3.2)	1.3 (0.8, 2.3)
Autism screen	Positive	1.2 (0.8, 1.7)	1.0 (0.7, 1.6)	1.0 (0.7, 1.6)	1.0 (0.4, 2.4)	1.1 (0.7, 1.7)
	Positive[E]	1.0 (0.6, 1.5)	0.9 (0.5, 1.5)	0.9 (0.5, 1.5)	2.2 (0.6, 8.0)	0.7 (0.4, 1.4)
Head circum	< −2	1.5 (0.9, 2.7)	1.5 (0.8, 2.8)	1.4 (0.7, 2.7)	1.3 (0.3, 4.9)	1.5 (0.7, 3.2)
Z-score (24 mn)	≥ −2, < −1	1.2 (0.8, 1.8)	1.0 (0.6, 1.7)	1.0 (0.6, 1.5)	1.0 (0.4, 2.7)	1.0 (0.6, 1.8)

[A] preeclampsia

[B] severe intrauterine growth restriction based on antepartum ultrasound examination, non-reassuring fetal testing, oligohydramnious, and Doppler abnormalities of umbilical cord blood flow

[C] preterm labor, pre-labor membrane rupture, abruption, cervical insufficiency

[D] Gross Motor Function Classification System

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$E_{\text{among those with GMFCS} < 1 \text{ (able to walk) and no vision or hearing abnormality}}$