

ORIGINAL ARTICLE

Reduced ability to produce reflex-evoked neurogenic inflammation, a sign of decreased defense against COVID-19 infection?

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Abstract

Background: A histamine skin prick test (SPT) generally evokes a wheal and a flare. The present study was initiated by an observation that histamine did not evoke a flare around a wheal in the skin of an 86-year-old man. Could that be of relevance to the findings that old men are prone to a more severe COVID-19 infection with a higher mortality than young ones?

Materials and methods: Histamine SPT was performed on the forearm of six old men, all above the age of 80. The skin reactions were photographed from above and from the side. The photographs taken from above were treated in a computer with LYNN, a program that increases color differences. With the help of ImageJ (NIH), the size relation between flare and wheal was calculated. On the photographs, taken as side views, areas, heights, and diameters of wheals were measured. Controls consisted of three groups of younger people.

Results: Among the old men, no or only a small flare was seen. All the controls had prominent flares. Histamine SPT evoked small wheals in the group of old men as compared to young men.

Conclusion: Reduced neurogenic inflammation evoked by histamine from mast cells in blood and tissue may reduce the defense against COVID-19 infection.

KEYWORDS

COVID-19, flare, histamine, old men, wheal

1 | INTRODUCTION

It is well known that mast cells evoke edema in the defense against allergens. In addition, mast cells can promote resistance against viral, bacterial, and fungal infections, well described in a recent review.¹ In the search for mechanisms in COVID-19 infections, mast cells have gained increasing interest.²

A rapid and large edema is suggested to be a sign of a more effective defense of microbes than a late appearing and small one. Histamine

injected into the skin, as in an ordinary histamine skin prick test (SPT) in allergy testing, may act as a model for the ability of mast cells to produce an edema. An edema, seen as a wheal in the skin, either evoked by histamine or allergens, is known to be surrounded by a flare, that is, a redness of the skin. A flare is a sign of dilated arterioles, a reflex-evoked inflammation, that exists also in, for example, respiratory mucosa.³

Recently, it was observed that a histamine SPT performed on the forearm of a man, 86 years old, did not evoke a flare. Furthermore, the wheal was rather small. High age is one of the main risk factors to

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die from COVID-19 infection.⁴ Men are about 60% more likely to be severely ill or to die from the complications of Covid-19 than women.⁵

2 | MATERIALS AND METHODS

2.1 | Subjects

Six men, 81–89 years old (mean age 85), took part in the study. They all considered themselves healthy. However, two men took an ACE-inhibitor for hypertension, one man an ACE-inhibitor and a β -adrenoceptor antagonist for cardiopathy, and a fourth man a statin for high cholesterol. Histamine SPT (histamine dihydrochloride solution, 10 mg ml^{-1} , Soluprick®, ALK-Abelló A/S) was set on the volar side of the forearm, with a generally used technique.⁶ Each subject received

two SPTs, the second one after 40 min and with a distance of 10 cm between the two SPTs.

2.2 | Methods

To document the findings, photographs were taken of the skin reactions and transferred to an iMac OS X. After the first SPT, photographs were taken from the side every second minute for 30 min. After the second SPT, photographs were taken from above every second minute for 14 min. On the 15th min, a cast of the histamine wheal was taken with a fast-stiffening material (ALGINoplast®, Heraeus Kultzer GmbH). That cast was later converted to a positive cast of plaster of Paris.

Photographs from the old individuals were compared to photographs taken in a previous study of two groups of healthy subjects,

