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Predictors of neonatal production of IFN- γ and relation to later wheeze

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Summary

Supernatant IFN- γ levels from mitogen-stimulated cord blood mononuclear cells were inversely associated with wheeze through age 2, but only among boys. This relation was not due to other factors associated with cord IFN- γ production.

Keywords

IFN- γ ; prenatal predictors; wheeze; children

To the Editor:

We have shown that IFN- γ production at 3 months and 9 months is inversely associated with frequent wheeze in the first year of life¹, and with wheeze up to age 13², respectively.

If early life IFN- γ production predicts later wheeze, it is important to consider whether there are prenatal predictors of IFN- γ , and if so, whether these factors may actually be the driving force for the relations with wheeze. For example, if parental smoking is associated with early IFN- γ production, an observed relation between IFN- γ production and wheeze could be attributable to passive smoke exposure. In addition, there appear to be sex-specific differences in both immune responses³ and prevalence of wheeze⁴, suggesting that potential modifications of the IFN- γ -wheeze relation by gender should be investigated. Thus, the objective of this study was to investigate the predictors of cord IFN- γ levels, to assess whether the relation of cord IFN- γ to early wheeze is actually attributable to these factors, and to determine if gender impacts these relations.

We used data from the Infant Immune Study, a birth cohort of non-selected children¹. Participants were healthy children born to pregnant women who planned to obtain care for

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their newborns from collaborating pediatricians. Blood specimens were obtained from the umbilical cord at birth and by venipuncture at 3 and 12 months. IFN- γ production was measured in supernatants from ConA/PMA stimulated blood mononuclear cells with Elisa as previously described⁵. IFN- γ levels were log-transformed for all analyses. Data on maternal and paternal asthma, maternal education, household smoking during pregnancy (defined as the presence of any person who smokes in the home), ethnicity, maternal age, number of children in the household, and the presence of cats or dogs in the house was obtained by questionnaire prior to the child's birth. Gender of the child, type of delivery, gestational age and the child's birth weight were ascertained soon after delivery. Wheeze was defined as report of wheeze in the past 12 months based on parent-completed questionnaires at age 1 (1.1 ± 0.1 years, $n = 265$), 2 (2.1 ± 0.2 years, $n = 233$), 3 (3.2 ± 0.3 years, $n = 237$), and 5 (5.1 ± 0.4 years, $n = 241$) years.

Relations between log-transformed IFN- γ levels and predictors were assessed using t-tests and linear regression models. Relations of IFN- γ to wheeze were assessed by logistic regression models and by Generalized Estimating Equations. Statistical significance for all analyses was defined by a two-sided alpha level of 0.05. All analyses were conducted using Stata version 10.0. The study was approved by the University of Arizona Institutional Review Board.

Children with both IFN- γ data at birth and wheeze data at 1, 2, 3 or 5 years were included in this analysis. Included children ($n = 277$) did not differ from those not included ($n=205$) with respect to most potential confounders. However, included children were more likely to have older mothers with more years of education and to live in non-smoking households (data not shown). Table 1 shows geometric mean IFN- γ levels overall and with respect to selected prenatal predictors. Maternal asthma, household smoking during pregnancy, the presence of other children in the household and gestational age were inversely related to IFN- γ production at birth. For most predictors, these relations were evident for both genders, although they were not always statistically significant. The presence of other children in the household was only inversely associated with IFN- γ production in boys ($P_{\text{interaction}} = 0.054$). There was no statistically significant association between cord IFN- γ production and gender, type of delivery, maternal age at delivery, maternal education, paternal asthma, ethnicity, the presence of cats or dogs in the house, or the child's birth weight (data not shown).

Of the 277 subjects included in this analysis, 92.4% (256) had data on both early wheeze (at either 1 or 2 years) and later wheeze (at either 3 or 5 years). The prevalence of active wheeze was 34.1% (90/264), 20.6% (48/233), 22.8% (54/237), and 24.9% (60/241) at age 1, 2, 3 and 5 years, respectively. Active wheeze prevalence was not significantly associated with gender at any age.

