Passive Transfer of Idiopathic Cold Urticaria to Monkeys

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Abstract. Serum from 3 out of 14 patients with primary acquired cold contact urticaria produced positive passive transfer reactions in monkeys.

Key words: Cold urticaria; Passive transfer; Monkeys

The pathophysiology of primary acquired cold urticaria (PACU) is unclear. That an immunological mechanism is involved is suggested by the reports in the literature (1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13) on patients with this condition, in whom a serum factor has produced positive passive transfer tests in humans. The exact nature of the serum factor is also unclear. It has been reported variously as being IgM (13) or IgE (1, 3 & 7). The overall proportion of patients with PACU who exhibit positive transfer reactions is unclear, various reports quoting 10% (6) to 50% (9). As it is now considered hazardous to do serum transfer experiments in humans because of the risk of transmissible diseases, the possibility of using monkeys as alternative recipients was investigated.

PATIENT SELECTION

14 patients (6 males, 8 females) with PACU, who had discontinued all medication for one week, were studied. No patient had evidence of active urticaria at the time of blood sampling. All but one showed a positive 15-min ice-cube skin response (local erythema and wealing). The duration of the disease was 1–15 years (mean 5 years). None of the patients showed elevated cryoglobulins, cryofibrinogens, cold agglutinin, or a positive serum test for syphilis. Five had a history of atopy (eczema, asthma or hayfever). Their IgE levels ranged from 25 to 400 IU/ml.

MATERIALS AND METHODS

Venous blood (10 ml) was drawn from patients into prewarmed (37°C) tubes and allowed to clot by standing in an incubator at 37°C. The serum was then separated by centrifuging at 37°C for 10 min at 2000 g (Mistral 6L, M.S.E.). The serum was transferred to preheated tubes and kept at 37°C till injected into the skin. Aliquots of these sera were heated at 56°C for 2 hours to inactivate their IgE antibodies.

One cynomolgous, 3 baboons and 3 rhesus monkeys were studied. The animals were sedated with an intramuscular injection of ketamine hydrochloride 15 mg/kg body wt. ('Vetlar', Parke-Davis). The chest and abdomen of the animals were shaved and reference squares marked. Each animal received intradermal injections from all patients' sera and control sera in a random order. Aliquots (0.1 ml) of the warm (37°C) undiluted sera were injected into duplicate sites on the shaved skin 24 hours and 5 hours prior to challenge. Control serum was obtained from patients known to be sensitive to house-dust mite, or grass pollen, but with no history of cold urticaria.

Prior to challenge, Evans Blue (2%) was injected intravenously (cynomolgous: 2 ml; baboons: 4 ml; and rhesus: 3 ml). The monkeys were observed for 5 min to detect any non-specific blueing. The injected areas were then challenged for 10 min by applying to the injection sites a plastic bag containing a crushed ice slurry. After that these sites were warmed up with hot air. Any blueing was then assessed visually. Thirty minutes later grass pollen and house-dust mite extracts (from Beecham Laboratories) in a dose of 1 mg/kg body wt. were injected intravenously to produce blueing at the control sites.

RESULTS

Serum from 3 out of 14 patients produced blueing after ice challenge (Table I). Blueing started about 10 min after the ice was removed and was maximal after 15–30 min. The blueing was not observed at control sites after ice challenge; however, these control sites became blue after intravenous grass pollen/house-dust mite challenge. Blueing at positive ice challenge sites was less intense than at the control sites after antigen challenge.

The sera of 2 subjects (E. L. & A. H.) produced a positive reaction at 5 hours in the rhesus monkey, but not at 24 hours. Serum of one (A. H.) also produced a positive reaction at one site out of two in the baboon tests. Serum of the third patient (H. R.) produced two positive reactions at 5 hours and one at 24 hours in the cynomolgous monkey.

On a separate occasion serum was again collected from the 3 positive patients and tested in a similar fashion in 2 other baboons and 2 other rhesus monkeys. However, no transfer (blueing) reactions occurred, so that attempts to determine the nature of the antibody involved by determing thermo-lability could not be interpreted.

Table I. *Passive transfer 3/14 cold urticaria patients*

Donor	Atopic status	Serum IgE (IU/ml)	Rhesus 5 h*	Rhesus 24 h*	Cynomolgous 5 h*	Cynomolgous 24 h*	Baboon 5 h*	Baboon 24 h*
E. L. ♂	+	60	+(2)	–	–	–	–	–
H. R. ♂	+	140	–	–	+(2)	+(1)	–	–
A. H. ♂	+	400	+(2)	–	–	–	+(1)	–

*= Number of hours after injection of donor serum at which the site was challenged by ice. Figures in parentheses refer to number of sites positive. Normal IgE levels up to 200 IU/ml.

DISCUSSION

As far as we are aware, this is the first report demonstrating the passive transfer to monkeys of a serum factor from patients (3 of 14) with primary acquired cold urticaria. These sub-human primates would appear to be unreliable recipients, however, because when the same positive serum was tested in 4 other monkeys no transfer was demonstrable. In contrast, positive results are usually more consistently obtained in human IgE anaphylactic antibody transfer studies in monkeys (4, 10). However, even in man-to-man transfer experiments using the same cold urticaria serum, positive passive transfer may be obtained in some human recipients and not others. For example, only 3 out of 5 human recipients were positive when using the serum from one patient with cold urticaria (5). For direct comparison of the sensitivity of obtaining positive passive transfer it would be necessary to inject both monkeys and humans with the same sera.

Houser et al. (3) have previously reported negative results in passive transfer experiments from a patient with PACU with attempted transfer to three different Macaca mulatta monkeys. This patient's serum had previously been shown to produce a positive transfer test in human volunteers. On the basis of our own experience, the most likely explanation for their negative results is that too few monkeys and species were tested. Another potential variable factor to be considered is the condition under which serum from cold urticaria patients is obtained and stored prior to transfer testing.

It is of interest that the 3 positive transfer subjects were atopic, whereas only 2 of the 11 who did not show passive transfer were atopic.

In conclusion, positive transfer has been demonstrated in a subgroup of patients with idiopathic acquired cold urticaria to this primate model. Monkeys may therefore be of value in elucidating the exact nature and role of the serum factor responsible for the passive transfer reactions.

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