DELAYED BLANCH PHENOMENON AS AN INDICATION OF ATOPY IN NEWBORN INFANTS*

WARD L. HINRICHs, M.D.,† GEORGE B. LOGAN, M.D.‡ AND R. K. WINKELMANN, M.D.§

In 1953, Lobitz and Campbell (1) first described the delayed blanch phenomenon that follows the intradermal injection of acetylcholine. In all 10 of their patients with atopic dermatitis an unusual paradoxic delayed blanch occurred within the flare, 3 to 5 minutes after injection, and persisted for 15 to 30 minutes. With acetylcholine, normal individuals display an erythematous wheal and flare without a subsequent blanch. They stated the belief that this unusual reaction might be specific for those with atopic dermatitis. The reactions and possible physiologic changes in normal and atopic individuals to intradermal injection of acetylcholine or its derivative methacholine are compared in table I.

In 1962 as a result of their study of 29 patients with hayfever or asthma or both, but without atopic dermatitis, West and associates (2) suggested that the delayed blanch reaction was found not only in patients with atopic dermatitis but also in those with other forms of atopy as well. One of the children studied and found to have a delayed blanch reaction was a 4½-year-old girl who had no atopic illness but had a definite family history of atopy. They, therefore, considered that this test might have value in predicting the subsequent development of atopic disease. If this proves to be true, then physicians might institute prophylactic care early in the patient’s life in the hope of preventing the development of atopic disease later. Thus, it seemed important to determine whether the test has value when performed on newborn infants.

The questions to be answered are: 1. Does the delayed blanch reaction occur in newborn infants? 2. Is the positive delayed blanch reaction evidence that atopic disease will subsequently develop in the infant? 3. Is the newborn infant with a family history of allergy more likely to have a delayed blanch reaction? 4. Is the newborn infant with a positive delayed blanch reaction more likely to have erythema toxicum neonatorum than one who does not show such a reaction?

METHODS

The study group consisted of a random sample of 100 healthy full-term infants, 3 to 4 days of age, who were born on the Mayo Clinic Obstetrical Service at St. Marys Hospital in Rochester, Minnesota, between November, 1963, and April, 1964. The group was comprised of an equal number of boys and girls; a sex distribution that was entirely fortuitous.

The tests consisted of injections into the skin of the back of the infant. The test injections were of 0.05 ml of 1:1000 dilution of methacholine (Mecholly), and the control injections were of 0.05 ml of 0.9 per cent sodium chloride and 0.05 ml of 1:100,000 dilution of histamine sulfate. The subsequent reactions (erythema, blanch, and wheal) were measured at 10 seconds and 5, 15, and 30 minutes and were photographed. (Initially injections of 0.1 ml of the test solutions were used as is customary in older children and adults, but the resulting reactions, especially to histamine, were too large. Therefore, a smaller volume of 0.05 ml, which gave smaller but adequate reactions, was used.)

After the intradermal injections and readings were completed, a detailed family history was obtained from the mother of each child with particular reference to eczema, asthma, hayfever, allergic rhinitis, hives, and reactions to drugs.

The blanching reactions were graded 1+ when the area of blanch measured at least 0.5 cm in diameter, 2+ when it measured 1 to 2 cm in diameter, and 3+ when it was larger than 2 cm. Precise measurement of the blanch area was difficult in crying infants and in those with jaundice. In some infants, peripheral blanching within the area of erythema appeared toward the end of the observation period. This type of reaction was graded 1+ and as with the other 1+ reactions can be called unquestionably positive. The 2+ and 3+ reactions, however, were more definite and could be measured more reliably. Satellite blanch areas that were several centimeters from the injection sites were noted in several infants, as were halo blanches around the injection site. These reactions were of questionable significance and were not the satellite wheals presumed to be due to lymphatic spread from the injection site.

The family history of allergy (3) was graded 1+ when a major allergy such as asthma, hayfever,
TABLE I

<table>
<thead>
<tr>
<th>Normal</th>
<th>Atopic</th>
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<tbody>
<tr>
<td>Flare: Onset 5 to 10 seconds, lasting 3 minutes (axon reflex dilatation)</td>
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<tr>
<td>Slow Prolonged Redness: (Local action of the drug on cutaneous vessels)</td>
<td>Delayed Blanch: Onset 2 to 3 minutes, lasting 15 to 30 minutes (possibly vasoconstriction or edema)</td>
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<tr>
<td>Sweating: (Local action of the drug on sweat glands)</td>
<td>Sweating: (Local action of the drug on sweat glands)</td>
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Allergic rhinitis, or atopic dermatitis was present in at least one parent, grandparent, or sibling. In our grading, we considered reactions to drugs as major allergies. The family history was graded 2+ when three or more different family members (sibling, parent, or grandparent) had a history of a major allergy. A family history was graded zero when there were no major allergies reported in the family history. The family history was graded as minor when it included only insect allergies and food allergies in siblings, parents, or grandparents or when major allergies occurred only in family members other than these. The family history also was evaluated as to the presence of major allergic disease either in the maternal or the paternal ancestry (unilateral), or in both maternal and paternal ancestry (bilateral), or in sibings.