Figure 1 shows the geometric mean production of cord IFN- γ by active wheeze at 1 and 2 years, stratified by gender. Boys who were wheezing in the first two years of life had lower IFN- γ production at birth than non-wheezers, a relation that did not exist for girls. Predictive relations of IFN- γ with wheeze to 2 years are shown in Table 2. For the group as a whole, cord IFN- γ levels were inversely associated with wheeze through age 2 years, though this relation was not statistically significant after adjustment for maternal asthma, household smoking, gestational age, and other children in the household. When stratified by gender, cord IFN- γ levels were inversely associated with wheeze for boys through age 2 years in both unadjusted and adjusted models. There was no relation of cord IFN- γ with wheeze to 2 years for girls ($P_{\text{interaction}} = 0.04$). IFN- γ production at 3 months was also inversely associated with wheeze through age 2, and again, this relation was primarily seen for boys (S-Table 1). There was no association between IFN- γ production at 12 months and wheeze through age 2 (S-Table 1). There was no association between IFN- γ production at birth, 3

months or 12 months with wheezing at ages 3 and 5, either overall or when stratified by gender (data not shown). Relations between IFN- γ production and wheeze were similar for infants who were atopic or non-atopic, as indicated by detectable allergen-specific IgE by age 2 years (data not shown).

Our results expand upon Guerra et al.¹ by utilizing a larger dataset from the same population, and by adjusting for prenatal predictors of cord IFN- γ . Whereas Guerra et al.¹ found no overall association between cord IFN- γ and wheeze, in the current analysis stratification by gender revealed an association among boys that persisted after adjustment for potential confounders.

In conclusion, this analysis reveals a relation of IFN- γ production at birth to wheeze that is only evident for boys, and is limited to the first two years of life. Further, predictors of IFN- γ production at birth do not account for these relations. These findings reinforce the importance of considering gender when evaluating the relation between risk factors and disease.

Acknowledgments

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Abbreviations

IFN- γ Interferon gamma

Figure 1.
Relation of IFN- γ levels at birth to active wheeze at 1 and 2 years, stratified by gender.

Geometric mean and 95% confidence interval for IFN- γ production at birth, by prenatal predictors and gender, in picograms per milliliter (pg/ml).

Table 1

		Birth IFN- γ levels (pg/ml)					
		All		Boys		Girls	
	N*	Geo. mean (95% CI)	N	Geo. Mean (95% CI)	N	Geo. Mean (95% CI)	
All Maternal asthma							
No	277	429 (364, 504)	140	399 (318, 502)	137	461 (365, 581)	
Yes	215	477 (399, 570)	115	428 (333, 550)	100	541 (419, 698)	
P-value [†]	52	241 (164, 354)	21	243 (124, 477)	33	239 (146, 392)	0.002
Household smoking							
No	222	474 (395, 568)	109	447 (344, 581)	113	502 (388, 648)	
Yes	52	295 (205, 424)	30	271 (166, 442)	22	332 (186, 594)	
P -value [†]		0.02		0.08		0.20	
Other children in household							
No	128	503 (407, 622)	61	563 (434, 739)	67	453 (326, 633)	
Yes	137	343 (268, 441)	72	281 (194, 407)	65	430 (309, 599)	
P -value [†]		0.02		0.004		0.82	
Gestational age							
Coef. (95% CI) [‡]	277	-0.09 (-0.13, -0.03)	140	-0.06 (-0.13, 0.02)	137	-0.14 (-0.24, -0.05)	
P -value [†]		0.004		0.15		0.003	

Abbreviations: CI (Confidence Interval); Coef. (Coefficient)

* Total N's vary as data on some subjects are missing for some factors.

[†] P -value obtained from two sample t-test using log-transformed IFN- γ levels.

[‡] From linear regression model, coefficient represents change in log-transformed birth IFN- γ levels for 1 week increase in gestational age. Bold indicates p-value less than 0.05.

Table 2

Odds ratios (OR) for relations of birth levels of IFN- γ to active wheeze at 1 and 2 years, from longitudinal models, for all children and stratified by gender.

	All (n = 272)		Boys (n = 137)		Girls (n = 135)		Gender by IFN- γ Interaction	
	OR (95% CI)	P-val	OR (95% CI)	P-val	OR (95% CI)	P-val	P-val	P-val
Unadjusted	0.5 (0.5, 0.9)	0.01	0.4 (0.3, 0.7)	0.002	0.9 (0.6, 1.5)	0.74		0.04
Adjusted*	0.8 (0.5, 1.2)	0.21	0.5 (0.3, 0.9)	0.02	1.4 (0.8, 2.4)	0.24		0.04

* Adjusted for maternal asthma, household smoking, gestational age and presence of other children in the household. Bold indicates p-values less than 0.05.