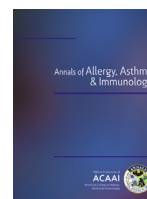




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Letter

Perinatal environmental influences on goat's and sheep's milk allergy without cow's milk allergy

Cow's milk (CM) allergy is the most common food allergy in children, and it can coincide with goat's and sheep's milk (GSM) allergy because of high sequence homology between the corresponding proteins.¹ Conversely, GSM allergy without CM allergy is extremely rare and mainly reported in countries with higher consumption of GSM products.² The reasons for the development of GSM allergy without CM allergy are unclear, but identical twin studies could shed light on this issue. We describe a case of monoamniotic identical twin girls with disparate food allergy. Twin A developed GSM allergy without CM allergy, and twin B has not yet manifested any food allergy.

Their mother was 41 years old and developed gestational diabetes that required insulin. She took only prenatal vitamins and had no other medical conditions. During pregnancy, she restricted meat consumption but continued to consume GSM products. In utero, the 2 umbilical cords were intertwined, resulting in intrauterine growth retardation, with absent end diastolic flow for 3 to 4 weeks before gestation and variable decelerations in twin A's heart rate. The mother underwent cesarean section at 35.6 weeks.

Twin A had a thin umbilical cord intertwined with the normal cord of twin B. Pathologic assessment of twin A's umbilical cord revealed 3 vessels but decreased spiraling, a finding associated with intrauterine growth retardation.³ There was no significant difference between the placental disks. Twin A was small for gestational age (1,840 g), and her initial blood glucose level was 18 mg/dL. She was immediately fed a formula for premature infants (Enfamil Premature Formula; Mead Johnson & Company, Evansville, Indiana), after which the hypoglycemia resolved. She had no further episodes and received no medications during her 6-day stay in the neonatal intensive care unit (NICU).

Twin B had a normal weight (2,495 g). She initially had a normal Apgar score but began grunting with mild respiratory difficulty and briefly required oxygen. Her blood glucose level was 27 mg/dL, so a glucose bolus was given, followed by an infusion for less than 24 hours. She was taken to the NICU, where she had normal chest and abdominal radiographs. She took a formula for premature infants (Enfamil Premature Formula) for 2 days followed by an advanced formula (Similac Advanced Formula; Abbott Laboratories, Abbott Park, Illinois) during her 6-day NICU stay.

At home, both sisters initially required formula supplementation but then transitioned to breastfeeding alone. They had no exposure to tobacco smoke and no other significant differences in their environmental exposures. Their mother was a gourmet cook, so they were exposed to unconventional foods at an early age. At 3 years of age, twin A ate goat's cheese and immediately developed anaphylaxis, with generalized hives, facial swelling, and nausea,

which improved with antihistamines. She had an elevated specific IgE level to sheep's milk (57.7 kU/L) and goat's milk (88.8 kU/L) but not to CM (<0.35 kU/L). She also had evidence of GSM allergy but not CM allergy by skin testing (Table 1). Twin B had negative skin test results to all foods and never developed food allergy.

To our knowledge, this is the first reported case of disparate GSM allergy without CM allergy in identical twins. This case offers the rare opportunity to observe the effect of environmental influences on the development of food allergies because genetic contributions are minimized. In this case, the only significant difference in the twins' experience was during the perinatal period. Compared with twin B, she had a more stressful prenatal period with impaired placental blood flow in utero. Several studies have linked stress and food allergies, although it is still not clear how stress modulates the allergic response. Experiments in rats suggest that chronic stress contributes to the development of food allergies by increasing transepithelial permeability and antigen uptake in the gut, sensitizing the host.⁴ Yang et al⁴ found that this process was dependent on corticotrophin-releasing hormone released in response to stress, and treatment with a corticotrophin-releasing hormone antagonist prevented antigen uptake and subsequent intestinal allergic response. Although human research is needed, this study found that stress may induce gut permeability and increase sensitization to luminal antigens, which could play a role in food allergic disease.

Epigenetic phenomena (ie, extrinsic factors that can produce heritable changes in gene expression without changing the underlying DNA sequence) may also have predisposed twin A to allergic disease. Environmental exposures may play a key role and lead to the modulation of gene expression via mechanisms such as DNA and histone methylation and changes in microRNA expression. Several findings suggest that intrauterine events play a critical role in the development of allergies and the mechanisms likely involve

Table 1
Results of prick-to-prick skin testing

Food tested	Twin A		Twin B	
	Wheal, mm	Flare, mm	Wheal, mm	Flare, mm
Goat's milk	30 ^a	42	2	5
Cow's milk	6	20	5	6
Pecorino (sheep's milk cheese)	15 ^a	30	5	6
Machego (sheep's milk cheese)	26 ^a	45	5	10
Feta (sheep's milk cheese)	21 ^a	42	5	10
Chevre (goat's milk cheese)	25 ^a	42	3	5
Gouda (cow's milk cheese)	6	8	5	7
Histamine (positive control)	16	55	13	40
Saline (negative control)	4	10	4	6

^aPositive reaction, defined by wheal 3 mm or larger than the negative control.

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epigenetic modifications.⁵ Lin et al⁶ found that in mice prenatal exposure to *Aspergillus fumigatus* during pregnancy was associated with diminished IgE levels, suggesting that prenatal environmental exposures to proinflammatory stimuli may help induce tolerance. Other murine studies have found that prenatal lipopolysaccharide exposure suppresses the T_H2 response in offspring, although the exact epigenetic changes have not been identified.⁷ In contrast, human studies have found that exposure to high microbial burden in utero leads to demethylation of the *FOXP3* gene.⁸ This epigenetic modification is associated with enhanced FoxP3 expression and neonatal regulatory T-cell function and may be protective against asthma and allergy. In this case, twin B received relatively more blood flow than twin A and may have been exposed to more maternal antigens in utero, which may have played a protective role. Overall, however, studies have been conflicting on whether prenatal exposure to antigens offers a protective benefit. For example, maternal peanut consumption during pregnancy was associated with increased peanut specific IgE in atopic infants.⁹ It is possible that the timing and intensity of prenatal allergen exposure affects the development of tolerance.

This case is unique for several reasons. GSM allergy without CM allergy is rare, as suggested by the few published reports of this condition.² Because the differential sensitization to GSM occurred in identical twins, genetic factors are largely controlled for, suggesting that environmental influences may have contributed to this unusual food allergy. Although several factors may be responsible for discordant food allergies in identical twins, this case emphasizes the potential importance of the prenatal period, when the twins had markedly different experiences. Larger studies are needed to further investigate this issue.

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