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Relation Between Infantile Colic and Asthma/Atopy: A Prospective Study in an Unselected Population

José A. Castro-Rodríguez, MD; Debra A. Stern, MS; Marilyn Halonen, PhD; Anne L. Wright, PhD; Catharine J. Holberg, PhD; Lynn M. Taussig, MD; and Fernando D. Martinez, MD

ABSTRACT. Objective. To assess whether children with history of infantile colic may be at increased risk of subsequently developing asthma and/or atopy.

Methods. We used data collected in a large, prospective study from an unselected population. Infantile colic and concurrent feeding method were determined from the 2-month well-infant visit form completed by the physician for 983 children who were enrolled at birth. Markers of atopy (total serum immunoglobulin E and allergy skin prick test), allergic rhinitis, asthma, wheezing, and peak flow variability were the main outcome measures studied at different ages between infancy and 11 years.

Results. Ninety (9.2%) children had infantile colic. Prevalence of colic was similar among children fed either breast milk or formula. There was no association between infantile colic and markers of atopy, asthma, allergic rhinitis, wheezing, or peak flow variability at any age.

Conclusion. Our data cannot support the hypothesis that infantile colic provides increased risk for subsequent allergic disease or atopy. Pediatrics 2001;108:878–882; infantile colic, asthma, atopy, feeding, wheeze.

ABBREVIATIONS. IgE, immunoglobulin E; PEF, peak flow; GM, geometric mean; CI, confidence interval.

Infantile colic—excessive crying in otherwise healthy, thriving infants—is a common problem during the first months of life, affecting about 10% of infants.1–4 The colicky period usually has its onset in the first 2 to 3 weeks of life, peaks at 6 to 8 weeks, and resolves by 3 to 4 months of age.5

Despite over 40 years of research, the cause of infantile colic remains unclear.2 Allergy to cow’s milk protein has often been implicated as a cause of colic.2,5 According to this theory, specific immunoglobulin E (IgE) to milk protein is associated with an IgE-mediated reaction that results in abdominal pain and crying6 and removal of the offending allergen should reduce symptoms.2 Supportive evidence includes the observation of increased numbers of IgE-producing plasma cells in the jejunal mucosa of a small group of colicky infants after exposure to cow’s milk protein.6 In addition, elimination of cow’s milk protein from the diet of infants with colic and substitution with hypoallergenic formula milks (but not with soy formula) has been shown to be an effective treatment.2 Studies done in selected populations or retrospectively seeking to determine whether a direct relation exits between family history of atopy and infantile colic have shown contradictory results.7–9

Asthma is associated with the presence of specific IgE to aeroallergens,10,11 airway inflammation, and bronchoconstriction of airway smooth muscle, which responds to bronchodilators and anticholinergic drugs.12 Personal and parental history of atopy/allergy is one of the most recognized risk factors for asthma.13 Moreover, allergic sensitization in susceptible asthmatic patients may begin with food allergens possibly through increased intestinal permeability to macromolecules. Similarly, it is thought that colic may be associated with the production of specific IgE to milk protein and may be regarded as a very early manifestation of an allergic predisposition.6 Additionally, anticholinergic drugs, such as dicyclomine (which decrease gut contractions by direct relaxation of gastrointestinal smooth muscle), are an effective treatment for colic.2 Therefore, there is suggestive evidence that common mechanisms (alteration in smooth muscle contraction and/or IgE-mediated events) possibly underlie both diseases. Using data from a large, unselected population enrolled at birth, we assess whether infantile colic is related to the development of asthma or atopy later in life.

MATERIALS AND METHODS

Subjects participating in the present study were enrolled in the Tucson Children’s Respiratory Study at birth (N = 1246).14 Parental history of physician diagnosed of asthma and allergic rhinitis as well as maternal education, maternal smoking, and ethnicity were determined from the enrollment questionnaire. The presence of colic was determined from the well-infant visit form completed by the physician at the time of the 2-month well-infant visit. The same group of physicians saw all children and it was up to the discretion of the physician, in conjunction with parental responses to questioning, as to whether colic was recorded as present on the form. In addition, on the same form, the physician reported concurrent information on breastfeeding, formula feeding, type of formula, and consumption of other foods such as meats, vegetables, and/or vitamins. Detailed health questionnaires were completed by the parents for the child at the Yr2 survey (mean age ± standard deviation, 1.6 ± 0.4 years), Yr3 survey (2.9 ± 0.5 years), Yr6 survey (6.3 ± 0.9 years), Yr8 survey (8.6 ± 0.7 years), Yr11 survey (10.9 ± 0.6 years), and the Yr13 survey (13.5 ± 0.6 years).
Asthma and Wheezing

The presence of asthma in the child was ascertained at the time of the Yr6, Yr8, Yr11, and Yr13 surveys by parental report of a physician diagnosis of asthma plus at least 1 exacerbation of asthma during the previous year. Parents were also asked if the child’s chest had sounded wheezy or whistling during the past year and how often this had occurred. Children were considered to have frequent wheeze if they had ≥3 episodes of wheezing during the previous year and any wheeze if they had ≥1 episode of wheezing during the previous year. Similar wheezing groups were created for the Yr3 survey using a slightly different scale for wheezing frequency.