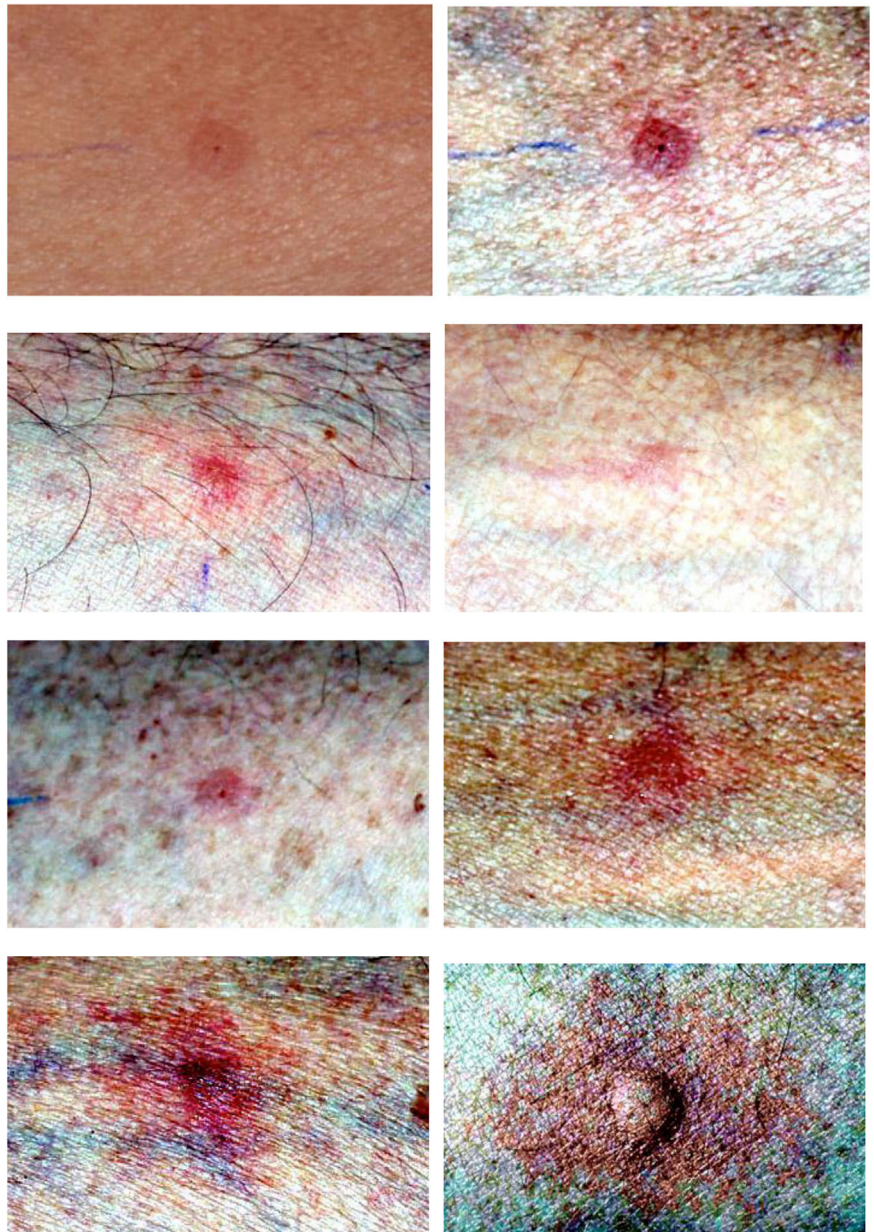


FIGURE 1 Color-increased photographs of skin reactions 14 min after a histamine SPT of six old men and one young student together with one of the original photographs are shown. Four of the old men had no flare. The fifth man had a flare and a wheal of equal size. For the sixth old man, the area of the flare was eight times the area of the wheal. The young student had a flare 14 times larger than the wheal

histamine skin prick tested in the same way.⁷ In that study, LYYN, a computer technique that increases color difference of photographs, was used. Relations between the size of flares and the size of wheals of LYYN-treated photographs of the old men were compared to those of the first group from the previous study. That group consisted of six young medical students, three men and three women (mean age 26 years). In the article of that study, only changes of the brightness of the wheals were described.

Area, height, and diameter of wheals on side view photographs of the old men were compared to side view photographs of the other group from the previous study. That group consisted of four men and two women (mean age 59 years), with wheals photographed every second minute for 30 min with the same technique as in the present study.

The positive casts of the old subjects were photographed from the side and compared to similar photographs of casts of six healthy men (mean age 50) presented in a recent study by the author.⁸ The technique to take the casts was the same as in the present study. It was thus possible to compare the results of the old men with three different series of results of the six younger men. All the side view photographs included a mm-scale.