RESULTS

Positive delayed blanch reactions (2+ and 3+) occurred in 16 of the 100 infants tested (table II). It is noteworthy that these infants with one exception had neither a 2+ nor a bilateral family history. It is likewise interesting that a number of the infants who did not display delayed blanch reactions had 2+ and bilateral family histories.

In 24 instances, one or more siblings of the tested infant had had major allergic disease. Fourteen of these infants also had a parent or a grandparent with a major allergy.

Eight of the infants had clinical erythema toxicum during their neonatal period. Seven of these had a family history of allergic disease, but only two of the eight had a definite delayed blanch reaction.

Ninety-eight of the infants had wheals that were 0.5 to 1.5 cm in diameter as well as erythema that was 3 to 4 cm in diameter as a reaction to the intradermal injection of histamine (1:100,000). The wheals and erythema persisted for 30 minutes or more.

The control injections of 0.9 per cent sodium chloride solution provoked an erythematous reaction in all of the infants, but this disappeared usually within 20 minutes.

The delayed blanch reaction was not noted in any of the areas injected with histamine or with saline.

COMMENT

The mechanism of the delayed blanch production is still uncertain. Lobitz and Campbell (1) suggested that it might be due to a paradoxic arteriolar vasoconstriction spreading peripherally from the intradermal wheal. This, they supposed, was due to either (1) acetylcholine itself acting to give a motor (constrictor) response rather than the usual inhibitor (dilator) response or (2) some other vasoconstricting substance being released after acetylcholine had been injected. However, Davis and Lawler (4) studied the delayed blanch reaction in 15 patients with atopic dermatitis by means of capillary microscopy and observed dilated capillaries in the blanched area. They attributed the blanching to the presence of edematous fluid. This explanation was not supported by Kalz and Fekete (5) who used intravenously injected coomassie blue dye to facilitate the demonstration of edematous fluid in the skin. In their 20 patients whose skin was normal, the intradermal injection of methacholine resulted in small wheals that did not develop bluing. In 12 patients with atopic dermatitis, the injection of methacholine produced larger, flat wheals with some bluing, but the peripheral blanched zones, which occurred in all of them, did not exhibit bluing. Therefore, they did not consider that the blanch response was caused by the leakage of plasma from dilated capillaries.

West and associates (2) reported that the delayed blanch reaction occurred in about 70 per cent of patients with atopic dermatitis. Lobitz and Campbell (1), Davis and Lawler (4), and Kalz and Fekete (5) did blanch tests with methacholine on three groups (10, 15, and 12 patients) with atopic dermatitis and found that every patient showed a delayed
Delayed blanch phenomenon. Reed and Kierland (6) found that 37 (90 per cent) of their 41 patients with atopic dermatitis had delayed blanch reaction. West and associates (2) studied 29 patients who had hayfever or asthma or both but who did not have atopic dermatitis and found that only 48 per cent of these had positive delayed blanch reaction. This was in contrast to no such abnormal responses in 20 control individuals without atopy.

Matheson and co-workers (7) found that, in infants, the scratch testing with solutions of histamine ranging in dilution from 1:8000 to 1:512,000 resulted in erythematous but not whealing reaction. We found that the intradermal injection of 0.05 ml of a 1:100,000 dilution of histamine resulted in both erythema and wheal in 98 per cent of infants.

In our study, there was no apparent correlation between a family history of allergic disease and a positive delayed blanch reaction. There was no correlation between the occurrence of erythema toxicum and a positive delayed blanch reaction. Whether this test will have value in predicting the probability of atopic disease ultimately developing in any given infant can only be answered when this group of infants has been traced for 10 years or more.

It should be both interesting and enlightening to trace this group through childhood, not only to observe whether atopic disease develops but also to repeat the skin test at various intervals. This length of follow-up should be helpful in deciding whether delayed blanch reaction is an innate, genetically determined characteristic, or whether it is an acquired trait that presents itself only after an atopic disease becomes manifest. There may be no correlation at all between this response to methacholine and the development of atopic disease later. However, if this reaction proves to be an indication of atopy, appropriate prophylactic and therapeutic measures may be instituted at such a time as to be of most benefit to that individual.

**SUMMARY**

Methacholine was injected intradermally into 100 infants who were 3 to 4 days of age. Sodium chloride and histamine solutions were used as control injections. The paradoxic delayed blanch reaction to methacholine was definitely present in 16 infants, questionably present in 21, and absent in 63.

There was no correlation between a positive delayed blanch reaction and a family history of allergy. There was no correlation either between a positive blanch reaction to methacholine or a whealing reaction from injection of histamine and the occurrence of erythema toxicum neonatorum.

The accuracy and reliability of this method for the detection of an atopic individual can only become apparent as the reactions of these infants are studied through childhood and adolescence.
REFERENCES