Allergic Rhinitis and Eczema

Allergic rhinitis was defined by a physician diagnosis and the presence of active symptoms during the previous year at the time of the Yr3, Yr6, and Yr11 surveys. Eczema was defined by a physician. Tests of skin prick tests were performed on the children at the Yr6 survey and again at the Yr11 survey. Allergens were retested at the Yr11 survey except house dust mite; in addition, cat and Dermatophagoides pteronyssinus were added to the test panel. Tests were read at 20 minutes and wheal size was expressed in IU/mL.

Markers of Atopy

Total serum IgE levels were measured with the paper radioimmunosorbent test (Pharmacia Diagnostics, Piscataway, NJ) in samples obtained from cord blood, from blood at a median age of 9.3 months (referred to as the 9-month sample), and from blood at the time of the Yr6 and Yr11 surveys. At the time of the Yr6 survey, total serum IgE levels were determined from parental blood samples. All samples were assayed in duplicate and the lower limit of detection in this assay is 0.1 IU/mL.

Allergy skin prick tests were performed on the children and the parents at the time of the Yr6 survey and again on the children at the time of the Yr11 survey. House dust mite, Alternaria alternata, Bermuda grass, careless weed, olive tree, mesquite tree, and mulberry tree were tested at the Yr6 survey (all allergens were obtained from Hollister-Stier Laboratories, Everett, WA). These allergens were retested at the Yr11 survey except house dust mite; in addition, cat and Dermatophagoides pteronyssinus were added to the test panel. Tests were read at 20 minutes and wheal size was recorded as the sum of the 2 diameters (in mm); wheal sizes of 3 mm or greater were considered positive. A positive response to at least 1 allergen was considered positive for skin test reactivity in general.

Peak Flow Variability

At the time of Yr11 survey, children, previously trained, took home peak flow meters to measure peak flow (PEF) 3 times daily for 1 week. Only children who recorded PEF measurements at least twice per day for at least 4 days were included in the analysis. Positive PEF was considered to be present in subjects with amplitude percent mean values above the 90th percentile for a healthy reference subgroup; more detailed information about this technique has been published.15

Statistical Analysis

Survival analysis was performed using the risk-time for developing asthma, frequent wheeze, and any wheeze (asthma/wheeze). Risk-time was defined as the age of the first questionnaire in which a positive report of asthma/wheeze occurred or the age of the last questionnaire in which no asthma/wheeze occurred. For those children in which the age of the first questionnaire reporting asthma/wheeze was followed by a missing questionnaire, we considered the mean age between the last 2 questionnaires as the age of the asthma/wheeze data. Statistical analyses for total serum IgE values were performed using log-normally distributed values and are reported as the geometric mean (GM) and 95% confidence interval (95% CI) and expressed in IU/mL. \( \chi^2 \) was used for proportions and Student t test for means. Statistical significance was defined by a 2-sided \( \alpha \) level of 0.05. Informed consent was obtained from the parents of participating children and the study was approved by the Human Subjects Committee of the University of Arizona.

RESULTS

Of the children enrolled in the study, 983 (79%) completed the 2-month well-infant visit (11.5% at the first month of life and 88.5% at the second). Of these children, physician-reported infantile colic occurred in 9.2% (90/983). Prevalence of infantile colic was similar among males and females (10.3% and 8.1%, respectively; \( P = .2 \)). There was no association of infantile colic with the maternal level of education, parity, ethnicity, or antecedents of prenatal maternal smoking and maternal smoking during the first year of life. Children with infantile colic had slightly older mothers compared with children without infantile colic (mean ± standard deviation, 28.3 ± 4.8 vs 27.3 ± 4.6 years of age, respectively, \( P = .04 \)). The 263 children who did not complete the 2-month well-infant visit were similar in demographic characteristics and in the prevalence of asthma/atopy compared with those who did complete the 2-month well-infant visit except for ethnicity. Children with at least 1 Anglo parent were more likely to have follow-up information compared with children with non-Anglo parents (81% vs 71%, respectively; \( P < .01 \)).