For all measurements, ImageJ (NIH) was used, a program that gives arbitrary figures of sizes of areas and lengths plotted on a computer screen by a cursor. Heights in mm were measured with a digital caliper and diameters with a ruler on the photographs of the screen. Areas were only possible to measure in arbitrary units. Each area or length was measured six times and mean values were used for the comparisons. All the measurements of the side view photographs were done in a blinded way both regarding the old men and all the younger subjects, the latter measured once more for the present study.

2.3 | Statistics

Mean values and SD of means are given. *p*-values of less than 0.05 were considered significant. *T*-test was used for comparisons between the groups.

2.4 | Ethical permission

Ethical approval was obtained by the Ethics Review Authority, Sweden (Number 2020-06778). All six subjects gave written consent to participate in the study.

3 | RESULTS

Four of the old subjects had no flare around the wheal. The fifth one had a flare equal to the size of the wheal and the sixth one a flare eight times larger than the wheal. One original photograph from the 14th min after the SPT and six LYYN-treated ones of the old subjects together with an LYYN-treated photograph of a young student are shown in Figure 1.

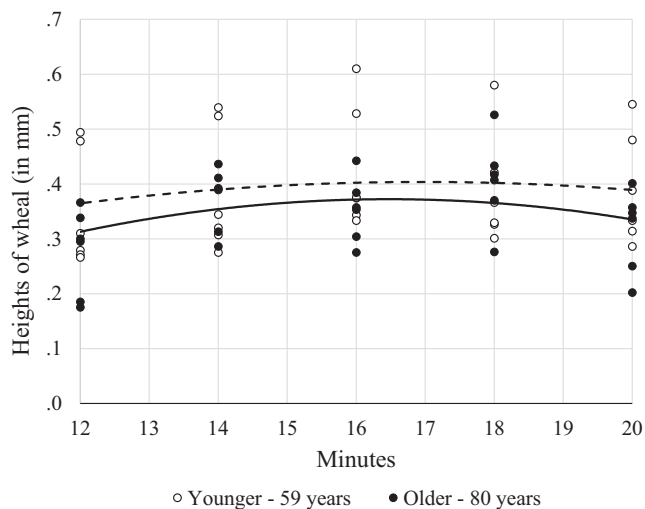


FIGURE 2 Heights of the wheals in mm of the old subjects and the subjects with a mean age of 59 years (dashed line) from the 12th to the 20th min are shown. The curves are fitted quadratic functions. There is no difference between the groups at any of the measured minutes from the 12th to the 20th min. Nor is there any difference between the groups when calculated as area under the curve (AUC)

The LYYN-treated photographs of the students had flares that were 39, 26, 24, 23, and 14, respectively, 13 times larger than corresponding wheal.

The mean heights in mm of the wheals from the 12th to the 20th min of the old subjects and the subjects with a mean age of 59 years are shown in Figure 2. The SDs of the six measurements of each of the side views of the photographs of the wheals were around 8% of the mean values. There were no differences of heights, diameters, or areas between the old men and the younger controls. The wheals seemed to peak at the same time for both groups.

The SDs of the six measurements of each of the side views of the photographs of the casts were around 4% of the mean values. There were no differences regarding the heights or diameters between the old men and the six men with the mean age of 50. However, the old men had smaller areas. When compared to the areas in the abovementioned three series of the six younger men, the *p*-values were 0.002, 0.013, and 0.017.

4 | DISCUSSION

In six men, 81–89 years old, subjected to histamine SPT on the forearm, the flares were absent or small around the wheals in contrast to what was seen in young subjects. There are few reports on similar results. In one study, 365 subjects were histamine skin prick tested. The authors wrote that “all subjects had a flare, but in some older than 70 years, the flare reaction was small.”⁹ In another study, substance P was injected into the forearm of diabetics and healthy controls. A smaller flare was found with increasing age in both diabetic patients and controls.¹⁰ Not only old people but also diabetic patients have an increased mortality in

COVID-19 infections.¹¹ Thus, reduced flare may be added to the signs of increased vulnerability for the disease.

The histamine wheals were not smaller in the old men than in the two groups of younger people, when height or diameter was calculated. However, areas of the elevation of casts, representing histamine wheals, were smaller in the old men. The results indicate that neurogenic inflammation is of importance for the size of histamine-evoked edema. Then, if a small edema as compared to a large one implies lowered defense against viruses remains to be demonstrated.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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