

Atopy Patch Test for Early Diagnosis of Cow's Milk Allergy in Preterm Infants

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ABSTRACT

Atopy patch test may help early diagnosis of cow-milk allergy in preterm infants. In the retrospective analysis of 5 girls and 9 boys, born at 31 ± 2 (mean $\pm$ SD) weeks of gestation and presenting digestive symptoms at age 42 ± 18 days, 10 had a complete recovery following the shift to an exclusive feeding with an amino acid–based formula. Cow-milk–skin prick tests and specific immunoglobulin E were always negative, whereas the atopy patch test was positive in 7 of the 10 infants with complete recovery.

Key Words: atopy patch tests, cow-milk allergy, diagnostic, preterm infants

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In preterm infants, the difficulty of reaching full enteral feedings is significantly associated with a poorer mental outcome, so that optimization of enteral nutrition without increasing the risk of necrotizing enterocolitis is a priority (1). Feeding difficulties and digestive symptoms such as rectal bleeding, vomiting, and diarrhea participate in the cohort of early symptoms of cow-milk (CM) allergy (CMA) (2,3). In clinical practice, the switch toward an elimination diet using an extensively hydrolyzed formula or an amino acid–based formula (AAF) relies on clinical decision trees. The usual allergic workup, that is cow-milk–specific immunoglobulin E (CM–IgE) measurement and CM–skin prick testing (CM–SPT), is almost often negative, CMA being mostly non-IgE mediated at this age (3). The atopy patch test (APT) has been proposed in the diagnosis of CMA, especially in non-IgE-mediated reactions (4). In addition, a recent study valued the role of APT in the early diagnosis of allergy to house dust mites, at an age at which IgE-mediated processes still remain undetectable (5). CM patch testing was rendered easier in some European countries because of the availability of a ready-to-use CM–APT, Diallertest, shown in older children (5–78 months) to exhibit good sensitivity (76%, confidence interval 59.2–92.7), specificity (93.8%, 81.9–100), and test accuracy 82.9% (range 71.3%–94.5%), without adverse events (6).

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We thus tested the potential of this ready-to-use APT among the usual CMA diagnostic tools to help neonatologists adopt a feeding policy adapted to the hypothesis of CMA in preterm infants.

PATIENTS AND METHODS

The retrospective analysis of the systematic testing of infants with symptoms suggesting CMA in the neonatal ward during 2006 comprised 5 girls and 9 boys born at 31 ± 2 (mean $\pm$ SD) weeks of gestation (WG), ages 42 ± 18 days, who presented with rectal bleeding ($n = 6$), vomiting (5), and diarrhea (3) while receiving a standard CM-based preterm formula. None of them was breast-fed.

In the presence of symptoms suggesting CMA, infants were tested as per routine protocol, using specific CM–IgE measurement, CM–SPT, and the ready-to-use CM–APT, Diallertest. They were then shifted to an AAF (Neocate, SHS International, Liverpool, UK). The outcome of symptoms was evaluated 1 month later, before deciding to shift or not to shift the child back to a standard CM-based preterm formula. Those who did not improve under the AAF were shifted back to the standard CM-based preterm formula.

Sera CM–IgE were analyzed using the RAST Cap System (Phadia, Uppsala, Sweden). References data for specific CM–IgE were those of the manufacturer, with values <0.10 kU/L considered nondetectable.

SPT were performed with a drop of pasteurized half-skimmed cow's milk on the volar part of the forearm. Histamine dihydrochloride (ALK, Copenhagen, Denmark), 10 mg/mL, and glycerosaline were used as positive and negative controls. A positive reaction after 15 minutes implied a wheal diameter 3 mm larger than the negative control.

The ready-to-use CM–APT (Diallertest, DBV Technologies, Boulogne-Billancourt, France) is 26 mm large and has the form of a small chamber. The back of the chamber has a central transparent plastic membrane (11 mm diameter) of polyethylene, coated with a homogeneous monolayer of powdered defatted milk (250 μ g microgranules of CM, 60% casein, and 40% whey). The chamber is mounted on an adhesive nonwoven film. When the patch is applied, the sweat allows the powder to solubilize, mimicking the presence of milk in the small chamber (6). The active patch and the control patch (same structure deprived of powder) were applied on the back of the child for 48 hours and then removed and the reading was done 24 hours later. All of the tests were performed by the same nurse and the reading performed by 2 different practitioners.

RESULTS

Among the 14 preterm infants, 4 did not improve under AAF and were shifted back to a standard CM-based preterm formula without any immediate or delayed reactions, and were negative for all of the tests. Ten infants (71.4%) had complete clearance of digestive symptoms under AAF and, among those, 2 had an immediate relapse of symptoms during an attempted early refeeding with a CM-based formula at 6 months of age. In those 10 infants,



FIGURE 1. A ready-to-use milk atopy patch test (Diallertest) on a premature infant's back, allowing comparison of the redness and infiltration of the milk patch (right) and the absence of reaction on the control patch (left).

7 had a positive APT (Fig. 1), contrasting with negative CM-SPT and CM-IgE.

In the 5 preterm infants born before 30 WG, the clinical benefit of the AAF diet was concordant with the positive results of the APT. In the 9 preterms born after 30 WG, 3 improved under AAF despite a negative APT.

DISCUSSION

The present study shows for the first time that skin reactivity to milk may be evidenced even at a young age, using a milk APT, even though a larger series is necessary to analyze the exact rate of positivity in this clinical situation.

Feeding difficulties are one of the major issues in the neonatal ward, and studies analyzing their frequency, origin, and management are strongly needed (1). In the recent follow-up of 193 premature infants, Kvenshagen et al (3) indicates CMA in 4.9%, thus suggesting that a certain number of preterm infants may experience CMA in the neonatal ward. In this cohort, they indicate that the most frequent and the earliest digestive complaints were pain behavior and gastrointestinal symptoms, in good agreement with the usual observation of digestive problems in preterm infants. Moreover, CM-IgE positivity tended to be exceptional (7).

In the present study, despite the good concordance observed between the results of the APT and those of the AAF diet, no diagnosis of CMA may be considered to be perfectly confirmed. The gold standard for diagnosing CMA is the double-blind, placebo-controlled food challenge (8), which was not performed in preterm infants. Implementation of such a double-blind, placebo-controlled food challenge raises practical difficulties particularly related to a lack of standardization. Furthermore, in this age range,

diet manipulation tends to be risky, and in a child suspected of having CMA, reintroducing a CM-based formula may not be ethical, owing to the risk of a severe relapse of symptoms, especially of bloody stools or even of CMA-related necrotizing enterocolitis (9).

Despite those limitations, the present study suggests that a noninvasive diagnostic tool such as the APT may help in assessing the potential relevance of a CM-free diet because these limited data allowed predicting clinical improvement in 70% of the cases. No further calculation of the accuracy of the test may be done in the absence of a control group in such a pilot trial. The study also confirms the complete lack of contribution of CM-IgE and CM-SPT. Finally, in concordance with the previous study of Boralevi et al (5) with house dust mites, this study suggests that APT may be the allergy diagnostic tool more helpful in younger infants, either using a ready-to-use APT or using fresh food, to compare the accuracy of both systems (10).

CONCLUSIONS

In conclusion, this study suggests the potential help of APT as a noninvasive diagnostic tool in deciding whether a switch to a CM-elimination diet is a relevant feeding choice. This is the first indication that a perfectly noninvasive diagnostic tool may help orient the feeding choice in a population needing high food intake amounts. Whether this diagnostic tool will find a place in clinical practice awaits confirmation by larger and controlled studies.

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