Using the physician-recorded feeding information, we found no difference in prevalence of infantile colic with either breast- or formula-feeding (Table 1). Likewise, there was no significant association of infantile colic with the use of either type of milk formula (cow’s milk vs soy-based). Among children who were only formula-fed, the prevalence of infantile colic was 12.9% (4/31) for soy-formula versus 6.9% (19/271) for cow’s milk formula (\( P = .4 \)). Among children who were both breast- and formula-fed, the prevalence of infantile colic was 15% (3/20) for soy-formula versus 9.5% (18/189) for cow’s milk formula (\( P = .7 \)). At the 2-month well-infant visit, only 3 (0.3%) infants were consuming meat and 35 infants (3.6%) consuming vegetables. Of those infants who were consuming vegetables, 22.9% had infantile colic compared with 8.6% of those who did not consume vegetables (\( P = .004 \)). There was no association of infantile colic and the consumption of vitamins (data not shown).

There did not seem to be any increased prevalence of infantile colic among offspring of parents with asthma or positive skin test reactions (Table 2). Maternal and paternal total serum IgE levels of infants

<table>
<thead>
<tr>
<th>Type of Feeding</th>
<th>Colic (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive breast-feeding</td>
<td>9.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Exclusive formula</td>
<td>7.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Breastfeeding and formula</td>
<td>10.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Soy-based formulas include Isomil (Ross, Abbott Park, IL), Prosobee (Mead Johnson, Evansville, IN), and Nursoy (Wyeth-Ayerst, Philadelphia, PA).

Cow-milk formulas include: Similac (Ross, Abbott Park, IL), Enfamil (Mead Johnson, Evansville, IN), SMA (Wyeth-Ayerst, Philadelphia, PA), and whole milk.
with colic were similar to those of infants without colic. Geometric mean total serum IgE in mothers of infants with colic (N = 57) was 31.2 IU/mL (95% CI: 20.3–48.0) and 31.0 IU/mL (95% CI: 27.2–35.4) in mothers of infants without colic (N = 545), P = 1.0; geometric mean total serum IgE in fathers of infants with colic (N = 49) was 53.4 IU/mL (95% CI: 33.9–84.0) and in fathers of infants without colic (N = 405) was 52.1 (95% CI: 44.8–60.5), P = 9. The prevalence of infantile colic was similar in infants with a parental history or no parental history of allergic rhinitis (Table 2). However, there was a slightly increased risk of colic among infants with maternal history of allergic rhinitis (Table 2).

The survival distribution was similar for children with and without infantile colic for asthma, any wheezing (Fig 1), and frequent wheezing (data not shown). In addition, infantile colic was also not associated with positive peak flow variability (4.9%/241) in children with infantile colic and 10.3% (42/409) in children without colic, P = .3.

Infants who had colic did not have a significantly increased prevalence of allergic rhinitis or eczema at the time of Yr3, Yr6, or Yr11 surveys (for colic vs no colic: prevalence of allergic rhinitis at the yr3, yr6, and yr11 surveys were 20.3% vs 17.2%, 28.9% vs 24.0%, and 27.8% vs 22.7%, respectively; prevalence of eczema at the yr3, yr6, and yr11 surveys were 7.0% vs 6.1%, 5.3% vs 5.4%, and 9.6% vs 6.0%, respectively). There was no association of infantile colic with increased positive skin test reactivity to any specific aeroallergens (Yr6 survey: 32.1% [18/56] vs 38.6% [216/560], for infants with colic vs those without colic, respectively, P = .3 and at the Yr11 survey: 61.5% [32/52] vs 57.0% [262/460], respectively, P = .5). Cord-serum IgE levels were also unrelated to infantile colic (N = 87, GM = 0.09 IU/mL, 95% CI: 0.07–0.12 in children with colic compared with N = 801, GM = 0.09 IU/mL, 95% CI: 0.08–0.1 for those without colic, P = .9). Moreover, total serum IgE levels at 9 months (for colic N = 68, GM = 3.86, 95% CI: 2.72–5.48 and for no colic N = 661, GM = 3.98, 95% CI: 3.61–4.41, P = .8), Yr6 (for colic N = 39, GM = 31.4, 95% CI: 18.2–54.3 and for no colic N = 394, GM = 35.5, 95% CI: 30.0–42.1, P = .7), and Yr11 (for colic N = 47, GM = 50.0, 95% CI: 27.7–86.5 and for no colic N = 446, GM = 61.8, 95% CI: 51.9–73.5, P = .4) surveys were similar for infants who had infantile colic compared with those who did not have colic.

**DISCUSSION**

This study indicates that children who received a colic diagnosis by a pediatrician during their first 2 months of life did not have an increased risk of asthma or wheeze at preschool and school ages compared with children without infantile colic. Markers of atopy, including total serum IgE levels, positive skin test reactions, and the prevalence of eczema and allergic rhinitis were not associated with a history of infantile colic. Moreover, infantile colic was not associated with a parental history of asthma or allergic disease. In addition, our data did not indicate any relation between colic and breast or formula feeding in infancy.

The prevalence of colic in the first 2 months of life diagnosed by the pediatricians in our unselected population (9.2%) was very similar to other population-based studies. Canivet et al, using the classic definition of Wessel, reported an occurrence rate of 9.3% in the first 3 months of life. In agreement with
other authors, the present study shows a similar prevalence of infantile colic between males and females. Crowcroft and Strachan reported an association between children with infantile colic and some social factors (eg, increased parental age, lower parity, and lower socioeconomic status). We found a significant relation between infantile colic and older age in the mother but not with parity or socioeconomic status as represented by the level of maternal education.

The present study supports the concept expressed by others that breastfed infants have similar rates of infantile colic compared with formula-fed infants. Similarly, we did not find a significant protective role for the development of infantile colic among those children with soy formula compared with those who used lactose formula milk during their first 2 months of life. However, one limitation of our study could be that we do not know the reason for the specific type of formula milk consumed at this age.

The early introduction of solid foods was reported to be associated with an increased development of eczema, respiratory illness (coryza, cough, or wheeze, and persistent cough), and infantile colic. In our study, only the early introduction of vegetables, but not other solid foods, was significantly associated with higher prevalence of infantile colic at 2 months. However, because <10% of the children with colic were eating vegetables at that age and because we do not know if the physicians suggested adding vegetables to the diet in response to symptoms of colic, this finding cannot be generalized.

The relation between family or personal history of atopy/allergy diseases and infantile colic has been investigated in the past. Some retrospective studies have suggested that the prevalence of colic was higher in those infants with family history of atopy/allergy disease, but another study has not supported this finding. However, a prospective study that followed 79 infants with a family history of infantile colic at 2 months did not find any relation between colic and atopic dermatitis or positive skin tests in infancy. In this large and prospective population-based study, the prevalence of colic was not related to parental history of allergic disease (allergic rhinitis or positive skin test reactivity or high level of total serum IgE). Only maternal allergic rhinitis in our study was related to an increased prevalence of infantile colic, but because this was the only parental marker of allergy/atopy related to colic in the child, this may be attributable to the large number of comparisons made. Furthermore, among our infants who had a diagnosis of colic, there was no increased risk for the development of eczema, allergic rhinitis, and either positive skin test reactivity or higher levels of total serum IgE at preschool and school age.

Previous retrospective studies did not find any relation between infantile colic and asthma/wheeze in infancy or in school-aged children. In this study, children with a history of infantile colic had similar survival curves for asthma (from Yr6 to Yr13 surveys), for frequent wheeze and for any wheeze (from Yr3 to Yr13 surveys) compared with those children without infantile colic. Furthermore, bronchoconstriction, as assessed in our population at the time of Yr11 by PEF variability, was similar in children with a diagnosis of infantile colic and those without. Therefore, the promising hypothesis of the potential relation between bronchial constriction of airway smooth muscle in asthma and the constriction of intestinal smooth muscle in colic cannot be supported with our data.

CONCLUSION

Our data cannot support the hypothesis that infantile colic is associated with the increased risk of asthma, allergic rhinitis, wheeze, or markers of atopy in childhood nor with formula or breastfeeding.

ACKNOWLEDGMENTS

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REFERENCES

BIOETHICISTS FIND THEMSELVES THE ONES BEING SCRUTINIZED

“As the march of medical science raises questions once reserved for theology alone, researchers, elected officials, and companies are increasingly turning to bioethicists for advice. Just today (August 2, 2001), 3 ethicists were among witnesses who testified before a Senate subcommittee about cloning and embryonic stem cell research . . . And the field has yet to develop rules on working with industry. Some bioethicists accept corporate donations for their university programs, and others work as paid consultants for biotechnology companies, leading colleagues to charge that they are being used to public relations tools and damaging the field’s credibility . . . a professor of law and medical ethics at the University of Wisconsin said, “Anybody can stand up and claim to be an ethicists—there is no licensing, there is no accreditation.” . . . And that, critics say, is a big problem with bioethics . . . “The bioethicists have set themselves up, almost like Napoleon crowing himself emperor as the arbiters of what is moral and ethical in health care,” said Wesley J. Smith, author of Culture of Death: The Assault on Medical Ethics in America, published last year by Encounter Books. “A hairdresser has to have a license.””


Noted by JFL, MD
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